UNIVERSIDADE D
COIMBRA

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Pharmacist Intervention in the Identification of Risk Factors and Optimization of Pharmacotherapy for Cardiovascular Disease

Doctoral Thesis in Pharmaceutical Sciences, specialization in Pharmacology and Pharmacotherapy, supervised by Professor Isabel Vitória Figueiredo and by Professor Margarida Castel-Branco and presented to the Faculty of Pharmacy of the University of Coimbra

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Dedico este trabalho a quem me dedicou tudo.

Aos meus Avós.

Aos meus Pais, Sérgio e Isaura.

Às minhas manas, Tina e Mena.

Aos meus sobrinhos, especialmente ao meu Miguel.

Aos meus queridos filhos Lara e Tomás.

Ao Amor da minha vida, Dito!

Agradecimentos

O trabalho agora apresentado é fruto de um desafio pessoal, profissional e uma enorme vontade de perceber como evidenciar o farmacêutico como profissional de saúde valioso e que merece ser reconhecido como tal. Rapidamente percebi que precisaria de muito mais ajuda do que pensava. Assim, o chegar a bom porto deste percurso deve-se à preciosa ajuda de muitos intervenientes.

Os meus sinceros agradecimentos às minhas orientadoras, Professora Doutora Isabel Vitória Figueiredo e Professora Doutora Margarida Castel-Branco pela oportunidade e por me orientarem, no verdadeiro sentido da palavra. Pela orientação científica, pelos incentivos e esforços desenvolvidos para levar a cabo o trabalho apresentado.

Ao Professor Doutor Fernando Fernandez-Llimos, pela orientação científica, pela disponibilidade em ensinar e pela partilha de tanto conhecimento indispensável neste percurso.

Ao Professor Doutor Tácio Lima, que do outro lado do Atlântico, prontamente se juntou ao nosso projeto e foi indispensável em várias etapas deste trabalho.

À minha Amiga Margarida, sempre ao meu lado!

À Dra. Maria Luísa Costa, com quem aprendi a gerir a responsabilidade que uma farmacêutica tem ao "estar ao balcão". Ao Dr. António Carlos Costa, que tornou o percurso deste Doutoramento possível. A todos os colaboradores da farmácia Gama, especialmente à minha colega e amiga Dra. Bárbara Correia. Saudades!

A todos os utentes da Farmácia Gama, que dediquei 20 anos da minha vida e que me retribuíram com enorme carinho.

Às dezenas de estagiários que passaram pela farmácia durante o seu percurso académico, com quem tanto aprendi e partilhei conhecimento.

A todos o meu Bem hajam!

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Abstract

Cardiovascular disease (CVD) remains the leading cause of human mortality. Assessing the patients' CVD risk, controlling the risk factors, and ensuring guideline-adherent cardiovascular pharmacotherapy are crucial interventions to improve cardiovascular health outcomes. As accessible and qualified health professionals, community pharmacists can be included in the early detection of patients at risk for CVD by implementing CVD screening programs and by improving cardiovascular pharmacotherapy.

The aim of this research was, on the one hand, to evaluate the feasibility of implementing screening programs for individuals at risk of cardiovascular disease in a Portuguese community pharmacy, and on the other hand, to assess the potential of pharmacist intervention in the optimization of pharmacotherapy in users who were already on cardiovascular therapy.

A cross-sectional study was conducted in a community pharmacy in Portugal. The reasons for which the customers entered the pharmacy were registered and subsequently, they were invited to be interviewed by the pharmacist, who recorded their willingness to participate. The pharmacist performed in-pharmacy point-of-care testing on the participants who accepted to evaluate the cardiovascular risk, and also collected the participants' data and biochemical and physical parameters in order to assess their cardiovascular risk by applying the Systematic COronary Risk Evaluation (SCORE) model. On those participants who were not eligible for the SCORE-based risk assessment, the pharmacist considered the major modifiable CVD risk factors - hypertension, dyslipidemia, smoking habits, obesity, impaired fasting glucose, and sedentary behavior - according to the European Society of Cardiology (ESC) guidelines. For the participants who were already on cardiovascular pharmacotherapy, the pharmacist reviewed patients' pharmacotherapy, based on ESC guidelines.

In terms of customers profile, picking up medication was the most prevalent reason (69.8%) for entering the pharmacy. Of the customers who entered the pharmacy to acquire medication, 36.2% acquired at least one medicine from the CVD pharmacotherapy. More than half (64.1%) of the customers were regular customers, the majority (65.6%) were under 65 years of age, and the male customers were older ($t=4.793$, $p<0.001$). Among the contacted customers, 56.4% (n=621) agreed to have their CVD risk assessed, and 53.4% (n=588) actually attended the cardiovascular risk assessment. There was no difference in

acceptability between male and female pharmacy customers, and the pharmacy customers who were more likely to accept the risk evaluation were those who entered the pharmacy for the acquisition of medicines ($p=0.004$), elderly customers ($p<0.001$) and regular customers ($p<0.001$).

Of the 588 participants, 56.6% (n=333) were already on cardiovascular pharmacotherapy and were therefore not eligible for screening. Of the 43.4% (n=255) cardiovascular pharmacotherapy-naïve participants, 94.9% (n=242) were screened with at least one CVD risk factor; 52.9% (n=135) were not eligible for the SCORE assessment, of which 92.6% (n=125) presented CVD risk factors. Of the 120 SCORE-eligible participants, 80.0% (n=96) were at least at moderate risk of CVD.

Of the 333 patients who were already on cardiovascular pharmacotherapy, 63.1% were in the high/very high-risk category, 91.9% showed at least two uncontrolled modifiable risk factors, and in 61.9% of patients, the cardiovascular pharmacotherapy was non-adherent to the current guidelines, failing to reach treatment goals. The lipid-lowering therapy was the least guideline adherent, with a suboptimal use of statins. However, we found no statistically significant difference between the guideline-adherent and the non-adherent group in terms of risk factor control. The pharmacist recommended 603 interventions to adhere to the guidelines.

The feasibility of CVD risk screening in Portuguese community pharmacies was determined, as a high customer acceptability rate was found, the reasons for nonattendance were evaluated, and a high prevalence of CVD risk factors was found and at-risk patients were detected. Furthermore, it was shown that community pharmacists are able to identify opportunities to optimize cardiovascular pharmacotherapy and support patients to achieve cardiovascular risk factor goals, based on evidence-based guidelines, contributing to the improvement of CVD management. The opportunity exists for Portuguese community pharmacists to take an active role in the early detection of CVD and to be included in the healthcare team members that are responsible for the optimization of cardiovascular pharmacotherapy and the achievement of cardiovascular risk factor goals of the patients.

Keywords: cardiovascular disease; risk factors; risk assessment; guideline adherence; pharmacists.

Resumo

A doença cardiovascular continua a ser a principal causa de morte dos seres humanos. Avaliar o risco cardiovascular dos doentes, controlar os fatores de risco, e garantir a concordância da terapêutica cardiovascular com as recomendações clínicas são intervenções cruciais para melhorar os resultados em saúde cardiovascular. Como profissionais de saúde acessíveis e qualificados, os farmacêuticos comunitários podem ser incluídos na deteção precoce de doentes em risco de doença cardiovascular, implementando programas de rastreio de doença cardiovascular e otimizando a terapêutica cardiovascular.

O objetivo deste trabalho de investigação foi, por um lado, avaliar a viabilidade da implementação de programas de deteção precoce de indivíduos com risco de doença cardiovascular numa farmácia comunitária portuguesa e, por outro lado, avaliar o potencial da intervenção farmacêutica na otimização terapêutica dos utentes que já se encontravam sob terapêutica cardiovascular.

Realizou-se um estudo observacional transversal numa farmácia comunitária em Portugal. Procedeu-se ao registo das razões pelas quais os utentes entraram na farmácia e, posteriormente, estes foram convidados a ser avaliados pelo farmacêutico, que registou a sua prontidão em participar. Durante a entrevista o farmacêutico recolheu dados sociodemográficos e avaliou parâmetros fisiológicos e bioquímicos nos participantes que aceitaram avaliar o risco cardiovascular; seguidamente determinou o risco cardiovascular aplicando o algoritmo SCORE. Nos participantes que não eram elegíveis para a avaliação de risco baseada no SCORE, o farmacêutico considerou os principais fatores de risco de doença cardiovascular modificáveis - hipertensão, dislipidemia, tabagismo, obesidade, glicémia em jejum alterada, e sedentarismo - de acordo com as recomendações da Sociedade Europeia de Cardiologia. Nos participantes que já estavam sob terapêutica cardiovascular, o farmacêutico procedeu à revisão da medicação dos doentes, com base nas recomendações da Sociedade Europeia de Cardiologia.

Relativamente ao perfil dos utentes, a aquisição de medicamentos foi a razão mais prevalente (69,8%) para entrar na farmácia. Dos utentes que entraram na farmácia para adquirir medicamentos, 36,2% adquiriram pelo menos um medicamento do foro cardiovascular. Mais de metade (64,1%) dos utentes eram utentes habituais, a maioria (65,6%) tinha menos de 65 anos de idade, e os utentes do sexo masculino eram mais velhos

(t=4,793, p<0,001). Entre os utentes contactados, 56,4% (n=621) concordaram com a avaliação do seu risco cardiovascular, e 53,4% (n=588) efetivamente voltaram para avaliar o seu risco cardiovascular. Não houve diferença na aceitação entre os utentes do sexo masculino e feminino, e os utentes mais suscetíveis de aceitarem a avaliação do risco cardiovascular foram os que entraram na farmácia para a aquisição de medicamentos (p=0,004), os utentes idosos (p<0,001) e os utentes habituais (p<0,001).

Dos 588 participantes, 56,6% (n=333) já se encontravam sob terapêutica cardiovascular, pelo que não foram elegíveis para o rastreio. Dos 43,4% (n=255) participantes sem terapêutica cardiovascular, 94,9% (n=242) foram rastreados com pelo menos um fator de risco de doença cardiovascular; 52,9% (n=135) não eram elegíveis para a avaliação SCORE, dos quais 92,6% (n=125) apresentavam fatores de risco de doença cardiovascular. Dos 120 participantes elegíveis para o SCORE, 80,0% (n=96) apresentavam, pelo menos, risco moderado de doença cardiovascular.

Dos 333 doentes que já se encontravam sob terapêutica cardiovascular, 63,1% estavam na categoria de risco alto ou muito alto, 91,9% apresentavam pelo menos dois fatores de risco modificáveis descontrolados, e em 61,9% dos utentes, a terapêutica cardiovascular não estava em conformidade com as recomendações atuais, não conseguindo atingir os objetivos terapêuticos. A terapêutica hipolipemiante foi a menos concordante com as recomendações clínicas, com uma utilização subótima de estatinas. No entanto, não observámos diferença estatisticamente significativa entre os grupos "concordante" e "não concordante" com as recomendações, em termos de controlo dos fatores de risco. O farmacêutico identificou 603 oportunidades de intervenção passíveis de ajuste da terapêutica.

Demonstrámos a viabilidade do rastreio de risco de doença cardiovascular nas farmácias comunitárias pela elevada percentagem de utentes que aceitaram avaliar o seu risco cardiovascular, pela avaliação das razões de não aceitação e pela elevada prevalência de fatores de risco e de doentes em risco de doença cardiovascular detetados. Além disso, foi demonstrado que os farmacêuticos comunitários são capazes de identificar oportunidades para otimizar a terapêutica cardiovascular e ajudar os utentes a alcançar os objetivos terapêuticos dos fatores de risco cardiovascular, com base em recomendações baseadas na evidência, contribuindo para a melhoria da gestão da doença cardiovascular. Existe a oportunidade de os farmacêuticos comunitários portugueses assumirem um papel ativo na deteção precoce da doença cardiovascular e de serem incluídos na equipa de profissionais

de saúde responsáveis pela otimização da terapêutica cardiovascular e dos objetivos terapêuticos dos fatores de risco cardiovascular dos doentes.

Palavras-Chave: doença cardiovascular; fatores de risco; avaliação de risco; concordância com recomendações clínicas; farmacêuticos.

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List of abbreviations and acronyms

ACC - American College of Cardiology

ACE - angiotensin-converting enzyme

AHA - American Heart Association

AMI - acute myocardial infarction

ARBs - angiotensin receptor blockers

ASCVD - atherosclerotic cardiovascular disease

BMI - body mass index

BMQ - The Beliefs about Medicines Questionnaire

BP - blood pressure

CCBs - calcium channel blockers

CHD - coronary heart disease

CKD - chronic kidney disease

CVD - cardiovascular disease

DALYs - Disability-Adjusted Life Years

DBP - diastolic blood pressure

DM - diabetes *mellitus*

DRP - drug related problem

ESC - European Society of Cardiology

ESH - European Society of Hypertension

GLP-1RA - glucagon-like peptide-1 receptor agonist

HbA1c - glycated hemoglobin

HDL-C - high-density lipoprotein cholesterol

HMG CoA - hydroxymethylglutaryl-coenzyme A

IHD - ischemic heart disease

LDL-C - low-density lipoprotein cholesterol

NCD - Noncommunicable disease

PCNE - Pharmaceutical Care Network Europe

PRISMA - Preferred Reporting Items for Systematic Reviews and Met-Analysis

RAAS - renin-angiotensin-aldosterone system

RCT - randomized controlled trial

SBP - systolic blood pressure

SCORE - Systematic Coronary Risk Estimation

SGLT2 - sodium-glucose cotransporter-2

TG - triglycerides

WHO - World Health Organization

General introduction and objectives

Cardiovascular disease accounts for nearly half of all non-communicable disease deaths. Reducing premature mortality from non-communicable diseases by 25% is the World Health Organization's target for 2025. With the purpose of showing the burden of CVD, this work starts with a global overview of the mortality of cardiovascular disease worldwide, in Western Europe, and more specifically in Portugal. To reduce the CVD burden, the management of cardiovascular disease needs a multifactorial and multi-professional approach, as CVD has multiple risk factors, which have a synergistic effect on the risk of CVD. Lifestyle changes, risk factor detection, and control, and ensuring adherence to cardioprotective medication regimes are crucial in the management of CVD, as per guiding evidence-based clinical recommendations.

The work continues with a review of the most important cardiovascular risk factors, their relation to CVD, and the recommended targets, as well as the review of emerging cardiovascular risk factors.

The synergistic effect of CVD risk factors is measurable with cardiovascular disease risk assessment tools. Thus, this work proceeds with the review of the most used risk assessment tools.

Success of the management of CVD relies on collective work through effective interdisciplinary team-based care with the same goals, clearly defined roles, and effective communication. The role of community pharmacists in CVD management is analyzed through an umbrella review. Following the review of the community pharmacists in CVD management, the Portuguese reality of pharmacy services and its context is explored.

Finally, the study itself is presented, consisting of four major parts with the following objectives:

- To assess the feasibility of cardiovascular risk screening in Portuguese community pharmacies, the characterization of the profile of community pharmacy users and evaluation of their acceptability towards cardiovascular risk assessment by the community pharmacist and reasons for nonattendance were evaluated.
- To evaluate the role of pharmacists in the early detection of at-risk customers in a community pharmacy, a cardiovascular risk factor screening study in a

community pharmacy of cardiovascular pharmacotherapy naïve participants was conducted.

- To assess the potential of pharmacists to optimize the adherence to pharmacotherapy guidelines and the achievement of risk factor goals among patients who attend a community pharmacy, the evaluation of the cardiovascular pharmacotherapy guideline adherence and risk factor control of patients already on cardiovascular pharmacotherapy was performed.
- To evaluate other health outcomes of the study the health status - EuroQol-EQ-5D-3L; the Beliefs about Medicines Questionnaire (BMQ); the cardiovascular pharmacotherapy in the analyzed patients; the type 2 diabetes risk assessment; and the medication review, with the results of the drug-related problems and interventions, were analyzed.

Meanwhile, the ESC published the new risk prediction algorithms SCORE2 and SCORE2-OP, and the evaluation of the sample in light of these new charts was carried out.

The overall aim of this work was to comprehend the role that Portuguese community pharmacists can assume in the struggle against CVD.

CHAPTER I - Management of cardiovascular disease

1. Introduction

Cardiovascular disease continues to be the main cause of death worldwide. In 2019, CVD was responsible for 29.9% of deaths in Portugal (Instituto Nacional de Estatística, 2020). CVD is also among the main cause of morbidity, disability and potential years of life lost in the Portuguese population (Direção-Geral da Saúde, 2004; Ribeiro et al., 2013). For this reason, it is essential to adopt preventive measures in individuals at risk of developing CVD (primary prevention) and measures that prevent the recurrence of events in individuals with established CVD (secondary prevention).

2. Cardiovascular disease

CVD is a term used to refer to the range of diseases that affect the heart and blood vessels. CVD as a diagnostic category includes four major areas:

- Coronary heart disease (CHD), manifested by fatal or non-fatal myocardial infarction, angina pectoris, and heart failure.
- Cerebrovascular disease, manifested by fatal or non-fatal stroke and transient ischemic attack.
- Peripheral artery disease, manifested by intermittent claudication and critical limb ischemia.
- Aortic atherosclerosis and thoracic or abdominal aortic aneurysm.

According to the 'Global Atlas on CVD prevention and control' published by the World Health Organization (WHO) (World Health Organization et al., 2011), CVD is considered a group of disorders that include vascular diseases of the brain, diseases of the heart and diseases of blood vessels, which in terms of causes can be classified into two different types:

- CVD due to atherosclerosis, which includes ischemic heart disease or coronary artery disease, cerebrovascular disease, diseases of the aorta and arteries, including hypertension and peripheral vascular disease.
- Other CVD, which includes congenital heart disease, rheumatic heart disease, cardiomyopathies and cardiac arrhythmias.

3. Cardiovascular disease worldwide, in Western Europe and Portugal

Noncommunicable diseases (NCD), also known as chronic diseases, kill 41 million people each year, equivalent to 71% of all deaths globally. CVD is the leading NCD in terms of premature deaths and account for most NCD deaths annually (17.9 million), followed by cancers (9.0 million), respiratory diseases (3.9 million), and diabetes (1.6 million). Worldwide, 56 million people died in 2017 and 17.9 million died from CVD. This means that almost 32% of the world population died from CVD, confirming that CVD remains the leading cause to the burden of mortality across the world (Ritchie & Roser, 2019).

The ESC released the 'Cardiovascular Disease Statistics 2017 Atlas' that was compiled by the European Heart Agency to document CVD statistics of the 56 ESC member countries and present a global overview of the causes of death (Timmis et al., 2018). The data sources of the referred Atlas include the WHO, the Institute for Health Metrics and Evaluation and the World Bank to document risk factors, prevalence, and mortality of CVD and national economic indicators and to provide a comparison between causes of death across countries (Ritchie & Roser, 2019). The authors conclude that the causes of death across the world remain heterogeneous and continue to change as global population increases, life expectancy rises and living standards improve. Due to this heterogeneity, it is important for each country to look at its numbers and to work towards its improvement.

The share of deaths shown in Figures 1, 2, and 3 present the percentage of total deaths in 2017 and reveal the causes of death worldwide, in Western Europe and in Portugal, respectively.

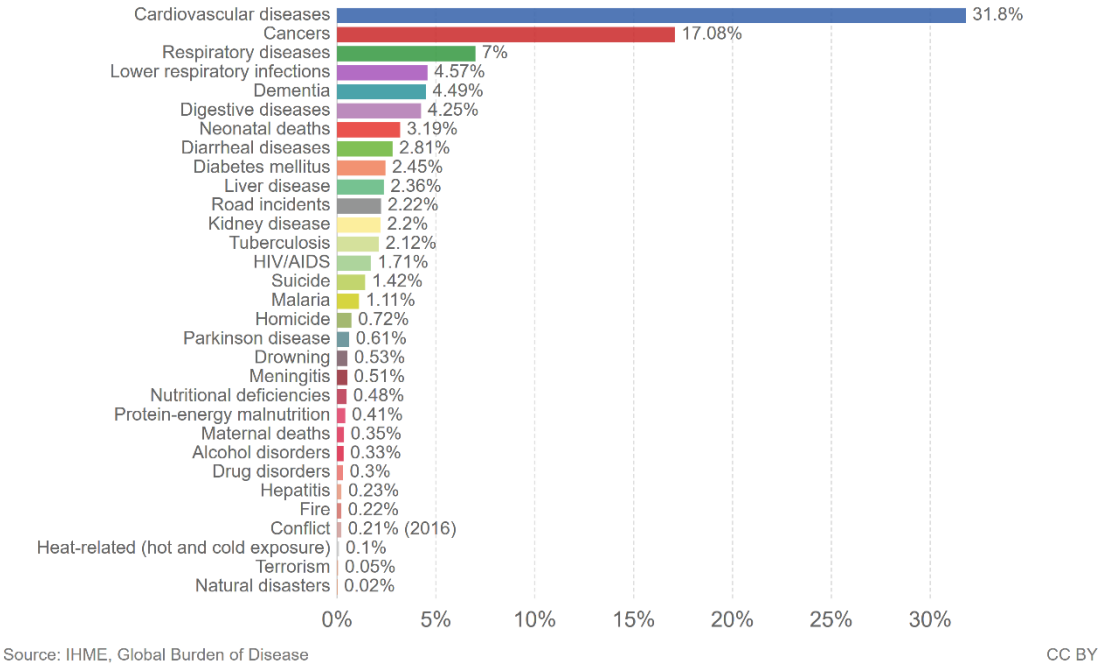

Figure 1 - Share of deaths by cause, worldwide.

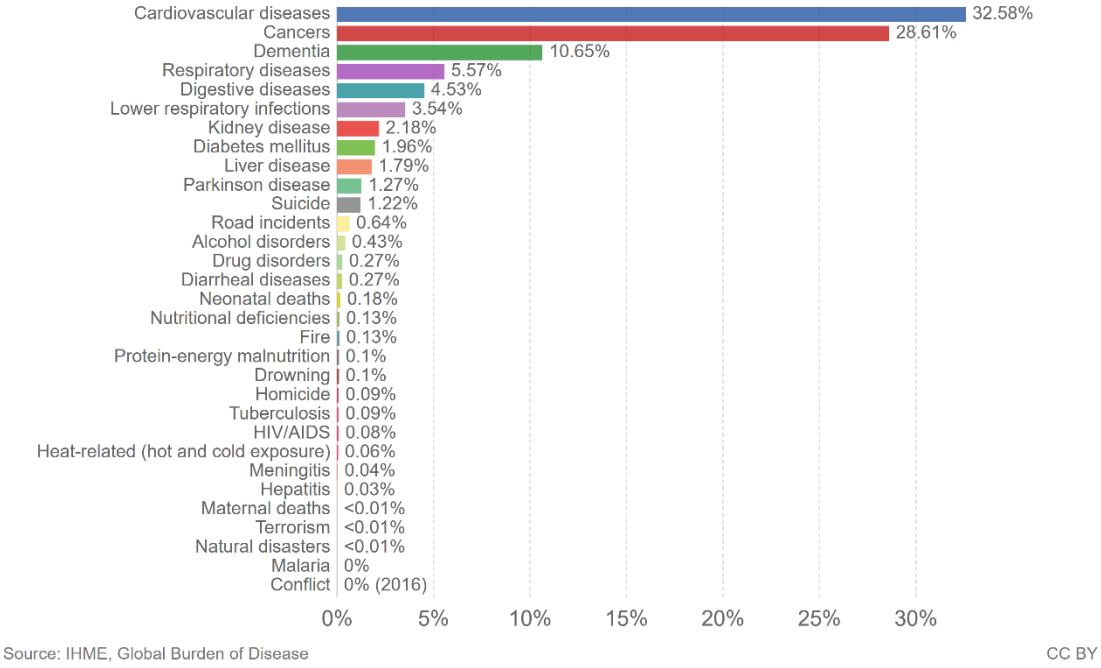

Figure 2 - Share of deaths by cause in Western Europe.

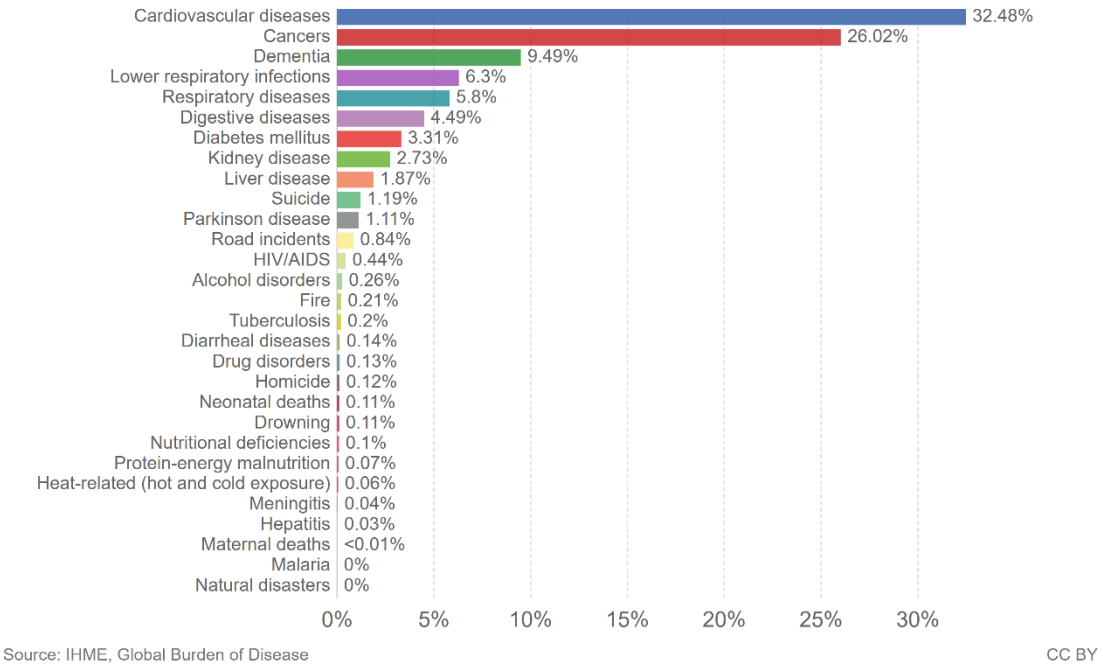

Figure 3 - Share of deaths by cause in Portugal.

The causes of death vary significantly by country and income levels across the world, but CVD is the global top cause of death. The map in Figure 4 shows the death rates from CVD across the world in 2017, and it is noticeable that there is a strong East-West divide in CVD death rates.

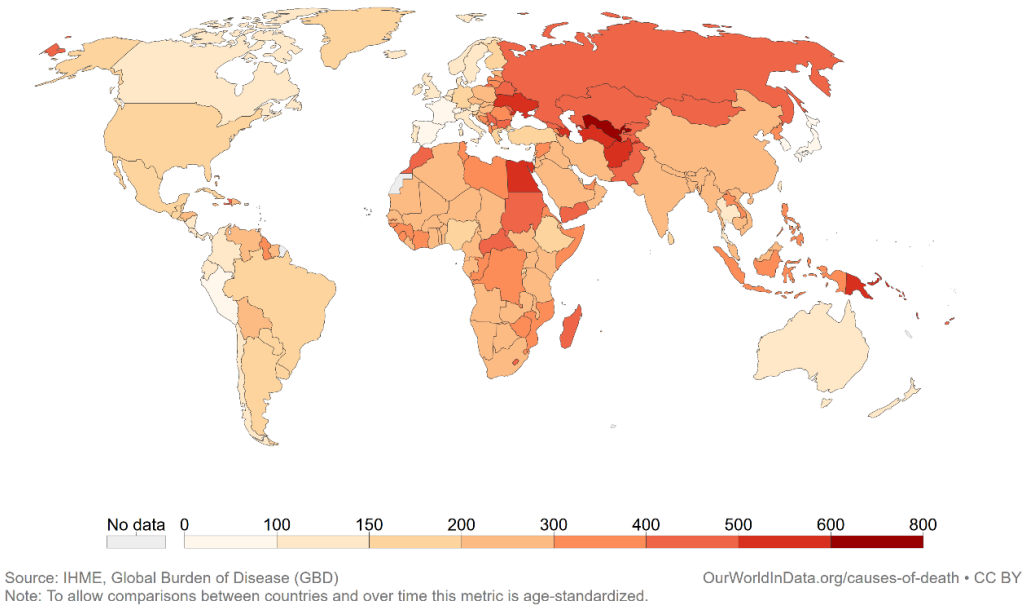

Figure 4 - Death rate from CVD - annual number of deaths per 100 000 people.

The graphs in Figures 5 and 6 show the breakdown of deaths from CVD by age category, reporting annual number of deaths from CVD differentiated by age category. As referred globally approximately 17.9 million people died from CVD in 2017. The majority (63%) of deaths occurred in the age bracket of 70 years and above. Just below 30% were aged 50-69, and the remaining 7-8% aged 15-49. These data clearly depict the age burden of CVD.

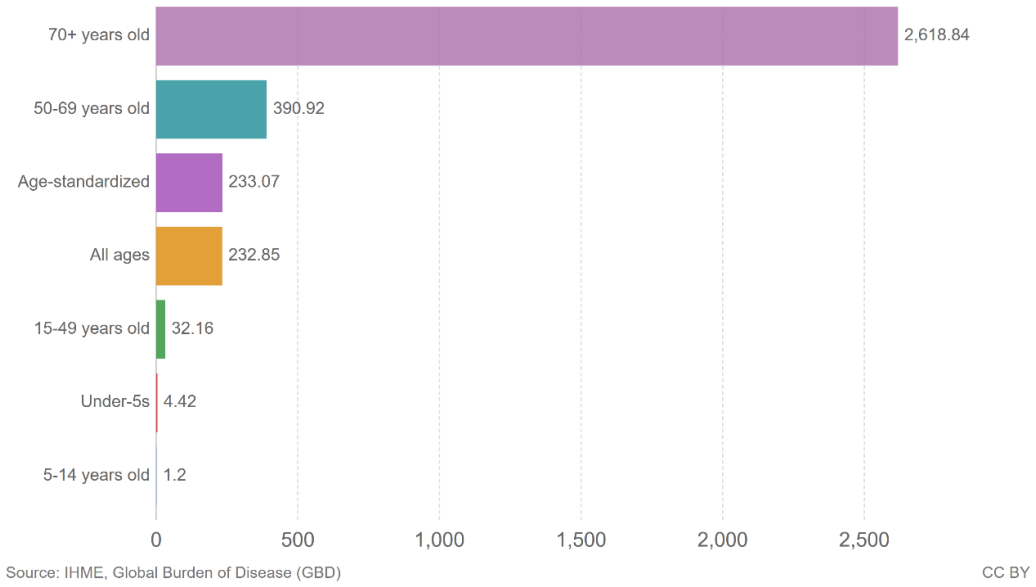

Figure 5 - Cardiovascular disease death rates by age, worldwide.

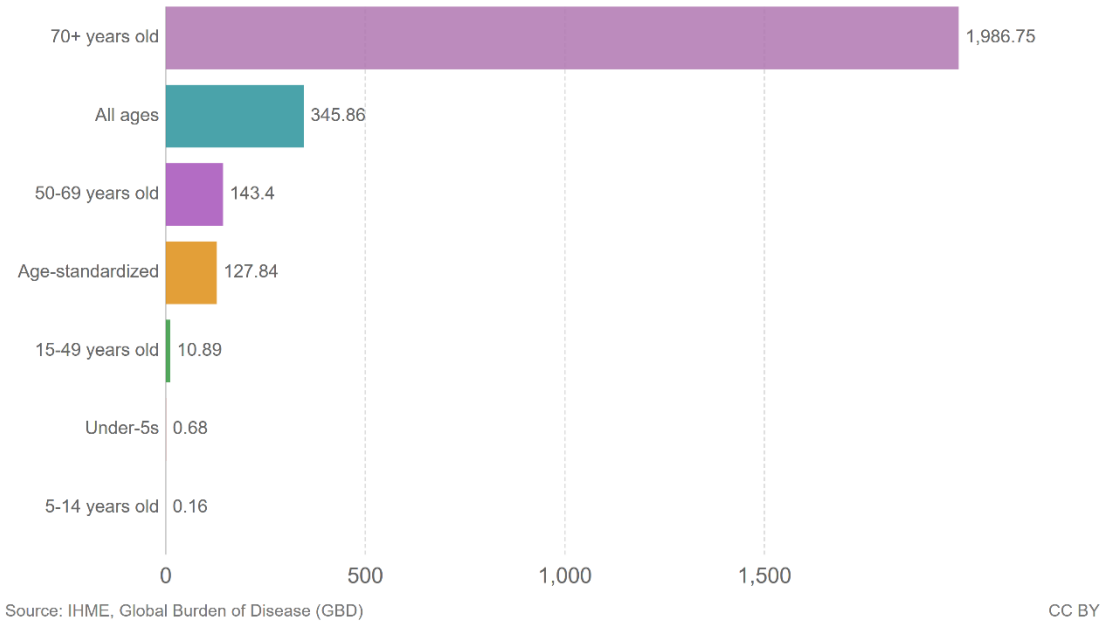

Figure 6 - Cardiovascular disease death rates by age in Portugal.

However, in high-income countries and some Latin American countries CVD death rates are, in fact, decreasing steadily, and the declines have been ongoing for decades without slowing down. These positive trends coincide with the decline in smoking and other risk factors such as blood pressure (BP) and serum cholesterol levels, confirming the beneficial effect of controlling cardiovascular risk factors on CVD. These decreases also coincide with improvements in health care, including primary prevention, diagnosis, and treatment of acute CVD, as well as in post-hospital care, especially over the past 40 years. Although in many countries the prevalence of CVD has decreased in the last two decades, cardiovascular conditions such as CHD and stroke remain the two most common causes of disease worldwide, accounting for a combined 15.2 million deaths in 2016. These diseases have remained the leading causes of death globally in the last 15 years (World Health Organization, 2016a; Roth et al., 2017).

In Portugal, CVD is the main cause of death and is one of the most important causes of morbidity and disability (Ferreira et al., 2016) and its management remains at the top of the priorities in terms of health planning. In 2014, ischemic stroke alone accounted for around 20000 episodes and 250000 days of hospitalization (Direção-Geral da Saúde, 2015a). Despite the improvement in cardiovascular mortality and morbidity indicators in Portugal and the Mediterranean region, it is necessary to reduce premature deaths and delay the development of CVD. For this purpose, it will be important to continue promoting health education with a focus on lifestyles and to monitor the evolution of risk factors and cardiovascular events (Rocha & Nogueira, 2015). Currently, heart failure has a significant economic impact, representing 2.6% of Portuguese public health expenditure, which is expected to increase in the future. This fact should be taken into account by health policymakers, alerting them to the need for resource management in order to mitigate the impact of this disease (Gouveia et al., 2020). In addition to the large number of expected heart failure patients, it is estimated that the hospitalizations and mortality associated with this syndrome will significantly increase its economic impact. Therefore, it is important to raise awareness of heart failure, as this will favor diagnosis and early referral of patients, thus facilitating better management and help decrease the burden it imposes on Portugal (Fonseca et al., 2018). In 2017, the stroke mortality rate in Portugal was 53.85 per 100 000 individuals, which can be compared to the global age-standardized stroke mortality rates represented in the Figure 7.

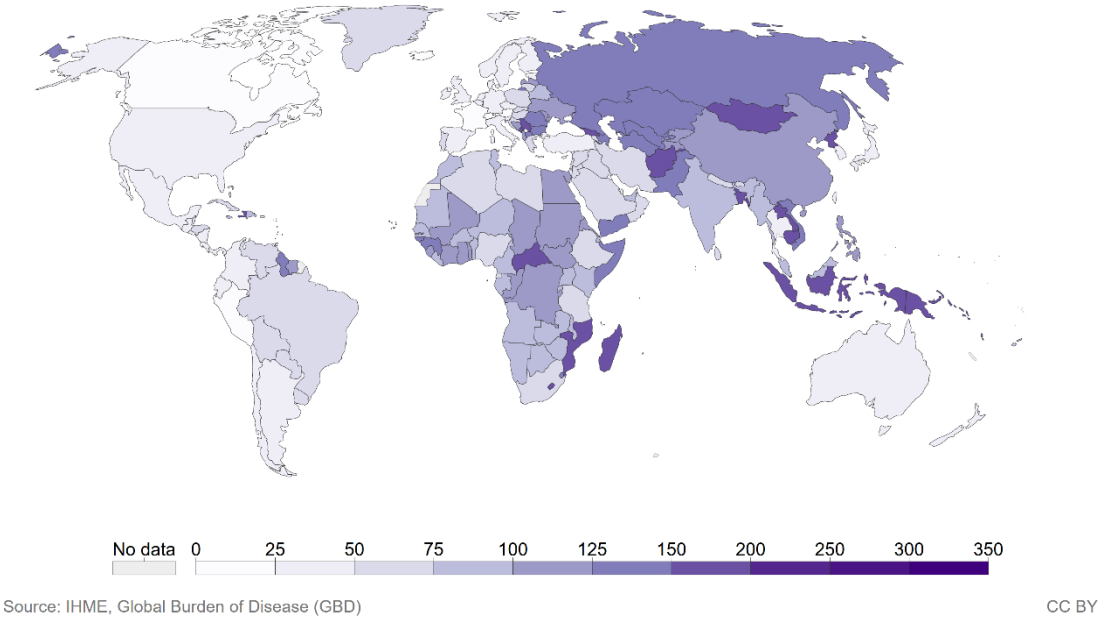

Figure 7 - Stroke mortality rate.

The impact of morbidity of CVD is measured by the total disease burden, which is measured in Disability-Adjusted Life Years (DALYs) both from Years of Life Lost due to premature mortality in the population and the Years Lost due to Disability for people living with the health condition. One DALY equals one lost year of healthy life. The burden of CVD mortality and morbidity is the most prevalent worldwide and one of the most prevalent in Europe and Portugal, where only cancer slightly exceeds the numbers, as shown in Figure 8.

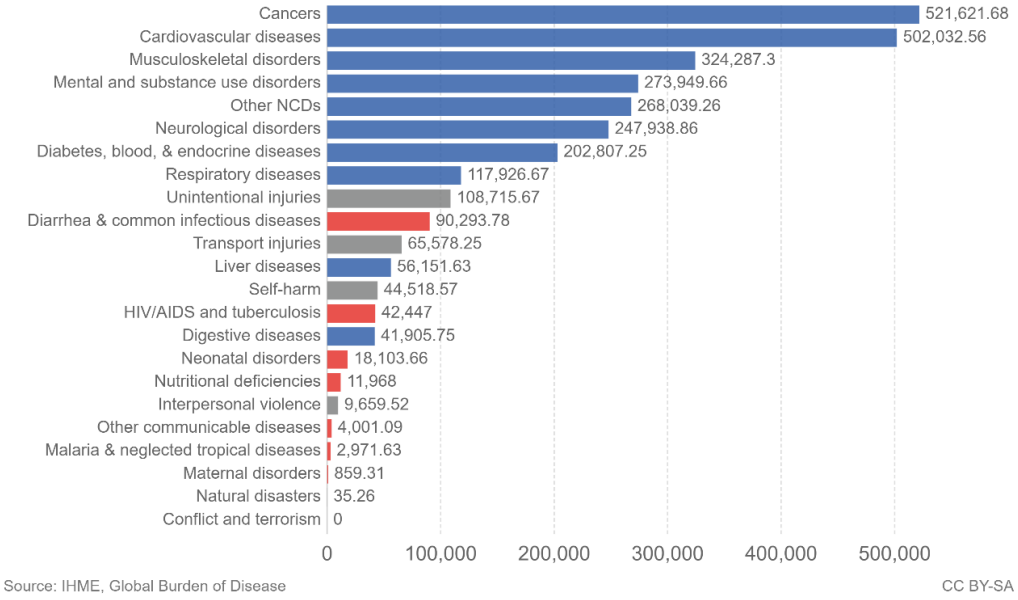

Figure 8 - Burden of disease by cause in Portugal.

4. Clinical guidelines in the management of cardiovascular disease

A large number of CVD guidelines have been developed by societies and organizations with the aim of recommending health professionals the best management strategies for patients with a given condition and to support the decision-making in daily practice. These guidelines are regularly updated based on available scientific evidence, which is constantly evolving.

Since the 1960s, the role of risk factors in CVD has been proven and intervention studies have been underway. Evidence from landmark clinical trials has supported the development of guidelines for CVD prevention, recommendations and management, developed by professional organizations and national societies in the past decades. The aim of guidelines in the management of CVD is to establish thresholds and target levels of cardiovascular risk factors, which are established and defined as normal for the lowest risk group, and also to recommend the interventions needed to achieve these goals for individuals at different risk levels (Visseren et al., 2021). Thus, to effectively reduce the incidence of CVD, efforts must be made to modify lifestyle trends and to reduce risk factors, which must be taken into account in public policy and education. Moreover, the identification of high-risk patients and their management, including pharmacological interventions, is mandatory and should be based on clinical evidence. Equivalent contributions of prevention initiatives, pharmaceutical developments and technological improvements have led to an important success in the reduction of mortality related to CVD in some countries of the Western world (van Camp, 2014). In the last three decades, more than half of the reduction in cardiovascular mortality has been attributed to changes in risk factor levels, mainly reductions in cholesterol and blood pressure levels and smoking. This favorable trend is partly outweighed by an increase in other risk factors, primarily obesity and type 2 diabetes (O'Keeffe et al., 2013; Mason et al., 2014). Global deaths from CVD increased by 41% between 1990 and 2013 despite a 39% decrease in age-specific death rates. This increase was determined by a 55% increase in mortality due to the aging of populations and a 25% increase due to population growth (O'Keeffe et al., 2013).

Since 2003, the ESC has published clinical practice guidelines on cardiovascular specific issues to present relevant evidence and provide knowledge for everyday clinical decision-making. The ESC cardiovascular disease guidelines have been updated with the most recent publication, the guidelines on diabetes, pre-diabetes, and CVD, developed in collaboration with the European Association for the Study of Diabetes (Cosentino et al., 2020), the

guidelines for the management of dyslipidemias (Mach et al., 2020), and the Guidelines on cardiovascular disease prevention in clinical practice (Visseren et al., 2021). With the same aim of preventing CVD, improving the management of people who have these diseases through professional education and research, the American College of Cardiology (ACC) and the American Heart Association (AHA) develop guidelines, standards, and policies that promote optimal patient care and cardiovascular health. The ACC and AHA have collaborated with the National Heart, Lung, and Blood Institute and stakeholders and professional organizations to develop clinical practice guidelines for assessment of cardiovascular risk and have been publishing their update guidelines on primary and secondary prevention of CVD (Levine et al., 2019). These guidelines are mostly in accordance with recommendations from the WHO and other international clinical societies, which state that CVD is strongly connected to lifestyle, especially the use of tobacco, unhealthy diet habits, physical inactivity, and psychosocial stress.

The international and European clinical guidelines recommend that general practitioners, nurses and allied health professionals implement strategies for CVD prevention for high-risk patients, including lifestyle changes, risk factor management and pharmacological optimization. Moreover, the European clinical guidelines recommend that patient follow-up should be carried out by the health care team, which should include physicians, nurses, and pharmacists in a concerted activity (Piepoli et al., 2016; World Health Organization, 2018a). The 2016 European Guidelines on CVD prevention in clinical practice represent an evidence-based consensus of the sixth European Joint Task Force involving and developed by 10 professional societies, to support health care professionals communicating with individuals about their cardiovascular risk and the benefits of a healthy lifestyle and early modification of their cardiovascular risk. Guidelines and clinical documents of the ESC, the ACC often in collaboration with the AHA Joint Committee on Clinical Practice Guidelines, the Canadian Cardiovascular Society, and the National Institute for Health and Care Excellence, provide a framework of evidence-based clinical statements and guidelines developed by leaders in the field of cardiovascular medicine. In Europe, the ESC guidelines are endorsed by most cardiac societies and national health systems and are continuously updated, as shown in Table 1.

Table I - ESC guidelines and scientific documents release.

Year	Guideline or Expert Consensus Document
2002	Guidelines for the Interpretation of the Neonatal Electrocardiogram
	Management of Chest Pain
2003	Estimation of Ten-Year Risk of Fatal Cardiovascular Disease in Europe: the SCORE Project
	Medical Practice Guidelines: Separating Science from Economics
2004	Expert Consensus Document on β-Adrenergic Receptor Blockers
	ESC Expert Consensus Document on Angiotensin Converting Enzyme Inhibitors in CVD
	Expert Consensus Document on the Use of Antiplatelet Agents
2007	The Role of Endomyocardial Biopsy in the Management of CVD
2010	Focused Update - Device Therapy in Heart Failure
2014	Hypertrophic Cardiomyopathy
	Aortic Disease
	ESC/ European Atherosclerosis Society - Non-Cardiac Surgery: Cardiovascular Assessment and Management
2015	Infective Endocarditis
	Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death
	Pericardial Disease
	Pulmonary Hypertension
2016	Position Paper - Cancer Treatments and Cardiovascular Toxicity
2017	Peripheral Arterial Disease
	Focused Update on Dual Antiplatelet Therapy
	Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation
2018	ESC/ESH Arterial Hypertension
	ESC/EACTS Myocardial Revascularization
	Fourth Universal Definition of Myocardial Infarction
	Cardiovascular Diseases during Pregnancy
	Syncope
2019	Diabetes, Prediabetes and Cardiovascular Disease
	Supraventricular Tachycardia
	Dyslipidemias
	Chronic Coronary Syndromes
	Acute Pulmonary Embolism
2020	Sports Cardiology and Exercise in Patients with CVD
	Atrial Fibrillation
	Adult Congenital Heart Disease
	Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation
2021	Heart Failure
	Valvular Heart Disease
	Cardiac Pacing & Cardiac Resynchronization Therapy
	CVD Prevention

CVD – Cardiovascular cardiovascular disease; EACTS - European Association for Cardio-Thoracic Surgery; ESC - European Society of Cardiology; ESH - European Society of Hypertension; SCORE - Systematic Coronary Risk Estimation.

In Portugal, CVD continues to be the main cause of morbidity and mortality, representing a high cost in socio-economic terms and health systems have been investing in its prevention. At the primary health care level, the clinical recommendations encourage the use of mathematical models to assess the risk of cardiovascular events with the aim of supporting clinical decision of therapeutic and non-therapeutic preventive measures to be

adopted. Thus, in accordance with the Portuguese standard No. 05/2013 of 19/03/2013, updated on 21/01/2015, of the Directorate-General of Health, the use of the SCORE (Systematic COronary Risk Evaluation) algorithm is recommended for the evaluation of the 10-year fatal cardiovascular risk (Direção-Geral da Saúde, 2013). The former recommendation implies the standard No. 019/2011 of 28/09/2011, updated on 11/05/2017 of the General Directorate of Health on the therapeutic approach to dyslipidemias in adults and the standard No. 026/2011 of 29/09/2011, updated on 19/03/2013 of the General Directorate of Health on the therapeutic approach to hypertension.

The risk factor goals and target levels for important cardiovascular risk factors recommended by the ESC guidelines will be presented further on, when approaching each cardiovascular risk factor.

5. Cardiovascular risk factor management

Risk factor is a measurable element or characteristic that is causally associated with an increased rate of a disease and that is an independent and significant predictor of the risk of presenting a disease (O'Donnell & Elosua, 2008b). Therefore, cardiovascular risk factors are elements or characteristics which increase the probability of suffering from CVD. The term risk factor in association to CVD was first introduced by a leader of the Framingham Heart Study in 1961 (Kannel et al., 1961). Since then, the concept of a risk factor has become deeply embedded into CVD prevention and practice (Greenland & Lloyd-Jones, 2018). Over time, and since the initial 4 risk factors underlying CVD - hypertension, hypercholesterolemia, left ventricular hypertrophy, and diabetes *mellitus* (DM) - were described in 1961 by Kannel et al., there were some main findings and landmarks where a clear association of risk factors and CVD was established, as illustrated in Figure 9 (O'Donnell & Elosua, 2008b).

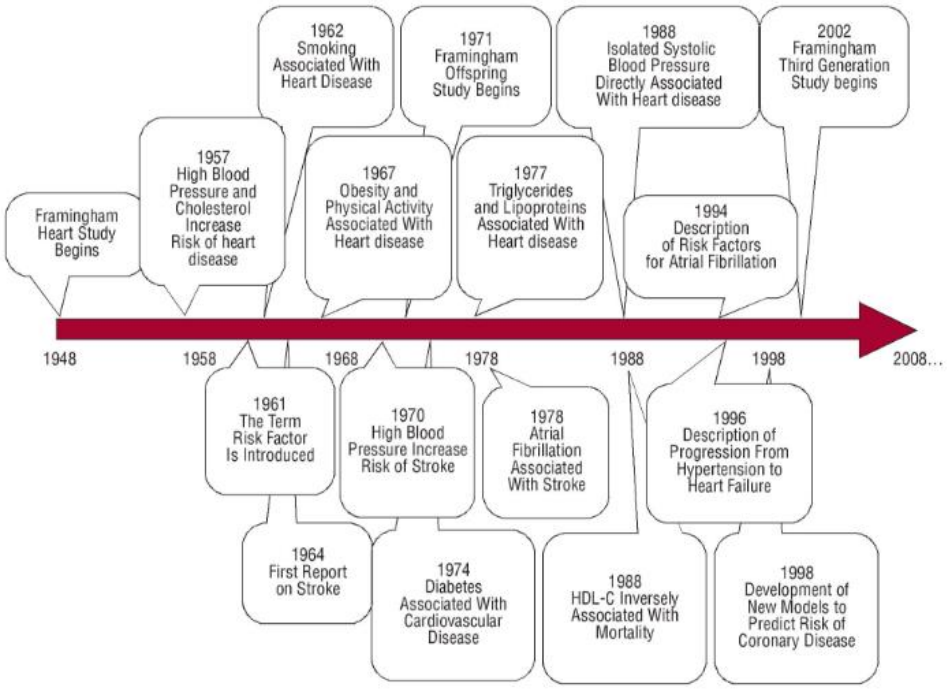

Figure 9 - Main findings and landmarks of the Framingham Heart Study.

The findings of the Framingham study have been widely validated, and their global importance was confirmed in INTERHEART, a case-control study conducted in 52 countries, which showed that nine potentially reversible risk factors and health behaviors - smoking, raised ApoB/ApoA1 ratio, history of hypertension, diabetes, abdominal obesity, psychosocial factors, lack of daily consumption of fruits and vegetables, regular alcohol consumption and lack of regular physical activity - account for more than 90% of the population attributable risk of acute myocardial infarction (AMI) in all regions of the world (Yusuf et al., 2004). The authors concluded that these findings suggest that approaches to prevention can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction.

The following graphs show the estimates of the numbers of deaths attributed to specific risk factors in 2017. There are several dominant risk factors for death, especially those related to dietary and activity lifestyle factors - blood pressure, physical activity, body-mass index, blood sugar, dietary intake, and smoking, among others - which varies significantly depending on the country. Whilst the Global Burden of Disease assessment assigns each death to one specific cause that initiated the series of events leading to death, it is known that the risk of disease burden and health outcomes are closely linked to several risk factors. These include risk factors across four broad categories: behavioral, environmental, occupational, and metabolic risks. For most high-income countries, the dominant risk factors are those related to healthy diets, smoking, and alcohol intake.

Available evidence suggests that targeting modifiable risk factors, especially hypertension, would result in a significant reduction in the burden of stroke. The development of preventive programs for stroke has to be both global and region-specific, considering that some variations in the frequency and the relative importance of individual risk factors for stroke were found (O'Donnell et al., 2016). The data in Figures 10 and 11 are presented as the number of deaths by risk factor, measured across all age groups and both sexes (Roth et al., 2018).

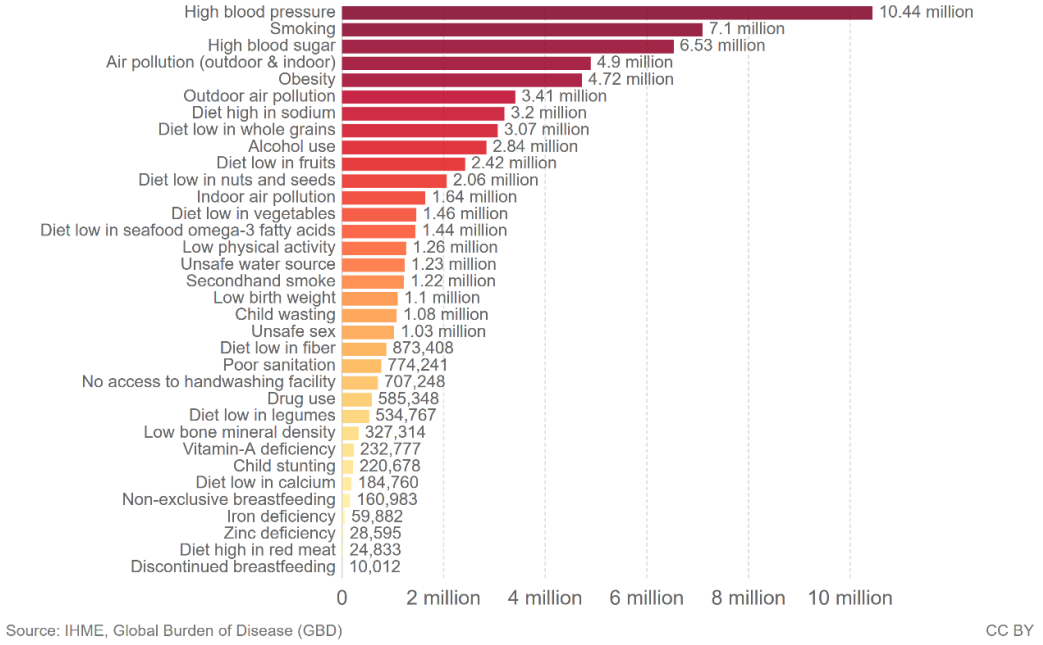

Figure 10 - Number of deaths by risk factor, World, 2017.

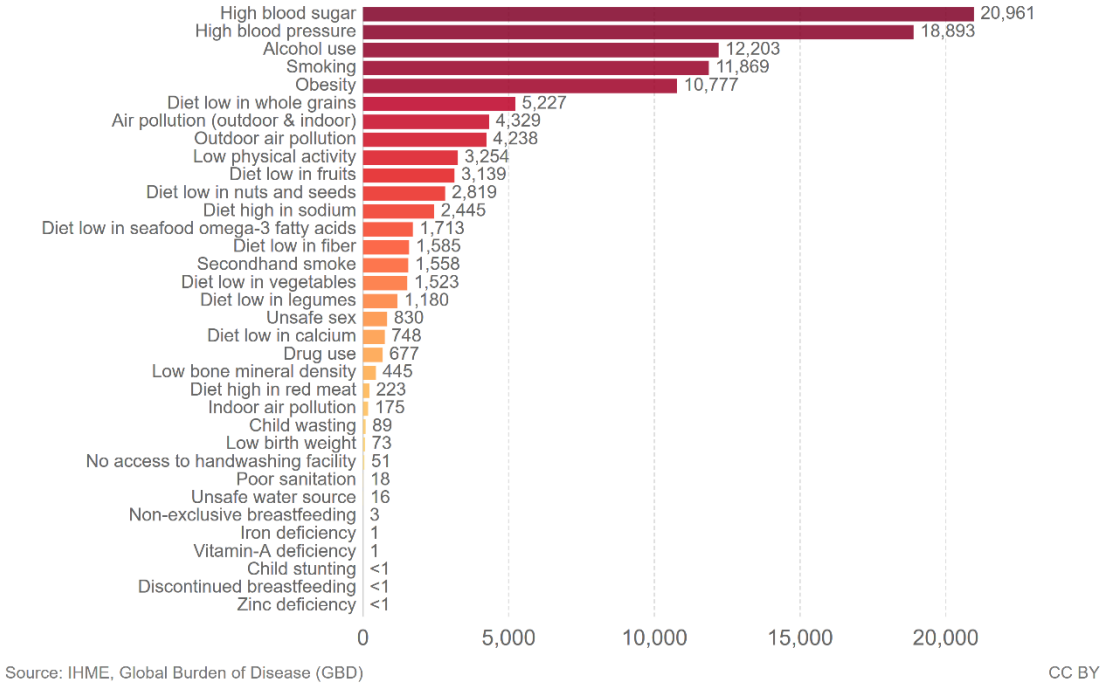

Figure 11 - Number of deaths by risk factor, Portugal, 2017.

In Portugal, the risk factors responsible for the largest number of deaths are high blood sugar, high blood pressure, alcohol use, smoking, and obesity. It is important to look at the number of deaths by risk factor through the different age categories. Figures 12 to 14 illustrate how, in Portugal, in 2017, the number of deaths were attributed to specific dominant risk factors in the several age categories.

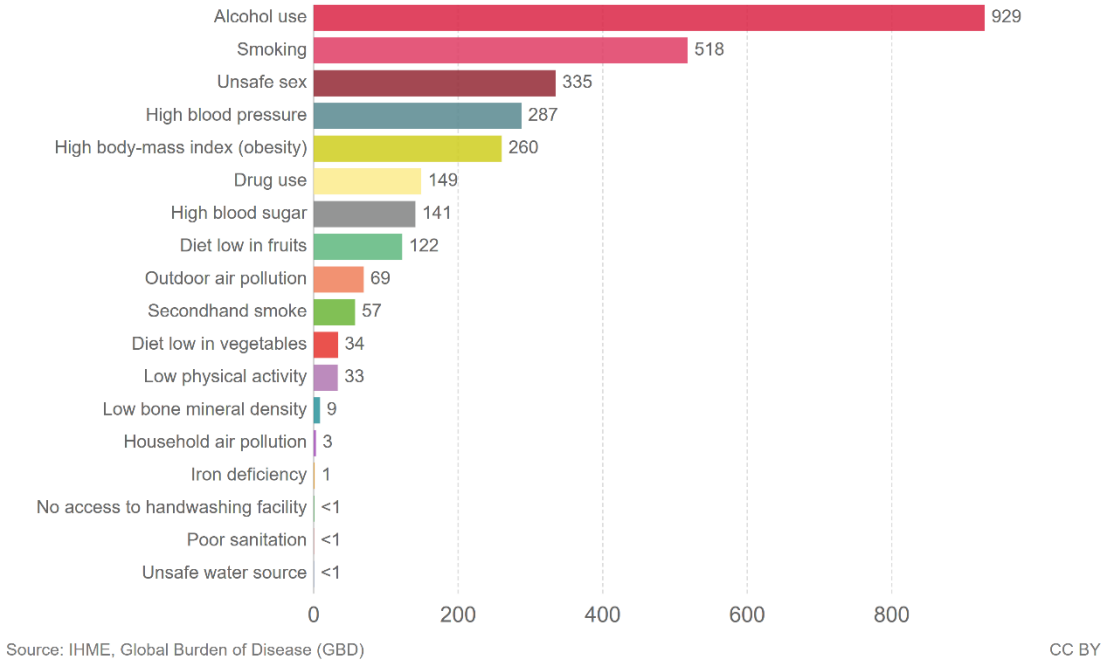

Figure 12 - Number of deaths by risk factor aged 15-49, Portugal, 2017.

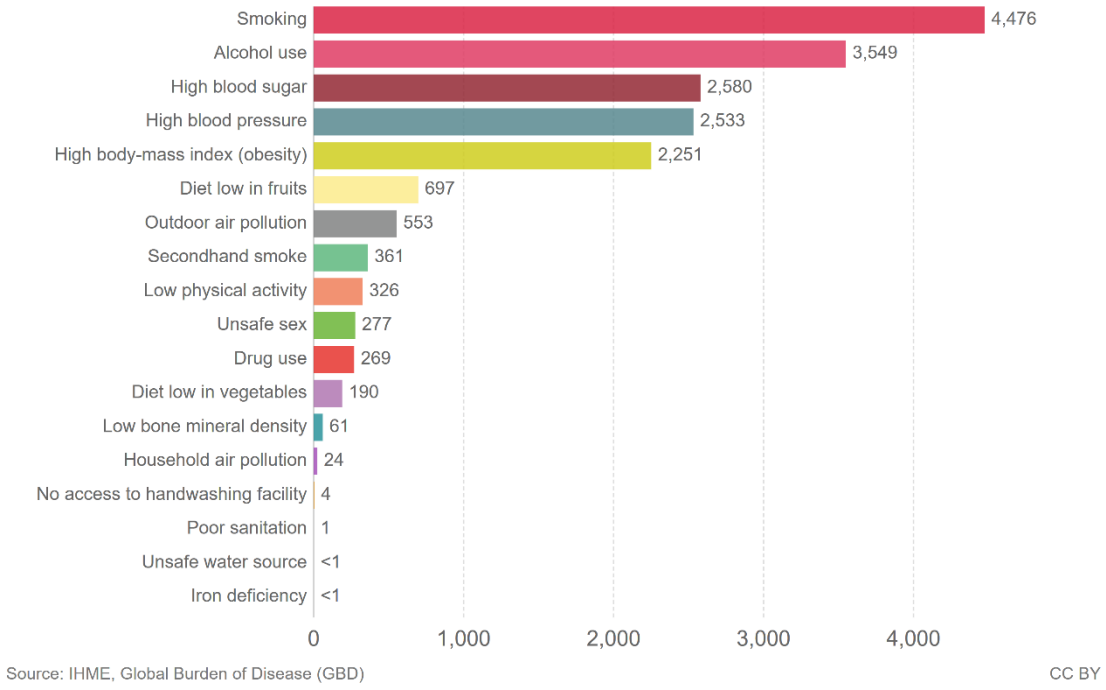

Figure 13 - Number of deaths by risk factor aged 50-69, Portugal, 2017.

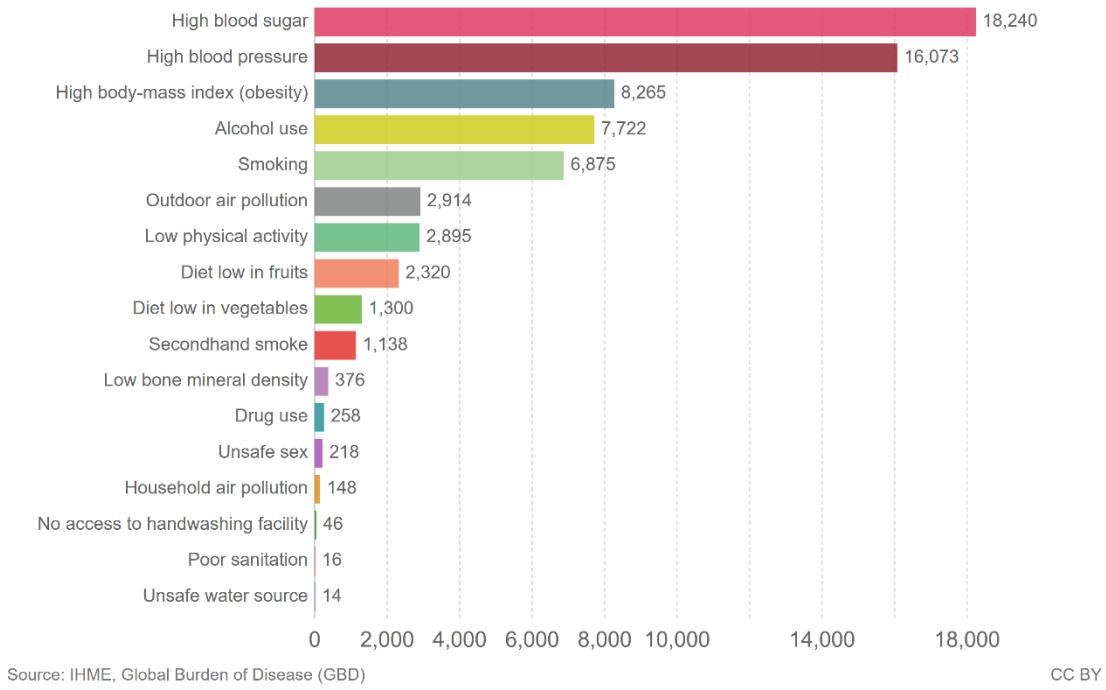

Figure 14 - Number of deaths by risk factor aged 70+, Portugal, 2017.

As shown in the graphs of Figures 12 to 14, risk factors such as high blood sugar, high blood pressure, obesity, alcohol use, smoking, low physical activity, and diet low in fruits and vegetables become prevalent in younger ages, which means that preventive interventions are crucial from young ages on. Figure 15 shows the risks that lead to death in perspective and in comparison with other common risks.

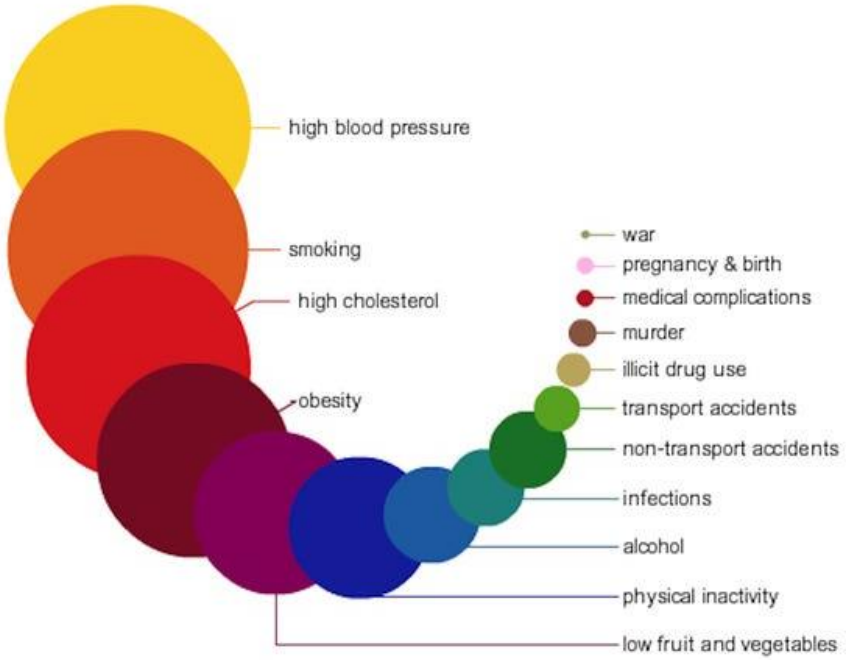

Figure 15 - Risks leading to death in perspective.

As stated by the WHO and depicted in Figure 16, the most important behavioral risk factors of heart disease and stroke are tobacco use, unhealthy diet, and physical inactivity, the effects of which may manifest in individuals as raised blood pressure, raised blood glucose, abnormal blood lipids, and overweight or obesity. In addition to the former risk factors, there are further underlying determinants of CVD, like globalization, urbanization, population aging, poverty, stress, and hereditary factors (World Health Organization, 2017a).

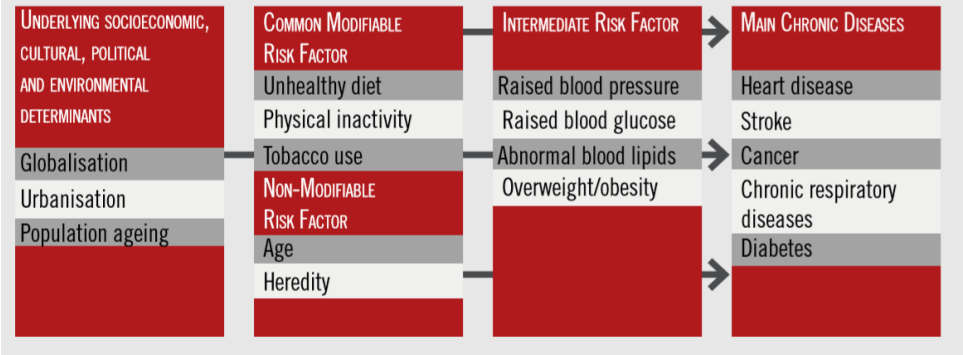

Figure 16 - WHO model of the causes of chronic diseases.

Globally, 61.0% of deaths were attributed to risk factors in the Global Burden of Disease study in 2017. The leading risk factor was high systolic blood pressure (SBP), representing 10.4 million deaths, followed by smoking, representing 7.1 million deaths, high fasting plasma glucose, representing 6.53 million deaths, and high body-mass index, representing 4.72 million deaths (Roth et al., 2017). The enormous impact of multiple comorbidities on total risk of CVD must also be considered, as in the INTERHEART study the risk of CVD was proven to be more than 40-fold higher when smoking, hypertension, diabetes, and dyslipidemia are present at the same time (Yusuf et al., 2004). On the other hand, interventions in one risk factor may diminish or even withdraw other related risk factors, such as in people with diabetes, who are at high risk for CVD, kidney disease, and retinopathy, all of which may be reduced with appropriate blood pressure management (de Boer et al., 2017).

It is important to establish the normative levels of each risk factor, that means considering the optimal risk factor level when it reaches the level at which associations with risk for disease are at their lowest magnitude, so that clinical practice guidelines can launch treatment and intervention thresholds for the risk factors.

There are some clearly identified cardiovascular, also called, "classical" risk factors, which can be categorized into:

a) Modifiable risk factors for CVD
    - Hypertension
    - Diabetes *mellitus*
    - Dyslipidemia
    - Smoking
    - Obesity (body mass index and waist circumference)
    - Physical Inactivity
    - Unhealthy diet
    - Stress
    - Harmful use of alcohol

b) Non-modifiable risk factors for CVD
    - Family history of premature CVD
    - Age
    - Sex

The following sections will focus on the cardiovascular risk factors, their definition, their link to CVD and their prevalence. When modifiable cardiovascular risk factors are addressed, the mechanisms of disease progression and treatment based on current guidelines, their control, and management will be referred, to define how to decrease CVD. Management of CVD includes screening and treating the risk factors. Essential CVD interventions can be delivered through a primary health care approach to strengthen early detection and timely treatment. Evidence shows that early provided interventions are excellent economic investments, as they reduce the need for more expensive treatment.

5.1. Modifiable risk factors

As referred earlier, CVD is associated with a set of causal factors that are called risk factors. Some cannot be modified, such as heredity, sex, and age. Others, on the other hand, can be modified with lifestyle and pharmacological interventions. Modifiable risk factors can be divided into different categories, namely biological risk factors, such as hypertension, obesity, diabetes, dyslipidemia, and lifestyle risk factors, such as unhealthy diet, sedentarism, smoking, alcohol consumption, and stress.

5.1.1. Blood pressure

The heart beats to supply our tissues and organs with oxygenated blood through the circulatory system, and in doing so, it creates pressure on the walls of the arteries, veins, and capillaries. This BP is the result of two forces: systolic pressure, which occurs as blood pumps out of the heart and into the arteries, and diastolic pressure, which is created as the heart rests between heart beats.

Longitudinal studies, genetic epidemiological studies, and randomized controlled trials (RCTs) have shown that raised BP or hypertension is one of the most important preventable causes of premature morbidity and mortality and one of the strongest risk factors for both atherosclerotic and nonatherosclerotic CVD (Kjeldsen, 2018). There is a continuous relationship between BP and cardiovascular and renal events, which makes the distinction between normotension and hypertension, based on threshold BP values, difficult (Ettehad et al., 2016). Nevertheless, in order to manage decisions about diagnose and treatment of hypertension in clinical practice, threshold BP values are used and defined. The absolute benefit of reducing SBP depends on absolute risk and the absolute reduction in SBP, except if lower SBP limits are imposed for tolerability and safety issues (Lewington et al, 2002). In fact, the association between high SBP level and atherosclerotic cardiovascular disease (ASCVD) events start even in levels as low as 90 mmHg, which is below the definition of hypertension (Whelton et al., 2020).

According to the ESC and the European Society of Hypertension (ESH) Guidelines, and presented in Table 2, hypertension is defined as office SBP values ≥140 mmHg and/or diastolic BP values ≥90 mmHg and recommend that BP is classified as optimal, normal, high normal, or grades 1 to 3 hypertension, according to office BP.

Table 2 - Categories for conventionally measured seated office blood pressure[a].

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension [b]	≥140	and	<90

[a] Blood pressure category is defined according to seated office blood pressure and by the highest level of blood pressure, whether systolic or diastolic; [b] Isolated systolic hypertension is graded 1,2, or 3 according to systolic blood pressure values in the ranges indicated.

Definitions of hypertension have also to be considered according to ambulatory and home BP categories, besides office BP categories. Hypertension is considered in ambulatory BP in daytime (awake) when the mean value of BP ≥135 and/or ≥85 mmHg, just as in home BP; in nighttime or asleep when the mean value of BP ≥120 and/or ≥70 mmHg; and in 24 hours when the mean value of BP ≥135 and/or ≥80 mmHg. Uncontrolled and prolonged elevation of BP leads to a variety of changes in myocardial structure, coronary vasculature, and conduction system of the heart. These changes can lead to the development of left ventricular hypertrophy, coronary artery disease, various conduction system diseases, and systolic and diastolic dysfunction of the myocardium, complications that manifest clinically as angina or myocardial infarction, cardiac arrhythmias (especially atrial fibrillation), and congestive heart failure (Guyton & Hall, 2000), accounting for almost 10 million deaths and over 200 million DALYs. Recent estimates are that 874 million adults worldwide have an SBP of 140 mmHg or higher (Forouzanfar et al., 2017). In international surveys, the rate of elevated SBP increased substantially between 1990 and 2015, as well as deaths associated with elevated SBP (Roth et al., 2017). The age-standardized prevalence of hypertension varies across the ESC member countries, ranging from 15.2% in the UK to 31.7% in Estonia and is lower in women than in men, with averaged rates of 20.2% and 28.4%, respectively. According to time series data, the SBP in ESC member countries, BP levels had a trended downwards change between 1980 and 2014, which were more obvious in high-income countries. When stratified by national income status, the average prevalence of hypertension in women and men was 18.3% and 27.3% in high-income ESC member countries and 23.5% and 30.3% in middle-income countries (Timmis et al., 2018).

The recent e_COR study estimated prevalence rates for arterial hypertension in the Portuguese population of 43.1% and higher rates in male gender and increasing significantly with age (Boubon et al., 2019). Before the e_COR study, four major studies were performed to estimate the prevalence, awareness, treatment, and control of hypertension among the Portuguese adult population, which are summarized in Table 3.

Table 3 - Studies on prevalence, awareness, treatment, and control of hypertension among the Portuguese adult population.

Study	**PAP Study** (Macedo et al., 2005)	**Valsim study** (Cortez-Dias et al., 2009)	**Physa Study** (Polonia et al., 2014)	**INSEF Study** (Rodrigues et al., 2017)
Year	2003	2008	2011-2012	2015
Sample	5023	16856	3720	4911
Ages	18-90	≥18	18-90	25-74
Prevalence of hypertension	42.1%	42.6%	42.2%	36.0%
Awareness of hypertension	46.1%	-	76.6%	69.8%
Receiving pharmacological treatment	39.0%	54.5%	74.9%	69.4%
BP control	11.2%	-	42.5%	71.3%

The results of the PAP study indicated that hypertension is highly prevalent in Portugal and that the percentages of those people with hypertension that are aware of their condition, that are treated and controlled are unacceptably low, evidencing the urgent need to develop national strategies to improve prevention, detection, and treatment of hypertension in Portugal (Macedo et al., 2005).

The VALSIM study was performed in primary care settings, involving 719 general practitioners and representatives of all regions of Portugal and exposing a high prevalence of hypertension in Portugal. This study also identified different patterns of treatment according to sex, age and region of residence and a very high proportion of hypertensive patients under monotherapy instead of combination antihypertensive therapy, which would probably improve BP control.

The objective of the Physa study was to determine prevalence, awareness, treatment, and control of hypertension in the Portuguese adult population and to examine their changes from the former similar PAP study. Although salt intake was found to be almost double of the WHO recommendations (Polonia et al., 2014), the conclusions of the Physa study were that hypertension prevalence among Portuguese adults remained stable in the past decade, but proportions of awareness, treatment and control of hypertension improved significantly.

The aim of the INSEF study was to estimate the distribution of prevalence, awareness, treatment, and control of hypertension in the Portuguese population in 2015. Results

suggest a reduction in hypertension prevalence and a more effective control, when compared to similar previous studies performed in Portugal. However, important differences in hypertension prevalence were found between specific population groups (Rodrigues et al., 2017), according to age (reaching 71.3% in individuals aged between 65 and 74 years), sex (39.6% of males) and level of education (62.6% with low levels of education), which highlights the importance of population strategies in public health policies (Rodrigues et al., 2019). The differences between these former studies may be related to the characteristics of their target populations: PAP and PHYSA - 18 to 90 years, mainland Portugal; INSEF - 25 to 74 years, includes Autonomous Regions of Madeira and Azores.

Given the high prevalence of hypertension and its relationship with the incidence of several cardiovascular events, the major recommendations of the national and international guidelines focus upon the diagnosis and management of hypertension. To ascertain the diagnosis, it is important to categorize BP and establish cut-off values to initiate interventions. The management of hypertension, as for pharmacological and non-pharmacological interventions, has to be risk-orientated and consider comorbidity.

The prevention strategies of CVD and the treatment recommendations are based on BP category and the assessment of total cardiovascular risk, which may be estimated with different models and all include the risk factor BP. The 2018 ESC/ESH arterial hypertension guidelines recommend that the diagnosis of hypertension is based on repeated office BP measurements or on out-of-office BP measurements with ambulatory BP monitoring or home BP monitoring. In respect to treatment thresholds, it is recommended to consider initiating antihypertensive drug therapy at high normal BP (130-139/85-89 mmHg) when cardiovascular risk is very high due to established CVD, especially coronary artery disease. In patients with grade 1 hypertension at low to moderate-risk and without evidence of hypertension-mediated organ damage, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention. Provided that treatment is well tolerated, BP-lowering drug treatment and lifestyle intervention are recommended in fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140-159 mmHg).

As BP treatment targets, it is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients and, if the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower in most patients. In patients <65 years, it is recommended that SBP should be lowered to a BP range of 120-129 mmHg

in most patients. In older patients (≥65 years), it is recommended that SBP should be targeted to a BP range of 130-139 mmHg. For patients aged over 80 years, provided that they are in good physical and mental condition, a SBP target range of 130-139 mmHg is recommended, if tolerated and not a SBP target between 140-150 mmHg, with an initial SBP ≥160 mmHg (Williams et al., 2018).

Regarding the treatment of hypertension, effective lifestyle changes may be sufficient to prevent or delay the need for pharmacological therapy, even in patients with grade 1 hypertension, such as smoking cessation, dietary sodium restriction, moderation of alcohol consumption, high consumption of vegetables and fruits, weight reduction, and maintaining an ideal body weight and regular physical activity. Nevertheless, most patients will require pharmacological therapy for hypertension in addition to lifestyle measures to achieve optimal BP control. Regarding pharmacological therapy, five major drug classes are recommended for the treatment of hypertension: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics - thiazides and thiazide-like diuretics such as chlortalidone and indapamide.

Several meta-analysis reported that the associations between BP-lowering treatments and outcomes were not significantly different, irrespective of drug class, except for heart and renal failure and stroke (e.g., inferior stroke and renal failure prevention with beta-blockers; inferior heart failure and superior stroke prevention with CCBs, and superior heart failure prevention for diuretics) (Emdin et al., 2015; Thomopoulos et al., 2015; Ettehad et al., 2016; Thomopoulos et al., 2017). Although there are contraindications for each class of drug and preferential use of some drugs for some conditions, which must be taken into consideration, overall studies show that major cardiovascular outcomes and mortality were comparable independently of the five major classes of treatment and therefore, should form the basis of antihypertensive therapy.

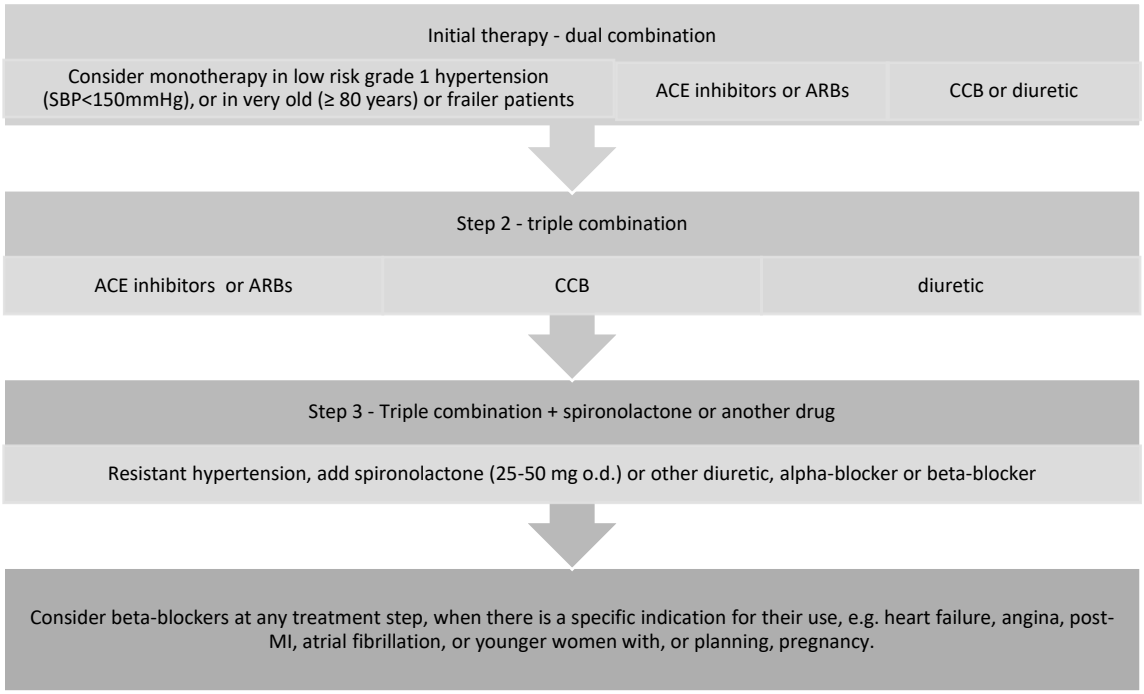

Figure 17 - Core drug treatment strategy for uncomplicated hypertension.

As depicted in Figure 17 and as recommended by the 2018 ESC/ESH Guidelines for the management of arterial hypertension, the treatment strategy for hypertension is based on the fact that among all antihypertensive drugs, ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and cardiovascular events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies. Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a renin-angiotensin system blocker (either an ACE inhibitor or an ARBs) with CCBs or diuretics. Other combinations of the five major classes can be used. It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g., angina, post-myocardial infarction, heart failure, or heart rate control, to initiate an antihypertensive treatment with a two-drug combination, preferably in a single-pill combination. Exceptions to this recommendation are frail older patients, those at low risk, and with grade 1 hypertension, particularly if SBP is <150 mmHg. If BP is not controlled with a two-drug combination, treatment should be increased to a three-drug combination, usually a renin-angiotensin system blocker with CCBs and thiazide/thiazide-like diuretics, preferably as a single-pill combination. If BP is not controlled with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of

other diuretics, a beta-blocker, or an alpha-blocker; the combination of two RAS blockers is not recommended (Williams et al., 2018).

Hypertension rarely occurs isolated, and often clusters with other metabolic cardiovascular risk factors such as dyslipidemia and glucose intolerance, which has a synergetic effect on cardiovascular risk (Berry et al., 2012).

5.1.2. Diabetes *mellitus*

Diabetes *mellitus* is a metabolic disease which is characterized by hyperglycemia resulting from insulin secretion or action abnormalities, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially heart, and blood vessels, but also the eyes, kidneys, and nerves. Most cases of diabetes fall into two etiopathogenic categories, type 1 diabetes where the cause is an absolute deficiency of insulin secretion and type 2 diabetes, the more prevalent category, where a combination of resistance to insulin action and an inadequate compensatory insulin secretory response is observed (American Diabetes Association, 2009).

According to the 2019 ESC Guidelines on diabetes, pre-diabetes and CVD, developed in collaboration with the European Association for the Study of Diabetes, the diagnosis of diabetes and pre-diabetes should be based on fasting plasma glucose or glycated hemoglobin (HbA1c). An oral glucose tolerance test is necessary to diagnose impaired glucose tolerance and individuals with established CVD should be screened using HbA1c or fasting glucose. An oral glucose tolerance test can be carried out if fasting plasma glucose and HbA1c are inconclusive (Cosentino et al., 2020).

As shown in Table 4, the diagnostic criteria of DM and prediabetes (impaired fasting glycemia and impaired glucose tolerance) are according to and based on recommendations from the WHO (World Health Organization, 2006, 2011) and the American Diabetes Association (American Diabetes Association, 2014, 2018) as presented in the 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases (Cosentino et al., 2020).

Table 4 - Diagnostic criteria for DM and prediabetes according to the 2006/2011 WHO and 2018 ADA recommendations.

Diagnosis/ measurement	WHO 2006[a]/2011[b]	ADA 2018[c]
DM	If measured, ≥6.5% (48 mmol/mol)	≥6.5% (48 mmol/mol)
FPG	≥7.0 mmol/L (126 mg/dL)	≥7.0 mmol/L (126 mg/dL)
	or	or
2hPG	≥11.1 mmol/L (≥200 mg/dL)	≥11.1 mmol/L (≥200 mg/dL)
RPG	Symptoms plus ≥11.1 mmol/L (≥200 mg/dL)	Symptoms plus ≥11.1 mmol/L (≥200 mg/dL)
IGT		
FPG	<7.0 mmol/L (<126 mg/dL)	<7.0 mmol/L (<126 mg/dL)
2hPG	≥7.8 to <11.1 mmol/L (≥140-200 mg/dL)	≥7.8 to <11.0 mmol/L (≥140-199 mg/dL)
IFG		
FPG	6.1-6.9 mmol/L (110-125 mg/dL)	5.6-6.9 mmol/L (100-125 mg/dL)
2hPG	<7.8 mmol/L (<140 mg/dL)	<7.8 mmol/L (<140 mg/dL)

2hPG - 2 h plasma glucose; ADA - American Diabetes Association; DM - diabetes *mellitus*; FPG - fasting plasma glucose; IFG - impaired fasting glycaemia; IGT - impaired glucose tolerance; RPG - random plasma glucose; WHO - World Health Organization. [a] (World Health Organization, 2006), [b] (World Health Organization, 2011), [c] (American Diabetes Association, 2018).

The diagnostic category *prediabetes* was introduced in 2002 and characterizes patients at very high risk of diabetes and its cardiovascular complications (Bansal, 2015). Currently, HbA1c, which measures an individual's average blood glucose level over the past three months, has been accepted as an alternative diagnostic test for type 2 diabetes with a positive predictive value (Goldenberg et al., 2011; World Health Organization, 2011).

It was estimated that, for every point increase in HbA1c, the relative risk of CVD increases by 18% (di Angelantonio et al., 2014). Type 1 diabetes, type 2 diabetes, and prediabetes are independent risk factors for ASCVD, increasing risk of ASCVD by about two-fold, as shown in a meta-analysis of 102 prospective studies (The Emerging Risk Factors Collaboration, 2010). Individuals with DM also have an increased incidence of hypertension and abnormalities of the lipoprotein metabolism (American Diabetes Association, 2009). The link between DM and CVD proves to be the most prevalent cause of mortality and morbidity in diabetic populations (Matheus et al., 2013) in both men and women, many without prior signs or symptoms of CVD (Booth et al., 2006).

Thus, the primary goal in patients with type 2 diabetes is to improve their cardiovascular risk, which is a challenging task considering that cardiovascular risk factors including obesity, hypertension and dyslipidemia are so common in these patients (Leon, 2015).

Long-term consequences of type 2 diabetes include microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (stroke, myocardial infarction) complications (The Emerging Risk Factors Collaboration, 2010), which are recognized to have an onset years before both clinical diagnosis and treatment and associated with increased metabolic abnormalities, clinical manifestations, and risk of death (Samuels et al., 2006). Therefore, patients who develop DM at a younger age have a high complication burden, greater mortality, and an unfavorable CVD risk (Constantino et al., 2013).

Patients with DM show overexpression of many cytokines by adipose tissue including tumor necrosis factor alpha, interleukin (IL)-1, IL-6, leptin, fibrinogen and angiotensin (Xu et al., 2014), C-reactive protein (Janowska et al., 2016), decreased adiponectin production (Shoelson, 2006), which contributes to endothelial dysfunction, inflammation and lipid accumulation, increases the uptake of oxidized low-density lipoprotein, development of atherosclerotic plaques, autonomic neuropathy myocardial infarction and cardiomyopathy (Duncan et al., 2003; Matheus et al., 2013), and directly contribute to the development of CVD. Insulin resistance has also been linked to cardiomyopathy in diabetics via cardiomyocyte hypertrophy and contractile dysfunction (Belke et al., 2002).

Hypertension is very common among patients with type 1 and type 2 diabetes, with prevalence rates of 30% and 60%, respectively (Matheus et al., 2013). Hypertension is closely tied to the development of diabetic nephropathy (Schena & Gesualdo, 2005) with structural changes that increase filtration pressure and often lead to microalbuminuria. The increase in filtration pressure leads to a compensatory activation of the renin-angiotensin system and progresses to hypertension, adding even more stress on the glomeruli and causing additional damage to the nephrons of diabetic patients (Lim, 2014).

Insulin-resistant fat cells increase the release of free fatty-acid, negatively impacting low-density lipoproteins and very low-density lipoproteins, which promotes triglyceride production, which in turn stimulates the secretion of apolipoprotein B and very low-density lipoproteins cholesterol increased glycosylation and oxidation, decreasing vascular compliance and facilitating the development of atherosclerosis, increasing the risk of developing dyslipidemia and therefore CVD (Mooradian et al., 2007; Hamilton & Watts, 2013).

According to the WHO, the number of people with diabetes worldwide has risen from 108 million in 1980 to 422 million in 2014, particularly in low-and middle-income countries,

and 1.6 million deaths are directly attributed to diabetes each year. In Europe, there are an estimated 61 million people living with diabetes, one in 11 adults. The number of adults with diabetes is expected to reach 67 million by 2030 and 69 million by 2045. Over one in 3 (36%) adults living with diabetes are undiagnosed. The countries with the highest number of people with diabetes are for the most part in Western Europe, including Germany, Spain, Italy, France, and the UK. To a large degree, the high prevalence of type 2 diabetes and impaired glucose tolerance are a consequence of the aging of these region's population, as age is an important risk factor for type 2 diabetes (Roth et al., 2018; International Diabetes Federation, 2021).

The studies presented in Table 5 aimed to determine the prevalence of type 2 diabetes in the Portuguese population.

Table 5 - Studies about the prevalence of type 2 diabetes in the Portuguese population.

Study	**PREVADIAB** (Gardete-Correia et al., 2010)	**e_COR Study** (Boubon et al., 2019)	**Observatório Nacional da Diabetes** (Sociedade Portuguesa de Diabetologia, 2016)	**INSEF** (Barreto et al., 2017)
Year	2008/2009	2012-2014	2015	2015
Ages	20-79	18-79	20-79	25-74
Prevalence of type 2 diabetes	11.7%	8.9%	13.3%	9.9%
Prevalence Male/Female	14.2%/9.5%	11.1%/7.0%	15.9%/10.9%	12.1%/7.8%
Prevalence pre-diabetes	23.2%	-	27.4%	19.0%
Total prevalence of Diabetes	34.9%	-	40.7%	-
With established diagnosis	6.6%	-	7.5%	9.8%
Without established diagnosis	5.1%	-	5.8%	-

Lifestyle intervention is recommended to delay or prevent the conversion of pre-diabetic states, such as impaired glucose tolerance, to type 2 diabetes and its cardiovascular complications (Li et al., 2014). Reduced calorie intake is recommended for lowering excessive body weight and smoking cessation guided by structured advice is recommended in all individuals with diabetes and prediabetes (Jennings et al., 2014). Moderate-to-vigorous physical activity, notably a combination of aerobic and resistance exercise, for >150 min/week is recommended for the prevention and control of DM, unless contraindicated (Colberg et al., 2016). A Mediterranean diet, rich in polyunsaturated and monounsaturated

fats, should be considered to reduce cardiovascular events (Snorgaard et al., 2017; Estruch et al., 2018).

As mentioned, the mainstay for initial treatment of type 2 diabetes includes therapeutic lifestyle change. In addition, metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes in most patients with no contraindications, such as stage 4 or 5 chronic kidney disease (CKD), advanced heart failure, or a history of lactic acidosis. Early combination therapy and introduction of insulin can also be considered if there is evidence of ongoing catabolism, if symptoms of hyperglycemia are present, or when HbA1c or blood glucose levels are very high (HbA1c >10%, blood glucose ≥300 mg/dL). In sum, a patient-centered approach should be used to guide the choice of pharmacologic agents, including cardiovascular comorbid conditions, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (Doyle-Delgado et al., 2020).

In Figure 18, the treatment algorithm in patients with type 2 diabetes and ASCVD, or high/very high cardiovascular risk is shown. The treatment algorithm is divided in two pathways: for (A) drug-naïve and (B) metformin-treated patients with DM (Cosentino et al., 2020).

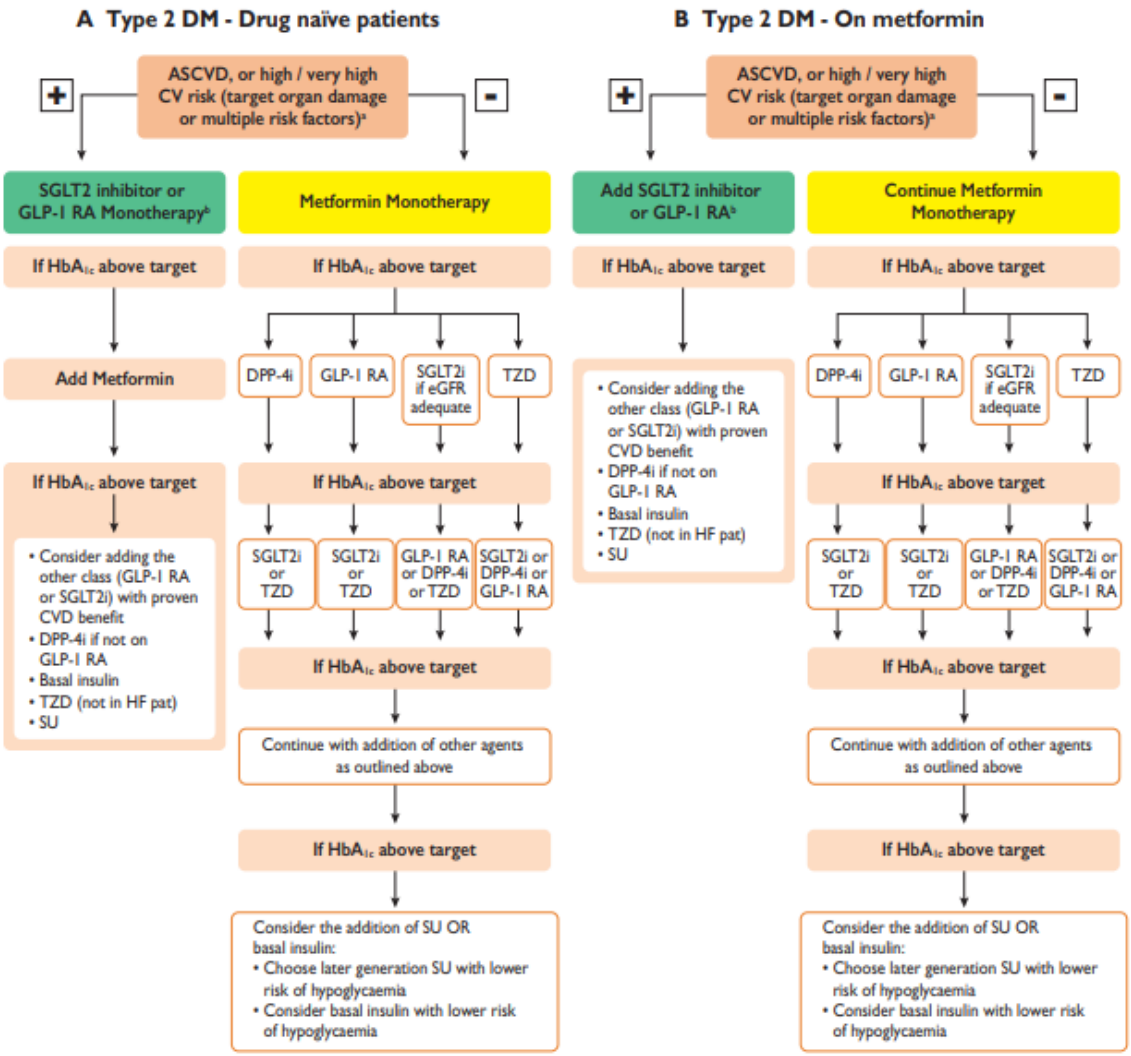

Figure 18 - Treatment algorithm in patients with type 2 diabetes and ASCVD, or high/very high cardiovascular risk - [a]age, hypertension, dyslipidemia, smoking, obesity; [b]use drugs with proven CVD benefit.

In patients with DM, cardiovascular risk categories are stratified as followed:

- Very high-risk: patients with DM and established CVD or other hypertension-mediated organ damage; or three or more major risk factors; or early onset type 1 diabetes of long duration (>20 years).
- High risk: patients with DM duration ≥10 years without hypertension-mediated organ damage plus any other additional risk factor.
- Moderate risk: young patients (Type 1 DM aged <35 years or Type 2 DM aged <50 years) with DM duration <10 years, without other risk factors.

Hypertension-mediated organ damage is considered whenever the patient presents proteinuria, renal impairment defined as estimated glomerular filtration rate 30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy. Additional risk factors are considered age, hypertension, dyslipidemia, smoking, and obesity (Williams et al., 2018).

Antihypertensive drug treatment is recommended for people with DM when office BP is >140/90 mmHg. It is recommended that patients with hypertension and DM are treated in an individualized manner and the BP goal is to target SBP to 130 mmHg and <130 mmHg if tolerated, but not <120 mmHg and in older people (aged >65 years), the SBP goal is to a range of 130-139 mmHg. An on-treatment SBP of <130 mmHg may be considered in patients at particularly high risk of a cerebrovascular event, such as those with a history of stroke. Moreover, it is recommended that diastolic blood pressure (DBP) is targeted to <80 mmHg, but not <70 mmHg (Cosentino et al., 2020).

Cardiovascular disease - coronary artery disease and stroke - is the major cause of mortality among people with type 2 diabetes (Einarson et al., 2018). However, interventional studies have been inconclusive in demonstrating that optimized glycemic control in patients with type 2 diabetes is linked to a reduction in CVD. This shifts the attention to the provision of therapeutic agents with a positive cardiovascular effect, meaning a new therapeutic approach to mitigate the development of diabetic cardiovascular complications (Sardu et al., 2019).

Type 2 diabetes is a preventable or at least a postponable metabolic disease, which renders the screening for subjects who are at increased risk for diabetes as an urgent and mandatory task. Cost-effective, convenient, and sensitive screening tools exist and should be applied in the primary care setting, to detect people at risk, to assess the diabetes risk and to detect undiagnosed type 2 diabetes, and ultimately to direct interventions toward individuals at increased risk for the disease (Lindstrom & Tuomilehto, 2003).

5.1.3. Obesity - Body mass index and waist circumference

The WHO defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to health, that is, a disease in which accumulated excess body fat may reach levels that negatively affect health. Body mass index (BMI) is a measure of weight adjusted for height, expressed as weight in kilograms per squared height in meters (kg/m^2).

According to the WHO and adopted worldwide, a BMI ≥25 kg/m^2 is classified as overweight, a BMI ≥30 kg/m^2 is classified as obesity. Obesity is subdivided into three classes: class I, BMI=30.0-34.9 kg/m^2, class II, BMI=35.0-39.9 kg/m^2 and class III, BMI ≥40.0 kg/m^2 to further stratify health risk.

A well-established predictor of cardiovascular risk is the location of body fat, since visceral fat is associated to a higher cardiovascular risk than subcutaneous fat. Several measures of abdominal fat are available, of which waist circumference is the simplest to measure, and WHO thresholds are widely accepted in Europe. The classification of two levels of risk of complications associated with obesity is admitted, with clinical and epidemiological value:

- Waist circumference ≥94 cm in men and ≥80 cm in women - represents the threshold at which no further weight should be gained.
- Waist circumference ≥102 cm in men and ≥88 cm in women - indicates an increased risk and represents the threshold at which weight reduction should be advised.

These thresholds are calculated for Caucasians, and different cut-offs for anthropometric measurements are required in different ethnicities (World Health Organization, 2016b). Although BMI and waist circumference are strong and continuously associated with CVD and type 2 DM, BMI generally suffices in routine practice, but it does not take into consideration whether excess body weight results from different body composition compartments, since excess abdominal fat, also known as central or upper-body fat is associated with an increased risk of cardiometabolic disease (Prado et al., 2015). The distribution of fat mass has diverse effects on the cardiovascular system and metabolism (Després, 2012). Thus, determining the location of fat mass helps to identify individuals with similar BMI and fat mass, but with different CVD risk profiles.

Accumulation of visceral fat mass has been recognized as a major cardiometabolic risk factor, which involves changes in body composition that can affect hemodynamic and alter the heart structure, inducing cardiac dysfunction (Tchernof & Després, 2013). Moreover, visceral fat mass favors the production of pro-inflammatory cytokines and adipokines, produced by the adipose tissue itself, with cardiodepressant and pro-atherosclerotic properties and promote the formation of atherosclerotic plaques (Ballak et al., 2015; Carbone et al., 2019).

Due to the important prognostic role of visceral fat mass, its clinical assessment is typically performed indirectly (e.g., waist circumference) and should be encouraged in routine clinical and research settings. There are other measures of adiposity, such as waist-to-hip ratio, waist-to-height ratio, skinfold thickness, and percentage body fat mass, which define overweight or obesity and further improve the risk prediction (Klein et al., 2007; Gaya et al., 2017; Iliodromiti et al., 2018). Studies revealed that obesity is a strong

independent predictor of CVD, even in lack of other risk factors, and reported the relationship between the BMI and mortality/morbidity (di Angelantonio et al., 2016). However, interestingly, after onset of CVD the relationship between increasing BMI and CVD events is not linear. Thus, obesity increases the risk for CVD in primary prevention (Lavie et al., 2018). In fact, CVD death and all-cause mortality is lowest with a BMI of 20-25 kg/m^2, and maintaining a healthy weight has a favorable effect on metabolic risk factors, such as blood pressure, blood lipids, and glucose tolerance. On the other hand, obesity is associated with numerous comorbidities, including hypertension, type 2 diabetes, dyslipidemia, obstructive sleep apnea and sleep-disordered breathing, and certain cancers. Because of its maladaptive effects on various cardiovascular risk factors and its adverse effects on cardiovascular structure and function, obesity has a major impact on heart failure, CHD, sudden cardiac death, and atrial fibrillation, and is associated with reduced overall survival (Lavie et al., 2009).

Worldwide, the prevalence of overweight and obesity is high and has increased substantially in recent decades, in children, adolescents, and adults. Overweight and obesity increases the risk of most CVD, metabolic diseases such as type 2 diabetes, and their related risk factors (NCD Risk Factor Collaboration (NCD-RisC), 2016; Abarca-Gómez et al., 2017; Khan et al., 2018). According to the WHO fact sheet on obesity and overweight, worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults (39%), 18 years and older, were overweight, of these over 650 million (13%) were obese; 39 million children under the age of five were overweight or obese in 2020; over 340 million children and adolescents aged 5-19 were overweight or obese in 2016. According to the Global Burden of Disease GBD study, worldwide, at least 2.8 million people die each year as a result of being overweight or obese, and an estimated 35.8 million (2.3%) of global DALYs are caused by overweight or obesity, and in 2017, obesity was the fifth in ranking of number of deaths by risk factor worldwide and in Portugal (Roth et al., 2018). In short, even though obesity is preventable, most of the world's population live in countries where overweight and obesity kills more people than underweight.

The first Portuguese nationwide representative survey about obesity, with objective anthropometric measurement, was undertaken from 1995 to 1998 and the second study was undertaken from January 2003 to January 2005. In the later survey, the main findings were that 39.4% were overweight, 14.2% obese and 45.6% of the sample suffered increased cardiovascular health risks associated with high waist circumference. The overall overweight/obesity prevalence increased from 49.6% (in 1995-1998) to 53.6% (in 2003-

2005) (do Carmo et al., 2007). The majority of the Portuguese recognized the risks of abdominal obesity and most consequences of excessive weight, independently of their BMI, but showing gaps regarding prevalence, calories and BMI diagnosis (Henriques et al., 2019). In Portugal, the Valsim Study revealed the increased prevalence of metabolic syndrome related to age, BMI and abdominal perimeter and an important association between metabolic risk factors and the occurrence of stroke and DM (Fiúza et al., 2008). The national prevalence of obesity was shown to be 22.3% (95%CI: 20.5-24.0), significantly higher in women (24.3%, 95%CI: 21.9-26.7 vs. 20.1%, 95%CI: 17.5-22.7), and increasing with age, with the lowest prevalence in children (7.7%, 95%CI: 4.6-10.9) and the highest in the elderly (39.2%, 95%CI: 34.2-44.2). The prevalence of pre-obesity at national level was shown to be 34.8% (95%CI: 32.9-36.7), higher in men (38.9%, 95%CI: 36.0-41.7) than in women (30.7, 95%CI: 28.1-33.2), and in the elderly (41.8%). On the other hand, approximately 40% of the Portuguese population (43.0%, 95%CI: 40.7-45.2) was shown to be underweight or normal weight (Oliveira et al., 2018). Since obesity is considered the second preventable cause of death, after smoking, and considering the high prevalence of overweight and obesity, the Portuguese Ministry of Health justifies the need for a *National Program to Combat Obesity*. It was implemented by the Directorate General of Health in January 2005. This program was based on a process of cooperation and partnership between public, private and non-governmental sectors working in the health area, with responsibilities at local and regional level. Other sectors, such as education, municipalities, and companies were also called upon to collaborate and assume responsibilities in the operationalization of the program (Sérgio et al., 2005).

It is recommended that subjects with healthy weight (BMI 20-25 kg/m^2) and waist circumference <94 cm (men) or <80 cm (women) maintain their weight and that overweight and obese people achieve a healthy weight, or aim for a reduction in weight. Even moderate weight losses of 5 to 10% from baseline reduces BP, dyslipidemia and risk of developing type 2 diabetes, and thus improves the cardiovascular risk profile (Zomer et al., 2016). The cornerstone of weight management is lifestyle change, including energy restriction and increases in physical activity and cardiorespiratory fitness levels (Lavie et al., 2018). Hypocaloric diets that aim to reduce ASCVD include plant-based and Mediterranean diets, with modifications to suit local food availability and preferences.

Pharmacological approach for weight loss in Europe is approved for orlistat, naltrexone/bupropion, and high-dose liraglutide, with favorable effects on blood pressure, glycemic control, and CVD mortality (Kane et al., 2019).

5.1.4. Dyslipidemia

Dyslipidemia may be defined as increased levels of serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), or decreased serum high-density lipoprotein cholesterol (HDL-C) concentrations, and is a confirmed risk factor for CVD (Yusuf et al., 2004). However, new evidence from genetic, epidemiologic, and intervention studies established that low-density lipoprotein and other ApoB-containing lipoproteins causes ASCVD and that lowering both, the duration of exposure, and plasma LDL, reduce the risk of ASCVD events (Ference et al., 2017). Current ESC guidelines focus on non-high-density lipoprotein cholesterol as an input in the Systemic Coronary Risk Estimation 2 (SCORE2) and SCORE2-Older Persons (SCORE2-OP) risk algorithms. Non-HDL-C is calculated by subtracting HDL-C level from total cholesterol level. Since non-HDL-C levels contain the same information as a measurement of ApoB plasma concentration and includes all atherogenic (apo-B-containing) lipoproteins, its relationship to cardiovascular risk is equivalent to that of LDL-C (The Emerging Risk Factors Collaboration*, 2009; Pencina et al., 2019). Low HDL-C is associated with increased cardiovascular risk, but interventions to increase HDL-C have not been associated with a decreased cardiovascular risk.

As in other cardiovascular risk factors, lifestyle and dietary changes are also recommended for the reduction of atherogenic lipoproteins. Treatment goals for LDL-C depend upon the total cardiovascular risk and should guide the intensity of the intervention (Holmes et al., 2015). Current guidelines propose a stepwise approach to risk factor treatment and subsequent treatment intensification (Visseren et al., 2021), while targets and goals for LDL-C remain as recommended in recent ESC Guidelines (Mach et al., 2020).

- In primary prevention for individuals at very-high risk, but without familial hypercholesterolemia and in secondary prevention for patients at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.
- In primary prevention for individuals with familial hypercholesterolemia at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.
- For patients with ASCVD, who experience a second vascular event within 2 years (not necessarily of the same type as the first event), while taking maximally tolerated

statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.

- In patients at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.
- In individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.
- In individuals at low risk, an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.
- Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
- ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
- Triglycerides have no goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.

As recommendations for lipid analyses for cardiovascular disease risk assessment, LDL-C is the primary method for lipid analysis for screening, diagnosis, and management; non-HDL-C evaluation is recommended, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels. HDL-C analysis is recommended to further refine risk estimation using the online SCORE system, TG analysis is recommended as part of the routine process for lipid analysis, and ApoB analysis is recommended, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels.

Evidence has confirmed that the key initiating event in atherogenesis is the retention of low-density lipoprotein cholesterol and other cholesterol-rich apolipoprotein ApoB-containing lipoproteins within the arterial wall, and that ASCVD is the major component of CVD. Furthermore, clinical trials have clearly indicated that the lower the achieved LDL-C values, the lower the risk of future cardiovascular events, with no lower limit for LDL-C values, or 'J'-curve effect (Ference et al., 2017; Mach et al., 2020). To appraise the clinical and genetic evidence that low-density lipoproteins cause ASCVD, Ference et al. assessed whether the association between LDL and ASCVD fulfills the criteria for causality by evaluating the totality of evidence from genetic studies, prospective epidemiologic cohort studies, Mendelian randomization studies, and randomized trials of LDL-lowering therapies. Separate meta-analyses of over 200 prospective cohort studies, Mendelian randomization studies, and randomized trials including more than 2 million participants with over 20

million person-years of follow-up and over 150 000 cardiovascular events demonstrate a remarkably consistent dose-dependent *log*-linear association between the absolute magnitude of exposure of the vasculature to LDL-C and the risk of ASCVD. This effect appears to escalate with increasing duration of exposure to LDL-C (Ference et al., 2017).

Table 6 - Prevalence of dyslipidemia in Portugal.

Study	**Valsim** (Cortez-Dias et al., 2013)	**INSEF** (Romana et al., 2019)	**e_COR** (Boubon et al., 2019)
Year	2006-2007	2015	2017
Ages (years)	≥ 18	25-74	18-79
Sample	16159 (TC) 9956 (LDL-C) 16 074 (HDL-C) 16 494 (TG)	4862 (2265 male/ 2645 female)	1688 (848 male/ 840 female)
Dyslipidemia target	TC ≥200 mg/dl LDL-C≥130 mg/dl HDL-C <40 mg/dl TG≥200 mg/dl	TC ≥190 mg/dl	TC>240/≥200 mg/dl LDL-C≥160/130 mg/dL TG≥200/>150 mg/dL HDL-C<40 mg/dL
Prevalence of dyslipidemia	TC 57.9% LDL-C 38.4% HDL-C 12.8% TG 12.7%	TC 52.3% Include population taking lipid lowering therapy 63.3% (IC95%: 61.2-65.4)	TC 31.3/56.3% LDL-C 31.5/51.5% TG 8.6/ 18.6% HDL-C 14.0%
Prevalence Male/Female	-	TC 62.8%/63.8%	TC>240 mg/dl 30.7/32.1% TC≥200 mg/dl 56.7/5.1% LDL-C≥160 mg/dL 34.0/29.4% LDL-C≥130 mg/dL 57.0/46.9% TG≥200 mg/dL 11.9/5.8% HDL-C 21.6% vs 7.5%
With established diagnosis	On statin treatment 44.7%	-	TC 49.2%; on treatment 39.9% LDL-C 73.3%; on statin treatment 71.4% LDL-C 51.3%; on treatment 43.6% TG≥200mg/dL 24.7%; on treatment 24.7%

As reported in the studies summarized in Table 6, dyslipidemia is highly prevalent in Portugal. National and European Guidelines recommend that LDL-C should be the main treatment target in cardiovascular risk reduction, as it has a causal role in ASCVD, and individualized treatment goals should be established. Thus, a statin lowering LDL-C approach is recommended, which is supported by extensive evidence from large, prospective studies (Cholesterol Treatment Trialists' Collaborators, 2005). In men and

women at an equivalent risk of CVD, statin therapy is of similar effectiveness for the prevention of major vascular events (Cholesterol Treatment Trialists, 2015). Statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about one fifth per mmol/L reduction in LDL-C and is the only pharmacological treatment for dyslipidemia with robust evidence to reduce the risk of ASCVD both in primary and secondary prevention and intervention settings (Taylor et al., 2013).

According to the ACC and the AHA, the equivalence of statins dosing and classification of intensity is as depicted in Table 7 (Stone et al., 2014).

Table 7 - Statin dosing and ACC/AHA classification of intensity.

	Dosage		
Statin	**Low-intensity (LDL-C reduction <30%)**	**Moderate-intensity (LDL-C reduction 30% to <50%)**	**High-intensity (LDL-C reduction >50%)**
Atorvastatin	NA	10 to 20 mg	40 to 80 mg
Fluvastatin	20 to 40 mg	40 mg bid; 80 mg	NA
Lovastatin	20 mg	40 mg	NA
Pitavastatin	1 mg	2 to 4 mg	NA
Pravastatin	10 to 20 mg	40 to 80 mg	NA
Rosuvastatin	NA	5 to 10 mg	20 to 40 mg
Simvastatin	10 mg	20 to 40 mg	NA

LDL-C - low-density lipoprotein cholesterol; NA - not applicable.

The selection criterion for the statin and its dose, that is the intensity of the statin, should consider the intended reduction of LDL-C levels and depends on the former assessed cardiovascular risk, and the lowest cost for equal effectiveness. It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk and if the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended (Visseren et al., 2021). In Portugal and up to date, the best cost-effective statins are: 10 mg simvastatin for low-intensity statins, 20 or 40 mg simvastatin and 10 or 20 mg atorvastatin for moderate-intensity statins and 40 or 80 mg atorvastatin for high-intensity statins (Direção-Geral da Saúde, 2011).

In the IMPROVE-IT trial, the combination therapy with ezetimibe provided an additional benefit to post-acute coronary syndrome in line with the Cholesterol Treatment Trialists' Collaboration meta-analysis, supporting the conception that LDL-C reduction is

key to the achieved benefit independent of the approach used (Cannon et al., 2015). The importance of ASCVD prevention remains undisputed and should be delivered at the general population level by promoting healthy lifestyle behavior and by reducing increased levels of LDL cholesterol (Mach et al., 2020).

5.1.5. Smoking

Smoking is by definition considered the inhalation of the smoke of burning tobacco encased in cigarettes, pipes, and cigars. Cigarette smoking is still the most common form of tobacco use worldwide. Nevertheless, nowadays in addition to cigarettes, there are many other forms of tobacco use, which have to be considered:

- e-cigarettes a type of electronic smoking device - "vaping", are available in a wide variety of flavors and can be refilled with liquid, which often contains nicotine and are the tobacco product teens use the most, as shown by a recent Centers for Disease Control and Prevention survey (Office on Smoking and Health, 2019).
- Heat-Not-Burn Tobacco Products - are marketed by tobacco companies as a better alternative to smoking, once tobacco is heated, not burned. However, these products still contain nicotine and additive chemicals.

The U.S. Food and Drug Administration has asserted that cigarettes and smokeless tobacco should be considered as nicotine delivery devices. Although there are many available tobacco products including water pipe tobacco, various smokeless tobacco products, cigars, cigarillos, roll-your-own tobacco, pipe tobacco, bidis and kreteks, all forms of tobacco are harmful, and there is no safe level of exposure to tobacco (Gupta et al., 2019).

Since very early, epidemiologic studies strongly supported the statement that cigarette smoking increases total death rates (Hammond & Horn, 1958). Data from the Framingham study gave good evidence to support the statement that cigarette smokers have about twice as much CHD as non-smokers, measured by deaths, prevalence, or incidence of new events (Kannel et al., 1961). In 1964, the Surgeon General released, at Public Health Reports, the official journal of the United States Public Health Service, a landmark report on the dangers of smoking and its link to diseases (U. S. Department of Health and Human Services, 2014). Smoking continues to be one of the most important modifiable risk factors, as it is responsible for 50% of all avoidable deaths, with half of these due to ASCVD (Doll et al., 2004). Tobacco accounts for over 7.2 million deaths every year, including the effects of

exposure to second-hand smoke, and is projected to increase markedly over the coming years (Ritchie & Roser, 2019).

The goal and target level for smoking is no exposure to tobacco in any form as well as passive smoking, since evidence does not establish that a reduction of cigarette consumption reduces the risk of CVD, nor is there a safe level of exposure to tobacco smoke (Piepoli et al., 2016; Hackshaw et al., 2018). Thus, it is recommended to stop all smoking of tobacco products, as this is strongly and independently a cause of CVD and substantially contributes to the overall cardiovascular burden (Roth et al., 2017).

Decades of research allowed scientists to describe the mechanisms by which smoking causes diseases, especially in relation to CVD. Exposure to cigarette smoke and their oxidizing chemicals and nicotine are responsible for endothelial injury and dysfunction, and activation of the blood-clotting cascade in both coronary and peripheral arteries, leading to an increased risk of thrombosis and the initiation of atherogenesis, which has a major role in the pathogenesis of acute cardiovascular events (Centers for Disease Control and Prevention et al., 2010; Leone & Landini, 2013; Messner & Bernhard, 2014). Cigarette smoking produces a procoagulant chronic inflammatory state, that induces an atherogenic lipid profile, essentially due to the oxidation of lipoproteins, an increase in TG and a decrease in HDL-C (Messner & Bernhard, 2014), and increases the levels of inflammation biomarkers, known as powerful predictors of cardiovascular events (Kianoush et al., 2017). The e-cigarettes, water pipes, and heat-not-burn tobacco products, in an emerging trend, especially among younger generations, have also proven to have a negative impact on endothelial function (Münzel et al., 2020). There are still gaps in the knowledge about the effects of smoking on CVD, but the major evidence of its damage is the smoking cessation which is the most effective measure for reversing damage that has already occurred and preventing fatal cardiovascular outcomes (Messner & Bernhard, 2014).

Despite recent data by the WHO indicating that in the last two decades global tobacco use has dropped and European Union and national governments' tobacco control policy measures - regulation of tobacco products; advertising restrictions; creation of smoke-free environments; tax measures and activities against illicit trade - 28% of the European population is still a smoker and tobacco related disease account for an estimated 700 000 premature deaths every year (Timmis et al., 2018).

In Portugal, smoking affects about 20 to 26% of the population, with a prevalence of three and a half men for each woman (World Health Organization, 2017b) and smoking was the fourth in ranking of number of deaths by risk factor, responsible for 11869 deaths (Roth et al., 2018). In 2005, the burden of disease attributable to smoking in Portugal was still very high and about 12,600 people had died from illnesses due to tobacco consumption, which represents 11.7% of all deaths (Borges et al., 2009). The evaluation of the smoking habits in the Portuguese population has been the objective of several studies, which are summarized in Table 8.

Table 8 - Prevalence of the smoking habits in the Portuguese population.

Study	Smoker male/female	Findings
5th INS study (Instituto Nacional de Estatística I.P., 2016)	20.0% 27.8%/13.2%	The age group from 25 to 34 years had the highest prevalence of daily consumers: 25.9% in both sexes - 34.0% in men and 18.0% in women.
1st National Health Survey (Namorado et al., 2017)*	12.8% 28.3%/16.4%	*In men, the highest prevalence of consumption was observed: in groups with intermediate schooling; in the unemployed (43.0%); in the 25 to 34 age group (45.6%) and in the Autonomous Region of the Azores. In women, except for higher education, consumption increased according to the degree of schooling; in the unemployed (27.0%); in the 25 to 34 age group (25.1%) and in the Algarve region, regardless of age.
4th Survey on the consumption of psychoactive substances (Balsa et al., 2017)	26.3% 32.2%/20.6%	The 25 to 34 age group had the highest consumption (42.0%).
e_COR (Boubon et al., 2019)	25.4% 32.1%/19.6%	The prevalence decreased significantly with age: 35.7% of smokers in the 18-34 age group, 26.7% in the 35-64 age group, and 6.1% in the latter age group.
Portuguese Program for Smoking Prevention and Control report (Nunes, 2021)	22.8% 18.6%/ 4.4%	Based on estimates from the Institute of Health Metrics and Evaluation - tobacco contributed to 19.6% of all deaths from cancer, 28.1% of deaths from chronic respiratory disease, 8.7% of deaths from brain- cardiovascular disease and 9.8% of deaths from type 2 diabetes (IHME University of Washington, 2018).

Over the past few years, there has been a clear increase in the number of women smoking between the ages of 15 and 64 and a decrease in the number of men smoking in the same age group. The data for 2001, 2007, 2012 and 2016/2017 are 17.6%, 19.0%, 18.0%, 24.8% for women and 40.1%, 40.1%, 35.1%, 36.4% for men (Nunes, 2021). Tobacco continues to tempt young people and one in two with the age of 15 consider it easy or

very easy to have access to tobacco and therefore starting their tobacco consumption in their adolescence - 13 years (12%);14 years (22%); 15 years (32%); 16 years (43%); 17 years (54%); 18 years (59%) (Feijão, 2015).

The understanding of patterns and trends in tobacco use and exposure to tobacco smoke helps policy-makers to design stronger and more targeted tobacco control policies. Thus, in November 2016, the governmental Order no. 14202-A/2016, in the scope of the National Program for Smoking Prevention and Control, established several initiatives to encourage smoking cessation, with emphasis on the possibility of co-payment of medicines and access to consultations for intensive smoking cessation support. On January 1, 2017, one of the first-line drugs - varenicline - was reimbursed 37% by the national health service. In the first quarter of 2017, this measure boosted the use of varenicline with an increase of about 68.2% (plus 6196 packages) in the dispensing of varenicline in pharmacies, compared to the same period of the previous year. There was also an increase in the accessibility of smoking cessation consultations and 31,800 intensive support consultations on smoking cessation were conducted at the regional health centers and hospital units of the national health service, representing an increase of 3.5% compared to 2015 (Nunes, 2021).

Smoking cessation is the most cost-effective of all preventive measures, with benefits at any age. The recommendations for smoking intervention strategies are based on offering follow-up support, brief interventions with advice to stop smoking, all types of nicotine replacement therapy (Hartmann-Boyce et al., 2018), varenicline (Cahill et al., 2016), and bupropion (J. R. Hughes et al., 2014) with greater effectiveness of drugs in combination, except for nicotine replacement therapy plus varenicline (Rigotti & Clair, 2013; Visseren et al., 2021).

5.1.6. Physical inactivity and sedentarism

The use of the terms "physical inactivity", "sedentarism", and "sedentary behavior" have become arguable in terms of interpretation and definition, and it is essential to standardize their use (Caspersen et al., 1985; Yates et al., 2011). One of the most frequently used methods for assessing physical activity is the metabolic equivalent method, which corresponds to the level of energy expenditure while resting quietly (metabolic equivalent of 3.5 mL O_2/kg/min). Physical activity has been classified as of light-intensity (<3 metabolic equivalents), moderate-intensity (3-6 metabolic equivalents), and vigorous-intensity (>6 metabolic equivalents) physical activity (González et al., 2017). The physical activity

recommendations are generally based on the former definition and aim to state the minimum requirement for physical activity to benefit health. Evidence shows that there is an optimal level of physical activities to promote health, but there is also an optimal level of sedentary behavior, beyond which developing chronic disease is more likely. Therefore, the importance of reducing sedentary behavior is added to the importance of being physically active (González et al., 2017). Investigation designs should include data of both conditions in order to establish a global perspective about the specific contribution of each one to chronic disease (Thyfault et al., 2015). To accurately measure and monitor levels of physical activity and sedentary behavior and evaluate its impact on global population health, a cost-efficient and valid assessment method is required (Lee et al., 2011; Gibbs et al., 2015; Tremblay et al., 2017; Cleland et al., 2018). The benefits of regular physical activity have been known since ancient Greek. Nevertheless, in the previous Century the scientific knowledge has progressed enormously, starting with the early studies of Morris et al., who demonstrated that physical activity at work reduced incidence of CVD and mortality (Morris et al., 1953). At present, numerous research studies demonstrate that almost all individuals can benefit from regular physical activity and evidence regarding health benefits of physical activity is overwhelming. Physical activity results in increased exercise capacity and cardio respiratory fitness, which may lead to many health benefits - lower blood pressure, improved glucose tolerance, prevention of obesity, improvement of lipid profile, lower rates of all-cause mortality, enhanced fibrinolysis, improved endothelial function, and decreased sympathetic tone (Bull et al., 2017). The aforementioned benefits of physical activity have a positive prognostic utility to prevent many chronic NCDs, including CVD, by reducing obesity, the development of metabolic syndrome, diabetes, hypercholesterolemia and can be applied as a therapeutic strategy (Health and Human Services, 2009; Kimata et al., 2018; Lavie, Kachur, et al., 2019). National and international organizations consider the increased levels of physical inactivity and time spent in sedentary activities, due to globalization, one of the leading modifiable risk factors for cardiovascular morbidity and mortality. Even a moderate level of occupational or recreational activity confers a significant protective effect (Prasad & Das, 2009; Booth et al., 2012; Moore et al., 2012; Lavie et al., 2019). The facts show that a significant percentage of the worldwide population, in particular the European population, have high levels of sedentary behavior and physical inactivity and the percentage of those exercising at a regular level is greater in men than in women. However, global progress to increase physical activity has been slow, largely due to lack of awareness and investment. In 2017, the number of deaths by risk factor revealed that 1.26 million deaths were attributed to insufficient physical activity

worldwide (Ritchie & Roser, 2019) and the ninth in ranking of number of deaths by risk factor in Portugal (Roth et al., 2018). The close relation to another CVD risk factor as overweight and obesity is clear, as physical activity contributes to lower prevalence of overweight and obesity at all ages. As public health measures have failed to stop the obesity epidemic in the last 3 decades, there is clearly a need to change the paradigm (González-Gross & Meléndez, 2013).

According to the National Program for the Promotion of Physical Activity, it is estimated that in Portugal physical inactivity is responsible for 8% of cases of coronary artery disease; 11% of cases of type 2 diabetes; 14% of cases of breast cancer and 15% of colorectal cancer, representing an overall estimated percentage of mortality attributed to physical inactivity of 14%. That is, if the Portuguese State achieves a 10% reduction in its prevalence - a target assumed for 2025 - around 1,500 deaths could be avoided every year. The total cost of physical inactivity in Portugal was estimated to be between 210 million and 460 million Euros, including direct costs and productivity losses with premature mortality (O'Donnell et al., 2016). The prevalence of physical inactivity patterns in the Portuguese population is shown in Table 9.

Table 9 - Prevalence of physical inactivity patterns in the Portuguese population.

Study	Prevalence of physical inactivity pattern	Findings
Sedentarism in a Portuguese urban population (Gal et al., 2005)	84% sedentarism during leisure time, in both genders	More likely to occur in those with higher levels of education and in white-collar workers
Prevalence of PA of Azoreans (Santos et al., 2009)	36.4% low PA level, 31.4% moderate PA level, 32.2% health enhancing PA level, 32.5% inactive (no PA/week), 10.5% insufficient PA, 57.5% sufficient PA and 48.1% sitting time ≥3h/day	Azorean women do not do enough PA to attain health benefits - sufficient PA (≥150 min/week of moderate to vigorous PA or ≥20 min/week of vigorous PA)
PA among Portuguese adolescents (10-18 years) (Seabra et al., 2011)	Age was positively related with moderate and high PA. Boys and adolescents of high socio-economic status were more likely to participate in moderate and high PA. Adolescents were more likely to participate in high PA when their mother also participated. Peers had a positive influence on participation in moderate and high PA, while physical education teachers did not have an influence.	
Special Eurobarometer: Sport and PA - European Commission (NS opinion & Social, 2018)	71.0% have sufficient PA for optimal health benefits - 66.7% are insufficiently active - 68% is most likely to never exercise or play sport	Men are 1.6 x more likely than women to be sufficiently active, less likely to be sedentary and slightly more likely to sit for at least 6hrs/day
PA prevalence in Portuguese adults (Teixeira et al., 2019)	42.3% were low active 30.6% moderately active 27.1% highly active	Frequent activities and most popular leisure-time activities: walking, health/fitness activities, running, group gymnastics classes, swimming/pool activities, football/futsal, and cycling

e_COR (Boubon et al., 2019)	28.6% of sedentarism 29.2% of low level of PA 29.9% of moderate level of PA 40.9% of high level of PA	The low level of PA did not differ significantly by sex or with age.
National survey on diet and activity behaviors (IAN-AF, 2015/16; Martins et al., 2020)	37.3% - "higher risk"- low PA/high sitting time -was likely associated with a middle household income, and with having ≥12 years of education. 26.6% - "lower risk" - high PA/low sitting time - was likely associated with middle-aged adults and with having a lower educational level.	

PA - physical activity.

The WHO recommends that adults aged between 18 and 64 years should accumulate at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or perform a combination of both forms of physical activity (Global recommendations on physical activity, 2010). According to the current ESC Guidelines and based on the physical activity guidelines advisory committee, the risk factor goal for the important cardiovascular risk factor physical activity, is that adults should perform at least 150-300 min a week of moderate-intensity physical activity, or 75-150 min of vigorous-intensity physical activity, or an equivalent combination of both, spread throughout the week (Visseren et al., 2021). Additional benefits on premature mortality are gained with even more physical activity, at any intensity, and less time spent sedentary, with a non-linear dose-response pattern in middle-aged and older adults (Ekelund et al., 2019). Based, among others, on the former study, the current ESC guidelines consider that regular physical activity is a pillar of cardiovascular prevention, as it decreases all-cause and cardiovascular mortality, and recommend physically inactive adults to reduce sedentary time and to engage in at least light activity, even as little as 15 minutes a day, is likely to produce benefits (Visseren et al., 2021). To consider that older adults or individuals with chronic conditions should be as active as their abilities and conditions allow, as any level of physical activity is considered better than none. Moreover, physical activity should be implemented by physicians in the same way as drug prescription and should also be promoted by other health care professionals. Thus, physical activity should be individually assessed and prescribed in terms of frequency, intensity, duration, type, and progression. Interventions are recommended to be based on behavior theory, such as goal-setting, re-evaluation of goals, self-monitoring, and feedback, and to encourage activity that people enjoy and can include in their daily routines, so that they are sustainable, such as walking, jogging, and cycling. It is important to stress that population-level interventions are also effective in promoting physical activity and should be applied in different environments, such as schools in different age ranges, companies, and workplaces in general.

5.1.7. Unhealthy diet

Diet strongly affects CVD, as dietary habits influence cardiovascular risk, through an effect on other risk factors such as cholesterol, blood pressure, body weight, and DM, with a synergetic interaction. In the development of CVD, as in other diseases, both genetic and environmental factors play an important role, with diet and physical activity being key environmental factors. Alcohol use, tobacco use, high blood pressure, high BMI, high blood cholesterol, high blood glucose, low fruit and vegetable intake, and physical inactivity are the eight risk factors that collectively account for 61% of cardiovascular deaths globally. Seven of these risk factors are related to diet and physical activity (World Health Organization, 2009), and therefore a key factor in the interventions to reduce the risk of CVD (Gambardella & Santulli, 2016).

The dietary pattern influences CVD directly by contributing to the accumulation of vascular plaques and indirectly by determining the rate of aging (Brandhorst & Longo, 2019). Excessive glucose intake produces oxidative stress by activating the NF-kB pathway that induces an increase in superoxide production in mononuclear cells and leukocytes (Dandona et al., 2005). A single high-fat meal can trigger endothelial activation, an oxidative mechanism that increases expression of specific adhesion molecules (Nappo et al., 2002). Moreover, meat consumption is positively associated with inflammatory biomarkers (Turner-McGrievy et al., 2015), while the Mediterranean diet has shown to reduce some inflammatory biomarkers (Esposito et al., 2004).

From the Global Burden of Disease study, it is known that in Portugal, in 2017, a diet low in whole grains, fruits, nuts and seeds, fiber, vegetables, and seafood omega-3 fatty acids was responsible for 5227, 3139, 2819, 1585, 1523, 1713, 1180 deaths respectively. Furthermore, a diet high in sodium and red meat was responsible for 2445 and 223 deaths respectively (Roth et al., 2018).

An Energy-adjusted Dietary Inflammatory Index score to quantify the effect of diet on systemic inflammation confirms benefits of the recommendations to increase the intake of an anti-inflammatory diet (fruits and vegetables), and lower the intake of simple carbohydrates and fats (Puddu et al., 2020). A meta-analysis reported a decrease of 4% in cardiovascular mortality for each additional serving of fruits and vegetables per day (Wang et al., 2014), a risk reduction for stroke of 11% for three to five daily servings of fruits and vegetables and of 26% for more than five servings compared with less than three servings (He et al., 2006) and a 4% decrease in risk of coronary artery disease for each additional

serving of fruits and vegetables per day (Dauchet et al., 2006; Miller et al., 2017). The risk of coronary artery disease is reduced by 2-3% when 1% of energy intake from saturated fatty acids is replaced by polyunsaturated fatty acids, which also lower LDL-C levels (Astrup et al., 2011).

Minerals, sodium, and potassium play an important role in CVD prevention, more specifically in the lowering of blood pressure. There is evidence from the Dietary Approaches to Stop Hypertension (DASH) trial that a dose-response relation between sodium reduction and blood pressure reduction exists, and it was shown that even a modest reduction in sodium intake of 1 g/day reduces SBP by 3.1 mmHg in hypertensive patients and 1.6 mmHg in normotensive patients (He & MacGregor, 2002). To realize the importance of specific nutrients in the prevention of CVD, in 2017, 4.1 million deaths have been attributed to excess sodium intake (Ritchie & Roser, 2019). Increased potassium intake reduces blood pressure in people with hypertension, and was associated with a 24% lower risk of stroke (Aburto et al., 2013).

A 7 g/day higher intake of total fiber is associated with a 9% lower risk of coronary artery disease (Threapleton et al., 2013), a 10 g/day higher fiber intake is associated with a 16% lower risk of stroke (Zhang et al., 2013), a 6% lower risk of type 2 diabetes for a 2 g/day increment in cereal fiber intake (Yao et al., 2014), a high fiber intake reduces postprandial glucose and insulin responses in healthy adults (Stewart & Zimmer, 2018) and lowers total cholesterol and LDL-C levels (Zhou et al., 2015). A meta-analysis of prospective cohort studies has shown that each incremental serving per day of nut intake (rich in unsaturated fatty acids, fiber, high-quality vegetable protein, and minerals) reduces the risk of CVD by almost 30% (Luo et al., 2014). Prospective cohort studies show a dose-response analysis, indicating that every 15 g/day increment of fish intake decreased the risk of cardiovascular mortality by 6%. Thus, eating fish at least once a week results in a 16% reduction in the risk of coronary artery disease compared with eating less fish (Zheng et al., 2012).

Soft drinks are one of the main sources of calories and its regular consumption has been associated with overweight, metabolic syndrome and type 2 diabetes. The WHO guideline recommends a maximum intake of 10% of energy from sugar, which includes all sugars from those added to those present in the fruits and fruit juices (World Health Organization, 2015).

Assessing the impact of a "dietary pattern" shows the preventive effect of a diet, since it combines the impact of several favorable dietary habits. The Mediterranean diet is considered one of the most studied diets regarding the benefit on CVD and contains many of the nutrients and foods that have been studied, mentioned earlier in the text, and linked to the protective effect of CVD. The Mediterranean diet is characterized by a high intake of fruits, vegetables, legumes, whole grain products, fish, and unsaturated fatty acids (olive oil); moderate consumption of alcohol and low consumption of red meat, dairy products, and saturated fatty acids. A meta-analysis of prospective cohort studies has demonstrated that a 2-point increase in adherence to the Mediterranean diet was associated with a 10% reduction of cardiovascular incidence or mortality and an 8% reduction in all-cause mortality, confirming the significant and consistent protection provided by adherence to the Mediterranean diet (Sofi et al., 2010). In fact, the *PREvención con DIetaMEDiterránea* study was the largest dietary intervention trial that publicized the preventive effects of the traditional Mediterranean diet on CVD (Estruch et al., 2006; Estruch et al., 2013) and a sub study of the PREDIMED study concluded that a high dietary polyphenol intake is associated with reduced all-cause mortality, lower incidence of cardiovascular events, lower SBP and DBP, higher plasma high-density lipoprotein cholesterol, and lower plasma levels of inflammatory biomarkers (Medina-Remón et al., 2017). These former studies gathered considerable evidence and had a major impact on the Mediterranean Pyramid being, therefore, held and adopted as the healthy eating pattern for the prevention of CVD. Current ESC guidelines based on the compiled evidence of the former studies also state that a healthy diet is a cornerstone of CVD prevention in all individuals, and that adopting a Mediterranean or similar diet lowers the risk of CVD. Moreover, a healthy diet can be achieved by restricting alcohol consumption to a maximum of 100 g per week; eating fish, preferably fatty, at least once a week and restricting processed meat; replacing saturated with unsaturated fats; reducing salt intake to lower blood pressure; choosing a more plant-based food pattern, rich in fiber, that includes whole grains, fruits, vegetables, pulses, and nuts; restricting free sugar consumption, in particular sugar-sweetened beverages, to a maximum of 10% of energy intake and energy intake should be limited to the amount of energy needed to maintain, or obtain, a healthy weight, that is, a BMI >20.0 but <25.0 kg/m^2 (Visseren et al., 2021).

Unfortunately, dietary patterns of many regions are affected by Westernization eating habits and the changes introduced by the economic crisis in the last decade have decreased the adherence to the Mediterranean diet around the world. Hence, it is important to sustain

the dietary traditions and lifestyle habits within the Mediterranean region to prevent increasing rates of chronic disease (Vilarnau et al., 2019). In Portugal, while facing a severe economic crisis, a high prevalence of food insecurity - limited or uncertain access to adequate food - was found and associated with low adherence to the Mediterranean diet, lower quality of life, and higher consumption of health resources, with consequent public health problems (Gregório et al., 2018). The Portuguese government, aiming to improve the dietary habits of the population, assigned a working group, led by the Ministry of Health, which developed a strategy with its framework based on WHO and European Commission recommendations, as well as on relevant data from the last Portuguese dietary intake survey (2015/2016). The project encompasses four different strategic areas, namely (1) creation of healthier food environments, (2) improvement of the quality and accessibility of healthy food choices for consumers, (3) promotion and development of literacy, to encourage healthy food choices, and (4) promotion of innovation and entrepreneurship. Under the scope of this strategy, Portugal has already implemented several actions, including (1) definition of standards for food availability at all public healthcare institutions; (2) implementation of a sugar tax on sweetened beverages; (3) implementation of a voluntary agreement with the food sector industry for food reformulation; (4) design of a proposal for an interpretative model of front-of-pack food labelling; (5) improvement of the nutritional quality of food aid programs for low-income groups; and (6) regulation of marketing of unhealthy food for children (Graça et al., 2018).

5.1.8. Psychosocial stress

Recently, greater attention has been devoted to the role of psychosocial stress in CVD, as a result of increasing knowledge of its adverse physiological consequences for both mental and physical health. A significant body of evidence indicates that psychosocial risk factors such as low socio-economic status, social isolation, stress, type-D personality, depression, and anxiety increase the risk of CHD (Pogosova et al., 2015; Gomez et al., 2020). Bonnet et al. studied the association of anxiety and depression with unhealthy behaviors - physical inactivity, smoking, and poor diet - combined to produce a global unhealthy lifestyle and concluded that depression, and to a lesser extent anxiety, are associated with a cluster of unhealthy behaviors in subjects at risk of CVD, making it difficult to modify lifestyles in patients with anxious-depressive disorders (Bonnet et al., 2005).

The ESC identifies depression, anxiety, and psychosocial stressors, such as work-related stress or poor social support, as risk factors for incident CVD and adverse outcomes in patients with existing CVD. The ESC recommends that psychosocial risk factors should be assessed, using clinical interview or standardized questionnaires in order to identify possible barriers to lifestyle change or adherence to medication in individuals at high CVD. Moreover, the ESC acknowledges that more work needs to be done to identify effective treatments to reduce their impact on CVD, and considers stress symptoms and psychosocial stressors as CVD risk modifiers. In addition, guidelines from major societies also reflect the growing recognition of the connection between mental and cardiovascular health (Cohen et al., 2015).

The INTERHEART study has shown that a cluster of psychosocial risk factors (i.e., social deprivation, stress at work or in family life, and depression) is associated with increased risk for myocardial infarction (Yusuf et al., 2004). AMI is triggered by various factors and the found exposure prevalence ranged from 0.04% to 100% in the following order: use of cocaine, heavy meals, smoking of marijuana, negative emotions, physical exertion, positive emotions, anger, sexual activity, traffic exposure, respiratory infections, coffee consumption, and air pollution (Nawrot et al., 2011). Lower socio-economic status patients experience poorer functional recovery following AMI (Alter et al., 2013) and interventions to increase social support improve the prognosis of coronary artery disease (Barth et al., 2010). Short-term psychological stress, like brief episodes of anger, trigger the onset of AMI, acute coronary syndromes, ischemic and hemorrhagic stroke, and ventricular arrhythmia. All analyzed studies found that there was a higher rate of cardiovascular events in the 2h following outbursts of anger and after the death of a significant person, the incidence rate of AMI is elevated 21-fold during the first 24 hours (Mostofsky et al., 2012; Mostofsky et al., 2014). The relation between psychosocial stress (job strain) and CHD was 3.4%, suggesting that prevention of workplace stress might decrease disease incidence (Kivimäki et al., 2012) and that employees who work long hours have a higher risk of stroke (Kivimäki et al., 2015). The prospective cardiovascular population study - Copenhagen City Heart Study - concluded that both psychosocial and traditional risk factors affect CHD. In effect, vital exhaustion was one of the most important risk factors found for CHD, which highlights the importance of including psychosocial factors in risk prediction scores (Schnohr et al., 2015).

Stress, anxiety, chronic stress and depression affect the cardiovascular system through immune, neuroendocrine and behavioral pathways, as neuropsychological, hormonal, and

immune functions influence the cardiovascular homeostasis. In fact, psychosocial stress is associated with changes in the autonomic function, dysregulation of the hypothalamic-pituitary-adrenal axis, sympathetic nervous system with increased release of catecholamines impacting inflammatory processes and inducing endothelial damage, leading to atherosclerosis, the core of CVD events (Dal Lin et al., 2015; Fioranelli et al., 2018). Evidence suggests that elevated cortisol levels are associated with both the incidence of CVD and poorer recovery and treatment outcomes and are linked with established cardiometabolic risk factors for CVD including hyperlipidemia, insulin resistance, hyperglycemia, hypertension, abdominal adiposity, and dyslipidemia. Thus, hair cortisol is a promising biomarker of chronic cortisol excess due to chronic stress which may contribute to both the pathogenesis and prognosis of CVD (Whitworth et al., 2005; Iob & Steptoe, 2019).

On the other hand, CHD and its associated treatments may also lead to distress in patients, including anxiety and depression. Thus, a multimodal behavioral intervention, integrating psychological counseling for psychosocial risk factors, coping with illness and psychopharmacological treatment should be included within comprehensive cardiac rehabilitation in patients with clinically significant symptoms of distress (Pogosova et al., 2015; Blumenthal et al., 2016).

ESC guidelines recommend that patients with ASCVD and stress should be considered for referral to psychotherapeutic stress management to improve cardiovascular outcomes and reduce stress symptoms; patients with CHD and moderate-to-severe major depression should be considered for antidepressant treatment with a selective serotonin reuptake inhibitor. However, in patients with heart failure and major depression, selective serotonin reuptake inhibitor, serotonin-noradrenaline reuptake inhibitors, and tricyclic antidepressants are not recommended.

5.1.9. Harmful use of alcohol

According to the International Classification of Diseases (ICD-10) the diagnosis of harmful use of alcohol is based on a pattern of psychoactive substance use and only considered harmful when it causes damage to health.

Current ESC guidelines recommend restricting alcohol consumption to a maximum of 100 g per week. However, results from epidemiological studies have suggested that, for

CVD subtypes except myocardial infarction, there were no risk thresholds below which show that lower alcohol consumption stopped being associated with lower disease risk (Wood et al., 2018). These data challenge the concept that moderate alcohol consumption is universally associated with lower CVD risk. In addition, any amount of alcohol increases BMI, since alcohol is energy-dense, providing 7 kcal/g, increases blood pressure (Holmes et al., 2014), and secondary dyslipidemias can also be caused by alcohol abuse. Alcohol use has complex effects on CVD, which are influenced by many other behavioral, genetic, and biologic factors. Although low-to-moderate alcohol intake induces elevations of HDL-C, Apo A-I and adiponectin, decreases hemostatic factors, and levels of fibrinogen, which affects positively atherosclerosis and inflammation, providing support for a protective effect, the over-consumption of alcohol causes mitochondrial dysfunction, changes in circulation, increases inflammatory cytokines, deteriorates insulin resistance, results in an increase of very low-density lipoproteins cholesterol and TG, oxidative stress, and apoptosis, as well as anatomical damage to the cardiovascular system (Piano, 2017; Yanai & Yoshida, 2021). The mortality rate of CHD is 65%, higher in male, heavy drinkers, and more than double in female heavy drinkers (Brien et al., 2011). An association exists of a protective effect of hydroxytyrosol-related foods - wine and virgin olive oil - along with its biological metabolite homovanillyl alcohol on CVD. This duality of effect is largely determined by the dose and pattern of alcohol consumption (de la Torre et al., 2017). Numerous epidemiological studies have observed the complex relationship between the volume and patterns of alcohol consumption and the occurrence of CVD. There appears to be a beneficial effect of low alcohol consumption without heavy drinking episodes, whereas episodic and chronic heavy drinking do not provide any beneficial effect on ischemic heart disease (IHD). Thus, average alcohol consumption is not sufficient to describe the risk relation between alcohol consumption and IHD (Roerecke & Rehm, 2014) and the presence of proposed beneficial non-alcoholic components in wine (particularly in red wine, as resveratrol) suggest that this beverage type might afford extra coronary artery disease protection (O'Keefe et al., 2014; Klatsky, 2015). Likewise, volume and patterns of alcohol consumption have been shown to increase the risk of hypertensive heart disease (Briasoulis et al., 2012; Whitman et al., 2017), cardiomyopathy (Klatsky, 2015), atrial fibrillation, and flutter (Kodama et al., 2011; Voskoboinik et al., 2016). There is also a linear dose-response association between increasing consumption and increasing risk of hemorrhagic stroke, whereas ischemic stroke showed a curvilinear association, where low to moderate consumption shows a protective effect, and increased risk for higher consumption (Patra et al., 2010). Heavy drinking prematurely ages the arteries and increase the levels of TG, which combined with high

LDL-C or low HDL-C is associated with the formation of atheroma plaque, increasing the risk of IHD, AMI, and stroke (Klop et al., 2013; Leong et al., 2014). Alcohol consumption has a U-shaped relationship with type 2 diabetes for both sexes. This means that low to moderate alcohol consumption is protective for type 2 diabetes in men and women, but a higher alcohol consumption (>60 g alcohol/day in men and >50 g alcohol/day in women) is harmful and increases the risk of developing diabetes (Baliunas et al., 2009).

Globally, in 2017, heavy chronic alcohol use caused an estimated net CVD burden of 593 000 deaths (3.3% of all CVD deaths). When analyzed by cause, alcohol caused 9.5% of all hemorrhagic stroke deaths, 7.4% of all hypertensive heart disease deaths, 6.8% of all cardiomyopathy deaths and 2.7% of all IHD deaths (World Health Organization, 2018b). The harmful use of alcohol is a causal factor in more than 200 diseases and injury conditions. In 2017, of all deaths attributable to alcohol consumption worldwide, 19% were due to CVD. Men (7.6%) are nearly twice as likely as women (4%) to suffer from deaths attributable to alcohol (Ritchie & Roser, 2019).

Total alcohol *per capita* consumption in the world's population over 15 years of age rose from 5.5 liters of pure alcohol in 2005 to 6.4 liters in 2010 and remained at that level until 2016, where more than half (57%, or 3.1 billion people) had abstained from drinking alcohol in the previous 12 months, but 2.3 billion people are current drinkers. Alcohol is consumed by more than half of the population in only three WHO regions - the Americas, Europe and Western Pacific. The highest levels of *per capita* alcohol consumption are observed in countries of the WHO European Region (World Health Organization, 2018b).

According to the e_COR study, the prevalence of alcohol consumption in the Portuguese population, between 18 and 79 years of age, was 18.8%, and statistically lower in the female sex (10.0%) than in the male sex (29.2%). The percentage of heavy drinkers increased significantly with age (18-34 years: 9.7% / 65-79 years: 24.2%) (Boubon et al., 2019).

Policies and population-based interventions for addressing the harmful use of alcohol, such as increasing alcoholic beverage taxes, restricting access to alcoholic beverages and prohibitions on advertising, and the promotion of alcoholic beverages, are cost-effective and bring numerous benefits (Visseren et al., 2021). The analysis of the relationship between the use of alcohol and tobacco allows reducing their consumption with a common

intervention, enabling policymakers to approach both simultaneously and thus, to achieve extended health and economic gains (Reis et al., 2018).

5.2. Non-modifiable risk factors

5.2.1. Family history of premature CVD

Family history of premature CVD, as defined by the ESC guidelines, is a fatal or non-fatal CVD event or an established diagnosis of CVD in first-degree male relatives before 55 years or in first-degree female relatives before 65 years, and recommended being included in the cardiovascular risk assessment (Visseren et al., 2021). If affirmative, the CVD risk is increased, providing an easily assessed, simple, inexpensive indicator in clinical practice that produces a comprehensive risk assessment, and the most accessible way of evaluating the inherited component of CVD and the relationship between environmental and genetic factors, increasing the accuracy of risk assessment tools (Banerjee, 2012; Veronesi et al., 2014). In studies that assessed the effects of family history and genetics at the same time, the family history remained significantly associated with CVD, after adjusting for genetic scores. However, not all risk calculators include family history of CVD and in some risk calculators its definition is either not explicit or differs among them. Current ESC guidelines recommend systematic global CVD risk assessment in the target population, which includes individuals with any major vascular risk factor, where family history of premature CVD is included. Thus, family history should be inquired about routinely, and an affirmative answer should be followed by a comprehensive CVD risk assessment. In the SCORE risk calculator, family history of premature CVD is considered a risk modifier that is likely to have reclassification potential and increase CVD risk, when present (Visseren et al., 2021).

Family history of premature CVD has been studied as an independent risk factor for CHD events, and it was found that adding genetic information and family history to traditional risk factors, risk stratification is improved. After adjustment for traditional risk factors and genetic scores, family history was associated with a persistent increase in both CHD and CVD mortality risk (Bachmann et al., 2012; Tikkanen et al., 2013). However, limited data exist regarding the ability of a family history to improve CVD prediction in addition to conventional and established cardiovascular risk factors (Sivapalaratnam et al., 2010). Nevertheless, family history should be included in low-incidence populations, in long-term CVD risk scores, in men, and added to the baseline model for improving prediction

of early onset of CHD events (Hughes et al., 2012; Veronesi et al., 2014). Family history and heredity is responsible for passing genetic factors from one generation to the next, including factors likely to play some role in high blood pressure, heart disease, diabetes, and obesity, but also common environments, with unhealthy lifestyle choices, such as smoking, physical inactivity, and unhealthy eating patterns, that may increase their risk for CVD (Osadnik et al., 2018).

A large international case-control study found an increased risk of myocardial infarction if one parent had myocardial infarction (OR=1.67), one parent had myocardial infarction before age 50 (OR=2.36), both parents had myocardial infarction (OR=2.90), and both parents had myocardial infarction before age 50 (OR=6.56) (Chow et al., 2011). Moreover, siblings of patients with CVD have about a 40% risk increase, while offspring of parents with premature CVD have a 60% to 75% risk increase. Along these lines, it is important to consider that risk from family history of CVD depends on the number of first-degree relatives affected and the age CVD developed, this in turn demands a clear and consistent definition of family history of premature CVD, enabling a better estimate of the true attributable risk. Taken together, a positive family history should favor more intensive interventions, while a negative family history should favor less intensive treatment (Kolber & Scrimshaw, 2014).

The ability of genetic markers to predict cardiovascular events beyond traditional cardiovascular risk factors and even family history of premature CVD was found only in some studies. There is a lack of agreement regarding which genetic markers should be included, in addition to being less easy and more expensive to get, and therefore not recommended in clinical practice (Tikkanen et al., 2013).

The estimated prevalence of family history of premature CVD in mainland Portugal was 11.8% (I.C. 95%: 10.3-13.3), higher in females (14.6% I.C. 95%: 12.2-17.0) than in males (8.4% I.C. 95%: 6.5-10.3) and does not differ significantly with age (Boubon et al., 2019). The recent Precise study reported a prevalence of family history of CVD in patients with hypertension assisted in Portuguese Primary Healthcare centers of 11.0% (I.C.95%: 9.9;12.2) in CHD and 26.8% (25.2; 28.5) in other CVD (Marques da Silva et al., 2019).

5.2.2. Age

Most epidemiological studies consider age as the traditional non-modifiable risk factor that triumphs other risk factors for developing CVD. For that reason, all CVD assessment risk scores currently available include "age" as a predicting variable, showing an increased risk with age. It is known that age plays a vital role in the deterioration of cardiovascular functionality and that some key genes are involved in regulating cellular health, such as SIRT sirtuins, AMP-activated protein kinase, mTOR-mammalian target of rapamycin, and insulin-like growth factor 1 (North & Sinclair, 2012; Yu et al., 2021). The intrinsic aging, the molecular biology of aging pathways and the physiological changes of the cardiovascular system worsens the progression of the disease. This explains the high prevalence of CVD in the older population and its relationship with increased oxidative stress, inflammation, clinical manifestations of atherosclerosis, changes in lipid and glucose metabolism, apoptosis and overall myocardial deterioration, and degeneration (Curtis et al., 2018; Yu et al., 2021). The large elastic artery stiffening, which is associated with pathophysiological conditions, such as hypertension, stroke, left ventricular hypertrophy, subendocardial ischemia, and cardiac fibrosis, and the endothelial dysfunction at the tissue level via inflammation and oxidative stress in the older population, are independent predictors of CVD development (Donato et al., 2018). Recent evidence recognizes that accumulation of somatic mutations in hematopoietic cells with increasing age may represent a new causal risk factor for ASCVD and several studies examined the casual role of gene mutations including TET2, JAK2V617F and DNMT3A on the pathogenesis of CVD (Jung et al., 2020; Li et al., 2021). Along the aging process levels of blood inflammatory markers increases in a process that is known as *inflammageing*, contributing, therefore to an amplified susceptibility to chronic morbidity and premature death. It is a risk factor not only for CVD, but also CKD and DM, which, in turn, are CVD risk factors. Among the outlined causes of the potential mechanisms of *inflammageing* were central obesity, increased gut permeability, changes to microbiota composition, oxidative stress, and chronic infections (Ferrucci & Fabbri, 2018).

Along with the physiological aging process and the pathogenesis of CVD, there is a cumulative acquisition of other CVD risk factors and the time of exposure to these factors, that determines the multifactorial cause of CVD. Following this line of argument, it has been suggested that the contribution of age in multivariate models may be a result of the intensity and duration of exposure to other traditional risk factors for CVD. The prevalence of most types of CVD is considerably higher among older adults as compared with the general population (Benjamin et al., 2019). The Framingham Study has followed data on age-related

incidence of CVD, and a multivariable analysis of the prospective data clearly indicate an independent effect of age on CVD incidence while considering all the major risk factors. Further multivariable analysis, adjusting for the associated burden of risk factors, shows an independent contribution of age to the development of ASCVD, indicating that an age over 65 in women and over 55 in men is a risk factor in itself. In fact, the incidence of all CVD increases with age, with more than 80% of individuals who die from CVD being over 65 years of age. Our average lifespan, and consequently, the proportion of people in older age groups is increasing. Within the age group of people older than 65 years, CVD is the leading cause of death (Roth et al., 2018). As advanced age is the major risk factor for the development of ASCVD, the social and financial burden attributable to ASCVD will continue to rise due to the projected demographic aging. The Framingham study also showed that the influence of age on CVD risk is not uniform along age groups and varies depending on the burden of other cumulative risk factors, and that old age survivors have a resistance to cardiovascular risk factors (Kannel & Vasan, 2009).

Besides absolute risk, there is the concept of "risk age" of a person with several cardiovascular risk factors, which reflects the age of an older person of the same sex with the same level of risk, but with ideal levels of risk factors. Therefore, risk age is an intuitive and easily understood way for communicating about risk, demonstrating that a young person with many risk factors may have the same level of risk as an older person with no risk factors. This concept was clearly illustrated with the relative risk chart in the ESC guidelines, which illustrated how a young person with a low absolute risk, due to young age, may conceal a very high relative reducible risk, and may help in advising them of the need for intensive preventive efforts.

Recent updates of the SCORE charts have extended the age range from 40 to 89 years and have incorporated the interaction between age and each of the other risk factors, thus reducing the overestimation of risk in older persons in the original SCORE charts. In addition, lifetime benefit charts, which express the "years of median life expectancy free from myocardial infarction or stroke", gained by controlling or treating uncontrolled risk factors, have been included (Visseren et al., 2021).

5.2.3. Sex

Sex and gender are usually used interchangeably, contributing to an assumed thinking that both are constant or fixed, without the notion that gender itself is a potentially

modifiable target for CVD prevention. Their influence on other risk factors and thus, the onset and progression of CVD have to be considered. The current European prevention guidelines recognize the importance of integrating sex, gender, and gender identity considerations into the risk assessment, as gender interacts with biological sex to shape cardiovascular health from conception, through early life when health behaviors and risk factors are shaped, into adolescence and adulthood. Gender is a performative, behavioral, learned and dynamic process that is shaped by social construct and context, whereas sex is a biological, physiological, and anatomical characteristic. As for risk stratification, the applied factor is sex and the gender influence on other risk factors are already represented in lifestyles, such as smoking habits, physical activity, and alcohol consumption, among others.

Evidence exists on the risk modifying effect of sex and on sex-specific clinical conditions, which have to be considered in clinical management strategies. Sex-specific responses to treatment and clinical conditions, such as menopause, pregnancy disorders, and gynecological conditions represent a sex-specific pathophysiological mechanism of CVD, through genetic and hormonal influences. On the other hand, the epigenetic effect, which influences determinants of access to health care, health care utilization, disease perception, decision-making, and perhaps therapeutic response are important risk modifiers, such as lifestyle, nutritional habits, exercise, smoking, and perceived stress (Mauvais-Jarvis et al., 2020).

The INTERHEART study indicated a different influence of risk factors, such as smoking, alcohol use, high-risk diet, and physical inactivity, for the incidence of myocardial infarction between men and women, which was significantly higher in women than in men (74.3; 95% CI, 67.9-80.7 *versus* 67.3; 95% CI, 63.9-70.8). Even though CHD is a leading cause of death among men and women globally, women experience their first AMI on average 9 years later than men, which can also be explained with the fact that men show higher risk factor levels at younger ages (Yusuf et al., 2004). The Framingham study cohort has been followed biennially for development of ASCVD for over more than 5 decades, so it was possible to estimate the lifetime risk of developing stroke events in men and women of this cohort. The study proves stroke events to be higher in women, presumably because of their longer life expectancy (Kannel & Vasan, 2009). The AHA 2019 Heart Disease and Stroke Statistical Update support the former results, where the incidence of CVD was reported to be 77.2% in males, 78.2% in females, from ages 60-79 years, and 89.3% in males and 91.8% in females,

in adults above 80 years of age (Benjamin et al., 2019). In fact, sex-specific differences exist in CVD, which are summarized in the following studies:

Disease differences

- Women have a higher mortality and worse prognosis after acute cardiovascular events (di Giosia et al., 2017).
- Population data show that heart disease develops at a later age for women compared to men, yet have been increasing among younger women (Lerner & Kannel, 1986) possibly because of the changes in Western lifestyles of younger women (Vogel et al., 2016).
- Women are significantly older at their first-ever stroke and present a higher incidence of stroke above 85 years of age and with longer periods of post-stroke disability (Petrea et al., 2009).
- Age, hypertension, total cholesterol, LDL-C and body weight have a greater influence in men and smoking, diabetes, triglyceride, and HDL-C levels mainly have effect on women. Diabetes appears to be a stronger risk for ischemic heart disease in women when compared to men, and rates of impaired glucose are higher among women than in men (Pathak et al., 2017).
- CVD is also affected by some female-specific risk factors, such as polycystic ovary syndrome, primary ovarian insufficiency, pregnancy-induced hypertension, preeclampsia, gestational DM, and preterm birth (Gao et al., 2019).
- Polycystic ovarian syndrome and postmenopausal status have been associated with increased incidence of hypertension among women (Goodman et al., 2015; Dargham et al., 2018).
- Women have a longer repolarization phase (longer QT duration on electrocardiogram), which may increase a woman's risk for ventricular arrhythmias in the setting of certain drugs including antidepressants (Cardiovascular Clinical Study Group, 2016).
- The decline in hormone levels, primarily of estrogen and testosterone, may play a significant role in the development of CVD in older men and women. Despite this, hormone replacement therapies are largely shown not to improve outcomes in older patients and may even increase the risks of cardiac events in older adults (Rodgers et al., 2019).

Therapeutic differences

- Sex differences are also present in enzyme formation, pharmacokinetics and pharmacodynamics altering efficacy, compatibility and side effects of pharmacological interventions (Baggio et al., 2013).
- Differences in the pathophysiology and in the clinical presentation of CVD (Gao et al., 2019).
- Sex differences exist related to the pharmacokinetics of many cardiac drugs: oral bioavailability, clearance, body fat distribution, plasma protein binding, and metabolism.
- Estrogen has been studied extensively for its potential cardioprotective activity, including high-density lipoprotein production (Garcia et al., 2016).

Based on the previous facts retrieved from the literature, it is important to consider the sex impact in the prevention, diagnosis, and treatment of CVD. Not taking sex into account when setting diagnostic criteria and treatment thresholds can lead to poorer CVD outcomes in women. Already in 1999, the AHA developed the first women-specific clinical recommendations for CVD prevention, which led to increased awareness of women's CVD risk, and to improved risk factor management and treatment of CVD in women (Mosca et al., 1999) and in 2014 AHA published separate guidelines for the prevention of stroke in women with atrial fibrillation (Bushnell et al., 2014).

Nevertheless, as stated in several studies, gender-related variables should also be defined and added to current risk assessment (O'Neil et al., 2018; Gao et al., 2019; H. den Ruijter, 2020).

5.2.4. Ethnicity

Every country has ethnic minority groups and immigrants from all over the world with different ethnic backgrounds in their population, and no single risk score performs adequately in all groups. Indeed, the existing guidelines on CVD management apply to the "general population" and specific recommendation on primary and secondary prevention for ethnic groups is limited. According to the Centers for Disease Control and Prevention, cardiovascular disease death rates by race vary a lot, from 85.5 per 100,000 persons in non-Hispanic Asian or Pacific Islander adults to 208 per 100,000 persons in non-Hispanic Black adults. There are racial-ethnic differences in cardiovascular health and a vast variability in risk factors documented in the literature, due to identified hindrances which contribute to

the increase in CVD risk factors, such as language barriers, limited access to health care services, and health illiteracy (Muncan, 2018). The QRISK3 gave us some data on CVD risk imposed by ethnicity, as calibration and discrimination in the validation cohort were determined separately for individual subgroups by ethnicity (Hippisley-Cox et al., 2017). Based on these data, the current ESC guidelines recommend applying a correction factor on CVD risk like follows: 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; and Black African and Chinese - multiply the risk by 0.7.

In conclusion, it is important to stress the interdependence and mutual influence of all the mentioned risk factors and how this is conducive to interventions in the struggle against CVD. It seems easy to understand and to demonstrate, as by simply increasing physical activity and having a healthier diet, the weight and abdominal circumference are reduced, improving the lipid profile, glucose resistance, and BP and by simply quitting smoking the lipid profile is improved, reducing the global CVD risk.

5.3. New cardiovascular risk factors

Cardiovascular risk prediction can incorporate both traditional risk factors and nontraditional, recent technologically generated diagnostic and therapeutic biomarkers. Biomarkers can be classified into inflammatory (high-sensitivity C-reactive protein and fibrinogen), thrombotic (homocysteine, lipoprotein-associated phospholipase A2), glucose and lipid-related markers (apolipoproteins) and organ-specific markers (renal, cardiac) (Upadhyay, 2015). Some may be causal - lipoprotein, reflecting a pathogenic lipid fraction, whereas others may reflect underlying mechanisms - C-reactive protein reflecting inflammation, or indicate early cardiac damage - natriuretic peptides or high-sensitivity cardiac troponin.

The aim of incorporating nontraditional risk factors is to improve the performance of traditional multivariable risk assessment for CVD. However, despite the many potential predictors studied, no new cardiovascular risk factor shows the predictive effect of the traditional risk factors and the contribution to the existing methods of cardiovascular risk assessment is probably small. Despite the improved understanding of cardiovascular pathophysiology and, an interest in new cardiovascular biomarkers individually or in a panel, none are sufficiently accurate and cost-effective for routine use in primary prevention (Gilstrap & Wang, 2012; Ghantous et al., 2020).

Nevertheless, some new potential cardiovascular risk factors have been studied. Atherosclerosis is an inflammation condition, induced by cholesterol, plaque formation, interleukin-1β, and interleukin-6, which are markedly elevated at the site of plaque rupture (Lüscher, 2018). The N-terminal pro B-type natriuretic peptide (NT-proBNP) is an inactive peptide released along with the active peptide hormone BNP, when the walls of the heart are stretched or in pressure overload. This peptide showed an incremental predictive value as a new risk factor to predict cardiovascular morbidity and mortality in older adults (Vaes et al., 2020).

Including coronary artery calcium, carotid intima-media thickness, ankle-brachial index, brachial flow-mediated dilation, high-sensitivity C-reactive protein as risk markers have been reported to improve on the Framingham Risk Score for prediction of CHD (Yeboah et al., 2012). However, Den Ruijter et al. analyzed 14 population-based cohorts contributing data for 45,828 individuals to determine whether common carotid intima-media thickness has added value in 10-year risk prediction of first-time myocardial infarction or stroke, above that of the Framingham Risk Score. The authors concluded that the net reclassification improvement with the addition of common carotid intima-media thickness was small and unlikely to be of clinical importance (den Ruijter et al., 2012).

Among the most extensively studied biomarkers is high-sensitivity C-reactive protein, which has shown consistency across large prospective studies, with relative risks approaching those of classical cardiovascular risk factors (The Emerging Risk Factors Collaboration, 2012; Piepoli et al., 2016). Nevertheless, new studies confirm that C-reactive protein has limited additional value (Lin et al., 2018).

Current ESC guidelines do not recommend genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods, such as intima-media thickness, contrast computed tomography angiography, arterial stiffness, and echocardiography to improve cardiovascular risk prediction or as risk modifiers (Visseren et al., 2021). However, ESC guidelines and the 2019 AHA and ACC guidelines for primary prevention of ASCVD recommend consideration of coronary artery calcium scoring for further risk assessment in borderline to intermediate risk individuals in whom management is uncertain (Lin et al., 2018; Dzaye et al., 2019).

Significantly improved risk discrimination of cardiovascular outcomes beyond traditional risk factors was demonstrated for estimated glomerular filtration rate and

albumin-to-creatinine ratio in general populations, and was especially evident in individuals with diabetes or hypertension, being greater with albumin-to-creatinine ratio than with estimated glomerular filtration rate (Matsushita et al., 2015). Indeed, ESC guidelines classify the patient's risk category in subgroups based on estimated glomerular filtration rate and albumin to creatinine ratio (Visseren et al., 2021), when these measures are already assessed for clinical purpose in populations with CKD.

6. Cardiovascular disease risk assessment tools

After reviewing the risk factors for cardiovascular disease, the need arises to understand how these risk factors combine in the individual. As far as what has been studied, CVD is the product of a number of causal risk factors and, the combination of risk factors slightly above ideal levels, may add a much higher cardiovascular risk than would be expected with each uncontrolled single risk factor. Rather than a simple additive effect, risk factors have been shown to have a synergistic and multiplicative effect, so that the overall cardiovascular risk of the individual is much more than the sum of the risk given by the sum of the isolated factors. This interplay between risk factors and their variable influence and the tendency for risk factors to cluster makes the determination of global CVD risk in apparently healthy individuals more complex, but absolutely necessary to address modifiable risk factors before the onset of disease (Hobbs et al., 2007). This assumption is the basis of all the available risk scores, which take into consideration the multifactorial nature of CVD. Thus, it is important to have prognostic assessment tools that can be used with maximum accuracy to estimate the overall cardiovascular risk.

Risk estimation systems have been developed from decisive cohort studies and aim to support health professionals to evaluate the effects of risk factor combinations in managing interventions (Cooney et al., 2009). The importance of evaluating the global cardiovascular risk and consequent risk stratification is to implement the risk factor management identified in individuals, and to establish the level of intensity of counseling and the adequate therapy to prevent cardiovascular disease.

In the late 20th century, studies based on large patient population samples demonstrated greater predictive value of multivariable risk assessment models compared with models based on demographic variables alone. Since then, a shift from the concept of treating patients based on individual risk factors to the management concept based on

overall cardiovascular risk have been seen. Population-based studies increased the knowledge in the incidence and causes of CVD, and some of these studies are at the basis of the development of existing risk scores. The performance of the risk estimation systems is similar when applied to comparable populations of those from which the risk estimation systems were derived.

The cornerstone of these cohorts is the Framingham Heart Study, which was started in 1948 in Framingham, a small town in Massachusetts, USA by the U.S. Public Health Service and shifted to the newly established National Heart, Lung, and Blood Institute of the National Institutes of Health in collaboration with the Boston University (Kannel et al., 1961). This study revealed much of the current knowledge about the cardiovascular risk factors like tobacco, dyslipidemia, hypertension, electrocardiographic abnormalities, menopause, atrial fibrillation, and obesity. The Framingham Heart Study continues to reveal results, since the descendants continue to be included in the initial cohort - The Offspring Cohort, which included 5124 sons and daughters in 1971, and The Third Generation Cohort, which included 4095 grandchildren in 2002 (D'Agostino et al., 2008). From the Framingham Heart Study, models were developed to predict CVD risk, resulting in the first extensively used multivariable CVD risk score, provided the basis for other risk scores, and is the most adopted screening tool in the United States. It is also recommended by The National Heart, Lung, and Blood Institute to assess an individual's CVD risk (Anderson et al., 1991). The latest version is included in the National Cholesterol Education Program guidelines and the Canadian Cardiovascular guidelines. Other national guidelines recommend adapted versions. This risk assessment tool combines the effects of age, sex, SBP, total cholesterol, HDL-C, smoking status, antihypertensive treatment status, and DM to estimate 10-year risk of CHD. During the past two decades, there has been a widespread development of additional cardiovascular risk estimation systems, based on different cohort studies, incorporating diverse variables input into mathematical equations and predicting cardiovascular outcomes. The most common cardiovascular disease risk prediction algorithm and their characteristics are summarized in Tables 10, 11 and 12.

Table 10 - Characteristics of cardiovascular disease risk prediction algorithm.

CV risk assessment tool	Study Design Data source Follow-up period	Population Sample size Statistical methods	Format used (charts, calculator, website)	Variables Age range
ASCVD: 2013 ACC/ AHA (Goff et al., 2014; Stone et al., 2014)	Prospective 4 pooled studies from the USA ≥12 years.	Men and women from White, African American, and other ethnic origins >25,000 Cox.	Available as an electronic risk calculator www.cvriskcalculator.com	Sex, age, race, total cholesterol, HDL-C, SBP-treated and non-treated patients, diabetes, smoking status. 40-79 years.
ASSIGN-SCORE (Woodward et al., 2007)	Prospective Scottish Heart Health Extended Cohort-SHHEC prospective study 1984 to 1987.	Random sample from general population in Scotland 6,540 men and 6,757 women Cox.	Online risk calculator available at: www.assign-score.com Dundee University, Scotland in 2006.	Sex, age, total cholesterol, HDL-C, SBP, smoking -number of cigarettes, diabetes, area-based index of deprivation, family history of CHD 30-74 years.
CRAX (Martineau et al., 2020)	Retrospective Manitoba Population Health Research Data Repository February 2001 to July 2008 4.4±1.2 years.	Patients who underwent SPECT-MPI at St. Boniface Hospital, Winnipeg, for suspected coronary artery disease 5842 Multivariable Cox proportional hazards regression.	Excel spreadsheet included as a supplementary file for interested readers, which is not intended or approved for clinical use. Will be used to optimize cardiac risk stratification after undergoing a SPECT-MPI.	Sex, age, congestive heart failure, cardiomyopathy, angina, valvular disease, dysrhythmias, diabetes, COPD, hypertension, hyperlipidemia, number of hospitalizations in the three years before myocardial perfusion imaging. Candidate imaging variables: need for pharmacological stress vs exercise, TID, sTPD, iTPD, rest TPD, and LVEF.
CUORE (Giampaoli et al., 2004; Ferrario et al., 2005)	Prospective 1982 to 1996 Mean 9.1 years.	Eleven cohorts-northwest, northeast, center and south of Italy, both gender groups 7520 men 13127 women Cox proportional hazard models.	www.cuore.iss.it GPs and other health professionals may download free of charge the cuore.exe software.	Sex, age, total cholesterol, SBP, smoking status, HDL-C, diabetes mellitus, antihypertensive treatment, and family history of coronary heart disease 35-69 years.
Framingham Heart Study-FHS (Dawber et al., 1951; KANNEL et al., 1979; D'Agostino et al., 2008)	Prospective Framingham Heart Study and Framingham offspring study (1968-1971,1971-1975,1984-1987) The latest version includes both/ 14 years.	General population, Framingham, Massachusetts, U.S.A. Volunteer and the majority of white race, but validated across different origins 8,491 (3,969 men, 4,522 women) Mean Age: 49 years Cox (Weibull-earlier versions).	Online calculator www.framinghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease-10-year-risk Simplified scoring sheets and portable calculator.	Sex, age, total cholesterol, HDL-C, SBP, smoking status, diabetes, antihypertensive treatment 30-75 years.

Globorisk (Hajifathalian et al., 2015)	Prospective extension of Framingham calculator and 7 more prospective studies [a] 1948-1993.	8 prospective studies from North America. 33 323 men, 16 806 women 1948-1993.	www.globorisk.org/risk-charts	Smoking status, total cholesterol, diabetes, SBP Age and sex were included in the risk score as a part of event rate 20-80 years.
PROCAM (Assmann et al., 2002)	Prospective 1979-1985.	Healthy employees Volunteer-not random 18,460 men 8,515 women Cox & Weibull Exploratory analysis with neural networks.	Simple scoring sheet and online calculators Online calculator available at: www.chd-taskforce.com/calculator	Age, sex, LDL-C, HDL-C, diabetes, smoking status, SBP 20-75 years.
QRISK1 (Hippisley-Cox et al., 2007) **QRISK2** (Hippisley-Cox et al., 2008) **QRISK3** (Hippisley-Cox et al., 2017)	Prospective/ QRESEARCH database- includes health records of general general practitioners in the UK-not random QRISK1: 6.5 yrs, median; QRISK2: 7.3 yrs mean; QRISK3: 4.4 yrs median 3 million patients with more than 10 yrs of follow-up, until 2008 Imputation of missing data.	QRISK1:1.28 million, 48-49 median age QRISK2: 2.29 million, 48-49 median age QRISK3: 7.89 million, 42.6-43.3 mean age Ethnic variables include: White, Indian, Pakistani, Bangladeshi, Black, Caribbean, Black African, Chinese Cox.	Online calculator available at: www.qrisk.co.uk QRISK2 includes interaction terms to adjust for the interactions between age and some of the www.qrisk.org/tree/index.php	QRISK1 - sex, age, total cholesterol to HDL-C ratio, SBP, smoking status, diabetes, area-based index of deprivation, family history, BMI, antihypertensive treatment QRISK2 - also includes ethnicity, chronic diseases, and medications (Antipsychotics, corticosteroids, etc.) 35-74 years.
Reynolds (Ridker et al., 2007; Ridker et al., 2008)	RCTs: Women- Women's Health Study; Men- Physician's Health Study II Women baseline: 1993-1996; Men baseline: 1997 10.2 years.	Women: Health Service employees >45 years; Men: Physicians Volunteer-not random >50years 24,558 women; 10,724 men Cox.	Online calculator: www.reynoldsriskscore.com	The Reynolds risk score adapts the calculation formula to women Sex, age, SBP, smoking, hsCRP, total cholesterol, HDL-C, family history of premature myocardial infarction -parent age <60 years, HbA1C 45-80 years.
SCORE (Conroy, 2003)	Prospective 12 pooled prospective studies from 11 European countries 1972-1991/ 2.7 million-person years.	Mostly random samples from general population, some occupational cohorts 117,098 men and 88,080 women Cox & Weibull.	Color-coded charts, HeartScore-online on www.heartscore.org/en_GB/access-heartscore-quick-calculator and CD-based stand-alone electronic version	Sex, age, total cholesterol or total cholesterol to HDL-C ratio, SBP, smoking status Two versions were developed for high and low-risk countries 40-65 years.

			Relative Risk Chart for younger persons.	
SCORE2 (Hageman et al., 2021)	Prospective Cohort data with baseline after 1990; WHO CVD mortality data from 49 countries-10.78 million individuals.	45 cohorts in 13 countries; 677684 individuals.	ESC CVD Risk app-freely available from app stores Recalibrated risk charts to four risk regions in Europe.	Sex, age, smoking status, SBP, total- and HDL-C 40-69 years.
WHO/ ISH (World Health Organization, 2007)	Comparative Not derived from prospective data, but relative risks were derived from the comparative risk assessment project.	Methods differ to other risk estimation functions, not based on prospective data Data combined with estimated absolute risks for each WHO subregion based on global burden of disease study.	Color-coded charts Development of risk predication models.	Sex, age, SBP, smoking status, diabetes, total cholesterol 40-79 years.

ACC/AHA - American College of Cardiology/American Heart Association; BMI - body mass index; CHD - coronary heart disease; COPD - chronic obstructive pulmonary disease; CVD - cardiovascular disease; ESC - European Society of Cardiology; GPs - general practitioners; HbA1c - glycated hemoglobin; HDL-C - high-density lipoprotein cholesterol; hsCRP - high-sensitivity C-reactive protein; iTPD - ischemic total perfusion deficit; LDL-C - low-density lipoprotein cholesterol; LVEF - Left ventricular ejection fraction; RCTs - randomized controlled trials; SBP - systolic blood pressure; SPECT-MPI - single photon emission computed tomography-myocardial perfusion imaging; sTPD - stress total perfusion deficit; TID - transient ischemic dilation; WHO - World Health Organization. [a] Atherosclerosis Risk in Communities, CV Health Study, Honolulu Program, Multiple Risk Factor Intervention Trial, Puerto Rico Heart Health Program, and Women's Health Initiative Clinical Trial.

Table 11 - Calculated outcomes, implemented guidelines, and advantages and disadvantages of cardiovascular disease risk prediction algorithm.

CV risk assessment tool	Calculated outcomes	Implemented Guidelines	Advantages	Disadvantages
ASCVD: 2013 ACC/ AHA (Goff et al., 2014; Stone et al., 2014)	10-year risk of the first CVD event Lifetime risk of the CVD event Non-fatal CAD Fatal CHD Fatal and non-fatal stroke.	Used by the AHA/ACC and USPSTF.	Derived from large prospective cohorts Include Caucasian and African American patients Provides both 10-year and lifetime risk of CVD.	Gathers other ethnicities into one group Does not include chronic diseases, family history, nor BMI as predictors.
ASSIGN-SCORE (Woodward et al., 2007)	10-year risk of CVD event.	Recommended by SIGN-Scottish Intercollegiate Guidelines Network.	Includes socioeconomic and rheumatoid arthritis as predictive variables.	Not enough studies on validation using ASSIGN-SCORE Disregards BMI and ethnicity as risk factors Developed from a Scottish sample.

CRAX (Martineau et al., 2020)	5-year risk of AMI, death, and MACE.	Will be used to optimize cardiac risk stratification after undergoing a SPECT-MPI.	Considers imaging and clinical variables, resulting in net reclassification improvement.	Rests on the availability of SPECT-MPI Excludes other import risk factors.
CUORE (Giampaoli et al., 2004; Ferrario et al., 2005)	10-year probability of first major CVD event (myocardial infarction or stroke).	CUORE Project, launched by the Italian Ministry of Health aims to prevent CVD through risk assessment by GPs (Giampaoli, 2007).	Collaboration project: Italian Ministry of Health +National Institutes of Health, to implement a training course for GPs to routine CV risk assessment in clinical practice.	Country specific.
Framingham Heart Study (Dawber et al., 1951; KANNEL et al., 1979; D'Agostino et al., 2008)	10-year risk of fatal+non-fatal CVD events, CAD, stroke, PAD, heart failure. Latest version: 10-year risk of CVD events NCEP ATP III version: 10-year risk of hard coronary events.	AHA; National Cholesterol Educational Program; Canadian CV Guidelines; Adapted version for: Joint British Society New Zealand guidelines.	Validated and updated in differed countries Provides fatal and non-fatal outcomes.	Does not consider ethnicity or socioeconomic variables Derived from a smaller sample size Patient were mainly of white race and of middle-income society.
Globorisk (Hajifathalian et al., 2015)	10-years risk of fatal CVD.			
PROCAM-Prospective Cardiovascular Munster Study (Assmann et al., 2002)	2 separate scores calculate 10-years risks of major coronary events and cerebral ischemic events.	International Task Force for Prevention of Coronary Disease guideline.	Logistic regression-accounts for variable duration of follow-up, censoring of subjects, proportionality of event occurrence, and time-to-event. Includes family history of CHD + triglycerides.	
QRISK1 (Hippisley-Cox et al., 2007) **QRISK2** (Hippisley-Cox et al., 2008) **QRISK3** (Hippisley-Cox et al., 2017)	QRISK1: 10-year risk of CVD events QRISK2: 1-15 years risk of developing CVD Lifetime risk of developing CVD, coronary artery disease, myocardial infarction, Stroke, TIA. QRISK3: 10-year risk of CVD events, Relative risk, Heart age.	NICE-guidelines on lipid modification; used in quality and outcomes framework; Department of health vascular guidance; NHS incorporation - general practitioners' systems, pharmacies, and hospitals; QRISK Lifetime recommended by JBS3 guidelines.	Derived and validated in large studies; includes ethnicity, socioeconomic status, and chronic diseases; provides patients with a time specific and lifetime risk prediction Extensively reviewed and externally validated.	Revealed to underestimate certain European groups Data derived exclusively from the United Kingdom.
Reynolds (Ridker et al.,	10-yr risk of incident myocardial	No	Sample size and power	Cohort is largely White with a relatively narrow

2007; Ridker et al., 2008)	infarction, stroke, coronary revascularization, or cardiovascular death.		Reclassified 40-50% of women at intermediate risk into higher- or lower-risk categories - improving accuracy of clinical algorithms.	socioeconomic range Data on BP, obesity, and family history were based on self-report.
SCORE (Conroy, 2003)	10-year absolute and relative risk of CVD mortality.	2016 European Guidelines on CVD prevention in clinical practice ESC.	Population-based cohorts with many participants.	Predicts only fatal CVD events, underestimating total CVD burden; Outside of Europe -difficult to choose the low or high-risk chart; Limited age range: 40-65 years; Cohorts recruited before 1986 - not recalibrated or statistically adapted to contemporary CVD rates; Does not include ethnicity.
SCORE2 (Hageman et al., 2021)	10-year fatal and non-fatal CVD risk in individuals without previous CVD or diabetes in Europe.	2019 ESC/ European Atherosclerosis Society Guidelines for the Management of Dyslipidemia ESC.	Broad age range: 40 to 90+; Sex-specific risk prediction models; calibrated to the most contemporary CVD rates; available for four distinct European risk regions; can be rapidly updated based on national CVD mortality rates published by the WHO.	
WHO/ ISH (World Health Organization, 2007)	10-year risk of CVD events: non-fatal coronary artery disease, fatal CHD, non-fatal stroke, fatal stroke.	WHO guidelines on primary cardiac prevention (World Health Organization, 2007) Development of preventive pocket guidelines for each continent or region.	Provides risk charts per each region Provides prediction of both fatal and non-fatal CVD events.	Does not include BMI, family history, nor socioeconomical variables Not well validated compared to other risk calculators.

BMI - body mass index; BP - blood pressure; CAD - coronary artery disease; CHD - coronary heart disease; CVD - cardiovascular disease; ESC - European Society of Cardiology; MACE - major adverse cardiac event; GPs - general practitioners; NHS - national health service; NICE - National Institute for Health and Care Excellence; PAD - peripheral artery disease; TIA - transient ischemic attack; WHO - World Health Organization.

Table 12 - Developments, internal and external validation of cardiovascular disease risk prediction algorithm.

CV risk assessment tool	Developments/ Comments	Internal validation - discrimination/ calibration	External validation discrimination
ASCVD: 2013 ACC/ AHA (Goff et al., 2014; Stone et al., 2014)	Not applicable.	10 x10 cross-validation technique of the Pooled Cohort Equations, yielding average discrimination C-statistics and calibration chi-squared statistics.	The 2 external cohorts consisted of Whites and African Americans from the Multi-Ethnic Study of Atherosclerosis MESA and the REasons for Geographic And Racial Differences in Stroke study (REGARDS).
ASSIGN-SCORE (Woodward et al., 2007)	Not applicable.	Observed 10-year CVD incidence rates: men 11.7%; women 6.4% Median ASSIGN: men 11.7%; women 6.2%.	Not applicable.
CRAX (Martineau et al., 2020)	Development of $CRAX_2MACE$ (Leslie et al., 2021), with 3896 individuals and including diabetes, besides the variables already included in the CRAX tool.	Internal validation group was drawn from the same population as the development group. Validated on subgroups of random sample.	Not applicable
CUORE (Giampaoli et al., 2004; Ferrario et al., 2005)	Ongoing collection and analysis of data since the 1980s, using standardized procedures and methodologies.	Not applicable.	Not applicable.
Framingham Heart Study (Dawber et al., 1951; KANNEL et al., 1979; D'Agostino et al., 2008)	Latest version includes version based on non-laboratory values only, substituting BMI from lipid measurement.	AUROC men: 0.76(0.75 to 0.78) AUROC women: 0.79(0.77 to 0.81)/ HL men: 13.48 HL women: 7.79.	PRIME study, Belfast: 0.68; PRIME study, France: 0.66; Dutch study: 0.86; Cleveland study: 0.5; China: men 0.75 (0.72 to 0.78); China: women 0.79 (0.74 to 0.85); THIN (UK): men 0.74 (0.73 to 0.74); women 0.76 (0.76 to 0.76); EPIC Norfolk: 0.71; UK women (BHHS): 0.66 (0.62 to 0.69).
Globorisk (Hajifathalian et al., 2015)	Recalibrations have been undertaken for 11 countries.	Not applicable.	
PROCAM (Assmann et al., 2002)	Recent change in the methods (Weibull) extension of risk estimation to women and broader age range The Updated including myocardial infarction and	AUROC 0.82 for coronary events AUROC 0.78 for cerebral ischemic events/ Not specified.	PRIME study Belfast: 0.61 PRIME study France: 0.64.

	stroke prediction as well (Assmann et al., 2007).		
QRISK1 (Hippisley-Cox et al., 2007) **QRISK2** (Hippisley-Cox et al., 2008) **QRISK3** (Hippisley-Cox et al., 2017)	QRISK2 includes interaction terms to adjust for the interactions between age and some variable.	QRISK2: AUROC men: 0.79 (0.79 to 0.79); AUROC women: 0.82 (0.81 to 0.82)/ Good correlation between observed and predicted risks in both men and women.	THIN database (UK): QRISK1: AUROC men: 0.76 (0.76 to 0.77); AUROC women: 0.79 (0.79 to 0.79).
Reynolds (Ridker et al., 2007; Ridker et al., 2008)	hsCRP and family history have been incorporated into risk prediction models for women the Reynolds Risk Score for women.	AUROC women: 0.808 AUROC men: 0.708/ HL women: 0.62 HL men: 12.9.	Not applicable.
SCORE (Conroy, 2003)	National, updated Recalibration.	AUROC high risk: 0.80 (0.80 to 0.82); AUROC low risk: 0.75 (0.73 to 0.77)/ Not specified.	Dutch study: 0.85 (0.83 to 0.87); Cleveland study: 0.73; Norwegian study: range for different age groups: men 0.65 to 0.68; women 0.66 to 0.72; Austrian study: men 0.76 (0.74 to 0.79); women 0.78 (0.74 to 0.82); Icelandic study: 0.80 (0.78 to 0.82)-SCORE high; 0.80 (0.77 to 0.82)-SCORE low.
SCORE2 (Hageman et al., 2021)	Countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population.	Discrimination was assessed using external validation cohorts by calculating Harrell's C-index, adjusted for competing risks.	Data from 25 additional cohorts in 15 European countries-1 133 181 individuals, 43 492 CVD events; C-indices from 0.67 (95%CI 0.65-0.68) to 0.81 (95%CI 0.76-0.86).
WHO/ ISH (World Health Organization, 2007)	In 2019, WHO has updated the CV risk charts through the WHO Cardiovascular disease risk chart working group, which were published in the Lancet Global Health.	Risk discrimination with Harrell's C index on randomly selected pair of participants from ERFC data - 85 cohorts, 376177 individuals with 19333 CVD events within 10 yrs. Internally validated C indices ranged from 0.666 (95% CI 0.661-0.672) in men with the non-laboratory-based model to 0.757 (0.749–0.765) in women with the laboratory-based model.	Analyze individual participant data from studies distinct from those used in model derivation - further 123 743 individuals from surveys in 79 countries collected with the WHO STEPwise Approach to Surveillance.

Many other less well-known risk charts exist:

- the RISCARD, based on three Italian epidemiological data: the Italian Rural Areas of the Seven Countries Study, the Gubbio Population Study and the ECCIS study, for a total of 9089 men and women aged 35 to 74 years and followed for a period lasting 5 to 6 years. The included risk factors were sex, age, BMI, mean blood pressure, non-HDL-C, HDL-C, diabetes, heart rate, and daily cigarette consumption. The considered endpoints were the first major coronary event, the first major cerebrovascular event, and the first major cardiovascular event (Menotti et al., 2002).

- the PRECARD developed in Denmark based on two Danish population studies (n=11,765) with 10 years of follow up, was used to establish the Copenhagen Coronary Risk Score for myocardial infarction and nine RCTs for calculating the effect of intervention. The included risk factors were age, sex, cholesterol, SBP, smoking, BMI, diabetes, familial predisposition, and previous heart disease. As results, the program yields a graphical or numerical presentation of absolute coronary risk and the potential benefit of intervention, the relative impact of modifiable risk factors and numbers needed to treat (Thomsen et al., 2001).

- the Arriba risk calculator was based on the Framingham risk algorithm and calibrated to the German setting, through a study conducted within the primary care scheme provided by a large healthcare insurer in Baden-Württemberg - AOK BW Allgemeine Ortskrankenkasse and whose general practitioners included their patients to constitute the cohort (Diener et al., 2013).

There are several algorithms to objectify the risk of cardiovascular diseases. None of them is sufficiently reliable to get a universal recommendation (Santos, 2020), but all the models are valid, although they present many differences about what they are actually estimating and the way the result can be integrated in clinical practice. A study identified 73 CVD risk calculators, where the same high-risk patient profile produced widely variable CVD risk stratification (Bonner et al., 2018). Thus, the question arises if the perfect cardiovascular risk assessment models are found (Abidov & Chehab, 2019), and the challenge to explore the value and limitations of existing scores for the assessment of cardiovascular risk (Cooney et al., 2009). Supposedly, cardiovascular risk estimation algorithm evaluates multiple CVD risk factors to determine total CVD risk, to individually tailor strategies and optimize the management and interventions on the cardiovascular risk

factors. In fact, the treatment of cardiovascular risk factors based on disease risk depends on valid risk prediction equations.

As mentioned above, assessment of individual global risk is the cornerstone of effective cardiovascular prevention and management. While the relative risk for CVD can be estimated by counting the number of traditional risk factors - hypertension, diabetes, cigarette smoking, premature family history of CVD, CKD, and obesity - a more precise estimation of the absolute risk for a first CVD event is necessary for making treatment recommendations for a specific individual.

Risk equations, in general, allow the estimation of fatal, non-fatal, and specific CVD, in certain periods concerning a certain age range, adjusted to a specific condition and with the input of numerous variables in the model. Based on former algorithms, a good deal of software has been developed.

In addition to conventional cardiovascular risk factors, new risk factors and prognostic markers are emerging and being added to the scales with the aim of improving risk stratification, such as ethnicity (Kurian & Cardarelli, 2007), blood and urine biomarkers (Gilstrap & Wang, 2012), and the coronary artery calcium (Lin et al., 2018). As highlighted by many authors, the combination of clinical and imaging variables shows improved results in terms of the prediction of cardiac risk and acute cardiovascular events (Koh et al., 2016; Betancur et al., 2018; Martineau et al., 2020). A confirmation of what was said before is the addition of the coronary artery calcium score in improving both, risk stratification (Osawa et al., 2016) and clinically significant adverse coronary events (Detrano et al., 2008) when combined with a risk calculator. Beyond the relevance of a well understood statistical method, the prediction model has to perform well for the particular research question and it also has to distinguish high and low-risk patients, since the objective is to improve health outcomes and reduce health care costs by identifying patients who would benefit from further interventions, and those who would not (Schummers et al., 2016). To be useful for clinical prediction modelling and to adequately classify patients into clinically distinct risk groups, the risk prediction model must be both strongly associated with the outcome and prevalent in the population. The authors of a systematic review concluded that although current strategies for providing CVD risk scores may slightly reduce CVD risk factor levels and increase preventive medication prescribing in higher-risk people without evidence of harm, there is uncertainty to whether it affects CVD events in primary prevention (Karmali et al., 2017). This ambiguity is due to multiple study limitations in the identified studies and

substantial heterogeneity in the interventions, outcomes, and analyses, requiring adequately powered studies to define the role of applying CVD risk scores. Many guidelines recommend risk assessment for the primary prevention of CVD in apparently healthy persons (Khanji et al., 2016).

The most applicable risk prediction algorithm for European countries and recommended by the ESC is the European SCORE algorithm. The original SCORE - risk chart estimated the 10-year risk of death due to coronary or noncoronary CVD for individuals between the ages of 40 and 65 (Conroy, 2003). The previous guidelines of the European Societies on Cardiovascular Disease Prevention recommend the use of the SCORE risk charts to calculate risk (Piepoli et al., 2016). These guidelines were recently updated, and the current guidelines of the European Societies on Cardiovascular Disease Prevention in clinical practice recommend use of the new SCORE2 and SCORE2-OP risk charts to calculate CVD risk (Visseren et al., 2021). Mortality by cardiovascular diseases presents a heterogeneous distribution in European countries, where a decrease from north to south and from east to west is verified. Although Portugal is the most southwestern country in Europe, the relative position in cardiovascular death is medial, mainly because of stroke incidence, which exceeds the mortality by ischemic heart disease (Santos, 2020). The SCORE2 and SCORE2-OP algorithms were defined according to country-specific CVD mortality by applying recalibrated models to each region using expected incidences and risk factor distributions. Thus, SCORE2 and SCORE2-OP are calibrated to four clusters of countries - low, moderate, high, and very high CVD risk that are grouped based on national CVD mortality rates published by the WHO. A multiplier approach has been used for converting CVD mortality rates to fatal and non-fatal CVD events (Pennells et al., 2019).

CHAPTER II - The role of community pharmacists in cardiovascular disease management

1. The role of community pharmacists in cardiovascular disease management - Umbrella review.

1.1. Introduction

The role expansion of pharmacists to a patient-oriented pharmacy practice has its roots in the clinical pharmacy movement (Berenguer et al., 2004). The foundations for a broader scope of pharmacy practice were laid down during the 1960s in some North-American hospitals and the term *pharmaceutical care* was applied to describe non-dispensing, direct patient care role as "the care that a given patient requires and receives, which assures safe and rational drug usage" (Mikeal et al., 1975). In 1980, another *pharmaceutical care* definition was introduced - "includes the determination of the drug's needs for a given individual and the provision not only of the drug required but also the necessary services to assure optimally safe and effective therapy" (Brodie et al., 1980). The terms developed throughout time until 1989, when Charles Hepler and Linda Strand published the breakthrough work in pharmaceutical care: "Opportunities and responsibilities in Pharmaceutical Care". In their words, pharmaceutical care is "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life", comprising a "process through which a pharmacist cooperates with a patient and other professionals in designing, implementing, and monitoring a therapeutic plan that will produce specific therapeutic outcomes for the patient" through three main tasks: identifying, resolving, and preventing potential drug-related problems (Hepler & Strand, 1990). Later, the International Pharmaceutical Federation embraced the Hepler and Strand definition and added patient's quality of life when evaluating outcomes (Wiedenmayer et al., 2006). The Pharmaceutical Care Network of Europe defined pharmaceutical care in 2013 as: "the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes" (Allemann et al., 2014).

As pharmacy practice evolves in different pharmacy settings across the world, there is a variation among pharmacists' patient care services terminology. In the literature, different terms are applied to describe pharmacists' practice and daily activities. Gernanta et al.

carried out a literature review of the variation of the terminology. The authors retrieved fifteen terms describing pharmacist services, which are included in Table 13, which had a spike and appeared in the literature after 1990. All the terms' definitions had in common the fact that pharmacists to provide the services use their clinical interventions to affect the patient's medication-related outcomes (Gernant et al., 2020).

Table 13 - Pharmacists' care services term definition and evolution.

Term	Year	Reference	Definition
Clinical Pharmacy	1969	Francke GN. Evolvement of clinical pharmacy	A concept or philosophy emphasizing the safe and appropriate use of drugs in patients, placing the emphasis on the patient, not on the product.
	2008	American College of Clinical Pharmacy	The area of pharmacy concerned with the science and practice of rational medication use.
	2022	European Society of Clinical Pharmacy	Aims to optimize the utilization of medicines through practice and research to achieve person-centered and public health goals.
Pharmaceutical Care	1990	Hepler and Strand	The responsible provision of drug therapy to achieve definitive outcomes that improve a patient's quality of life.
	2013	PCNE	The pharmacist's contribution to the care of individuals to optimize medicines use and improve health outcomes.
	2018	American Pharmacist Association	A patient-centered, outcomes-oriented pharmacy practice that requires the pharmacist to work in collaboration with the patient and the patient's other health care providers to promote health, to prevent disease, and to assure that drug therapy regimes are safe and effective.
Patient Counseling	1990	The Omnibus Budget Reconciliation Act of 1990 (OBRA '90)	Required pharmacists to provide counseling to Medicaid patients regarding their medications, and quickly extended counseling services to all patients receiving prescription drugs. The provided verbally counseling must cover: name of medication, intended use and expected action, route, dosage form, dosage, and administration schedule, special directions for preparation, administration, proper storage, common side effects, techniques for self-monitoring of drug therapy, potential drug-drug or drug-food interactions or other therapeutic contraindications, prescription refill information, and actions to be taken in the event of a missed dose.
	1997	Americas Society of Health-Systems Pharmacists	A responsibility of the pharmacy profession for providing patient education and counseling in the context of pharmaceutical care to improve patient adherence and reduce medication-related problems.
Drug Utilization Review/ Prospective Drug Review	1991	USSocial	A review of patients' prescription and medication data before, during and after dispensing to assure that prescriptions are appropriate, medically necessary, and not likely to result in adverse outcomes; Drug Utilization Review was originally required by the Center for Medicare & Medicaid Services for each State's Medicaid program.
	2009	Academy of Managed Care Pharmacy. Drug utilization review	An authorized, structured, ongoing review of prescribing, dispensing and use of medication, including a comprehensive review of patients' prescription and medication data before, during and after dispensing to ensure appropriate medication decision-making and positive patient outcomes. As a quality assurance measure, Drug Utilization Review programs provide corrective action, prescriber feedback and further evaluations.

Pharmacogenomics	1992	Straka	Pharmacogenetics defines inter-individual variability of the enzyme systems responsible for drug metabolism - genetic polymorphism, responsible for variability in pharmacokinetic and pharmacodynamic with clinical significance, which must be applied in clinical practice.
Pharmacogenetics	2011	Reiss	The use of genetic information to predict an individual's response to a drug.
Medication management	1993	Tett	Pharmacist interventions designed to assist people in managing their medication regimens.
	2018	Joint Comission	A spectrum of patient-centered, pharmacist provided, collaborative services that focus on medication appropriateness, effectiveness, safety, and adherence with the goal of improving health outcomes - Medication Therapy Management, Comprehensive Medication Management, Collaborative Medication Management, etc.
Collaborative Drug Therapy Management	1995	Zellmer	Legislative and regulatory provisions that allow for prescribing and related activities by the pharmacist as a component of pharmaceutical care.
	2012	Academy of Managed Care Pharmacy	A formal partnership between a pharmacist and physician or group of pharmacists and physicians to allow the pharmacist(s) to manage a patient's drug therapy.
Transitions of Care/ Care Transitions, Care Continuum	1996	Goldenberg	To develop a clinical pathway indicating a predictable course of care.
	2012	The Joint Comission	The movement of patients between health care practitioners, settings, and home as their condition and care needs change.
Medication Therapy Management	2003	H.R.1, Medicare Prescription Drug	A program to improve medication use, reduce the risk of adverse events, and improve medication adherence of the beneficiaries.
	2008	Medication therapy	Services that are dependent on pharmacists working collaboratively with physicians and other health care professionals to optimize medication use in accordance with evidence-based guidelines and include medication therapy review, a personal medication record, a medication-related action plan, intervention and referral, and documentation and follow-up.
Medication Reconciliation	2006	The Joint	The process of comparing a patients' medication orders to all the medication that the patient has been taking, to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions.
	2010	US Centers	The process of identifying the most accurate list of all medication that the patient is taking, including name, dosage, frequency, and route, by comparing the medical record to an external list of medications obtained from a patient, hospital, or other provider.
Comprehensive Medication Review	2010	US Centers	An annual, real-time, interactive, person-to-person, or telehealth consultation performed for a patient or caregiver by a pharmacist or another qualified provider that includes collecting patient-specific information, assessing medication to identify medication-related problems, developing a prioritized list of medication-related problems, and creating a plan to resolve them, and has a written summary in the Center for Medicare and Medicaid's standardized format.
	2017	Pagano	The pharmacist looking at the patient as a whole by reviewing the patient's medication list, medication allergies, immunization status, and any other clinical need for the patient.
	2010	US Center	A service Medicare Part D sponsors are required to provide to all beneficiaries enrolled in the sponsor's

Targeted Medication Review			Medication Therapy Management program that includes quarterly medication reviews and follow-up interventions as necessary.
	2017	Pagano	When the pharmacist focuses on one area of the patient's health care, for example, when a pharmacist counsels a patient with diabetes on the importance of being on statin therapy and then contacts their doctor to initiate a targeted medication review for them.
Compressive Medication Management	2012	Patient-Centere	A standard of care that ensures each patient's medication is individually assessed to determine that each medication is appropriate, effective, safe, and able to be taken by the patient as intended. Includes an individualized care plan that achieves the intended goals of therapy, with appropriate follow-up to determine actual patient outcomes. This all occurs because the patient understands, agrees with, and actively participates in the treatment regimen, thus optimizing each patient's medication experience and clinical outcomes.
	2016	America College	The standard of care that ensures each patient's medication (i.e., prescription, nonprescription, alternative, traditional, vitamins, or nutritional supplements) are individually assessed to determine that each medication is appropriate for the patient, effective for the medical condition, safe given the comorbidities and other medication being taken, and able to be taken by the patient as intended.
Pharmacists' Patient Care Process	2014	Joint Comission	A patient-centered approach in collaboration with other providers to optimize patient health and medication outcomes that includes: Collection of the necessary information; Assessment of the information collected to identify and prioritize problems; Development of an individualized patient-centered care plan; Implementation of the care plan; and Follow-up to monitor and evaluate the effectiveness of the care plan.
\Chronic Care Management	2016	United States	A service under the United States' Center for Medicare and Medicaid Services' Medicare Physician Fee Schedule consisting of at least 20 min clinical staff time directed by MD or other qualified health care professional per month furnished to Medicare patients meeting multiple chronic condition criteria.
	2018	Fixen	A fee-for-service program intended to encourage ambulatory care practices to use value-based care delivery and to compensate for coordinated healthcare provided outside the patient visit.
Medication Review	2012	(Blenkinsopp et al., 2012)	Aims to identify problems for action by the prescriber, the clinician conducting the review, the patient or all three, but can also be regarded as an educational intervention to support patient knowledge and adherence.
	2018	PCNE (Griese-Mammen et al., 2018)	A structured evaluation of a patient's medicine with the aim of optimizing medicines use and improving health outcomes. This entails detecting drug related problems and recommending interventions.

Adapted from (Gernant et al., 2020).

Wide variations remain in the terms and practice of pharmacy, not only between countries, but also within countries. Health service researchers, practicing pharmacists, and professional organizations should make the commitment to promote and adhere to pharmacy's standardized terminology across research, practices, and time.

The World Health Report 2008 on Primary Health Care refers to the primary care team as a coordination hub, as healthcare networks expand and becomes more crowded and pluralistic, and predicts a healthcare system in which pharmacists effectively participate in the scenario (World Health Organization, 2008). However, extending community pharmacy services require quality-driven incentives and collaboration between community pharmacists and general practitioners to achieve better integration within the patient's primary care pathway. This collaboration remains poor, and pharmacists and general practitioners perceive some barriers to successfullly implement and integrate pharmacy services. Furthermore, community pharmacists, despite their training, are the only health professionals who are not remunerated for delivering health care (Hindi, Jacobs, et al., 2019). All studies emphasize communication as a key in the success of establishing a highly productive interprofessional collaboration, besides trust, interdependence, perceptions, and expectations about the other health care provider, skills, interest for collaborative practice and role definition (Bardet et al., 2015).

New pharmacy services and new roles for pharmacists continue to emerge, but in the era of evidence-based practice, the services have to be proposed on evidence of their benefit, proving to be feasible, acceptable, cost-effective, and improve health outcomes. Evaluating the impact of pharmacist-delivered patient care on health-related outcomes is difficult, as it is challenging to evaluate which interventions are effective. The interventions in clinical pharmacy are targeted on the medication use process and the patient outcomes. The interventions focused on specific medical conditions, such as hypertension, dyslipidemia or DM, are easier to assess as outcomes are measurable, but interventions that target medication adherence and assess the impact of clinical pharmacy services in prescription appropriateness are more challenging because of the variability of methods to assess both.

Clinical pharmacy services vary with the setting and the autonomy pharmacists have to manage or prescribe medicine to the patient according to pre-defined clinical protocols. Clinical pharmacy services provided in community pharmacies identified in the literature can be divided in the following categories (Rotta et al., 2015; Omboni & Caserini, 2018):

- Educational activities focused on patients to promote the correct use of medicines and adherence to treatment - patient education and counseling, and drug safety management resorting to educational support, like printed materials or multimedia and compliance aids.

- Definition and application of disease management protocols for the detection, prevention, or control of specific risk factors - smoking cessation, point-of-care testing, screening services, and monitoring patients' outcomes.
- Medication review and drug therapy adjustments, with or without direct contact with the patient and improve the medication use process - review inappropriate prescribing, therapeutic regimen, treatment costs, or adverse effects, by recommending interventions to the patient or physician.
- Medication therapy management and medication follow-up with the aim of improving health outcomes.
- Provision of information directed at health care professionals - includes patient referral, documenting adverse drug reactions occurring to the patients or monitoring patient's adherence to physician's prescription.

Evidence of the effect of clinical pharmacy services is constantly growing in several areas, and regular systematic evaluation of the services is important and relevant to healthcare, especially in cardiovascular healthcare. Nowadays, besides a wide range of effective and safe pharmacotherapy, and availability of multidimensional non-pharmacological treatment, the rate of major adverse cardiovascular outcomes remains high. The pharmaceutical care available in the community pharmacy settings have a significant impact on outcomes in cardiovascular patients, as adherence to cardiovascular pharmacotherapy, level of blood pressure, total cholesterol, HbA1c or patients' health literacy. The predominant issue in delivering effective pharmaceutical care is to develop an evidence-based model. Further research, particularly based on real data on this topic, is needed and recommended (Swieczkowski et al., 2016).

1.2. Objective

The number of published studies on pharmacist intervention in CVD management is rising. Consequently, there is also an increase in the number of systematic reviews. An appropriate next step is to conduct reviews of the existing systematic reviews. The designation of these reviews is various, including umbrella reviews, overviews of reviews, reviews of reviews, a summary of systematic reviews, and a synthesis of reviews (Gates, 2020). Thus, this part of the study aims to conduct an umbrella review that will permit the review of the interventions of community pharmacists in CVD and risk factor management, and summarize the needed evidence from research.

1.3. Methods

The umbrella review is presented according to the PICO strategy and reported in conformity with the Preferred Reporting Items for Systematic Reviews and Met-Analysis (PRISMA) Protocols 2015 checklist (Page et al., 2021), as shown in Table 14. The aim of this review is to describe, appraise and gather information from systematic reviews assessing the impact of community pharmacist interventions on cardiovascular risk factors and outcomes. The used source was the MEDLINE database, using PubMed interface from database inception to May 2022 and the following search query was used:

((((pharmaceutical services [MeSH Terms]) OR (pharmacists) OR "medication review" OR "pharmaceutical care") AND ((hypertension[MeSH Terms]) OR (diabetes *mellitus*, Type 2[MeSH Terms]) OR (cardiovascular) OR (cholesterol, LDL[MeSH Terms]) OR "blood pressure" OR diabetes OR hypertension OR (cardiovascular risk factor) OR (smoking)))) AND ((primary OR ambulatory OR clinic OR outpatient OR pharmacies OR community))

The used limits were the search filter for *Systematic Reviews* available on PubMed. All the searched results were saved and sent to Mendeley Reference Manager, checked for duplicates and exported to Microsoft Excel (Microsoft, Redmond, WA, US). The cited references were examined after browsing reference lists.

Table 14 - The participants/population, intervention, comparator, outcome (PICO) framework.

Criteria (PICO)	Definition
Participants/ Population	Community pharmacy users aged 18 years and above.
Intervention	Community-pharmacist-led intervention aimed to impact cardiovascular disease management both pharmacological and non-pharmacological interventions.
Comparator	"Usual care", "no intervention", "standard care" and "intervention delivered by any other registered health care professional".
Outcome	Clinical outcomes - modifiable cardiovascular risk factors, such as lipids, glycated hemoglobin, blood pressure, and smoking. Health services utilization outcomes. Not economical outcomes.

PICO – Participants/ Population Intervention Comparator Outcome

The inclusion criteria for the umbrella review were systematic reviews based on RCTs on pharmacist-led intervention in cardiovascular disease risk factor management and cardiovascular disease clinical outcome report in community pharmacy settings.

The exclusion criteria were systematic reviews based on non-randomized controlled trials; systematic reviews published in other than the English, Portuguese, or German language; studies that were editorial studies, letters to the editor and conference abstracts; studies with no outcome of interest; interventions carried out by other professionals or beside from community pharmacy settings; protocols, reports, consensus, guidelines; overview of systematic reviews; and studies on animals or cells.

In the first stage, the study titles and abstracts were screened, and the studies that were clearly irrelevant to this study's aim and that did not meet the inclusion criteria were excluded. In the second stage, full texts of the relevant and potentially eligible studies were downloaded and reviewed against the study's inclusion and exclusion criteria. The citedreferences of the retrieved reviews were manually analyzed. This review was conducted as per the guidance of the PRISMA (Page et al., 2021).

1.4. Results

The PRISMA flow diagram illustrating the search and selection process of systematic reviews and the reasons for study exclusion is presented in Figure 19.

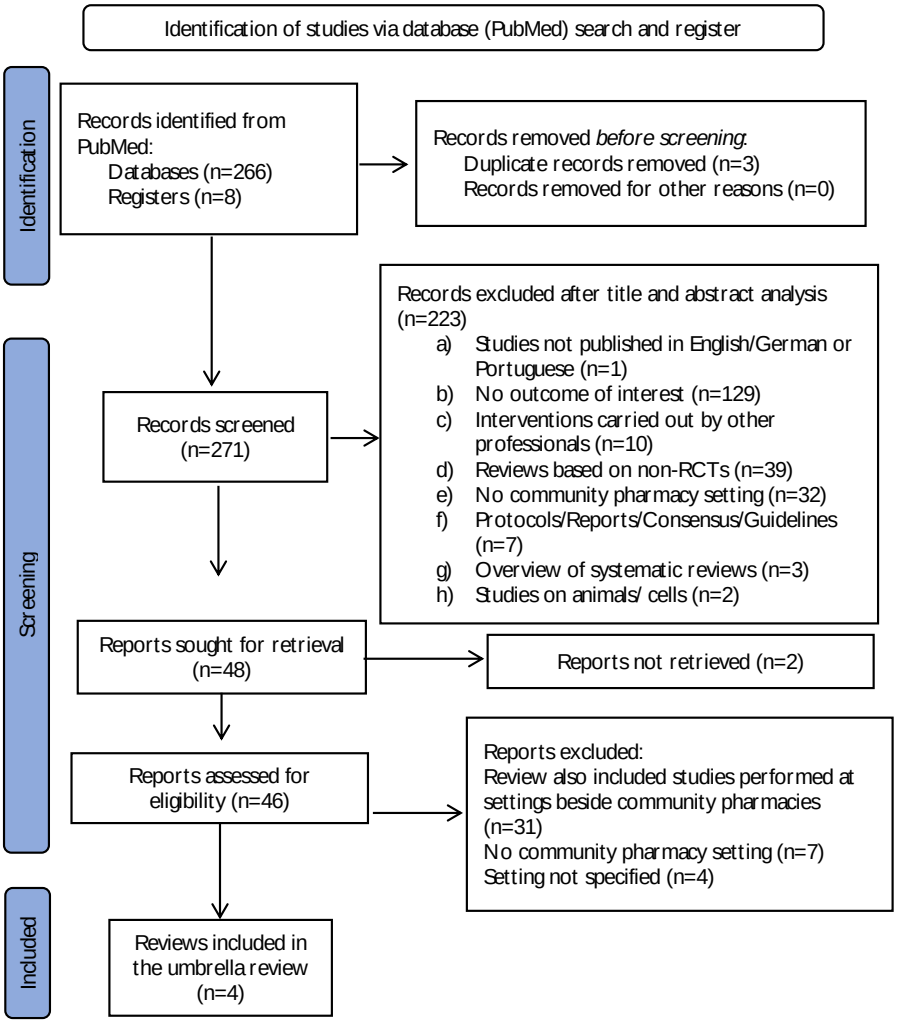

Figure 19 - PRISMA flow diagram illustrating the search and selection process of systematic reviews and the reasons for study exclusion.

The reviews included in the umbrella review are shown in Table 15 and summarize the databases searched and the date range of the search, number, and quality of studies, number, and details of patients included, type of intervention and comparator, existence of collaboration, objectives, results, and conclusion of the review, targeted risk factor and outcomes.

Table 15 - Summary of included systematic reviews characteristics assessing the impact of the pharmacists' intervention on cardiovascular disease and risk factors.

Year	1st Author /Reference	Searched Databases	Date range of search	Objectives of the review	Studies N	Participant details	Patients N	Type of Intervention
2014	**Cheema E** (Cheema et al., 2014)	Web of Science, Embase, The Cochrane Library, Medline Ovid, Biomed Central, Biosis Citation Index, CINAHL, PsycINFO	No start date and up to 30 November 2013	Assess the impact of community pharmacist-led interventions on blood pressure control in patients with hypertension	16 RCTs and 11 meta-analyses	Patients with hypertension, with or without cardiovascular related co-morbidities	3032 or 3034	Patient education on hypertension/ Management of prescribing/ Safety problems associated with medication/ Advice on lifestyle
2016	**Sabater-Hernández D** (Sabater-Hernández et al., 2016)	DEPICT through MEDLINE, Scopus, SciELO DOAJ	No start date and up to 30 November 2014	Identify community pharmacy evidence-based services designed to help prevent CVD/ Provide fundamental information that is needed to assess their potential adaptation to other community pharmacy settings	16 RCTs addressing 14 services	Population at CVD risk - Individuals with type 2 DM, hypertension, dyslipidemia, smokers; mean age >60 years, except for one study.	Not referred	Activities directed at patients, at health care professionals and assessments to gather patient-related information to support the previous activities
2019	**Carson-Chahhoud KV** (Carson-Chahhoud et al., 2019)	Cochrane Tobacco Addiction Group Specialized Register; clinicaltrials.gov and the International Clinical Trials Registry Platform	Up to January 2019	Assess the effectiveness of interventions to assist people to stop smoking, with or without concurrent use of pharmacotherapy	7 RCTs and pooled 6 studies	Clients who were smokers	Pooled 1614 from 1774	Support starting before quit day and continuing with weekly appointments for several weeks afterwards
2022	**Al-babtain B** (Al-babtain et al., 2022)	Cochrane Library, MEDLINE and Embase	From database inception up to 1 January 2020	Evaluate the effectiveness of community-pharmacist-based medication review programs among patients with long-term conditions	40 RCTs systematic review/ 12 RCTs for the meta-analysis	Patients aged 18 years and above receiving medication review led by community pharmacists	4815 patients with chronic diseases	Community-pharmacist-led medication review programs under different countries

CPs - community pharmacists; CVD - cardiovascular disease; DBP - diastolic blood pressure; Depict - Descriptive Elements of Pharmacist Intervention Characterization; DOAJ - Directory of Open Access Journals; FG - fasting glucose; GP - general practitioner; HP – health care professionals; MD - mean difference; MR - medication review; PCP - primary care physician; qol – quality of life; RCTs - randomized controlled trials; SBP - systolic blood pressure; SciELO - Scientific Electronic Library Online; TC - total cholesterol.

Year	1st Author /Reference	Comparator	Targeted risk factor outcomes	Reported results	Collaboration	Quality of studies rating	Conclusion of the Review
2014	**Cheema E** (Cheema et al., 2014)	Standard or usual care	Difference in blood pressure. Reduction in SBP and DBP	Significant reductions in SBP [11 studies (2240 patients); -6.1 mmHg (95% CI, -3.8 to -8.4 mmHg); p < 0.00001] and DBP [11 studies (2246 patients); -2.5 mmHg (95% CI, -1.5 to -3.4 mmHg); p < 0.00001].	None	Cochrane tool to assess risk of bias	CPs can make a clinically important contribution to the management of hypertensive patients with/without cardiovascular co-morbidities.
2016	**Sabater-Hernández D** (Sabater-Hernández et al., 2016)	Usual care	CVD risk factors - Improving the control of diabetes and hypertension; enhance patient adherence to statins and loop-diuretics; smoking cessation; enhancing the management of dyslipidemia	14 CPs services: Targeting patients - one-on-one information with support material for behavioral changes derived from performed assessments; follow-up/ treatment plans, discussing results and agreeing on goals. Targeting HP – information/ treatment recommendations; requesting clinical analysis to evaluate patients; discussing on treatment plans. Assessments performed by service providers to support decisions.	None	Cochrane tool to assess risk of bias	Provides pharmacy service planners and policymakers with a list of evidence-based services with the potential to be adapted to different settings to reduce the burden of CVD.
2019	**Carson-Chahhoud KV** (Carson-Chahhoud et al., 2019)	Usual support or any less intensive program	Smoking cessation rates at six months or more after the start of the intervention.	6 studies of 1614 participants were pooled with proven benefit of more intensive behavioral smoking cessation interventions delivered by CPs at longest follow-up - RR 2.30, 95% CI 1.33 to 3.97; I2 = 54%; low-certainty evidence.	None	GRADE Working Group grades of evidence	CPs can provide effective behavioral support to people trying to stop smoking.
2022	**Al-babtain B** (Al-babtain et al., 2022)	Standard care; intervention delivered by any other health professional	Disease-specific: SBP/DBP, lipid profile, FG, HbA1c and CVD risk. Non-disease-specific: medication adherence, DRP, mortality, QoI. Health services utilization: emergency depart., hospital admissions.	Blood pressure in patients with diabetes - MD in SBP: 6.82 (95% CI -11.33, -2.32); MD in DBP: 2.13 (95% CI -3.35, -0.92) and in the hypertension patients - MD in SBP: 6.21 (95% CI -13.26, 0.85); MD in DBP: 2.11 (95% CI -6.47, 2.26), HbA1c in patients with DM (MD -0.61; 95% CI -0.96, -0.25), and TC in patients with hyperlipidemia (MD -0.18; 95% CI -0.32, -0.05).	31 studies: MR in collaboration with GP/PCP; 9 studies: collaboration not clear	Cochrane tool to assess risk of bias	CP-led medication review can improve certain clinical and health care utilization outcomes in patients with long-term conditions.

The four systematic reviews included in the umbrella review are from 2014, 2016, 2019, and 2022, representing the more recent evidence-based pharmacy practice interventions reviews in community pharmacy practice. As shown in Figure 20, the count of the retrieved systematic reviews, made available by PubMed, reveal a significant increase from 2015 in indicating that around that time the research in the field of interest of this umbrella review started to raise.

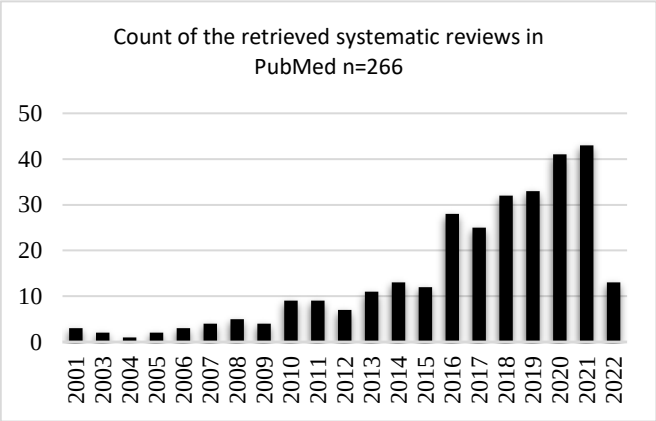

Figure 20 - Count of the retrieved systematic reviews.

From the results of the initial scoping search, it was anticipated that there would be few evidence from RCTs that met all the inclusion criteria, specially when taking account that RCTs were solely conducted in community pharmacies. This umbrella review included four systematic reviews, based on 79 original RCT studies. Due to the overlap of studies included and analyzed in each systematic review, these are actually based on 60 original studies. To indicate the overlap of the primary research studies in the included systematic reviews, a list of the repeated studies is presented in Table 16. The authors are cited, but not referenced.

Table 16 - Primary research studies assigned to each systematic review.

	Cheema E	Sabater-Hernández D	Carson-Chahhoud KV	Al-babtain B
Ali M et al., 2012	✓	✓	-	✓
Al-Tameemi D et al., 2017	-	-	-	✓
Amariles P et al., 2012	✓	✓	-	-
Armour C et al., 2013	-	-	-	✓
Aslani P et al., 2010	-	-	-	✓
Basheti IA et al., 2016	-	-	-	✓
Beaucage K et al., 2006	-	-	-	✓
Bernsten C et al., 2001	-	-	-	✓
Blenkinsopp A et al., 2000	✓	-	-	-
Bouvy ML et al., 2003	-	✓	-	✓
Burford O et al., 2013	-	-	✓	-
Caponnetto P et al., 2017	-	-	✓	-
Cheema E et al., 2018	-	-	-	✓
Clifford RM et al., 2005	-	-	-	✓
Cordina M et al., 2001	-	-	-	✓
Currie JD et al., 1997	-	-	-	✓
Dent LA et al., 2009	-	-	✓	-
Doucette WR et al., 2009	✓	-	-	✓
El Hajj MS et al., 2017	-	-	✓	-
Elliot RA et al., 2016	-	-	-	✓
Eussen SR et al., 2010	-	✓	-	-
Farley A et al., 2017	-	-	✓	-
Falami´c S et al., 2018	-	-	-	✓
Fornos JA et al., 2006	✓	✓	-	-
Garção JA et al., 2002	✓	✓	-	✓
Herborg H et al., 2001	-	-	-	✓
Hoffmann W et al., 2008	-	-	-	✓
Jahangard-Rafsanjani Z et al., 2015	-	-	-	✓
Jodar-Sanchez F et al., 2015	-	-	-	✓
Krass I et al., 2007	✓	✓	-	-
Maguire TA et al., 2001	-	✓	✓	-
Manfrin A et al., 2017	-	-	-	✓
McDonough RP et al., 2005	-	-	-	✓
McKenney J et al., 1978	✓	-	-	-
McLean DL et al., 2008	✓	-	-	-
Mclean W et al., 2003	-	-	-	✓
Mehuys E et al., 2011	-	✓	-	-
Mott DA et al., 2017	-	-	-	✓
Nola KM et al., 2000	-	-	-	✓
Planas LG et al., 2009	✓	-	-	✓
Richmond S et al., 2010	-	-	-	✓
Rickles NM et al., 2005	-	-	-	✓
Santschi V et al., 2011	✓	-	-	-
Sarkadi A et al., 2004	-	✓	-	-
Schoenmakers TWA et al., 2018	-	-	-	✓
Schulz M et al., 2019	-	-	-	✓
Sinclair HK et al., 1998	-	-	✓	-
Sookaneknun P et al., 2004	✓	✓	-	-
Stewart K et al., 2014	-	-	-	✓
Svarstad BL et al., 2003	✓	-	-	-
Tsuyuki RT et al., 1999	-	✓	-	-
Tsuyuki RT et al., 2002	-	✓	-	-
Tsuyuki RT et al., 2016	-	-	-	✓
Van der Meer HG et al., 2018	-	-	-	✓
Verdoorn S et al., 2019	-	-	-	✓
Villeneuve J et al., 2010	-	-	-	✓
Vinks TH et al., 2009	-	-	-	✓

Volume CI et al., 2001	-	-	-	✓
Vrijens B et al., 2006	-	✓	-	-
Zillich AJ et al. 2005	✓	✓	-	-

In the included reviews, it was shown that evidence-based pharmacist-led interventions are associated with improved clinical management and significant reduction of cardiovascular risk factors. The interventions intend the provision of safe and effective medication to patients, which is the main responsibility of pharmacists. The reviewed pharmacist-led interventions include a variety of practical applications from patient-aimed activities, to activities aimed at health care professionals and evaluation to collect patient-related information to support the previous activities. From there, the studies revealed the most mentioned services as patient education and information, management of prescribing and safety problems associated with medication, and advice on lifestyle. Community-pharmacist-led medication review programs in community pharmacy settings, despite differing nomenclature in different countries, stands out as having a positive impact on patient clinical and healthcare utilization outcomes.

All the authors strongly encourage pharmacy practice researchers to design and implement high-quality RCTs for inclusion in future reviews of evidence-based community pharmacy services designed for the prevention of CVD.

1.5. Discussion

Community pharmacists are the third-largest health care professional group in the world after physicians and nurses, and among the only one who are not primarily rewarded for delivering health care. A consensus among academics, professional organizations, and policymakers would be important to allow community pharmacists to contribute to the safe and effective use of medicines, particularly in people with multiple chronic conditions, strengthening integrated primary care delivery across the health system. The searched systematic reviews gathered evidence that support the expansion of the role of community pharmacists and pharmacists' medication expertise has been recognized as a valuable contribution towards improving patient clinical outcomes. Future policies should focus on effectively integrating community pharmacists into primary care, such as health professionals with the greatest depth and breadth of knowledge on pharmacotherapy.

Cardiovascular diseases are caused by modifiable risk factors, whose prevalence continues to increase. Screening, identifying and appropriately managing high-risk patients are strategies that can be provided by pharmacists. Pharmacists are an underutilized health resource despite robust evidence to support their roles as health team members and direct patient care providers. In many countries, community pharmacies have a long tradition of practice research resulting in several well-documented cognitive and clinical services, but few are being remunerated and implementation is still a challenge. Support from professional bodies and more patient-centered community pharmacy contracts, including remuneration for cognitive and clinical services, are required to foster progress in this area (Costa et al., 2017).

Community pharmacies provide the ideal conditions to conduct CVD management, ensuring access and proximity to people who may otherwise not regularly visit other healthcare facilities. The public authorities and all healthcare stakeholders have to recognize the role community pharmacies play in improving access to disease prevention, health promotion programs and health literacy; embrace the added-value pharmacies provide by improving access to screening services; support services that aim to improve patients' adherence to medicines by developing programs that support pharmacists' capacity to communicate with patients, and whilst helping to ensure the sustainability of the health systems.

Another service that needs to be developed is medication review and this objective can only be achieved if national professional organizations promote and support strategic alliances and projects fully involving community pharmacies in national health strategies, thus providing better pharmaceutical assistance to citizens and improving the efficiency of national health systems. Many methods have been used to improve CVD outcomes, one of which is to involve clinical pharmacists in the direct care of patients with CVD. The studies included in the present umbrella review have assessed the effectiveness of community pharmacy-delivered interventions and concluded that pharmacists may improve the clinical management of major risk factors for CVD prevention. Although wide variations exist in the organization of healthcare systems across Europe, the 2016 European guidelines on CVD prevention in clinical practice stated that the patient follow-up should be carried out by the health care team, which should include physicians, nurses, and pharmacists in a concerted activity (Piepoli et al., 2016). Accordingly, the 2018 ESC/ESH guidelines for the management of arterial hypertension highlight a key role for nurses and pharmacists in the longer-term management of hypertension and emphasize their role in the education,

support, and follow-up of treated hypertensive patients as part of the overall strategy to improve blood pressure control (Williams et al., 2018). The collaborations between health care professionals seem to be important, as highlighted by many authors, who view the role of the pharmacist as liaison between patients and other health care providers as essential for effective management of a patient's medication therapy and subsequent therapeutic outcomes' improvement (Cheng & Cooke-Ariel, 2014; Tan et al., 2014).

Pharmacy services are easily accessible and widely distributed in the community setting. RCTs show that pharmacists improve the control of hypertension, dyslipidemia or diabetes, promote smoking cessation and reduce hospitalization in patients in primary and secondary prevention of CVD. The pharmacist interventions are essentially patient education and counseling, drug safety management, medication review, detection, monitoring, and control of specific cardiovascular risk factors - blood pressure, blood glucose, serum lipids, and clinical outcomes. A multidisciplinary approach, adding medical input and specialist nurse to the pharmacist and a greater involvement of community rather than hospital pharmacists, seems to represent the most efficient and modern healthcare delivery model (Dunn et al., 2015; Omboni & Caserini, 2018). As mentioned, the most frequently used interventions retrieved were medication review, medication management, and education interventions, where pharmacists performed medication assessments and provided guideline-concordant recommendations to optimize CVD medication management in primary care teams and were able to help the patients to achieve CVD risk factor targets (Simpson et al., 2011; Santschi et al., 2012; Santschi et al., 2014; Alshehri et al., 2020; Nogueira et al., 2020). Regarding the outcomes, many systematic review and meta-analysis of RCTs showed that pharmacist-led interventions can significantly reduce the medical risk factors of CVD events and studies support, with proved benefit, the involvement of pharmacists as health care providers in improving the quality of the medication use process, health literacy and managing patients with hypertension, heart failure, diabetes, smoking habits and dyslipidemia; support with unclear benefit CVD mortality and morbidity, medication adherence and healthcare costs (Morgado et al., 2011; Charrois et al., 2012; Cheng & Cooke-Ariel, 2014; Fazel et al., 2017). As discussed before, the benefits of pharmacist's intervention on the patient with CVD or CVD risk factors may be complex and interrelated. The net effect of the pharmacist's intervention is the use of fewer healthcare resources and cost saving. There are still many limitations and it continues to be challenging to find out which interventions directly lead to certain changes and evidence still needs to be confirmed in large intervention trials with more well-designed studies, conducted with sufficient data in the provision of medication review, patient education, adherence

assessment, lifestyle advice, physical assessment, monitoring, prescribing, or adjusting and administering therapy from community pharmacists (Ifeanyi Chiazor et al., 2015; Yuan et al., 2019). Furthermore, it is necessary to apply more homogeneous criteria for the assessment of the outcomes and a standardized consensus of the guidelines for pharmaceutical care service, to improve homogeneity in the studies (Kang et al., 2016).

1.6. Conclusion

Effective CVD management requires a systematic, multidisciplinary approach in the community. The findings of the included reviews highlight the benefits of community pharmacist-led interventions in the management of cardiovascular risk factors.

Information provided in this umbrella review focuses on the CVD at-risk populations targeted by the interventions and provides a comprehensive list of evidence-based services to reduce the burden of CVD. One of the highlighted interventions is community-pharmacist-based medication review, which has a positive impact on clinical and healthcare utilization outcomes, resulting in a reduction in cardiovascular risk factors.

These results support greater involvement of the community pharmacist in the management of CVD.

2. Pharmaceutical care services – The Portuguese reality

2.1. Introduction

In Portugal, the Pharmacist profession has existed since the 13th century. Back then, these professionals were known as "boticários", which may be translated to apothecaries. Until the 1970s, their functions were product focused, that is, focused on medicine and medicinal products, from their preparation to their provision, assessment and the associated information provided in the treatment of diseases. That meant that the primary role of the pharmacist was to be an expert in medicines, with an obligation to certify that the medical substances were pure and properly prepared. In the late 1970s, with the industrialization of medicines, the magistral formulas were replaced by industrially prepared formulas and the pharmacists' focus moved to that of caregiver - the pharmacist becomes committed to a person-centered care, a health profession that has the responsibility of ensuring the safe, effective, and rational use of medicines (Ordem dos Farmacêuticos, 2018).

2.2. Pharmacy regulation in Portugal

In Portugal, the pharmacist is considered the medicine expert and the most accessible health professional to the public. The geographical distribution of pharmacies in Portugal is even and ensured by the existing regulation, which positively affects accessibility, especially in rural areas and in the interior of the country, where most of the time they are the only healthcare setting available to the population. In fact, due to the wide geographical coverage that pharmacies have in the national territory and the high technical-scientific competence of their human resources, these structures have become essential allies to guarantee the pillars recommended by the Portuguese national health service, which advocate accessibility to medication and equity in the provision of quality health care to all citizens, regardless of their geographical location. Considering this proximity, the community pharmacy is often the first setting visited by the patient when needing some health advice and the management of minor ailments - a 'front door' to the Portuguese national health service. Furthermore, the community pharmacies are the most visited health setting, receiving a citizen, on average, two to three times a month. Although the community pharmacy is a private institution it is heavily regulated by specific legislation, where National Authority for Medicines and Health Products INFARMED is the responsible entity for the supervision in order to ensure equal and safe access to medicines. Until 2007, pharmacies had to be owned by a qualified pharmacist. On the 31st of August 2007, however, the Ministry of Health approved the law of Property Liberalization - Health Ministry, Decree-Law No. 307/2007, August 31st, 2007, ending the exclusive pharmacy ownership by pharmacists, allowing the liberalization of the ownership of pharmacies to non-pharmacists, with the aim of improving the access to pharmacy services for the public whilst also imposing the requirement that technical management must be carried out on a permanent and exclusive basis by a pharmacist, thus guaranteeing and promoting the quality and improvement of the services provided to users. The only restriction being to have a maximum number of four pharmacies per owner. With this regulation, any singular person or commercial society is free to acquire, explore or manage a maximum of four pharmacies. It is still mandatory to have a technical pharmacist director with a degree in Pharmaceutical Sciences in each pharmacy for permanence, and exclusiveness, and the presence of one or more pharmacist is required. Currently, the community pharmacy is one of the Portuguese national health service pillars and contributes to the maximization of health gains, as well as an improvement in patients' quality of life. Regarding the evolution of these facilities, the number of pharmacies in Portugal has been increasing in past years. In 2008, the number of community pharmacies in the country was 2811, increasing to 2934 in 2015. This evolution

represents the creation of 123 new pharmacies, denoting a 4.4% growth in the business. In Portugal, independent community pharmacies remain a major segment of the overall pharmacy marketplace, since big national chain pharmacies are not allowed and small chains are only nowadays becoming a reality. Moreover, the majority of the community pharmacies are owned independently, and employ most of the pharmacists. As stated above, the presence of a responsible pharmacist - the technical director - is mandatory and a substitute has to be registered at the INFARMED, to assure the presence of a pharmacist all the time. The number of pharmacists has been growing gradually over the last 15 years. By the end of 2012, there were 12816 registered pharmacists and by the end of 2020, there were 15565 registered pharmacists, which represents an increase of 21.4% (Ordem dos Farmacêuticos, 2020). However, it remains low in comparison to similar systems such as the United Kingdom and Spain. In 2013, Portugal still had a low ratio of pharmacists (77 per 100 000 population) when compared with Spain (112 per 100 000 population) or the United Kingdom (80 per 100 000 population). Portuguese pharmacists are mostly female professionals, 79% are women, 68% under 45 years of age and the pharmacies have on average more than three pharmacists per pharmacy. According to OF, in 2019 there were 15 175 active pharmacists in Portugal, and data from 2016 show us that 58% worked in community pharmacies, 8% worked at hospital pharmacies, 6% in clinical analyses, 5% in pharmaceutical industry, 4% in wholesale distribution of medicines, and 19% in other professional areas (HMR Portugal Consulting Services, 2020).

Pharmacies have a national health service contract for dispensing medicines, establishing prescription medicines' profit margins and co-payments. Apart from dispensing, none of the provided services are supported by the Portuguese national health service remuneration. Pharmacies may offer services such as smoking cessation, minor ailment schemes, and adherence support services, all of which are supported by the patient's direct payments (S. Costa et al., 2006).

2.3. The role of Portuguese community pharmacies in the health service

The role of the pharmacist in the field of Public Health has been proving to be determinant in the last two decades. The community pharmacist is in a privileged position to intervene in areas such as therapeutic management, medication administration, determination of biochemical and biophysical parameters, identification of at-risk patients, early detection of various diseases and promotion of healthier lifestyles (Ordem dos Farmacêuticos, 2018).

Some services of different degrees of complexity stand out in the Portuguese community pharmacies and show the positive intervention in Public Health:

- The management and optimization of chronic therapy and framed in a continuous plan to achieve therapeutic objectives, identification, and resolution or prevention of drug-related problems, thus becoming called pharmacotherapeutic follow-up. This is a service of high complexity and assumes the co-responsibility of the pharmacist, the physician, and the patient, to obtain the best health outcomes. These are structured processes, which, according to the pharmacy, can be organized in a more targeted way for people with chronic therapies in general, or for specific groups of pathologies, namely diabetes, asthma and chronic obstructive pulmonary disease or hypertension and dyslipidemia.
- The revision of the medication, which can be performed isolated, using only the pharmacotherapeutic history of the patient, or articulated with the information from other sources; the promotion of the use of generic medicines, which is currently co-financed by the Portuguese national health service and plays an important role in promoting adherence to therapy when the non-adherence is related to economic and financial issues, as well as a determining role in the access to innovation by allowing important savings to the Portuguese national health service.
- The promotion of self-care and the guidance of the patients of the correct administration of medical devices, to optimize the therapy and the referral of the patient to various therapeutic adherence programs, available in various formats, from automated electronic alerts to individual medication preparation (Ordem dos Farmacêuticos, 2018).

A study carried out by Policarpo et al. regarding the public's perceptions of Portuguese pharmacies concluded that 94% of those who visited their pharmacy at least once in the previous year were either globally satisfied or very satisfied. The respondents of the study gave support to the development of new health services such as the automatic renewal of prescriptions for the chronically ill, support in maintaining chronic disease under control, home delivery of medicines, health care in pharmacies, and provision of certain medicines exclusively dispensed at the hospital pharmacy and in follow-up of treatment (Policarpo et al., 2019).

In primary care centers, only those vaccines that are part of the National Immunization Program, and therefore provided free of coinsurance, are dispensed directly by the institution. Otherwise, patients have to fill in their prescriptions in a community pharmacy. Since 2007, the range of pharmaceutical services provided has been widened with the introduction of immunization services, as the influenza vaccines and other vaccines in risk groups. In fact, studies show that since then, an increasing proportion of citizens prefer to be vaccinated in the pharmacy than in other health facilities due to the shorter waiting time and their great confidence in the pharmacist. In the 2008/2009 flu season, the National Association of Pharmacies developed a training program on immunization, which was conducted across the country, and was largely attended by pharmacists. During the flu season, 160 000 people received vaccination and 93.5% of all pharmacy-based immunizations were performed by pharmacists with no record of anaphylaxis among the immunized patients. For community pharmacists to be allowed to administer the seasonal influenza vaccination, Portuguese pharmacists have to fulfill a set of requirements: a training on vaccination; a recertification every five years; evidence of continued activity; a certification on basic emergency resuscitation, and a suitable room with all the necessary equipment, including those to adequately manage anaphylactic events, like adrenaline (Pharmaceutical Group of the European Union, 2018). A Portuguese patient survey showed that 98% of vaccinated patients in community pharmacies were highly satisfied with the experience and would recommend it to others. More importantly, in Portugal, almost 14% of the immunized patients were patients who had never been immunized before. These data suggest that community pharmacies reach patients that are otherwise not reached by other healthcare settings (Gary Finnegan, 2012).

In Portugal, a recent pilot project for HIV-positive patients to collect their antiretroviral drugs from community pharmacies instead of hospital pharmacy, increasing the accessibility of HIV drugs for HIV-positive patients, has evaluated the benefits for patients and the health system in primary care (Pharmaceutical Group of the European Union, 2018).

Other services such as disease management campaigns, health campaigns and home care support have also been introduced to the role of community pharmacists. It should be noted that community pharmacies in Portugal are not reimbursed by the national health care service for the provision of these services, but patients pay out of their own pocket for some of them (Martins & Queirós, 2015). These data show the importance and the

feasibility of a greater integration of community pharmacists into the national health care service to maximize benefits for the population.

The prevention of the disease and its complications involves the identification of risk factors, at-risk patients and timely referral to specialized medical care to manage the needed interventions. Pharmacists have been assessing blood pressure and measuring biochemical and biophysical parameters for over 30 years in the majority of the Portuguese community pharmacies. These activities are essential to screen patients who have not yet been diagnosed, to detect patients who need to improve their medication adherence, and to follow and monitor chronic ill patients. In almost all Portuguese pharmacies, customers can assess their blood pressure, glycemia and cholesterol levels, BMI, maximum instant expiratory debit or calculate their cardiovascular risk, among many others without an appointment and with the certainty of being assisted by a pharmacist. Pharmacists are also engaged in promoting the adoption of healthier behaviors, and in making its contribution to the preservation of the environment in the Public Health field, through the participation in recycling programs, like collection of radiographs, disused medicines, as well as their participation in the syringe collection program. The syringe collection program has been remunerated by the national health service since 2017, a clear demonstration of the recognition of its added value.

In 2004, due to political changes that seemed to reinforce the need to pursue the expanded scope of pharmacy business to a wider range of health services, the Portuguese National Pharmacy Association included and implemented disease management and pharmaceutical care programs to pharmacies which decided to provide these services. The accomplishments of the implementation of the comprehensive services reflected a high level of organization and unity among Portuguese pharmacies, which enabled them to expand their scope of intervention (S. Costa et al., 2006). The Great Recession started in Portugal in 2009 and was combined with severe austerity, with the reduction of public health expenditure and structural reforms in the healthcare sector. The troika period had a negative impact on health care services, leading to consumption restraints and worsening the access to health care services (Perelman et al., 2015; Morais Nunes et al., 2019). In 2011, the financial rescue plan agreed between Portugal and the European Commission, the European Central Bank, and the International Monetary Fund, imposed harsh policy conditions on the Portuguese Government, including measures reflected in the healthcare sector. One of the measures was a significant increase in the user charges, which potentially created an increased access barrier to health care - emergency services in primary care facilities rose from €2.70 in 2004 to €10.00 in 2012 (Barros, 2012).

At that time, in April 2018, the Portuguese Government published the ministerial order no. 97/2018 that broadened the scope of Portuguese pharmacists' practice. This was the first amendment to the ministerial order No. 1429/2007, which defined, for the first time, the pharmaceutical care services that may be provided by Portuguese community pharmacies. The authority justifies this amendment with the evolution of the pharmacy practice during the last ten years, with the aim of comprehending new health promotion services. With this diploma, the pharmacies extended the range of services that can be provided to date. In addition to the former services, the pharmacies are now allowed to promote campaigns and programs on health literacy, disease prevention and promotion of healthy lifestyles. The changing role of pharmacists and pharmacies is also being supported by the pharmacists' representatives, the Portuguese Pharmaceutical Society (Ordem dos Farmacêuticos), which was founded in 1972 and which accompanies the pharmacists and contributes to the professional development (Ordem dos Farmacêuticos, 2005).

2.4. The National Association of Pharmacies

The National Association of Pharmacies (Associação Nacional das Farmácias) was founded in 1975 and is an association for pharmacy owners, comprising almost 95% of the member pharmacies. The National Association of Pharmacies supports and outlines the trends of community pharmacy services in the national health service and has been responsible for the development of the community pharmacies over the past decades, since safeguarding the economic sustainability to investing in information technology systems, communication technologies and modernizing the architecture of pharmacies. Moreover, the National Association of Pharmacies has developed professional services such as point-of-care measurements, drug waste management, needle exchange and the methadone substitution program.

Just like in many other countries, in Portugal, all community pharmacies are privately owned, and the core activity is to dispense prescription and non-prescription medicines. Even though community pharmacies hold the exclusivity of the first, since 2005, dispensing of the latter was authorized outside of community pharmacies, implying considerable financial losses. Thus, access to additional pharmacy services may increase as market competition increases. Pro-competitive regulatory measures may have led to an asymmetric distribution of pharmacy services across the country, favoring more competitive urban marketplaces. To achieve a more symmetrical distribution of pharmacy services all over-

the-country, policy-makers are recommended to act to ensure equitable access to them (Martins & Queirós, 2015).

As mentioned above, prescription-only medicines could only be sold in a pharmacy, but on the 16th of August 2005, with the Decree-Law No. 134/2005 of the Ministry of Health, a major change occurred in the over-the-counter market, the selling of non-reimbursed, non-prescription medicines outside of pharmacies was approved, in specialized stores authorized by INFARMED. The government claimed that the consumers would benefit from this measure in terms of an increase of selling points, which would make accessibility easier, as well as benefit the price, and therefore promote the competition among different channels of distribution and commercialization - Health Ministry, Decree-Law No. 134/2005, 16 August 2005. After the publication of the Decree-Law No. 134/2005, around four hundred new selling points of non-prescription medicines were created in the country. According to INFARMED, this measure also allowed, a decrease in the price of the medicines as intended, which led to a decision to amplify the number of medicines that have the classification of non-prescription medicine, following the steps of other European countries. This created a new competitive environment for the Portuguese pharmacy scenario since the number of drug stores selling non-prescription medicines increased from 598 sites in 2007 to 1010 sites in 2014, representing an increase of 68.9% (INFARMED, 2020). In 2013, a subcategory of medicinal products for human use not subject to medical prescription, but dispensed exclusively in pharmacy was introduced in Portugal. The aim of this reclassification in establishing this subcategory was to promote the accessibility of treatment and to ensure safety and efficacy, with benefits to public health (Martins et al., 2016).

Another major change in community pharmacies has been the progressive reduction in the selling price of the generic medicines, the branded medicines and the global retail price, which are the main income of a community pharmacy representing on average 87% of sales and 81% of this represents reimbursed medicines. According to The National Association of Pharmacies, in April 2015, these changes resulted in a fifth of Portuguese pharmacies being in a situation of insolvency and 69% of pharmacies having a negative net result in drug dispensing, with the average pharmacy operating with a negative operating result of €869. In the same period, the pharmacies lost €0.17 for each service to dispensing medication (Gomes et al., 2017). To overcome the decreasing profit margins, pharmacies took some actions, to invert the current market scenario and clustered, following a reality that already exists in other markets such as the United Kingdom, to achieve synergies related with purchases, meaning best commercial conditions (Gregório et al., 2014).

2.5. The development of pharmacy services

Since the beginning of the 21st century, there has been an effort to develop and implement nationwide pharmaceutical care programs for diabetes and hypertension with the contribution of professional organizations such as the National Association of Pharmacies. In 2003, through the Second Agreement on the National Program for Diabetes Control between the Ministry of Health and the National Association of Pharmacies, the remuneration for the Diabetes Management Program was established and an amount of 15.00 euros (€) per patient per month was agreed. The Diabetes Management Program was aimed at diabetic patients on pharmacotherapy, who did not achieve their therapeutic goals. The program consisted of follow-up visits of the patients to the pharmacy, with the SOAP methodology, which consisted in registering Subjective, Objective, Assessment, and Plan notes sections. These follow-up visits programmed between the physicians' appointments, had the aim of detecting, preventing and solving Drug Related Problems (DRPs) - Dáder methodology, through an intervention at the patient level (information, adherence, and healthy lifestyle advice) and the referral to the physician, assessing the intervention's outcomes. Only certified pharmacists delivered the Diabetes Management Program, for which they had to complete the required courses on DRPs and pharmaceutical intervention, patient and physician communication, merchandising and marketing of the services. For the health checks and diabetes management the pharmacists were paid €15 per patient per month, 75% of which was reimbursed by the national health service, and 25% paid by the patient. The Diabetes Management Program was financially supported by the national health service from 2003, but despite positive results, ceased in 2010 as by the Government's decision, ending the first experience of remunerating pharmacies for patient care service in Portugal. At that time, 403 pharmacies were providing the service, with an average of three patients per pharmacy. However, as soon as the financial support ceased, most pharmacies ended the provision of the patient follow-up. Since then, many pharmacies have broadened their services to other professionals such as nutritionists, podiatrists, or nurses in an attempt to have more revenue to face the present financial constraints. These services provided by other health care practitioners inside the pharmacy are regulated and supervised by the Portuguese Health Regulation Authority (Gregório et al., 2014). At the present time, apart from dispensing prescription medicines, the national health service reimbursement supports none of the new services. The medicines' profit margins and patients' direct payments support these services entirely.

The prevention and management of the disease and its complications requires the identification of risk factors and adequate referral to specialized medical care to promote therapeutic and non-therapeutic interventions. In almost all Portuguese pharmacies, citizens can, at any time of the day and without an appointment, benefit from point-of-care services. The referral process is already a feature of Portuguese community pharmacists' daily activity, but most of the time it is done informally, with no remuneration associated (Barros, 2012). Several studies show the social and economic benefits of community pharmacy services provided by pharmacists in health care, consequently adding value to healthcare systems across the world. A study conducted by Félix et al. estimated that current non-remunerated pharmaceutical services provided in Portuguese community pharmacies result in a gain in quality of life of 8.3% and an economic value of 879.6 million euros in avoided expense with the consumption of health resources. Furthermore, an increase in the range of community pharmacy services and a greater integration in primary and secondary care, may add additional social and economic value (Félix et al., 2017).

Paulino et al. conducted a study with the aim of analyzing the views and experiences of a group of stakeholders regarding the interprofessional relationship between community pharmacists and physicians. The authors concluded that the relationship is in an early stage of development, and that there are differences between the perceptions that pharmacists had of their function and that physicians assumed they had. Furthermore, the physicians perceived little benefit of interprofessional work to patients and themselves, whereas pharmacists anticipated benefits for patients. Pharmacists as well as physicians considered the extension of the pharmacist's role to more clinical areas as an invasion of medical practice. However, the factors presented as facilitating the strengthening of the interprofessional relationship were the increase in knowledge about the function and services provided by the pharmacist, through mixed training and joint meetings and the existence of collaboration protocols and sharing of clinical data (Paulino et al., 2010). In line with the global trend for pharmacists to move from a focus on providing, dispensing and prescription checking service to a public health role, the expansion of Portuguese pharmacists' role, framed within a context of social expectations regarding organizations' community involvement, is generating favorable results for patients and pharmacists (Nunes et al., 2015). In fact, for the future of health care a wide public support for the health system and the good clinical skills of its health professionals is needed. In addition, since Portugal has an aging population and high levels of chronic diseases, pharmacists can play an important role, as they are ideally placed to collaborate in health promotion and disease prevention activities. An increased awareness of the costs of medicines and of patients not

taking them as prescribed and a new emphasis on patient empowerment, allows for opportunistic interventions in medication adherence and the prevention and detection of Drug-Related Problems with positive clinical, economic and humanistic outcomes (Crisp, 2015). The solution for increasing access to primary health care and reducing disparities among small areas seems to lie more in organizational changes than in allocation of resources (Carneiro, 2018).

In Portugal, there is positive evidence for the intervention in community pharmacies in smoking cessation (Martins & Capela, 2010; Condinho et al., 2015) and in evaluating and improving the inhaler technique use (Castel-Branco et al., 2017). Garção and Cabrita conducted a pharmaceutical care program in a rural community pharmacy for hypertensive patients. The intervention resulted in significant blood pressure control and showed that shortly as after 6 months the prevalence of uncontrolled blood pressure dropped by 77.4% in the intervention group ($p<0.0001$) and by 10.3% in the control group ($p=0.48$) and twenty-four of 29 (83%) detected actual DRPs were solved (Garçao & Cabrita, 2002). Morgado et al. conducted a RCT in an outpatient clinic for secondary care on 197 randomly assigned hypertensive patients. The pharmacist's intervention program aimed to enhance hypertension control during a 9-month period by improving medication adherence through educational interventions. Blood pressure control ($p=0.005$) and medication adherence (74.5% vs. 57.6%, $p=0.012$) were higher in the intervention group, illustrating that pharmacist intervention improves medication adherence and blood pressure control in patients treated with antihypertensive agents (Morgado et al., 2011). Costa et al. found positive evidence from pharmacist interventions in screening at risk and uncontrolled patients, in managing patients with diabetes, and in supporting self-monitoring strategies. Furthermore, the authors found room for improvements in health policies, intervention design and research methods. Concerning intervention design and research methods, the authors concluded that systematic reviews that assess clinical pharmacy services and which target specific conditions were more conclusive. This is attributable to well-defined interventions and unequivocal and tangible measured outcomes. On the other hand, for interventions with a broader target and with measured parameters that were not clearly established or inconsistently assessed, the results were inconclusive. In conclusion, the authors highlighted both the importance of defining clinical pharmacy services and the methods to assess the impact of the interventions on patient health outcomes (Costa et al., 2019).

HIPOS-PHARMA was a nationwide observational, cross-sectional, multicenter study conducted in community pharmacies, with the aim to assess type 2 diabetes patients at risk of mild to moderate hypoglycemia. The authors found that overall prevalence of mild to moderate hypoglycemic episodes was 17.8%, prevalence of severe hypoglycemia was 3.13% and that men and patients on antihyperglycemic therapies excluding secretagogues or insulin were less likely to have mild to moderate hypoglycemic episodes (Torre et al., 2018). Another example of Portuguese pharmacists' intervention was the study from Guerreiro et al. in the detection of at-risk patients for preventable drug-related problems and consequent prevention of unnecessary patient harm and waste of resources for the health care service. The authors found that about half of the assessed patients were at risk of a preventable drug-related morbidity event, and pharmacists had to provide risk minimization actions in 23 patients (Pereira Guerreiro et al., 2012). Portuguese community pharmacists also assess disease control in patients through the application of validated questionnaires. Lourenço et al. used the *Control of Allergic Rhinitis and Asthma Test*, a simple self-assessment questionnaire and showed that pharmacists can help to identify patients with uncontrolled allergic rhinitis and asthma disease by changing patients' knowledge about their disease, with the goal of improving outcomes (Lourenço et al., 2014). A study to assess baseline and change after 26-weeks in health-related quality of life among adults with type 2 diabetes initiating one of the new glucose lowering drugs - dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonist (GLP-1RA) or sodium-glucose cotransporter-2 (SGLT2) inhibitors, was carried out in community pharmacies. The authors found a mean positive change in the EQ-5D scores. Participants with worse health conditions at baseline were more likely to experience larger improvements in health-related quality of life (Torre et al., 2019).

Exploring the public's perceptions and attitudes towards community pharmacy in Portugal, a qualitative approach was undertaken by Cavaco and collaborators through semi-structured interviews. The participants presented general and contradictory ideas about the role of the pharmacist and a superficial understanding, confirming a low expectation level, which justifies the reduced wish for an extended role of the pharmacist in the community (Cavaco et al., 2005). In a study comprising 1114 interviews carried out by Policarpo et al., the authors assessed the utilization of community pharmacies and 36% of the respondents stated to use the pharmacy as a first resource when seeking to treat a minor ailment and 54% when seeking answers about medicines. The authors also assessed the level of acknowledgement of pharmacy services and the level of satisfaction of the users, which they concluded was high and with a strong positive attitude towards their community

pharmacy. Furthermore, the users stated that there could be more services available in pharmacies that are provided in other healthcare settings (Policarpo et al., 2019).

In Portugal, the provision of clinical pharmacy services is not yet fully recognized by other health care providers such as nurses and physicians. Portuguese nurses showed low expectations of pharmacists and considered them as external to the team. This perception is due to a lack of exposure to pharmacists' clinical skills and the inexistence of health policies that promote interprofessional collaboration (Salgado et al., 2013; Salgado et al., 2014). A recently created pilot-project is an example of collaborative models work - the USFARMÁCIA. In this project, general practitioners and pharmacists exchange therapeutic information to provide efficient health care to their patients. The care is provided based on the information and the education of the patients, to understand why their treatment is necessary and how they should take it.

In Portugal, a commitment was created to increase the use of the electronic prescriptions in the national health service, helping to improve patient safety and the sustainability of the wider health system.

CHAPTER III - Pharmacist intervention in cardiovascular disease management - The study

The present study aimed to reveal the opportunities Portuguese pharmacists have in managing cardiovascular disease in community pharmacies by detecting cardiovascular risk factors and at-risk patients. The objective was to assess the feasibility of the whole process, from the characterization of the pharmacy users, to the evaluation of their acceptability towards cardiovascular risk assessment by the community pharmacist and analysis of the reasons for nonattendance, to the detection of uncontrolled risk factors and the adherence of cardiovascular pharmacotherapy to clinical guidelines. In pursuit of these goals, the study was divided into the following parts:

A - Characterization of the profile of community pharmacy users and evaluation of their acceptability towards cardiovascular risk assessment by the community pharmacist and reasons for nonattendance.

B - Cardiovascular risk factor screening in community pharmacy of cardiovascular pharmacotherapy naïve participants.

C - Evaluation of the cardiovascular pharmacotherapy guideline adherence and risk factor control of patients already on cardiovascular pharmacotherapy.

The content of this chapter is partially supported by the scientific papers:

- Fonseca AA, Lima TM, Castel-Branco M, Figueiredo IV. Feasibility of cardiovascular risk screening in Portuguese community pharmacies. Pharm Pract (Granada). 2021 Apr-Jun;19(2):2255.
  doi: 10.18549/PharmPract.2021.2.2255. Epub 2021 May 25. PMID: 34188730; PMCID: PMC8203311.

- Fonseca A, Lima TM, Fernandez-Llimos F, Castel-Branco MM, Figueiredo IV. Evaluation of Cardiovascular Pharmacotherapy Guideline Adherence and Risk Factor Control in Portuguese Community Pharmacy Patients. Int J Environ Res Public Health. 2022 May 19;19(10):6170. doi: 10.3390/ijerph19106170. PMID: 35627707; PMCID: PMC9140328.

A - Characterization of the profile of community pharmacy users and evaluation of their acceptability towards cardiovascular risk assessment by the community pharmacist and reasons for nonattendance.

1. Introduction

Community pharmacies are widely used in Portugal, since the pharmacy is an easily accessible place where users are cared by qualified professionals. The services that community pharmacies provide are changing, with pharmacists expected to take on wider roles and responsibilities. Although, the impact of these changes will depend on how and who uses these health settings.

To describe the profile of Portuguese pharmacy users, it is important to analyze the reasons that lead them to enter community pharmacies. In many countries, more recently, community pharmacies have emerged as strategic settings to deliver services aimed at promoting public health. To explore how customers face this accessibility and experience the care intervention by their community pharmacist, it is essential to develop evidence-based approaches to public health interventions.

It is already known that developing a trusting relationship with the pharmacist is a decisive aspect in the context of the acceptability of community pharmacy for public health service by their users. On the other hand, the lack of awareness among the public about the extended role of community pharmacists is a potential barrier toward people using them as health care providers (Lindsey et al., 2017). The accessibility of community pharmacies for health care services by the public must be extended beyond the physical accessibility and addressed in a more complex acceptability-connotation. In other countries, the community pharmacists' services are supported and accepted by the majority of the users due to their potential benefits. These benefits are based on personal convenience, a trusting relationship with the community pharmacist and more time to talk, the absence of a judgmental attitude, and the fact that the community pharmacist can be consulted without an appointment (Bissell & Anderson, 2003; Lindsey et al., 2017; Hindi et al., 2018). The increasing involvement of pharmacists in public health will require changes in the behavior of both pharmacists and the public. Attitudes and beliefs are important determinants of behavior which ultimately influences the choices of the pharmacy users, and when analyzed

can be useful to support and improve the disclosure of pharmaceutical care service (Eades et al., 2011).

From the point of view of most of the pharmacists, public health services are important and are part of their public health role. However, their confidence in providing public health services is on the whole average to low. Pharmacists report time constraints, lack of demand, expectation of a negative reaction from customers, challenges as to the use of new technologies and social media, lack of awareness, commercial pressure from pharmacy owners, inadequate funding, government policy on the public health role of pharmacists, inadequate communication skills, lack of integration of undergraduate healthcare programs, logistics, as well as the fact that pharmacists qualify as scientists rather than as clinicians, and lack of an adequate private space as barriers to provide these services. A need for further training was identified in relation to specific public health services (Eades et al., 2011). Furthermore, some authors state that a clearer policy by the government on the public health role of pharmacists, supported by Schools of Pharmacy and relevant stakeholders, might be a way forward (Agomo et al., 2017). In a review, Hindi et al. searched the literature for patients and public views of community pharmacy service and divided them in two main themes: public cognizance - where they include promotional strategies, awareness, and use of pharmacy service, physicians' supremacy, perceptions of pharmacists - and attitudes towards services - where they include facilitators, barriers, service *versus* non-service users, and perceived impact. The public cognizance provides insights into expectations from these services and the attitudes towards services focuses on experience of using these services. The authors found that most pharmacy users had never been offered public health services by their pharmacist and did not expect them to be offered. Moreover, pharmacy users view pharmacists as appropriate providers of public health advice, but have mixed views on the pharmacists' ability to do this. The satisfaction rate was high in patients that had experienced pharmaceutical public health services. The study concluded that patients and the public appear to view pharmacists' services as beneficial, but the successful integration of the extended pharmacy services requires pharmacists' clinical skills to be recognized by patients and physicians and that future research should be undertaken to explore the approaches to increase this awareness (Hindi et al., 2018). A study on the confidence in the world of professions revealed that globally pharmacists are placed fifth with 86% of an overall index of confidence, after firemen (90%), nurses (89%), teachers (89%) and doctors (88%) (Frank, 2018). Consequently, the consumer is likely to accept the extended role of the pharmacy when introduced, based precisely on that

confidence. Another study, exploring the provision of flu vaccinations in primary care, showed that some people prefer using community pharmacy for vaccination and pay for it instead of benefitting from a free of charge vaccination on the Portuguese national health service, as the service was easier to access. The rationale of access given showed that it was more convenient, due to extended opening hours, pharmacy location and a preference for the pharmacy environment. This is an example of opportunities for pharmacy to support the Portuguese national health service (Anderson & Thornley, 2014). A study conducted by Lindsey and collaborators revealed that the majority of pharmacy users did not expect to be offered public health services in the pharmacy setting, although those that used public health services in the pharmacy were highly satisfied. Some respondents perceived lack of pharmacist ability and a lack of private space to put forth such services. The authors also found a general lack of awareness about pharmacists' educational programs, and their level of competence associated with delivering services, and the environment in which public health services are delivered, therefore being potential barriers for the pharmacy users (Lindsey et al., 2017).

The acceptability to users of pharmaceutical care provided in Portuguese community pharmacies is mainly determined by the perceptions of convenient access (shorter waiting time; flexibility of appointments; service organization; and proximity to home) and the development of a therapeutic relationship with the pharmacist. Patients' expectations concerning the service are not well-developed, but not necessarily low (Guerreiro et al., 2010).

Lack of awareness or knowledge, misunderstanding the purpose, aversion to preventive medicine, time constraints or competing priorities, difficulty with access in general practices and concern around the pharmacy as appropriate setting are some reasons why people do not attend health checks (Harte et al., 2018). To improve health check attendance, the findings particularly highlight the need for improved communication and publicity around the purpose of the Portuguese national health service Health Check program and the personal health benefits of risk factor detection (Harte et al., 2018). A study by the national health service on the CVD risk profile of the Portuguese population revealed a high prevalence of CVD risk factors and the need for health authorities to develop strategies to screen the general population for CVD risk factors (Boubon et al., 2019). Community pharmacists' responsibilities must expand to include these more direct patient care services to transform health care practice, but are consumers ready to accept this expanded community pharmacist patient care roles (Steckowych et al., 2018)?

As far as it is known, this is the first study, in Portuguese community pharmacies, that evaluates the whole process, from the analysis of the acceptability of users to assess their cardiovascular risk, the effective assessment of their global cardiovascular risk, to the analysis of the prevalence of major cardiovascular risk factors. To evaluate the feasibility of the process, this study characterized the profile of the community pharmacy users, evaluated their acceptability towards cardiovascular risk assessed by their pharmacist, and the reasons for nonattendance.

2. Objectives

This part of the study aimed to understand the profile of the community pharmacy users in Portugal, both in terms of their characteristics and also in terms of the purpose of entering the pharmacy, thus shaping the profile of the pharmacy utilization. The profile of the community pharmacy users was determined in two different periods in order to analyze the variability and the consistency of the sample.

Moreover, the study aimed to assess the feasibility of cardiovascular risk assessments in community pharmacies in Portugal, the acceptability of community pharmacy users towards cardiovascular risk assessment by their pharmacist, and their reasons for nonattendance, with the goal of evidencing that community pharmacists are health professionals that add value to the effort to reduce the burden of CVD.

3. Methods

Study design

This study was a single-center cross-sectional study conducted to characterize the profiles of pharmacy customers at two different time points, and evaluate the acceptability of community pharmacy customers towards cardiovascular risk assessment by their pharmacist.

The Decree-Law No. 307/2007 of 31st August establishes that Portuguese community pharmacy may provide the public with the following products:

(a) Medicines;

(b) Medicinal substances;

(c) Medicinal and veterinary products;

(d) Homeopathic medicinal products and homeopathic products;

(e) Natural products;

(f) Medical devices;

(g) Food supplements and special nutrition products;

(h) Plant protection products;

(i) Cosmetic and body hygiene products;

(j) Childcare articles;

(k) Comfort products.

Under this assumption, the reasons for attending the pharmacy were classified into the following categories:

1- Acquisition of medicines

2- Acquisition of health products

3- Assessment of physiological and biochemical parameters

4- Information on medicine and health product

5- Other reasons

Included in the category of *Acquisition of medicines* (1) there were prescription-only medicines (POM), non-prescription medicines "over-the-counter" (OTC), veterinary medicines and homeopathic medicines. In the category of *Acquisition of health products* (2) there were cosmetic and body hygiene products, plant protection products, food supplements and special nutrition products, childcare articles, comfort products and medical devices. In the category *Assessment of physiological and biochemical parameters* (3) the assessment of blood pressure, total cholesterol, triglycerides, and glycemia were considered. In the category *Information on medicine and health product* (4) users who entered the pharmacy only to request information on medicines and health products were included. In the *Other reasons* category (5) users who entered the pharmacy to accompany another user, make a purchase for another person, pick up a reservation, pay a bill or just to greet were considered. The reason to enter the pharmacy *Information on medicine and health product* was only reported when the user entered the pharmacy with this sole purpose. Nevertheless, users may enter the pharmacy to ask for advice while getting their medication, or ask all the other concurrent reasons. Thus, the considered categories are not mutually exclusive, i.e., a customer could have visited the pharmacy for more than one reason at the same time. Customers were considered as regular customers if they had visited the pharmacy at least once in the previous 3 months.

To assess the readiness of the users of community pharmacies to accept the assessment of their cardiovascular risk in the community pharmacy, when invited by their pharmacist, and to understand the main reasons why they did not accept, the research pharmacist invited each eligible customer via telephone and registered their readiness to accept, or the reasons pointed out by the customer for not accepting. The reasons for nonattendance were categorized as follows:

1) Lack of time
2) Not used to participate in this type of services
3) Bedridden or in an institution / Cognitive impairment / Deceased
4) Do not need follow up at the pharmacy / Followed up by the physician
5) Not the usual pharmacy/ (e)migrated /have no transport.

Setting

The recruitment process occurred in a community pharmacy of a central Portuguese city during two distinct periods of two 70-hour working weeks from Monday through to Saturday. The first period was in May 2015 and the second period was in December 2016. The enrollment process was carried out in two distinct periods to minimize the bias of seasonality and to analyze the variability.

The pharmacy, where the study was conducted, is located in Viseu, one of the largest cities in central Portugal. The pharmacy was considered representative of the reality of most pharmacies in the country. The Portuguese population has 2892 community pharmacies at its service (FFMS, 2018), with national coverage of excellence and a great equity in the geographical distribution, therefore making being Viseu being perfectly in line with the national context as shown in Figure 21 (Pharmaceutical Group of the European Union, 2015). Twenty-one pharmacies serve Viseu's municipality of about 96991 inhabitants (FFMS, 2018), resulting in a ratio of 4618 inhabitants per pharmacy, which is below the national average of 3522 and closer to the European Union average of 4550 (Pharmaceutical Group of the European Union, 2015).

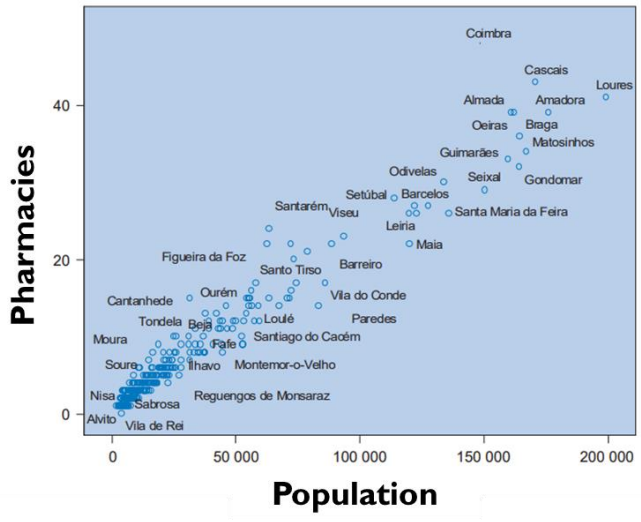

Figure 21- Source - Portuguese Pharmaceutical Society.

Portuguese pharmacies have a benchmark quality in terms of the number of pharmacists per pharmacy - 3.10 - exceeding the European average of 2.73 (Pharmaceutical Group of the European Union, 2015). The pharmacy where the study was conducted has three pharmacists at the service of its users, which can be considered as representative of the national reality.

Population

Previously, before the start of the study, an informative session to all the pharmacy team members was held by the pharmacist, with the objective of presenting the purpose of the study and the procedures to be adopted for the enrollment process. The pharmacy team members responsible for the enrollment process were three pharmacists, five pharmacy technicians, a pharmacist trainee and a collaborator of the dermo cosmetic products. During the enrollment process, the team members registered the name, date of birth, telephone number, day, and time of the customer attendance, collaborator responsible for the attendance, and the purpose of the customer entering the pharmacy, for all customers who entered the pharmacy, during the two distinct weeks. The exclusion criteria were customers below the age of 18, pregnant customers, or mentally disabled persons who were unable to consent. Afterwards each pharmacy customer of the second recruiting week was contacted by phone by the investigator pharmacist and invited to participate in a cardiovascular risk assessment study at the pharmacy by their pharmacist.

To avoid any selection bias, the pharmacist who contacted each customer used a standard invitation speech in every phone call, clarified possible doubts, scheduled an appointment for data and sample collection, and informed the customer about the requirement to fast beforehand and bring all their medications. The pharmacist registered the readiness to accept and the reasons for nonattendance indicated by the contacted customers. All contacts were made up to three attempts at different times on different days. To clarify the flow of participants throughout the study, a diagram is presented in Figure 22.

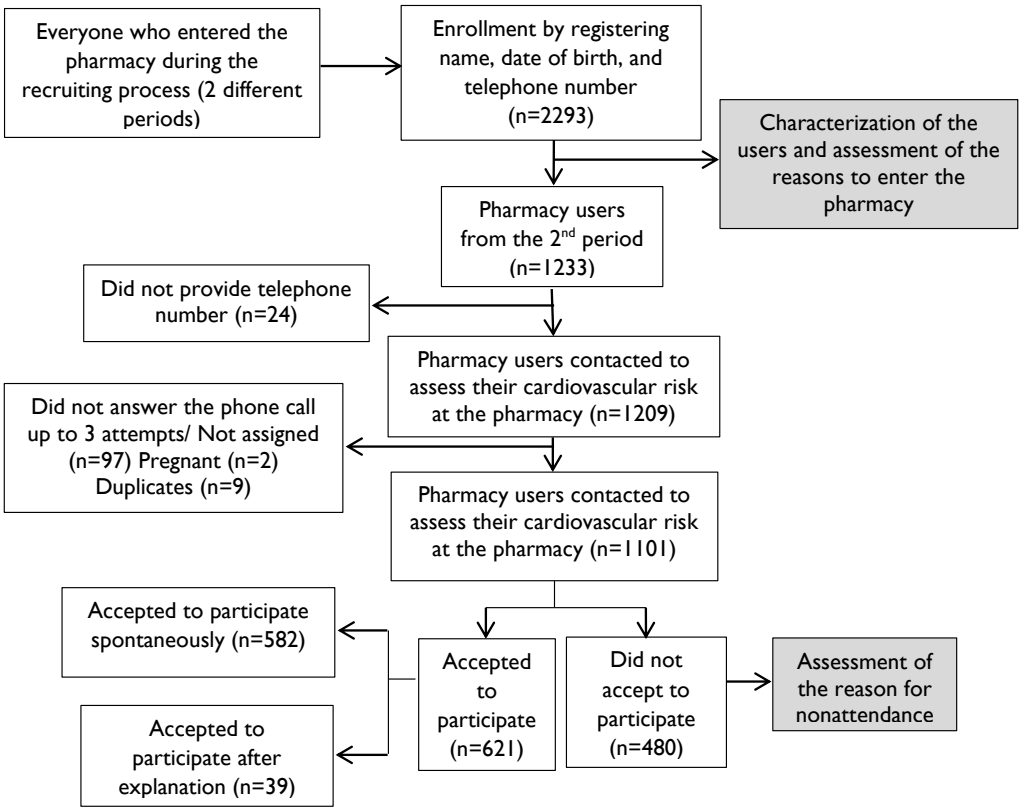

Figure 22 - Flow diagram of participants throughout the study.

Data analysis

Descriptive statistics to explore the characteristics of the study population were used. To analyze possible associations between variables, chi-squared and Kruskal-Wallis tests for categorical variables and t-tests and ANOVA for continuous variables were used. For the data analysis, SPSS v.24 (IBM, Armonk, NY, United States) was used and a p-value lower than 0.05 to be statistically significant was considered.

4. Results

In the two weeks of data collection, a total sample of 2293 customers was obtained - 1060 in the first period and 1233 in the second period.

Profile of the community pharmacy users

The descriptive characteristics of the sample of the pharmacy users in both periods, including the reasons for entering the pharmacy, are shown in Table 17.

Table 17 - Descriptive characteristics of the sample of the pharmacy users (n=2293)

		1st period	2nd period
Gender; n (%)			
	Male	447 (42.2)	516 (41.9)
	Female	613 (57.8)	717 (58.1)
Mean age in years; mean (SD)		55.26 (±17.48)	55.52 (±17.07)
	Male	59.78 (±17.25)	58.93 (±17.04)
	Female	51.83 (±17.83)	53.77 (±17.13)
	Minimum-Maximum	18-101	18-94
Regular customer; n (%)		659 (62.2)	811 (65.8)
Pharmacy staff member who attended the pharmacy customer; n (%)			
	Pharmacist	679 (64.1)	729 (59.1)
	Pharmacy technicians	363 (34.2)	484 (39.3)
	Non-clinical pharmacy staff	18 (1.7)	20 (1.6)
Reason that prompted the customer to come into the pharmacy; n (%)			
	Acquisition of medicines	847 (79.9)	753 (61.1)
	Prescription-only medicines	704 (66.4)	745 (60.4)
	Over-the-counter medicines	213 (20.1)	241 (19.6)
	Acquisition of health products	300 (28.3)	403 (32.7)
	Assessment of physiological and biochemical parameters	25 (2.4)	22 (1.8)
	Information on medicine and health product	10 (0.9)	44 (3.6)
	Other reason	55 (5.2)	150 (12.2)

The flow of customers varied during the day and the week, and the peaks during the day were different in the winter and in the spring period, as shown in Figure 23.

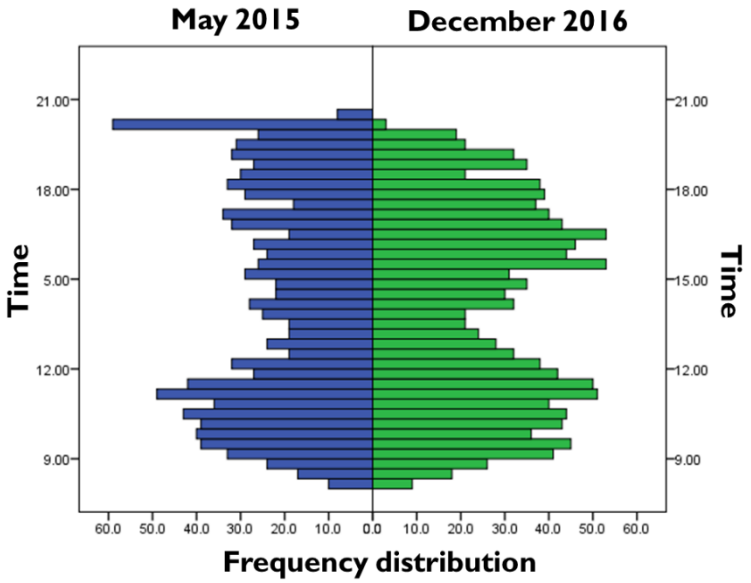

Figure 23 - Time of entry of the customers into the pharmacy, in the two distinct periods.

The percentage of male and female customers did not vary with the weekdays (p=0.849), nor with the different periods of the day (morning versus afternoon) (p=0.228), as shown in Figure 24.

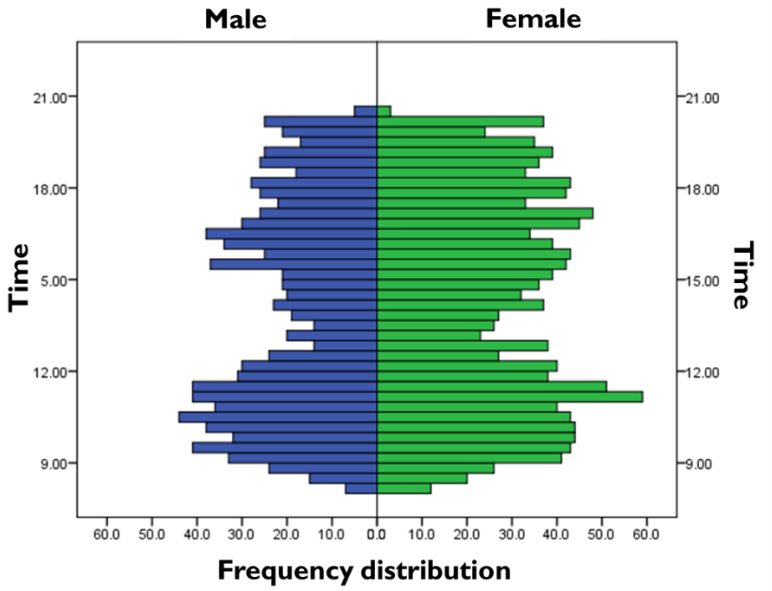

Figure 24 - Time of entry of male and female customers in the pharmacy.

The male customers were older than the female customers (t=4.793, p<0.001). On Tuesdays, there was a slight increase in the mean age of the customers due to a weekly fair that happens near the pharmacy and which is attended by the older population from the peripheral villages.

The pharmacy customer flow throughout the day increased during the morning, reaching its maximum at 11:00 am and was more concentrated in the early afternoon (4:00 p.m. to 5:00 p.m.), decreasing after 6:00 p.m. in the winter period and had a more concentrated flow in the late afternoon (6:00 p.m. to 8:00 p.m.) in the spring period. Moreover, concerning the number of pharmacy customers, Saturday was the least busiest day of the week, whilst Monday and Tuesday were the busiest weekdays.

Entering the pharmacy to acquire medication was the most prevalent reason, and it was more frequently reported in the morning period ($p=0.004$) and by male customers ($p<0.001$). More female customers visited the pharmacy to acquire other health products ($p<0.001$), and this reason showed no difference between the morning and afternoon period ($p=0.527$). The assessment of physiological and biochemical parameters was a reason for visiting the pharmacy that was not influenced by sex, but had more expression during the morning period ($p=0.028$). Asking for advice and information on medicine and health products was a reason for visiting the pharmacy that was not influenced by the period of the day ($p=0.122$) or the sex of the customer ($p=0.661$). Accompanying another customer and making a purchase for another person was more frequently reported by female customers ($p=0.006$) and in the afternoon period ($p<0.001$).

More than half 61.4% (n=1408) pharmacy users were taken care of by pharmacists, considering that the trainees were under the responsibility of the pharmacists. More than half 64.1% (n=1470) pharmacy users were regular customers. In the second period sample, among the 61.1% (n=753) pharmacy users who entered the pharmacy to acquire their medication, 38.0% (n=286) acquired at least one medicine related to CVD - antihypertensive, antidyslipidemic, antidiabetics.

Acceptability of the pharmacy users towards cardiovascular risk assessment

As shown at the flow chart in Figure 22, from the 1233 customers who entered the pharmacy in the second period, it was possible to contact 1101 customers. The customers who did not provide their telephone number during the enrollment period (n=24) were not regular customers - eight were living abroad and were in Portugal for the Christmas holiday, eight customers stated to have no telephone number or did not know the number, and the remaining simply did not provide their telephone number.

More than half of the contacted customers - 56.4% (n=621) - accepted the invitation of the study, and 53.4% (n=588) actually attended the cardiovascular risk assessment. Table 18 shows the results of the reasons for nonattendance.

Table 18 - Reasons for nonattendance to the appointment (n=1101)

Reason	n (%)
Accepted to participate	621 (56.4%)
Spontaneously accepted to participate	582 (93.7%)
Accepted to participate after explanation	39 (6.3%)
Did not accept to participate	480 (43.6%)
Lack of time	96 (20.0%)
Not used to participate in this type of services	46 (9.6%)
Bedridden or in an institution/Cognitive impairment/ Deceased	50 (46/1/3) (10.4%)
Do not need follow up at the pharmacy/Followed up by the physician	205 (42.7%)
Not the usual pharmacy/ Migrant /have no transport	83 (17.3%)

There was no difference in acceptability between male and female pharmacy customers, and the pharmacy customers who were more likely to accept the risk evaluation were those who entered the pharmacy for the acquisition of medicines ($p=0.004$), elderly customers ($p<0.001$) and regular customers ($p<0.001$).

5. Discussion

We have ascertained that pharmacies are a healthcare setting with a high number of users visiting them, with a wide range of ages and reasons for visiting, thus, many opportunities exist for public health initiatives to be provided in community pharmacies (Lindsey et al., 2017; Hindi et al., 2018).

During the two weeks of data collection, a total sample of 2293 customers was obtained, which represents almost 50% of the population assisted by the pharmacy in question - 4618 inhabitants per pharmacy in Viseu, which is a representative sample, even if it were assumed that there was repetition among the participants in the two distinct periods.

Profile of the community pharmacy users

The pharmacies are widely used in Portugal, as in most countries (Hindi et al., 2018). A 16.8 customers per hour rate was registered in the community pharmacy where the study was conducted. As expected, the main reason for customers to attend the pharmacy

was to get their medicines (Lindsey et al., 2017). In the two periods, 63.2% (n=1449) customers entered the pharmacy to get prescription-only medicines and 19.8% (n=454) customers entered the pharmacy to get over-the-counter medicines.

In the two distinct study periods slight variations in the profile of the users were observed, in the same pharmacy, and deserve a more careful analysis. In fact, changes in the supply chain had an impact on the profile of the customer's utilization of the pharmacy. During the second period, the Portuguese pharmacies experienced a lack in the supply of some medicines and the rate of "other reasons", which includes picking up a reservation, for having to wait for the medicine to be available, increased from 5.2% to 12.2%. Thus, external factors influence the dynamic of the community pharmacies and have to be safeguarded. Another aspect is that in Portugal, the profit of pharmacies depends almost exclusively on the margin that is obtained on the prices of the medicines. The reduction in medicines prices since 2011 resulted in a large proportion of pharmacies operating with a negative margin. In consequence, pharmacy owners had to shift the focus from medicines to other health products and services. In this study, it was found that the owners' policy affected the reasons to enter the pharmacy in the two periods, due to a more intensive and aggressive offer in health products in the pharmacy. Thus, in the analysis of the two periods separated by 19 months, the consumers who entered the pharmacy with the only objective of getting their medicines decreased from 64.1% (n=679) to 49.6% (n=612), whereas the consumers who entered the pharmacy with the only aim of getting health products increased from 12.4% (n=131) to 21.7% (n=268). Thus, marketing strategies affect community pharmacy customers and influence their selection of pharmacy (Kevrekidis et al., 2018).

A wide range of ages and reasons to visit pharmacies are found, which provides many opportunities for public health initiatives to be delivered in pharmacies. Furthermore, the flow of customers and the pattern of use of the pharmacy by the customers vary along the different periods, during the weekdays and along the day. It is important for each pharmacy setting to learn about these oscillations to allocate their collaborators and services efficiently. Gathering this information is critical while designing and tailoring the pharmacy services to be provided by a particular pharmacy and to improve and optimize health programs in community pharmacies. In the present study, 38.0% acquired at least one medicine related to CVD. Thus, many opportunities exist for public health initiatives to be provided in community pharmacies, targeting the management of CVD.

Acceptability of the pharmacy users towards cardiovascular risk assessment

Worldwide, community pharmacies are shifting their role in the healthcare system from simple medication dispensers to health care providers. High levels of satisfaction with pharmacy services were found in previous studies. The obtained participation rate in the present study indicates a good acceptability of the pharmacy users towards CVD screening by the pharmacist, as more than half of the contacted customers (56.4%) accepted the invitation to participate in the study. It is known that fewer than 25% of the approached patients accept invitations to participate in health intervention studies in the pharmacy (Gazmararian et al., 2010). However, the participation rates increased in patients already attending specialized pharmacies, from 5.9% in 2004 to 28.1% in 2007, suggesting that patient awareness and receptivity increased over time (Blalock et al., 2013). A study from Denmark aimed to investigate the determinants of attendance to a preventive health check program on 4853 eligible persons and to explore the homogeneity of the attenders. The authors found that more than half (55%) of the invited population attended, 49% were men. Moreover, those who accepted were more likely to be: of higher age; immigrants; cohabiting; have higher socio-economic status, higher use of preventive services and lower morbidity (Bjerregaard et al., 2017).

Barriers to the implementation of primary health care disease management models in Portuguese community pharmacies are related to workload and lack of demand and time. An observational study performed by Gregório et al. described community pharmacists' workload and estimated the demand of pharmaceutical care services. The authors found that between 67.0% and 81.8% of the registered activities were pharmacist-patient interactions, with a mean duration of 3.98 min per interaction and about one third of the day was spent performing administrative and non-differentiated tasks. These workload results were found to be very similar to findings from studies in other countries, which may be an indication of uniformity of community pharmacy practice across countries. The author concluded that the amount of time a pharmacist has at the counter to interact with a patient renders disease management or therapeutic management non-viable. Furthermore, the perception of "lack of time," many times reported, as a barrier for service provision, must be called into question, since substantial available time was found. It is therefore necessary to redesign work processes and define new roles to increase and enable patient follow-up services by community pharmacists (Gregório et al., 2017). Moreover, pharmaceutical services optimization requires a comprehensive understanding of resource usage and its costs. Thus, the development of a time-driven activity-based

costing model of pharmaceutical services is necessary to optimize healthcare system management and to inform policy makers of the elaboration of pharmaceutical care policies for community pharmacies costs. The calculated cost of a dispensing service in these pharmacies ranged from €3.16 to €4.29, the cost of a counseling service when no medicine was supplied ranged from €1.24 to €1.46, and the cost of health screening services ranged from €2.86 to €4.55 (Gregório et al., 2016).

Research to examine the factors that predict patient acceptability towards clinical services conducted in Portuguese community pharmacy has been scarce. A cross-sectional study involving patients enrolled in a community pharmacy-based diabetes care program found that self-reported intention to continue to participate in the program was associated with patients' beliefs concerning perceived susceptibility to diabetes complications and the extent to which program participation reduced their risk of developing these complications (Pinto et al., 2006). Thus, a big facilitator is the importance that the user attaches to the service provided. In the present study, the fact that the awareness and importance of CVD is a widespread concern may have positively influenced the participation rate. Moreover, the Portuguese community pharmacy users are accustomed to assessing their blood pressure and their biochemical parameters in the pharmacy.

Many studies report low or lack of awareness of extended pharmacy services, and this is cross-cutting through public or patients in different age groups with different social and educational backgrounds. There is also a perceived lack of awareness among the public about the extended role of community pharmacy, which is a potential barrier toward people using them (Lindsey et al., 2017). Saramunee et al. with the purpose of exploring the reasons for patients to seek advice at pharmacies concluded that key themes around choice of pharmacy were due to the convenience of professional advice, triage to general practitioner care if warranted, inaccessibility of general practitioner care, perceived non-serious nature of the condition and high levels of trust in their pharmacists. On the other hand, the authors identified lack of privacy and the potential for misdiagnosis as concerns of the interviewees. Almost all participants felt positive about their pharmacy care and would revisit it for future problems (Saramunee et al., 2015). In a study about experiences of and willingness to use medicines-related services among the public, the results of the specific issue of giving the pharmacist permission to telephone to follow-up about advice already provided was accepted by 65.6% (n=655) of the interviewees. The referred interviewees had experience of the medicines-related services (11.1%, n=111), or would be prepared to use it in the future (55.4%, n=553) (Krska et al., 2016). The former study

reported the concept of physicians' supremacy, as over two-thirds of respondents indicated that they would consider going to a pharmacy for advice if they did experience difficulties with a medicine, but the majority of the remainder of the respondents indicated that they would go to their general practitioner instead. The reasons for choosing to see a general practitioner were given as: greater general practitioner knowledge of them personally, health or illness in general, the pharmacist not being able to change medicines, and the expectation of being referred to general practitioner by pharmacist (Krska et al., 2016). Apart from this, pharmacy CVD screening users and non-users had different opinions on the pharmacy being a proper place for screening or if it should only be carried out by doctors (Taylor et al., 2012). In the present study, only one contacted user actually verbalized this concept, by asking "Shouldn't this evaluation be done by physicians?" However, the mentioned customer attended the CVD assessment.

In fact, the main reason for nonattendance was that the user "Do not need follow up at the pharmacy/ Followed up by the physician" (42.7%), which represents 18.6% (n=205) of the whole contacted sample. Thus, for services to improve, the pharmacy profession demands a better awareness of what the public, especially those with potential to benefit from these services, view as acceptable and desirable (Krska et al., 2016). Results showed that erroneous concepts and behaviors, and inappropriate users' perceptions of the pharmacists, exist within the Portuguese population in relation to the community pharmacists' role. This is a matter for pharmacy professional and educational bodies to consider when developing intervention strategies, and in particular when communicating with the public (Neves Cavaco & Peter Bates, 2007). Some customers accepted to participate in the study only after an explanation was given by the investigator pharmacist, hence showing a lack of acknowledgment that the pharmacist is qualified to deliver a CVD screening service. A study on responses to statements regarding CVD screening conducted by Taylor et al. showed a high level of agreement with the need for screening in both users and non-users of the service. The overall majority of service users had a positive experience of the screening service, agreeing that they were given enough time and that pharmacists made them feel at ease. A minority of non-users were aware of the pharmacy service and, although the majority (78.4%) were willing to be screened at a pharmacy, this result was significantly lower among males than among females. Perceived concerns about confidentiality and lack of privacy were among the identified barriers to screening. Upon these results, the authors concluded that the public accepts pharmacy-based CVD screening and that acceptability could be improved through increased awareness of the

service and by addressing concerns about privacy and confidentiality in promotional activities (Taylor et al., 2012; Fitzgerald et al., 2015).

In the present study, the pharmacy users who were more likely to accept the risk evaluation were those who entered the pharmacy for the acquisition of medicines ($p=0.004$), the elderly customers ($p<0.001$) and the usual customers ($p<0.001$). These results are in line with other studies, namely in a study conducted by Krska et al., where the respondents who were frequent pharmacy users, and those using regular medicines, were significantly more willing to agree than those not regularly using pharmacies or medicines (all $p<0.001$) (Krska et al., 2016).

For future perspectives, participants voiced a perception of different levels of service provided by independent pharmacies and larger national chains. Independents were perceived to provide more personalized service and advice. Some participants valued the opportunity to buy products within pharmacies, e.g., toiletries and cosmetics, while others felt this detracted from the role of the service (Wood et al., 2015). As pointed out in other studies, barriers have been identified such as, for example, existing business requirements, general negative views of the pharmacy settings, with a perception of a lack of integration not only with other services, but also of public and health professionals' awareness (Cooper & Tsoneva, 2017).

Community pharmacy has the potential to deliver public health services. Addressing the identified barriers could help to increase utilization and impact of pharmacy public health services. A study, intending to explore the experience of and willingness to use pharmacy public health services related to cardiovascular risk among the public in England, concluded that the public has been slow to utilize pharmacy public health services but are receptive to these services. A greater willingness to use services was shown by females, those in good health, with specific health needs and towards specific advisory services supporting their problems, like smokers, overweight individuals and those with alcohol-related problems. The public showed a lower willingness towards advisory services, than towards health check services. The authors concluded that pharmacists have to promote pharmacy public health services that target on relevant populations and maximize uptake by considering the barriers, which were identified as being frequent staff changes, seeing pharmacist as medicines suppliers and concerns about competence for these services (Saramunee et al., 2015).

General and preventive health checks are a key feature of contemporary policies of anticipatory care. Ensuring high and equitable uptake of such general health checks is essential to ensure health gain and prevent health inequalities. A literature review carried out by Dryden et al. explored the sociodemographic, clinical and social cognitive characteristics of those who do and who do not engage with general health checks or preventive health checks for CVD. The authors found that those least likely to attend health checks were men on low incomes, low socio-economic status, unemployed or less well-educated, single, individuals from other than white ethnic backgrounds, greater proportion of cardiovascular risk factors, smokers, younger people, value health less strongly, have low self-efficacy, feel in less control of their health and in those less likely to believe in the efficacy of health checks. Thus, the authors conclude that routine health check-ups are taken up inequitably, and that non attendees present greater clinical need or risk factors. This differential uptake may lead to suboptimal health gain and aggravate inequalities. The authors recommend that appropriate service redesign and interventions to encourage increased uptake among these groups is required (Dryden et al., 2012).

It was shown that older participants of community pharmacy services valued continuity of the service, the ability to build a trusting relationship and good communication. Older participants also voiced the perception of different levels of service provided by larger national chains and independent pharmacies, the latter providing more personalized service and advice. Community pharmacies need to take a more proactive role in promoting innovative services to older people, who may benefit from these services, accept and appreciate them (Wood et al., 2015).

The pharmacy where the study was conducted has long opening hours from 8:00 am to 8:00 pm through Monday to Friday and from 8:00 am to 6:00 pm on Saturday, allowing the participants to choose when to attend the CVD risk assessment. Even so, of the customers who did not accept the invitation, 20.0% (n=96) claimed "lack of time" as a nonattendance reason. Another reason for nonattendance was "Not the usual pharmacy or migrant or have no transport", which is a reality in the peripheral population of the pharmacy and in many locations in Portugal where citizens have poor access. If every pharmacy offered a cardiovascular risk assessment service, the mentioned nonattendance reason would be bypassed and the acceptability rate would increase from 56.4% to 63.9%. "Not used to participate in this type of services" was the reason pointed out by 9.6% (n=46) of the contacted customers, confirming a lack of awareness of the public towards this kind of services. Thus, public cognizance, awareness and previous use *versus* non-use of

pharmacy service, shape the attitudes towards the receptivity of the services acting as important determinants (Hindi et al., 2018). If this barrier was to be removed, the acceptability rate would increase to 68.1%. If the customers knew that community pharmacists were capable of assessing the risk of their patients and if they were aware of the benefits that must be conveyed upon evidence-based research and by accredited health care providers, as well as knowing that this service is a reliable complement to physician care, the nonattendance reason "Not used to participate in this type of services" and "Do not need follow up at the pharmacy/Followed up by the physician" would be bypassed, and the acceptability rate would increase to 75.7%. Data suggest that a pharmacist involved in the domiciliary hospitalization unit may have a positive impact on patients' health and safety (Brito et al., 2017). Thus, if community pharmacists were to be involved in domiciliary hospitalization and therefore able to evaluate the risk of their customers in the institutions, bypassing this further reason of nonattendance, the acceptability rate would increase to 90.9%. Customers who could not be reached by phone due to either not answering the phone call after 3 attempts or the phone number provided not being assigned, could have been reached by any other means. These customers had a mean age of 51.44 years (SD 18.61), younger than the mean age of the sample. Thus, alternative ways of contacting patients to provide the services should be considered.

The displayed theoretical barrier removal is a rather utopian approach, but nonetheless reveals the barriers that pharmacists, pharmacists' owners and health policymakers have to lead astray to effectively implement community pharmacy services. In terms of performance, this would also mean that the 2923 Portuguese community pharmacies would be able to assess at least 41.1% (3 437 488) of their adult population in one year. This shows the potential of community pharmacy assets for improving the public's cardiovascular health. Relying on the high participation rates, cardiovascular risk evaluation and especially risk factor screening should be carried out in Portuguese community pharmacies. The obstacles and barriers encountered provide a useful contribution to the development of larger-scale studies:

- Every hour, there is an opportunity to care for 56.4% of 17 x 2892 = 27 729 patients*.

  *56.4% rate of acceptability; 17 average customers per hour rate; 2892 Community pharmacies.
- Every working day, there is an opportunity to care for 8-hours x 27 729 = 221 832 patients.

- Every working year, there is an opportunity to care for 260-days x 221 832 = 57 676 320 patients.

The increasing involvement in public health will require changes in the behavior and understanding of the perspectives of all participants - pharmacists, physicians, public, and stakeholders - towards the role of community pharmacist and delivered services that may affect future development. Despite the change-aware environment, a lack of clarity about the existing and potential role and value of the pharmacist in this area remains. It is necessary to clearly define the role and limits of responsibility of pharmacist-led services in terms of integration into other existing professional peer structures, including traditional medical hierarchies, and clarification and safeguards of potential duplication or overlap with other health care structures and health policies (Hall et al., 2018; Nørgaard & Sporrong, 2019).

Strengths and weaknesses

This part of the cross-sectional study can be used to assess the health needs of the Portuguese population, and it disclosed findings that can be useful for planning and allocating CVD screening services in community pharmacies. It would be interesting to investigate the perceptions of primary care physicians regarding such a program. Additionally, it would be pertinent to gauge the acceptability of pharmacists in community pharmacies and to understand their willingness to provide CVD risk screening services.

Some customers claimed "lack of time" as a reason for nonattendance, and this is a type of sampling bias. Thus, it may be assumed that some members of our population were inadequately represented in the sample. In summary, if the non-attendees had been screened, the results of the study could have been different. To minimize nonresponse bias, the day before the encounter, the pharmacist made a second phone call to remind the participants.

The screening service was free of charge, positively influencing acceptability. Thus, the achievement of similar acceptability rates would depend on remuneration. The existing trusting relationship between regular customers and the pharmacist also had a positive influence on the acceptability rate, but ended up mirroring a real-life context.

The study was conducted in a single pharmacy, but would have been enriched by a multicenter study. Evaluating whether community pharmacists can include CVD screening

services along with their regular daily practices would also have been beneficial. However, the cardiovascular risk assessment strategy would be a combination of two basic services already supported by law, point-of-care testing and health screening, to be implemented as a standardized pharmacy-based CVD risk assessment service, which pharmacists have already included in their daily routine.

6. Conclusion

In this part of the study, it was revealed that pharmacist-delivered CVD risk screening in Portuguese community pharmacies is accepted by their customers. The characteristics of pharmacy customers were assessed, and high customer acceptability was found. Furthermore, the reasons for nonattendance were analyzed, and could be used in further studies.

B - Cardiovascular risk factor screening in community pharmacy of cardiovascular pharmacotherapy naïve participants.

1. Introduction

According to the WHO, CVD is the leading cause of global death. Worldwide, 56 million people died in 2017 and 17.79 million died from CVD. This means that 31.8% of the world population died from CVD, confirming that CVD remain the leading cause of the burden of mortality across the world (Ritchie & Roser, 2019). CVD is the main cause of death among the Portuguese population as well, and is also one of the most important causes of morbidity, disability and DALYs (Ferreira et al., 2016), justifying the fact of being at the top of the priorities for the national health plan. In 2014, ischemic stroke alone accounted for about 20 000 episodes and 250 000 days of hospitalization (Direção-Geral da Saúde, 2015). Despite the improvement in mortality and cardiovascular morbidity indicators in Portugal and the Mediterranean region, it is necessary to reduce premature deaths and delay the development of CVD. Promotion of lifestyle-focused health education and monitoring the evolution of risk factors and cardiovascular events are crucial interventions (Rocha & Nogueira, 2015). Assessing the global CVD risk in the individual is therefore of major importance to identify and to adequately manage patients and their modifiable risk factors, such as dyslipidemia, tobacco use, diabetes, hypertension, obesity, physical inactivity, harmful use of alcohol, and unhealthy diet. The modifiable risk factors account for approximately 90% of myocardial infarction risk in both sexes and in all age groups around the world (Yusuf et al., 2004).

The control of cardiovascular risk factors and the prevention of CVD require the involvement and coordination of all health professionals who assist patients. As a highly accessible health professional and medication expertise there is a public health need to have pharmacists take a proactive, responsible role in the patients' education in relation to preventive measures (Sabater-Hernández et al., 2011; Houle et al., 2015), and in cardiovascular health management (Horgan et al., 2010; George et al., 2011; Kaczorowski et al., 2011; Jahangard-Rafsanjani et al., 2017). Including global cardiovascular risk assessment and further interventions to the services provided in community pharmacies can improve patient outcomes (Tsuyuki et al., 2016) and the pharmacy users accept them (Al Harmarneh et al., 2018), as proven in the part A of the present study. Community pharmacies are already considered a potentially useful and easily accessed provider of health

services and Health Checks in other countries (Corlett & Krska, 2015). Even the Portuguese regulatory authorities state that the role of the pharmacist as a public health care professional has been decisive in the last two decades and that community pharmacists occupy a privileged position to contribute in areas such as therapeutic management, determination of biochemical parameters, identification of at-risk individuals, early detection of diseases and promotion of healthier lifestyles. In fact, due to the wide geographical coverage of the pharmacies in the Portuguese territory and the high technical-scientific competence of their human resources, these settings have become essential allies to guarantee the pillars advocated by the national health service: accessibility to medication and equity in the provision of quality health care to all citizens, regardless of their geographical location. In many areas of the national territory, pharmacies are the only available healthcare setting capable of health promotion and minor health disorders management by dispensing and advising on the rational use of medicines, therefore playing a key role in promoting health and a proper guidance of the citizen within the health system and favoring the best use of the scarce available resources (Ordem dos Farmacêuticos, 2018).

Early detection of at-risk patients is crucial to reduce the risk for development of chronic disease. One way of identifying individuals at risk is to invite the general population to attend intervention and screening programs (Simmons et al., 2012). Population-based prevention programs may prevent the onset and development of cardiometabolic diseases. The effectiveness of these programs depends on participation rates (Petter et al., 2015), which are satisfactory in Portuguese community pharmacy as previously shown. It is already a common practice to evaluate biochemical and biophysical parameters in Portuguese community pharmacies, but not as a structured comprehensive CVD risk assessment service. The necessary conditions are created for pharmacists to take on their responsibilities as health care professionals working in pharmacies, which are widely spread and whose network is best distributed throughout the territory, in collaboration with the professionals and institutions of the national health service.

The European scientific societies recommend that general practitioners, nurses and allied health professionals deliver CVD prevention for high-risk patients and that allied health professional-led programs should be considered to deliver CVD prevention across healthcare settings (Piepoli et al., 2016). Risk factors for cardiovascular disease have seen a large rise in prevalence recently, which has prompted interest in prevention through the identification of individuals at risk of CVD and has also seen increased investment in

screening interventions taking place in primary care. Community pharmacies have become increasingly involved in the provision of such interventions and are feasible sites for screening for those at risk of CVD. A significant number of previously unknown cases of CVD risk factors such as hypertension, hypercholesterolemia, and diabetes are identified, however a significant number of referred participants at high risk do not attend their practitioner for follow-up. Research priorities should include methods of increasing uptake to follow-up testing and early intervention, to maximize the efficacy of screening interventions based in community pharmacies (Willis et al., 2014).

2. Objectives

This part of the study aimed at evaluating the opportunity that community pharmacists have to identify and case-find at-risk pharmacy users who accepted to participate in the study. Thus, ultimately assessing the potential of a pharmacy as a healthcare setting in the struggle against CVD in Portugal.

3. Methods

Study design

This study was a single-center cross-sectional study. Ethics approval for conducting this study was received from the Ethics Committee of the Faculty of Medicine of Coimbra University in March 2017 (reference number: CE_Proc. CE-011/2017). Consent to publish was obtained from the participants as indicated in the Consent Participation Form, which was part of the ethics application forms submitted to the Coimbra University Institutional Review Board. The Technical Director of the pharmacy gave his written approval for the study to be carried out in the pharmacy in question. The customers gave their consent to register their name, date of birth, and telephone number to the pharmacist/pharmacy technician/trainee during the enrollment process, signing the digital consent form available on the informatic system Sifarma 2000 (Glintt, Lisbon, Portugal) developed by the Portuguese pharmacy association (ANF - Associação Nacional das Farmácias).

Setting

The enrollment process took place in a community pharmacy of a central Portuguese city during a normal 70-hour working week from Monday through to Saturday. Afterwards

the investigator pharmacist, who worked in the pharmacy, performed the CVD risk assessment of the participants, who accepted to take part in the study. The evaluation took place in a segregated area within the pharmacy with no interference to routine pharmacy processes.

Population

The pharmacy team members registered all the customers who entered the pharmacy during the enrollment period. The exclusion criteria were based on customers being younger than 18 years old, pregnant customers, or mentally disabled persons who were unable to consent. Then each pharmacy customer was contacted by phone, by the investigator pharmacist and invited to participate in a *Cardiovascular Risk Assessment Study* at the pharmacy by their pharmacist. To avoid any selection bias, the pharmacist that contacted each customer, used a standard invitation speech in every phone call, clarified possible doubts, scheduled an appointment for data and sample collection, and informed the customer about the requirement to maintain a 12-hour fasting and bring all their medications to the assessment. All contacts were made up of three attempts at different times/hours of different days. During the phone call, the investigator pharmacist confirmed pre-defined inclusion and exclusion criteria and scheduled the interview for data collection. To clarify the flow of participants throughout the study, a diagram is presented in Figure 25.

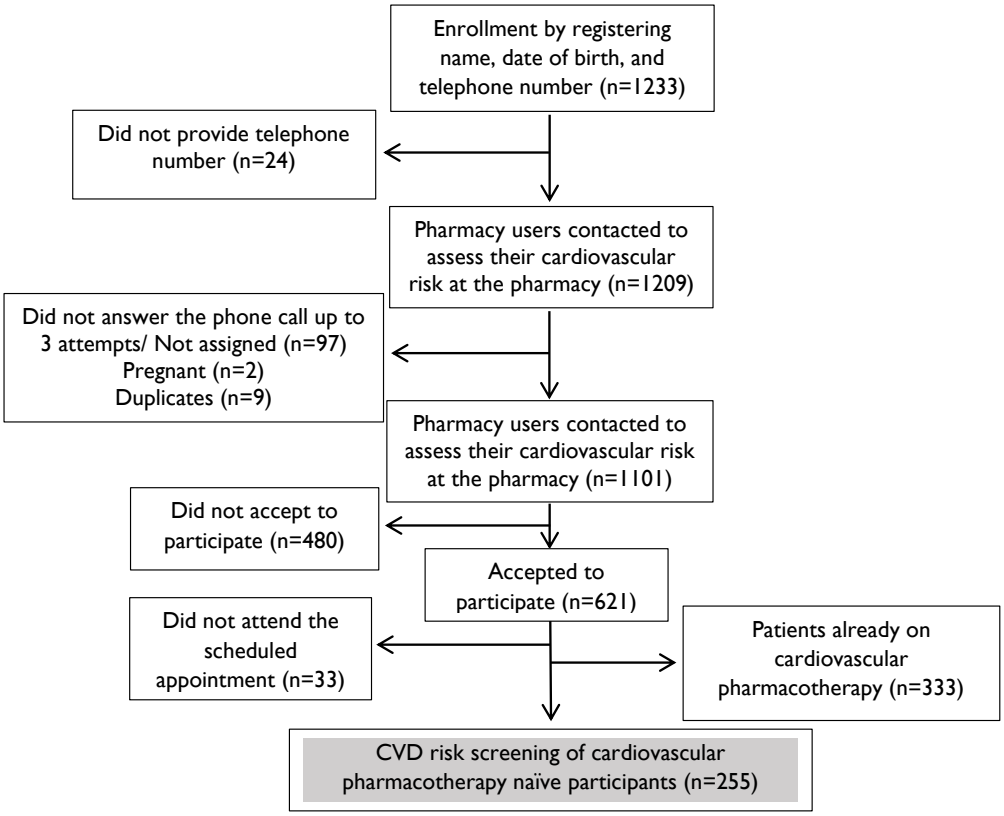

Figure 25 - Flow diagram of participants throughout the study.

Data analysis

Descriptive statistics to explore the characteristics of the studied population were used. To analyze possible associations between variables, chi-squared and Kruskal-Wallis tests for categorical variables and t-tests and ANOVA for continuous variables were used. For the data analysis, SPSS v.24 (IBM, Armonk, NY, United States) was used and a p-value lower than 0.05 to be statistically significant was considered.

Participants were considered at-risk for CVD, whenever in:

- Increased CVD risk categories or uncontrolled risk factors, risk factors clustered into metabolic syndrome.
- Risk for developing DM.

The participants who accepted to assess their CVD risk were asked to return to the pharmacy fasting and bring all the medication they were taking. The day before the appointment, the pharmacist investigator made a second phone call to remind the participants of the scheduled interview and also to recall the requirement to maintain a 12-hour fasting and bring all medications. During a seven-month period, the pharmacist investigator conducted the interviews, collected the participants' data, and performed the

CVD risk assessment for all participants who agreed to participate in the study in a dedicated counseling room, within the pharmacy, where privacy could be maintained with no interference by routine pharmacy processes. The following steps were included:

1- All participants who agreed to be interviewed gave their written, informed consent before initiating the interview. All the participants had the opportunity to clarify any doubt or ask any question they considered relevant before they began their participation. After all the clarifications had been given, every individual signed the informed consent form, thus accepting to participate in the study.
2- The following data were self-reported and ascertained via questionnaires: age, sex, level of education, professional situation, smoking status, alcohol consumption, physical activity, eating habits, medical, and family history of CVD events and deaths (first degree relatives) and personal history of associated diseases such as hypertension, hypercholesterolemia and diabetes, previous diagnosis of myocardial infarction or stroke, access and use of health services (hospitalizations, medical appointments and diagnostic exams) and current medications (including homeopathic, herbal and dietary supplements).
3- Capillary blood collection was performed, fasting, for analysis of various biochemical parameters (blood glucose level, HbA1c, total cholesterol, HDL-C, TG and calculated LDL-C); physical examination (evaluation of blood pressure, heart rate, weight, height and abdominal perimeter at waist level).
4- Once the physical examination was performed and the biological sample was collected, each participant was offered a card with the results obtained and the interventions to be taken.

The investigator pharmacist measured the fasting blood glucose level with Accu-Chek Performa device (Roche, Basel, Switzerland); HbA1c and lipids from whole blood (total cholesterol, HDL-C, TG and calculated LDL-C) with Cobas b 101 system (Roche, Basel, Switzerland), provided by Wocadi. The Accu-Chek Performa requires a 0.6 µL blood sample volume, and the Cobas b 101 requires a blood sample volume of 2 µL for HbA1c and of 19 µL for lipids.

The physical examination included the assessment of SBP and DBP and heart rate, and was performed with a Tensoval Duo Control (Hartmann, Heidenheim, Germany) according to Directorate-General of Health guidelines. The measurements were made twice, and the arithmetic mean was considered.

Height and weight measurements were performed with an electronic stadiometer (Exclusivas Iglesias, Cangas-PO, Spain) with the participants wearing light clothes and being barefoot, according to standard No. 017/2013 of the General Directorate of Health from 12/05/2013, just as the measurement of the waist circumference, which was performed with a proper anthropometric measuring tape.

Cardiovascular disease risk categories and risk factors

The CVD risk evaluation was performed using the ESC and ESH recommended scores. The following modifiable risk factors were considered: hypertension, smoking status, DM, obesity, BMI and waist circumference, dyslipidemia, physical inactivity, unhealthy diet, isolation, stress (anxiety and depression), harmful use of alcohol, and abnormal fasting glucose. The following non-modifiable risk factors were considered: family history of premature CVD, age, and sex.

The modifiable risk factors were divided and analyzed as two separate groups:

- Major modifiable risk factors - hypertension, smoking status, DM, obesity (BMI), dyslipidemia and physical inactivity.
- Obesity (waist circumference), unhealthy diet, isolation, stress (anxiety and depression), harmful use of alcohol, abnormal fasting glucose.

Waist circumference is an additional prognosis for obesity, and abnormal fasting glucose was analyzed while assessing the prevalence of the metabolic syndrome and also analyzed in the diabetes risk score questionnaire.

Smoking status

The current smoking status was self-reported by the participants and stratified into the "smoker" category considering that the participant was currently using any tobacco and nicotine product, either occasionally or regularly; categorized as "non-smoker" if the participant had not been using any tobacco and nicotine product for more than 5 years and counted as "ex-smoker" if the participants had not been using any tobacco and nicotine product for less than 5 years.

Sedentarism

As recommended by the ESC, healthy adults of all ages should perform physical activity at least for 150 minutes a week of moderate intensity or 75 minutes a week of vigorous intense aerobic physical activity or an equivalent combination. These were the considered cut-off points to classify sedentary behavior.

Diet

In the present study, an inadequate diet was evaluated as non-compliance with two recommendations - ESC and WHO - regarding the consumption of vegetables and fruit as a daily consumption of five portions. The information concerning the participants' diet was also included in the evaluation of risk of developing DM. In this context, the needed information was the frequency of vegetables and fruit intake, thus assessing if it was consumed on a daily basis or occasionally.

Blood pressure

The classification of office blood pressure and definition of hypertension grade were based on the ESC and the ESH Guidelines categories shown in Table 19 (Williams et al., 2018). These categories are also according to standard No. 020/2011 of the General Directorate of Health from 09/28/2011 updated to 03/19/2013, which defines and classifies hypertension.

Table 19 - Categories for conventionally measured seated office blood pressure[a].

Category	**Systolic (mmHg)**		**Diastolic (mmHg)**
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension [b]	≥140	and	<90

[a] Blood pressure category is defined according to seated office blood pressure and by the highest level of blood pressure, whether systolic or diastolic; [b] Isolated systolic hypertension is graded 1,2, or 3 according to systolic blood pressure values in the ranges indicated.

Obesity

The BMI was calculated and overweight classified as BMI ≥25 kg/m^2, obesity as BMI ≥30 kg/m^2. Sex-specific cut-off points for waist circumference were considered as increased risk, for >94 cm in male and >80 cm in female participants and as substantially increased risk for >102 cm in male and >88 cm in female participants, of metabolic complications. These categories are according to standard No. 017/2013 of the General Directorate of Health from 12/05/2013, which defines the evaluation of anthropometric measures in adults.

Cardiovascular risk evaluation - SCORE

To perform the cardiovascular risk evaluation, the following methods were applied:

- The SCORE model, whose charts were calibrated for individual European countries, including Portugal, as SCORE risk chart for low-risk countries, for 40 to 65-year-old participants, the relative risk chart for 18 to 39 years participants, as shown in Figure 26 (Piepoli et al., 2016) and the SCORE-OP for participants older than 65 years, as advocated by the ESC, shown in Figure 27 (Cooney et al., 2016).
- The electronic, interactive version of SCORE, known as HeartScore, available through www.heartscore.org, which was also to confront the obtained SCORE chart evaluation.

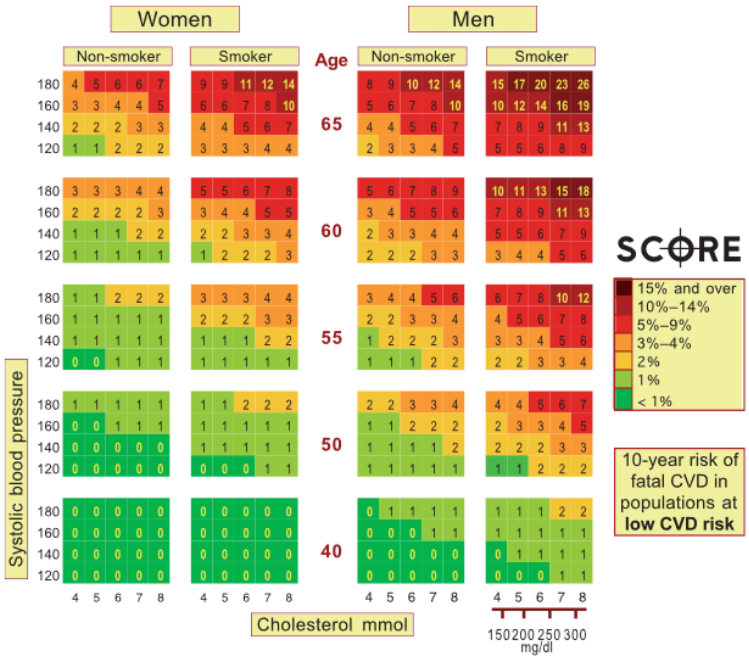

Figure 26 - SCORE - European low-risk chart: ten-year risk of fatal CVD in low-risk regions of Europe by sex, age, SBP, smoking status and total cholesterol.

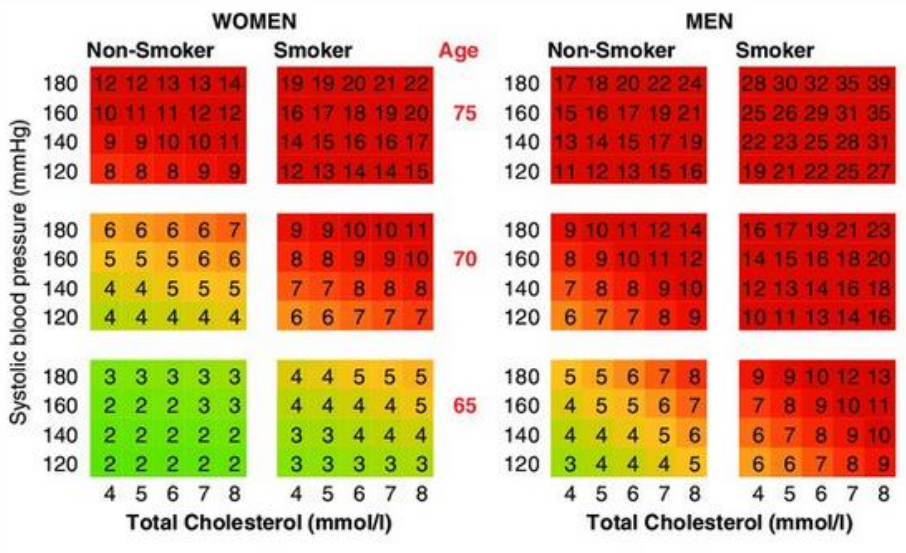

Figure 27 - SCORE-OP chart for use in low-risk regions. Numbers indicate estimated % of 10-year cardiovascular mortality risk.

The risk categories were classified according to ESC guidelines (Piepoli et al., 2016) and to 2016 ESC/ European Atherosclerosis Society Guidelines for the Management of Dyslipidaemias (Catapano et al., 2016) into the following risk categories:

- *Very high-risk of CVD*

  Participants with documented CVD - previous AMI, acute coronary syndrome, coronary revascularization and other arterial revascularization procedures, stroke and transient ischemic attack, aortic aneurysm and peripheral artery disease; DM with hypertension-mediated organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidemia; severe CKD with a glomerular filtration rate <30 mL/min/1.73 m2 or a calculated SCORE ≥10%.

- *High-risk of CVD*

  Participants with markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) or BP ≥180/110 mmHg; most other people with DM (except for young people with type 1 DM and without major risk factors that may be at low or moderate risk); moderate CKD (glomerular filtration rate 30–59 mL/min/1.73 m2) or a calculated SCORE ≥5% and <10%.

- *Moderate-risk of CVD*

  Participants with a SCORE ≥1% and <5% at 10 years.

- *Low-risk of CVD*

  Participants with a SCORE <1%.

Metabolic Syndrome is a complex disorder defined by a cluster of interconnected cardiometabolic risk factors and comorbidities that increase the risk of both ASCVD and type 2 diabetes (Zimmet et al., 2019). According to the International Diabetes Federation consensus, metabolic syndrome was considered whenever a patient showed three or more of the following measurements:

- Abdominal obesity (waist circumference >102 cm in male and >88 cm in female)
- Triglyceride ≥150 mg/dL
- HDL-C <40 mg/dL in male or <50 mg/dL in female
- SBP ≥130 mm Hg, or DBP ≥85 mm Hg or greater, or taking antihypertensive medication
- Fasting glucose ≥100 mg/dL, or taking oral antidiabetic medication

Fasting blood glucose was classified into normal blood glucose (<100 mg/dL), impaired glucose tolerance (100-125 mg/dL), and diabetes (≥126 mg/dL) and HbA1c≥6.5%.

4. **Results**

Descriptive characteristics of the participants

The descriptive characteristics and health care access of the sample of the participants are represented in Table 20. The median duration of the individual screening encounters was 18.2 (SD 6.3) minutes.

Table 20 - Descriptive characteristics and health care access of the sample of the participants (n=255).

Characteristic	**Description**	**n**	**%**	**p value***	
				Non-SCORE group (n=135)	**SCORE group (n=120)**
Sex				0.527	**0.023**
	Male	76	29.8		
	Female	179	70.2		
Age				0.244	**0.001**
	18-49 years	156	61.2		
	50-64 years	71	27.8		
	65-79 years	26	10.2		
	>80 years	2	0.8		
Regular customer	Yes	182	71.4	0.180	0.395
Level of education				0.360	0.367
	Illiterate/ 0 years	2	0.8		

	1-4 years	51	20.0		
	5-6 years	28	11.0		
	7-9 years	45	17.7		
	10-12 years	65	25.5		
	University or Master's degree	63	24.7		
	PhD	1	0.4		
Professional situation				0.894	**0.005**
	Employed	167	65.5		
	Unemployed	32	12.6		
	Retired	41	16.1		
	Student	11	4.3		
	Domestic	4	1.6		
Attributed primary care physician				0.356	0.102
	Yes	240	94.1		
	No or do not know	15	5.9		
Hospitalization last year	Yes	31	12.2	0.363	**0.026**
Resorted to the emergency services	Yes	75	29.4	0.698	0.967
Difficulty buying the medicines	Yes	28	11.0	0.768	0.125
	Mean	Median	Min./ Max.		
Medical tests in the last year	1.1	1.0	1/36	0.759	0.268
Pharmacy visits last 3 months	3.9	3.0	0/36	0.250	**0.007**
Physician visits last year	3.9	3.5	0/24	0.716	0.508

*Chi-square and Kruskal-Wallis for categorical variables and t-test and ANOVA for continuous variables.

Cardiovascular disease categories and risk factors

The modifiable CVD risk factors found in the cardiovascular pharmacotherapy naïve participants are shown in Table 21.

Table 21 - Modifiable CVD risk factors (n=255).

Variables	**Description**	**n**	**%**	**p value***	
				Non-SCORE group (n=135)	**SCORE group (n=120)**
Smoking status	Non-smoker	196	76.9		
	Ex-smoker (<5 years)	12	4.7	**0.001**	0.575
	Smoker	47	18.4		
Diet (vegetables/fruit)	Never	0	0.0		
	Sometimes	52	20.4	0.359	0.472
	Every day	203	79.6		
	≥ 5 servings/ day	66	25.9		
Sedentary behavior	No	108	42.3	**0.001**	0.398
	Yes	147	57.7		
Alcohol consumption	No	118	46.2		
	Yes	131	51.4	0.845	0.354
	>30g/day Male or 20g/day Female	6	2.4		
Anxiety/ Depression	No	119	46.7	0.095	0.264

	Moderate	115	45.1		
	Extreme	21	8.2		
Isolation	Living alone	27	10.6	0.513	0.095
Dyslipidemia	Yes		60.4		
	Total cholesterol >190 mg/dl	97	38.0		
	LDL-C (Very high-risk:>70 mg/dl; High-risk:>100 mg/dl; Low to moderate risk:>115 mg/dl)	67	26.3	**0.001**	0.384 **0.038** LDL-C
	HDL-C <40 mg/dl for M/ <46 mg/dl for F	44	17.3		
	TG >150 mg/dl)	59	23.1		
Obesity	Overweight BMI≥25 kg/m^2	137	53.7	**0.001**	0.369
	Obesity BMI≥30 kg/m^2	43	16.9		
	Waist circ.>94 cm M/>80 cm F	163	63.9		
	Waist circ.>102 cm M/>88 cm F	102	40.0		
Hypertension	Yes	106	41.6		
	High normal	49	19.2		
	Grade 1 hypertension	34	13.3		
	Grade 2 hypertension	13	5.1	**0.001**	**0.010**
	Grade 3 hypertension	1	0.4		
	Isolated systolic hypertension	9	3.5		
Fasting glucose levels	102-125 mg/dL	55	21.6	**0.029**	0.066
	≥126mg/dL	1	0.4		

*Chi-square and Kruskal-Wallis for categorical variables and t-test and ANOVA for continuous variables.

The global result of the SCORE risk evaluation is presented in the diagram in Figure 28.

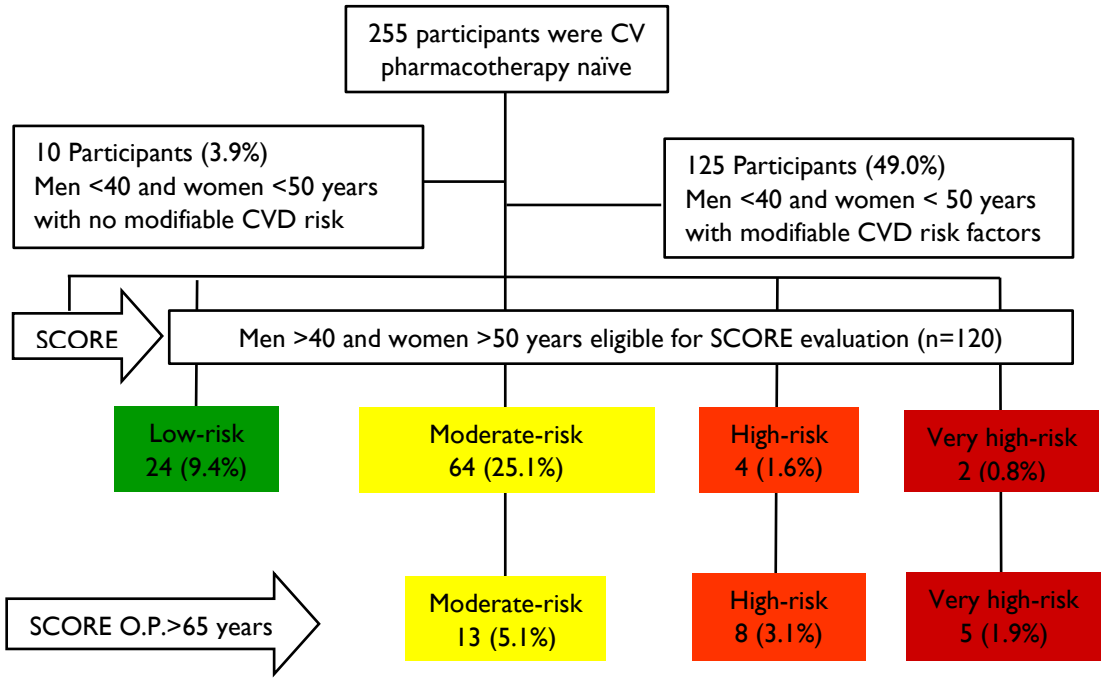

Figure 28 - SCORE risk evaluation and CVD risk factors found.

The 2016 European Guidelines on CVD prevention in clinical practice from the ESC state that systematic cardiovascular risk assessment in men <40 of age and women <50 years of age with no known cardiovascular risk factors is not recommended. It was found that 3.9% (n=10) participants met these criteria. In this case, the intervention was encouraging a healthy lifestyle. Systematic cardiovascular risk assessment is recommended in individuals at increased cardiovascular risk, i.e., with family history of premature CVD, familial hyperlipidemia, major cardiovascular risk factors, such as smoking, high blood pressure, DM or raised lipid levels, or comorbidities increasing cardiovascular risk. Within the group of men <40 of age (n=26) and women < 50 years of age (n=130), 80.1% (n=125) participants presented modifiable cardiovascular risk factors being at increased cardiovascular risk, with a mean number of 2.7 major risk factors and 7.2% (n=9) of these participants had no assigned physician. Applying the SCORE chart for populations of countries at low cardiovascular risk, as preconized for Portugal, women younger than 50 years of age always get a SCORE of zero and men may be underestimated in terms of CVD risk, achieving at most a SCORE of 2%. Therefore, in this subgroup (n=125), the Relative Risk Chart was used, as shown in Table 22 (Piepoli et al., 2016).

Table 22 - Relative Risk Chart score (n=125)

Relative Risk Chart	**women < 50 years of age**	**men <40 years of age**
SCORE = 0%	52	1
SCORE = 1%	33	11
SCORE = 2%	16	7
SCORE = 3%	3	1
SCORE = 6%	-	1
Total	105	22

Despite presenting major cardiovascular risk factors, the risk assessment tool underestimates the CVD risk, because of their age. In these cases, the individual risk factors have to be addressed, using the relative risk chart to demonstrate their risk age. One of the male participants, an immigrant from Bangladesh, reached a SCORE of 6 in the relative risk classification, being one of the participants with no assigned physician. Ten of the 125 participants included in his group met the criteria of metabolic syndrome. Thus, in this specific group, 56.5% of participants are at-risk. With the SCORE-OP chart, the lowest realizable risk SCORE is 2%, due to the high burden of age. Therefore, there is no participant with a SCORE ≤1% to be included in a low-risk category.

The participants with no attributed primary care physician were found to be at a higher risk (X2=2.4, p=0.118). Participants with <50 years of age with a family history of premature CVD should be tested for familial hypercholesterolemia and treated accordingly. In the present study 30 participants (<50 years) with positive family history of premature CVD were found and 14 (46.7%) presented dyslipidemia, and a mean number of modifiable risk factors of 3.07, and none of them were being treated for their hypercholesterolemia. There was also a positive relation between a heavier alcohol consumption and the obtained CVD risk SCORE (X^2=14.403; p=0.025). None of the 47 participants, who were smokers, were on nicotine replacement therapy, varenicline, or bupropion, either individually or in combination therapy, as recommended by the ESC Guidelines.

The presence of inclusion criteria for metabolic syndrome among the cardiovascular pharmacotherapy naïve participants was 19.6% (n=50), more prevalent among the participants at moderate cardiovascular risk (n=33) and in the older participants.

5. Discussion

A study carried out in the population of the Viseu municipality, in 1997, had the aim of assessing the prevalence of the main modifiable cardiovascular risk factors - smoking, hypercholesterolemia, and hypertension - showed that: smoking habits had a prevalence of 9.1% (15.9% in males and 5.2% in females), hypercholesterolemia had a prevalence of 34.9% (no significant differences between the sexes), and hypertension had a prevalence of 38.5%, higher in males (42.8%) than in females (35.9%). Thus, in comparison with the total sample of the present study, a higher prevalence of smoking habits (12.0%), similar prevalence of hypercholesterolemia (33.0%), and higher prevalence of hypertension (57.7%) were found (Nunes et al., 1997).

The *Amalia* study aimed to assess the self-reported prevalence and distribution, by sex, age-group and region, of the main cardiovascular risk factors for CVD in Portugal. The survey included 38893 individuals aged 40 or over. The prevalence of hypertension was found to be 23.5%, of hypercholesterolemia 19.7%, of diabetes 8.9%, of smoking 16.3%, of overweight/obesity 51.6% and of sedentarism 75.9%. The prevalence of hypertension, hypercholesterolemia, and diabetes was found to be higher in female participants and smoking had a higher prevalence in male participants. In terms of age-group, the prevalence of hypertension and diabetes increased with age, the prevalence of smoking decreased with age and the prevalence of hypercholesterolemia and overweight/obesity was higher in the

60-79 age group. The population in the Azores presented a lower prevalence of smoking, but a higher prevalence of hypertension, hypercholesterolemia, diabetes, and overweight/obesity, while the North and Algarve regions presented the lowest values of these risk factors. Another conclusion of the *Amalia* study was that these differences in prevalence of the major risk factors by sex and region should influence cardiovascular prevention strategies in Portugal (Perdigão et al., 2011).

In 2015, a study conducted by Gaio et al. characterized the cardiovascular risk of the Portuguese population between the ages of 40 and 65 using the parameters defined by SCORE and the data from the National Health Survey with Physical Examination (INSEF), a nationwide cross-sectional study with available data on sex, age, smoking, total cholesterol and SBP (n=2946). The cardiovascular risk was stratified by sex, age group, region, education, and income quintiles and presented in the four CVD risk SCORE categories. The authors concluded that 12% of the Portuguese population aged between 40 and 64 years presented a very high risk of CVD and that the very high cardiovascular risk was more prevalent in men, in the Autonomous Region of the Azores, in older individuals and belonged to the most disadvantaged socio-economic groups (Gaio et al., 2019).

In a study carried out at the Aveiro University in 2005/2006 with 378 enrolled first- to fourth-year students, the most prevalent risk factor for both sexes was sedentarism. Regarding the hypertension risk factor, there were significant sex differences within this young population of university students. Around a third belonged to the at-risk group with urgent need or intervention on healthy diet and lifestyles (Brandão et al., 2008).

The Portuguese National Institute of Health *Dr. Ricardo Jorge* released a study report on the prevalence of the main cardiovascular risk factors in the Portuguese population and on the perception of people regarding their health status and disease, treatment and control of DM, hypercholesterolemia, hypertriglyceridemia, and hypertension. This study was performed by the Research and Development Unit of the Department of Health Promotion and Prevention of Noncommunicable Diseases and the data collected between 2012 and 2014 were released in 2019. The data collection, namely questionnaires, the collection of biological samples and the physical examinations were performed by psychologists, nurses, and diagnosis technicians especially hired for this purpose. The authors found a high prevalence of several health determinants, namely: inadequate diet (71.3%); pre-obesity/obesity (62.1%); hypertension (43.1%); low level of physical activity (29.2%); smoking habits (25.4%); alcohol abuse (18.8%); hypercholesterolemia (LDL-cholesterol

≥160 mg/dL - 31.5%; LDL-cholesterol ≥130 mg/dL - 51.5%); family history of premature CVD (11.8%); DM (8.9%); hypertriglyceridemia (≥200 mg/dL - 8.6%; >150 mg/dL - 18.6%). The considered risk factors for CVD were DM, hypercholesterolemia, hypertension, pre-obesity/obesity and smoking, and 68% of the population presented two or more risk factors and 22% four or more. The authors highlighted the urgent need to define policies and develop campaigns that improve health literacy and promote the control of biological and lifestyle-related cardiovascular risk factors (Boubon et al., 2019).

The present study showed that the development of community pharmacy services to manage CVD in Portuguese pharmacies is feasible, accepted by the customers and results in an effective case-finding process of at-risk patients of CVD, clarifying that the Portuguese Health System would benefit in including their pharmacists in the struggle against CVD. The present findings, like other studies, demonstrated that a community pharmacy-based screening is feasible and accepted by the pharmacy users, improving awareness on their CVD risk status. The case-finding process also showed to be useful in detecting potentially uncontrolled and suspected new hypertensives, especially among young adults, to refer to general practitioners for confirmatory diagnosis or further evaluation (Pappaccogli et al., 2019). In the present study, participants revealed that they went 5.71 times to the pharmacy in the last 3 months. That means that in average they visit the community pharmacy 22.84 times in the year versus 4.68 visits to their physician. Thus, such frequent interactions with patients and the potential impact on CVD preventive interventions have to be seized. The crucial aspect is that pharmacists recruit and case find patients who are at-risk of CVD and can assume the role of liaison between patients and other health care providers in the healthcare system.

The PORMETS and the VALSIM were cross-sectional studies designed to estimate the prevalence of metabolic syndrome in Portugal. The reported prevalence rates of metabolic syndrome were 49.6% in the PORMETS study (Raposo et al., 2017) and 27.5% in the VALSIM study (Fiúza et al., 2008). More recently in 2021, Alves et al. released a study where the authors found a prevalence rate of metabolic syndrome of 33.4% (Alves et al., 2021). These studies showed that metabolic syndrome is highly prevalent in the Portuguese adult population. The presence of inclusion criteria for metabolic syndrome in the present study was lower (19.6%) than in the presented studies, given that the prevalence was evaluated in the group of cardiovascular pharmacotherapy naïve participants.

Knowing that CVD risk assessment is crucial to identify and to manage modifiable risk factors, that population-based prevention programs may prevent the onset and development of cardiometabolic diseases, and that the effectiveness of these programs depends on participation rates, community pharmacists should be included in primary prevention strategies to reduce the burden associated with CVD. Given that access to primary health care is a well-established social determinant of health, using community pharmacies as a platform to provide public health services does have the potential to reach those at-risk for CVD and thus impact on inequalities in health. The presented data support the possibility for health authorities to develop strategies to screen the general population for risk factors for CVD and promote appropriate lifestyle measures, and health literacy, through community pharmacists.

Strengths and weaknesses

This cross-sectional study can be used to assess the burden of CVD of the Portuguese population. However, a follow-up study to determine the health outcomes after the pharmacist's interventions on at-risk patients would have enriched the study. Future research is needed to describe clinical improvements in enrolled patients and to assess the efficacy of screening interventions. Investigating the response and collaboration of primary care physicians regarding pharmacists referring patients would also have been important.

Some data were self-reported and retrospective, with the risk of recall bias, as community pharmacists do not have access to the clinical information of the patients.

A total population sampling approach was adopted; nevertheless, health check-ups are inequitably taken up, and non-attendees may present an even greater clinical need or risk factor burden (Dryden et al., 2012). On the other hand, patients who do not visit their physician or are not included in routine health examinations might have been captured.

6. Conclusion

The present study was the first CVD risk case-finding study in a community pharmacy in Portugal with the sampling frame as the entire population of customers who entered the pharmacy in the study period. The community pharmacist was successful at identifying CVD at-risk participants, revealing that pharmacist-delivered CVD risk screening in Portuguese

community pharmacies is feasible. Cardiovascular risk factors and their clustering were common in the studied sample. Almost all the participants showed at least one risk factor, with the majority of the participants presenting two to three risk factors. This demonstrates an opportunity for an extended role of community pharmacists beyond the traditional dispensing of medicines. This feasibility study could be scaled up to a full pilot study, followed by an adequately powered RCT, to further investigate the interventions after the referral post-discharge.

C - Evaluation of the cardiovascular pharmacotherapy guideline adherence and risk factor control of patients already on cardiovascular pharmacotherapy.

1. Introduction

Cardiovascular disease remains the leading cause of death worldwide, as 17.79 million people died from CVD in 2017 (Ritchie & Roser, 2019). Assessing the global CVD risk in the individuals and controlling their CVD risk factors, such as dyslipidemia, hypertension, diabetes, tobacco use, obesity, physical inactivity, harmful alcohol use, and unhealthy diet, is important to adequately manage patients and cardiovascular events (Yusuf et al., 2004). Cardiovascular pharmacotherapy plays a major role in the management of CVD and CVD risk factors and has proven to be the most beneficial intervention (Kaski & Kjeldsen, 2019). However, although being on cardiovascular pharmacotherapy many patients do not achieve their risk factor goals, showing that CVD risk is not adequately addressed. Adherence to cardiovascular pharmacotherapy guidelines is associated with improved outcomes in primary and secondary cardiovascular prevention and reduces CVD (Blois et al., 2015; Witt et al., 2015; Agewall, 2017).

Many studies supported the involvement of pharmacists as health care providers in managing patients with hypertension, diabetes, and dyslipidemia and in optimizing CVD outcomes, by detecting uncontrolled cardiovascular risk factors, suboptimal and not guideline-adherent pharmacotherapy (Namara et al., 2019; Alshehri et al., 2020), and performing medication review to optimize drug use (Dunn et al., 2015; Jokanovic et al., 2017).

The increasing prevalence of chronic conditions in Portugal has profound consequences on the national health care service, requiring a shift in the current healthcare model. The Portuguese community pharmacist's scope of practice was expanded in 2018 by the Ministry of Health Portugal, with the first amendment to Directive 1429/2007, that defines the services provided by pharmacies, to include new services routinely provided and enforced by law: nutrition appointments; therapy adherence programs, medicine reconciliation, services utilizing multicompartment aids, and education programs on the use of medical devices; performance of rapid tests for HIV, HCV, and HBV screening (point-of-care tests), including pre-and posttest counseling and referral of positive cases to hospital care; and basic nursing services.

Pharmacies may also promote campaigns and programs for health literacy, disease prevention, and healthy lifestyle promotion. Most Portuguese pharmacies perform point-of-care tests that enable CVD risk evaluation. These services are freely priced by pharmacies and paid out-of-pocket by users, but there are no publicly available data on the number of services or pricing (Ribeiro et al., 2020). It was already demonstrated that community pharmacists play a relevant role in providing cardiovascular risk screening and detecting CVD risk factors and at-risk customers (Fonseca et al., 2021). However, there is currently limited research on the use of guideline-based cardiovascular therapy in Portugal.

2. Objectives

The objective of this study was to evaluate the opportunities pharmacists have in detecting non-adherence to cardiovascular pharmacotherapy guidelines and uncontrolled risk factors in community pharmacy patients and to demonstrate the role pharmacists can play in improving the quality of care through optimization of cardiovascular pharmacotherapy.

3. Methods

The population and setting were presented in the methods section of the previous part of the study. The diagram presented in Figure 29 shows the flow of participants throughout the study.

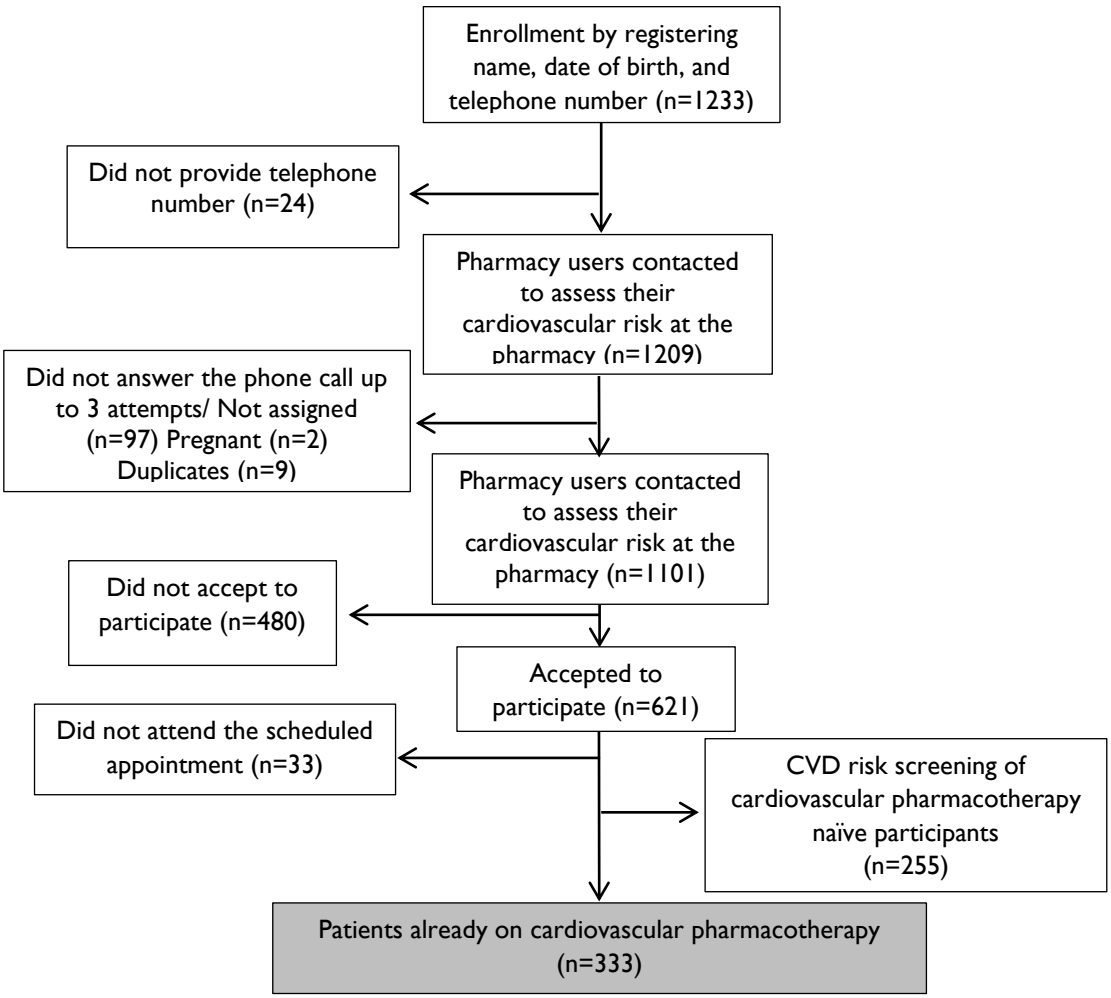

Figure 29 - Flow diagram of participants throughout the study.

Study design and data collection

A single-center, cross-sectional study was conducted to evaluate the cardiovascular pharmacotherapy guideline adherence and risk factor control. The enrollment process occurred in a community pharmacy in a central Portuguese city. All the customers who entered the pharmacy during a 70-hour working week (Monday through Saturday) were registered with name, date of birth, and telephone number. Then, the pharmacist contacted each pharmacy customer over the phone and made an invitation to participate in the study. The pharmacist performed a CVD risk assessment for the participants who agreed to participate in the study in a dedicated counseling room, where privacy could be maintained within the pharmacy with no interference by routine pharmacy processes, for seven months.

The inclusion criteria for this study were customers who were on cardiovascular pharmacotherapy. The customers who were not on cardiovascular pharmacotherapy were included in a screening program (Fonseca et al., 2021). The exclusion criteria were customers younger than 18 years, pregnant customers, or mentally disabled persons who were unable to consent. To avoid any selection bias, the pharmacist contacted each customer and used a standard invitation speech in every phone call, clarified possible doubts, scheduled an appointment for data and sample collection, and informed the customer about the requirement to maintain a 12-hour fasting and bring all medications. All participants gave their written informed consent before the interview was initiated, and they had the opportunity to raise doubts or questions before their assessment.

The sociodemographic characteristics and health data were self-reported and ascertained via questionnaires.

The pharmacist collected capillary blood for the analysis of blood glucose level, HbA1c, total cholesterol, HDL-C, and TG and calculated LDL-C for in-pharmacy point-of-care testing, obtaining the results in a 15-minute workflow. The pharmacist also performed a physical examination comprising an evaluation of the SBP and DBP, heart rate, weight, height, and abdominal perimeter at waist level. In the community pharmacy, these evaluations were performed by a licensed pharmacist. The devices and the training of the investigator pharmacist on equipment operation were provided by World Care & Diagnostics. The blood glucose levels were measured with an Accu-Chek Performa device (Roche, Basel, Switzerland); lipids were measured from whole blood with a Cobas b101 system (Roche, Basel, Switzerland). The physical examination was performed with a Tensoval Duo Control (Hartmann, Heidenheim, Germany), an electronic stadiometer (Exclusivas Iglesias, Cangas-PO, Spain), and an anthropometric measuring tape.

Based on the obtained results, the pharmacist performed the CVD risk assessment, by applying the Decree-Law SCORE model (Cooney et al., 2016; Cosentino et al., 2020; Mach et al., 2020).

Regarding smoking habits, only current smokers were considered as presenting this major modifiable CVD risk factor. Overweight patients presenting BMI ≥25 kg/m^2 and obese patients presenting a BMI ≥30 kg/m^2 were considered at-risk (Piepoli et al., 2016). The ESC recommends for healthy adults of all ages per-form at least 150 minutes a week of moderate-intensity or 75 minutes a week of vigorous-intensity aerobic physical activity

or an equivalent combination thereof (Piepoli et al., 2016). Less physical activity than recommended was considered as presenting sedentary behavior.

Fasting blood glucose was classified into normal blood glucose (<100 mg/dL), impaired glucose tolerance (100-125 mg/dL), and diabetes (≥126 mg/dL) and HbA1c ≥6.5%. The HbA1c targets were determined according to the recommendations of the 2019 ESC Guidelines on diabetes, pre-diabetes, and CVD (Cosentino et al., 2020).

The 2018 ESC/ESH Guidelines for the management of arterial hypertension, blood pressure thresholds for treatment initiation, and treatment targets in hypertensive patients were considered (Williams et al., 2018).

The dyslipidemia risk factor was considered positive when the patient presented: LDL-C >55 mg/dl for very high-risk patients, LDL-C >70 mg/dl for high-risk patients, LDL-C >100 mg/dl for moderate-risk patients, and LDL-C >116 mg/dl for low-risk patients or secondary lipid parameter non-HDL-C >85,100, and 130 mg/dl for very-high-, high-, and moderate-risk patients, respectively, a total cholesterol >190 mg/dl, or TG >150 mg/dl (Mach et al., 2020).

For the evaluation of cardiovascular pharmacotherapy guideline adherence, the pharmacist performed a type 2a medication review (Griese-Mammen et al., 2018b) and used the WHO Anatomical Therapeutic Chemical Classification System until the 4th level of the code to register the medication. The lipid-lowering therapy with statins was classified into three different dosage-intensity categories, high-, moderate-, and low-intensity statin, according to the ACC and the AHA guidelines (Stone et al., 2014a). In order to evaluate the ESC Guidelines adherence (Visseren et al., 2021), the treatment of the main cardiovascular risk factors, namely type 2 diabetes, dyslipidemia, and hypertension were focused (Williams et al., 2018; Cosentino et al., 2020; Mach et al., 2020).

For this purpose, quality indicators (QI) were established, which enabled the quantification of adherence to guideline recommendations. About guideline adherence in patients with hypertension, the recommendation of the inclusion of ACE inhibitors, or ARBs in patients who are intolerant to ACE inhibitors (QI-1) was considered; and it was considered that blood pressure control often requires multiple drug therapy with a renin-angiotensin-aldosterone system (RAAS) inhibitor, CCBs and diuretics (QI-2). Regarding guideline adherence in patients with type 2 diabetes, it was considered that metformin is recommended as first-line therapy in patients without previous ASCVD, CKD, or heart

failure and should be considered in persons with type 2 diabetes and ASCVD unless contraindications are present (QI-3); and that in patients with type 2 diabetes and ASCVD or in those who are at very high/high cardiovascular risk, the use of GLP-1RA or SGLT2 inhibitors is recommended to reduce cardiovascular and cardiorenal outcomes (QI-4). Regarding guideline adherence in patients with dyslipidemia, it was considered the recommendation that a high-intensity statin should be prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk category and if the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended (QI-5). In addition, the recommendation that all smoking of tobacco should be stopped, and that in smokers, offering follow-up support, nicotine re-placement therapy, varenicline, and bupropion individually or in combination was considered (QI-6). Moreover, and as antiplatelet drugs are the cornerstone of secondary cardiovascular prevention, it was considered that aspirin 75 to 100 mg daily is recommended for secondary prevention of CVD, or clopidogrel 75 mg daily in case of aspirin intolerance (QI-7); in patients with DM at high/very high risk, aspirin may be considered in primary prevention (QI-8); and that antiplatelet therapy is not recommended in individuals with low/moderate cardiovascular risk due to the increased risk of major bleeding (QI-9). The chosen QI were based on A level treatment evidence, except QI-3, which was based on B level evidence, and a strong recommendation class, except QI-8, where the treatment may be considered.

Data analysis

Descriptive statistics to explore the characteristics of the study population and chi-square to analyze possible associations between variables were used. For the data analysis, the SPSS v.24 (IBM, Armonk, NY, United States) was used, and a p-value lower than 0.05 as statistically significant was considered. For each QI the proportion of the patients that were treated adherent and not adherent to guideline recommendations were analyzed, and the degree of control of the risk factors in each group. To analyze possible associations between the main quality indicators of guideline adherence and CVD risk factors, chi-squared test was used.

Ethical statement

Ethics approval for conducting this study was received from the Ethics Committee of the Faculty of Medicine of Coimbra University in March 2017 (reference number: CE_Proc. CE-011/2017). Consent to publish was obtained from the patients as indicated in the Con-

sent for Participation Form, which was part of the ethics application forms submitted to the Coimbra University Institutional Review Board. The customers gave their consent to register their name, date of birth, and telephone number, to the pharmacist/pharmacy technician/trainee, at the enrollment process, signing the digital consent form available on the informatic system Sifarma 2000 (Glintt, Lisbon, Portugal) developed by the Portuguese pharmacy association (ANF - Associação Nacional das Farmácias).

4. Results

During the study period, 1261 customers entered the pharmacy. It was possible to contact 1101 and 513 did not accept to participate or did not attend the scheduled appointment, 255 did not meet the inclusion criteria, because they were not taking cardiovascular pharmacotherapy, and 333 met the inclusion criteria and were included into the study.

The descriptive characteristics of the patients and access to health care are shown in Table 23. The mean time spent with each patient in the interview was 27.1 minutes (SD= 6.40), with a minimum of 14 and a maximum of 55 minutes. The patients had a mean age of 65.00 years (SD=11.23). Of the 333 patients, 84.7% (n=282) were regular customers. The patients visited the pharmacy about four times more often than the physician.

Table 23 - Descriptive characteristics and health care access of the sample of the patients (n=333).

Characteristic	Description	n	%
Sex	Male	164	49.2
	Female	169	50.8
Age	18-49 years	27	8.1
	50-64 years	130	39.0
	65-79 years	147	44.2
	>80 years	29	8.7
Level of education	Illiterate 0 years	13	3.9
	1-4 years	191	57.4
	5-6 years	38	11.4
	7-9 years	34	10.2
	10-12 years	31	9.3
	University or Master's degree	25	7.5
	PhD	1	0.3
Professional situation	Employed	99	29.7
	Unemployed	18	5.4
	Retired	193	58.0
	Student	1	0.3
	Domestic	22	6.6
Attributed primary care physician	Yes	325	97.6
	No, or do not know	8	2.4
Hospitalization last year	Yes	54	16.2
Resorted to the emergency services	Yes	97	29.1

Difficulty buying the medicines	Yes	81	24.3
	Mean	Median	Min./Max.
Medical tests in the last year	1.5	1.0	0/12
Pharmacy visits (last 3 months)	4.8	3.0	0/36
Physician visits last year	4.9	4.0	1/31

Cardiovascular risk and risk factor assessment

It was found that 63.1% patients (n=210) were classified into a high or very-high cardiovascular risk category. According to the SCORE risk evaluation, of the 333 patients, 8.1% (n=27) were low-risk patients, 28.8% (n=96) were moderate-risk patients, 16.2% (n=54) were high-risk patients, and 46.9% (n=156) were very high-risk patients. The patients <40 years (n=6) were considered as low-risk patients, since none of them reached a relative SCORE >3. The modifiable cardiovascular risk factors of the analyzed patients are shown in Table 24.

Table 24 - Modifiable CVD risk factors of the patients.

Variables	Description	n	%
Smoking status	Non-smoker	297	89.2
	Ex-smoker (<5 years)	10	3.0
	Smoker	26	7.8
Diet (vegetables/fruit)	Never	0	0.0
	Sometimes	61	18.3
	Every day	270	81.1
	(Missing)	2	0.6
	≥5 servings/ day	89	26.7
Sedentary behavior	No	111	33.3
	Yes	221	66.4
	(Missing)	1	0.3
Alcohol consumption	No	147	44.1
	Yes	162	48.7
	>30g/day Male or 20g/day Female	23	6.9
	(Missing)	1	0.3
Anxiety/ Depression	No	124	37.2
	Moderate	166	49.9
	Extreme	40	12.0
	(Missing)	3	0.9
Isolation	Living alone	60	18.0
Dyslipidemia	Yes	235	70.6
	Total cholesterol >190 mg/dl	98	29.4
	LDL-C (>55, 70, 100, and 116 mg/dl, for very high-, high-, moderate, and low-risk)	217	65.2
	Non-HDL-C (>85,100, and 130 mg/dl, for very-high-, high-, and moderate-risk)	215	64.6
	HDL-C <40 mg/dl for M/ <46 mg/dl for F	76	22.8
	TG >150 mg/dl	118	35.4
Obesity	Overweight: BMI 25-29.9 kg/m^2	149	44.7
	Obesity: BMI ≥30 kg/m^2	103	30.9
	Waist circ.>102 cm M/>88 cm F	195	58.6
Hypertension	Yes	233	70.0

	High normal	74	31.8
	Grade 1 hypertension	50	21.5
	Grade 2 hypertension	25	10.7
	Grade 3 hypertension	8	3.4
	Isolated systolic hypertension	76	32.6
Fasting glucose levels	102-125 mg/dL	115	34.5
	≥126 mg/dL	44	13.2
HbA1c	≥6.5%	50	15.0

Regarding major modifiable risk factors, 0.9% (n=3) patients presented no risk factors, 27.6% (n=92) patients presented one or two risk factors, and 71.5% (n=238) patients presented three or more risk factors. Thus, 99.1% (n=330) had at least one modifiable CVD risk factor. Furthermore, the mean number of CVD risk factors increases as the CVD risk category increases: 2.37 (SD=1.01) in low-risk patients, 2.69 (SD=1.00) in moderate-risk patients, 3.02 (SD=1.01) in high-risk patients, and 3.31 (SD=1.01) in very high-risk patients. Apart from these CVD risk factors and after excluding the patients with diagnosed type 2 and type 1 diabetes (n=70), among the remaining 263 patients, 33.1% (n=87) patients had fasting glucose levels 102-125 mg/dL, 3.0% (n=8) patients had fasting glucose levels ≥126 mg/dL, and 3.8% (n=10) patients had HbA1c ≥6.5%. Moreover, the prevalence of the metabolic syndrome in the patients already on cardiovascular pharmacotherapy was 46.3%.

Evaluation of cardiovascular pharmacotherapy guideline adherence

The 333 patients were taking 821 prescription medications, comprising 995 drugs, considering the combinations of drugs in single-pill combination therapy, which resulted in a mean of 2.47 (SD=1.63) drugs per patient. The most prescribed medication were antihypertensives (n=399) [diuretics (n=139), ARBs (n=112), ACE inhibitors (n=78), beta-blocking agents (n=70)], statins (n=196), antithrombotic agents (n=109), and metformin (n=60). The most frequently used statin was atorvastatin 41.3% (n=81) and simvastatin 39.8% (n=78). In terms of statin intensity, 6.1% (n=12) patients were taking low-intensity statins, 91.3% (n=179) patients were taking moderate-intensity statins, and 2.6% (n=5) patients were taking high-intensity statins. Of the patients treated with antihypertensives, 19.0% (n=43) were treated with monotherapy, 75.3% (n=171) were treated with 2 or 3 antihypertensive drugs, and 5.7% (n=13) were treated with 4 or 5 antihypertensive drugs.

Of the 333 patients analyzed, 9.6% (n=32) showed high blood pressure, but were not treated for hypertension; 29.1% (n=97) showed high lipid levels, but were not treated for dyslipidemia; and 3.0% (n=10) showed high HbA1c, but were not treated for type 2

diabetes; 68.8% (n=229) were treated for hypertension, 60.7% (n=202) for dyslipidemia, and 20.1% (n=67) for type 2 diabetes; and from these 23.6% (n=54) reached blood pressure target, 38.1% (n=77) reached lipid targets, and 74.6% (n=50) reached HbA1c targets, respectively.

The results of the chosen QI for guideline adherence for the main CVD risk are shown in Table 25.

Table 25 - Analysis of the main quality indicators of guideline adherence for the CVD risk factors.

QI		Number of eligible cases	Guideline adherence		Guideline-adherent	Non-guideline-adherent	p-value*
			N	%	Controlled/non-controlled	Controlled/non-controlled	
1[a]	**Patients with hypertension on ACE inhibitors or ARBs.**	229	190	83.0	45/145	9/30	p=0.935
2[a]	**Patients with hypertension on multiple drug therapy with RAAS inhibitors, CCBs, and diuretics.**	229	54	23.6	17/37	37/138	p=0.118
3[b]	**Patients with type 2 diabetes without previous ASCVD, CKD, HF, or with ASCVD, on Metformin, unless contraindicated.**	65	57	87.7	43/14	5/3	p=0.436
4[a]	**Patients with type 2 diabetes and ASCVD or at very high/high CVD risk on a GLP-1RA or SGLT2 inhibitors.**	67	4	6.0	1/3	49/14	-
5[a]	**High-intensity statin is prescribed up to the highest tolerated dose and if the LDL-C goals are not achieved.**	202	5	2.5	3/2	74/118	p=0.578
6	**In smokers, follow-up support, NRT, varenicline, and bupropion individually/in combination should be considered.**	26	0	0	0/0	0/26	-

ACE - angiotensin-converting enzyme; ARBs - angiotensin receptor blockers; ASCVD - atherosclerotic cardiovascular disease; CCBs - calcium channel blockers; CKD - chronic kidney disease; CVD - cardiovascular disease; GLP-1RA - glucagon-like peptide-1 receptor agonist; HF - heart failure; LDL-C - low-density lipoprotein cholesterol; NRT - Nicotine replacement therapy; RAAS - renin-angiotensin-aldosterone system; SGLT2 - sodium-glucose cotransporter-2.

None of the 26 smokers had been prescribed with follow-up support, nicotine replacement therapy, varenicline, or bupropion individually or in combination (QI-6). Of the 39 patients in secondary cardiovascular prevention, 71.8% (n=28) were taking aspirin, as recommended by the guidelines (QI-7). Of the 60 patients with type 2 diabetes at high/very high risk in primary prevention, 33.3% (n=20) were taking aspirin, as recommended by the guidelines (QI-8). Of the 123 patients with low/moderate cardiovascular risk, 92.7%

(n=114) were not on antiplatelet therapy, as recommended by the guidelines, due to the increased risk of major bleeding (QI-9).

Almost 60.0% (n=120) patients treated for dyslipidemia were not reaching the LDL-C targets, but 98.3% (n=118) of these patients were on moderate and low-intensity statins or fenofibrates.

In terms of BP control, 76.4% of the treated patients were not reaching their BP targets and from these 28.7% (n=38) were treated with monotherapy. Indeed, the higher the CVD risk, the more intensive the antihypertensive therapeutic approach found, in terms of the number of antihypertensive drugs: low-risk (n=12) 1.58; moderate-risk (n=54) 1.83; high-/very-high-risk (n=161) 1.90 drugs. This approach resulted in an increased rate of control, low-risk (8.3%), moderate-risk (20.4%), and high-risk (39.5%), except for the very high-risk category where the rate of control dropped (20.3%). Within the group of patients in the high and very high CVD risk category, 16 patients were found to be on no antihypertensive treatment and with grade 1 or 2 hypertension.

It was found that 20.3% (n=54) nondiabetic patients with metabolic syndrome were treated with beta-blockers or thiazide diuretics, despite these antihypertensive drug classes may affect diabetes onset, and 68.5% (n=37) patients presented abnormal fasting glucose levels.

5. Discussion

A low adherence to cardiovascular pharmacotherapy guidelines, a lack of treatment intensification, and a poor risk factor control in Portuguese patients visiting a community pharmacy were found. In the light of the current ESC guideline recommendations, 61.9% (n=206) of treated patients were identified with cardiovascular therapy non-adherent with evidence-based guidelines, failing to reach target levels for CVD risk factors, leaving the patients at higher risk of CVD. In 333 patients, 603 opportunities were identified for intervention to increase adherence to the guidelines, manage cardiovascular therapy, improve outcomes, and reduce CVD risk. The lipid-lowering therapy was found to be the least guideline adherent, with a suboptimal use of statins. Moreover, a high prevalence of CVD risk factors was found, as 91.9% (n=306) of the analyzed patients showed at least two modifiable CVD risk factors.

Cardiovascular risk and risk factor assessment

The cardiovascular risk assessment conducted on the patients revealed a high prevalence of cardiovascular risk factors and a high cardiovascular risk status, as 91.9% presented at least two uncontrolled modifiable risk factors and most patients (63.1%) were classified into high to very-high cardiovascular risk category. The five most prevalent modifiable risk factors were overweight or obesity, dyslipidemia, hypertension, sedentary behavior, and abnormal fasting glucose levels. The data of the present study show a poor risk factor management and a high incidence of at-risk patients, who are already being followed and treated by their physician, corroborating the findings of other national studies. The results of the present study revealed that the treatment rates for hypertension (87.7%) are higher than most of the former national studies (PAP, 38.9%; PHYSA, 74.9%; INSEF, 69.4%; e_COR, 69.9%; Precise, 98.0%). However, the blood pressure control was lower with respect to former national studies, with only 23.6% of controlled patients - PAP 28.7%; PHYSA, 55.7%; INSEF, 71.3%; e_COR, 32.1%; Precise, 56.7% - (Macedo et al., 2005; Polonia et al., 2014; Rodrigues et al., 2017; Boubon et al., 2019; Marques da Silva et al., 2019).

Assessing the prevalence of cardiovascular risk factors and other comorbidities in patients with hypertension assisted in Primary Health Care was the aim of the Precise study. The authors also found a high prevalence of other cardiovascular risk factors and the persistence of uncontrolled hypertension and dyslipidemia in hypertensive patients, even when on antihypertensive treatment. These results suggest that current management of hypertension and cardiovascular prevention - gradually more complex, diagnostic, operational and therapeutic - is not adequate. In the authors' opinion, a structured interdisciplinary team to address the intended therapeutic goals is indispensable. The identification and screening of cardiovascular risk factors is therefore an imperative (Marques da Silva et al., 2019).

Moreover, the current ESC guidelines recommend more strict blood pressure and lipid targets, which render the control of hypertension and dyslipidemia an even more challenging task. Concerning LDL-C, lower treatment rates (60.7%) and lower control rates (38.1%) than in the e_COR study were found, with 71.4% patients treated and 52.1% controlled (Boubon et al., 2019).

It was found that 74.6% (n=50) patients with type 2 diabetes had HbA1c within their targets, which were individualized according to the duration of DM and comorbidities. The control rates observed in the present study were higher than those found by a Portuguese health examination survey (Barreto et al., 2018) and the e_COR study (Boubon et al.,

2019), with control rates of 63.2% and 64.0% respectively, but where HbA1c targets lower than 7.0% were generalized for all patients with type 2 diabetes, which in the present study would also result in lower control rates (67.2%). Most of the patients with type 2 diabetes failed to comply with the LDL-C (74.6%) and blood pressure (68.7%) recommended clinical targets. These findings were similar to the e_COR study (Boubon et al., 2019) where the authors found 71.9% and 59.0% patients with type 2 diabetes with uncontrolled LDL-C and high blood pressure, respectively. In the present study, 73.1% (n=49) participants with type 2 diabetes were found to have simultaneously hypertension, which confirms that hypertension and diabetes are inseparable partners in cardiovascular risk (Raposo et al., 2018). Moreover, 58.2% (n=39) type 2 diabetes patients presented simultaneously a dyslipidemia, hypertension, and obesity constellation.

As referred, the prevalence of the metabolic syndrome in the cardiovascular pharmacotherapy naïve participants was 19.6%. In the patients already on cardiovascular pharmacotherapy the prevalence of the metabolic syndrome was 46.3%. Overall, the prevalence of the metabolic syndrome in the present study was 34.7%, which is in line with other national studies, which found prevalence rates of 49.6% (Raposo et al., 2017), 27.5% (Fiúza et al., 2008), and 33.4% (Alves et al., 2021).

As in other studies, the results show a greater healthcare use in multimorbidity patients, both in primary and hospital care. The availability of scientific evidence regarding the use of health care services by patients with multimorbidity may support health policy changes, which could allow a more efficient management of these patients (Romana, Kislaya, Gonçalves, et al., 2019).

One of the major differences that the ESC guidelines (Cosentino et al., 2020), introduced to the 2016 European Guidelines on CVD prevention in clinical practice (Piepoli et al., 2016), was the cardiovascular risk categories classification in patients with diabetes, who are now considered to be at very high risk of CVD, when presenting three or more major risk factors (e.g.: age, hypertension, dyslipidemia, smoking, obesity). While with the previous guidelines 49.3% (n=33) patients in the present study would be classified as being at high risk and 50.7% (n=34) at very high risk, the new guidelines classify only 13.4% (n=9) patients with type 2 diabetes at high-risk and 86.6% (n=58) were classified as being at very high risk for CVD. These changes showed the previous underestimation of the CVD risk in patients with type 2 diabetes presenting a collection of CVD risk factors. Another

innovation of the new guidelines is the lower treatment targets for LDL-C across the cardiovascular risk categories in a stepwise approach.

The 2021 ESC Guidelines on CVD prevention in clinical practice were released in September 2021 (Visseren et al., 2021). In terms of target levels for the risk factors, the newest guidelines are in line with the previous guidelines on diabetes and pre-diabetes (2019) (Cosentino et al., 2020), on dyslipidemias (Mach et al., 2020), and on arterial hypertension (2018) (Williams et al., 2018). Another relevant difference is the new SCORE2 and SCORE2-OP charts, which predict the 10-year risk of fatal and non-fatal cardiovascular events, while the previous charts predicted the 10-year risk of fatal cardiovascular events. These new charts were calibrated to four clusters of countries (low, moderate, high, and very high CVD risk) that were grouped based on national CVD mortality rates published by the WHO. Based on these mortality rates, Portugal was considered as moderate risk region for CVD, which influenced the risk category stratification. Another difference compared to former guidelines is the stepwise approach to risk factor treatment and treatment intensification to reach risk factor goals. This approach is facilitated by the communication to patients of treatment benefits of risk factors in an understandable way, with charts showing the average lifetime benefit of smoking cessation, lipid-lowering, and BP-lowering, expressed as extra CVD-free life-years, which may improve the shared decision-making process.

Evaluation of cardiovascular pharmacotherapy guideline adherence

The analysis of the QI revealed many opportunities for improvement in the prescribed cardiovascular pharmacotherapy. The results of the adherence rate showed that the QI with the lowest degree of adherence was smoking cessation therapy (QI-6) because none of the smokers in the present study were on follow-up support, nicotine replacement therapy, varenicline, or bupropion.

Statin therapy (QI-5), SGLT2 inhibitors and GLP-1RAs (QI-4), and the multiple drug therapy in hypertension (QI-2) were the cardiovascular pharmacotherapy with the most opportunities for intervention, due to alarmingly low adherence with the level A evidence clinical recommendations. Thus, the lipid-lowering therapy was found to be the least guideline adherent, with a suboptimal use of statins in terms of intensity.

As stated by ESC guidelines, combination treatment is needed to control BP in most patients and the association of multiple pharmacological classes is frequently needed to improve BP control. Despite these ESC guideline recommendations, in the uncontrolled BP

group, a high number of patients treated with monotherapy was found. The high prevalence of vascular complications and the role of high BP is the leading global contributor to CVD (Fuchs & Whelton, 2020), which reinforces the need to improve BP management to minimize CVD risk.

Although SGLT2 inhibitors and GLP-1RAs are recommended in patients with type 2 diabetes and CVD, or at high/ very high CVD risk, to reduce cardiovascular events, in the present study only 6.0% (n=4) of eligible patients are receiving these therapies, which is coincident with other studies (Arnold et al., 2017; Vardeny & Vaduganathan, 2019).

The use of metformin in patients with type 2 diabetes without previous ASCVD, CKD, HF, or with ASCVD, unless contraindicated, showed a high adherence (87.7%) in the present study, probably because of the long experience with metformin in clinical practice. However, no statistically significant difference between the guideline-adherent and the non-adherent groups was found, in terms of risk factor control.

As in other countries (Hanbali et al., 2021), the use of guideline-based cardiovascular therapy in treated patients in Portugal is low. In this study, 603 opportunities for intervention were identified, to improve adherence to current ESC guidelines, improve therapeutic outcomes on blood pressure, lipid, and HbA1c targets, in patients with cardiovascular pharmacotherapy. In fact, in very-high cardiovascular risk patients, the probability to present not controlled risk factors was higher, confirming the importance of paying special attention to those patients, despite already being on cardiovascular pharmacotherapy.

Some limitations of this study are related to the fact that Portuguese community pharmacists do not have access to the patients' medical records. The pharmacist dependeds on point-of-care testing performed in the pharmacy and lab test results and the medication history provided by the patients during the interview. Some data used in this study were retrospective and self-reported, with the potential risk of recall bias. Moreover, the study was conducted in a single pharmacy, which may limit the generalizability.

6. Conclusions

A high cardiovascular risk factor prevalence and opportunities for intervention through medication review to optimize cardiovascular pharmacotherapy were identified, based on defined QIs and supported by evidence-based clinical recommendations. However, guideline adherence *per se* did not show improved risk factor control, proving that

cardiovascular disease management requires a multifactorial approach. This study may provide the groundwork for further, larger, multicentric studies, to prove the positive impact of pharmacist-led medication review on CVD.

D. Other outcomes of the studies

More than standing alone, the outcomes presented in this part of the study complement the former results, discussion, and conclusions. To evaluate the health status of the participants and how it correlates to the CVD risk, the EQ-5D-3L questionnaire was used. The BMQ was applied, as it has proven to be useful to measure patients' beliefs and associate them with non-adherence to treatment. Furthermore, cardiovascular pharmacotherapy in the analyzed patients is presented to characterize the sample. The type 2 diabetes risk assessment questionnaire was applied, as it is a practical tool to predict type 2 diabetes risk and to intervene among individuals at increased risk, and ultimately to prevent the onset of type 2 diabetes. The medication review process is explained in this part of the study. Finally, cardiovascular risk evaluation with the new risk prediction algorithms SCORE2 and SCORE2-OP is presented to compare the resulting data.

1. Health status - EuroQol- EQ-5D-3L

To evaluate the health status of the participants and how it correlates to the CVD risk, the EQ-5D-3L questionnaire was used (Ferreira et al., 2013). The *Anxiety* and *Depression* dimension comprised in the EQ-5D-3L questionnaire was included in the cardiovascular risk category assessment.

The EQ-5D-3L quality of life scale allows assessing the mobility, usual activities, self-care, pain/discomfort, and anxiety/depression dimensions. Each dimension has three levels - no problems, some problems, and extreme problems. The permission to use the EQ-5D-3L instrument paper version was obtained from the EuroQol Research Foundation. The valuation of the EQ-5D in Portugal was carried out by Ferreira et al., who estimated a value set for the EQ-5D for the Portuguese population (Ferreira et al., 2014). The results of the EuroQol - EQ-5D questionnaire with the five dimensions with three levels each - mobility, self-care, usual activities, pain/discomfort and anxiety and depression - are shown in Table 26.

Table 26 - Results of the EuroQol - EQ-5D questionnaire (n=588).

	Mobility		Self-care		Usual activities		Pain/ discomfort		Anxiety/ depression	
	n	%	n	%	n	%	n	%	n	%
Level 1 - No problems	441	75.0	535	91.0	459	78.1	235	40.0	243	41.3
Level 2 - Some problems	145	24.7	48	8.2	123	20.9	310	52.7	281	47.8
Level 3 - Extreme problems	0	0.0	3	0.5	4	0.7	41	7.0	61	10.4
Missing	2	0.3	2	0.3	2	0.3	2	0.3	3	0.5

No patient referred having "extreme problems" with mobility. The dimension where "extreme problems" were most reported was pain and discomfort, and anxiety and depression. As mentioned before, anxiety and depression are modifiable cardiovascular risk factors and have to be addressed, and were found to be very prevalent.

The EQ-VAS is comprised in the EuroQol- EQ-5D-3L questionnaire and reflects the respondent's self-rated general state of health. The EQ-VAS is assessed by asking the participants to mark, on a vertical scale of 0 to 100, the point that best characterizes their state of health, where 0 is labelled as "The worst imaginable health state" and 100 is labelled as "The best imaginable health state". The found global mean EQ-VAS score in the present study was 73.3%. There was no statistically significant difference between the EQ-VAS score and the CVD risk categories, as the found results for participants at low, moderate, high, and very high risk for CVD were 69.4, 77.3, 72.7, and 71.7 respectively.

2. The Beliefs about Medicines Questionnaire

The BMQ-Specific has proven to be useful to measure patients' beliefs and associating them with non-adherence to treatment in several illness groups. The BMQ was validated for use in patients and has been shown to predict adherence to treatment. People with strong beliefs in the necessity of taking medication to maintain their health were found to be more adherent to treatment, and those with higher levels of concern about medication, commonly about the dangers of dependence and long-term side effects, were more likely to be non-adherent (Horne & Weinman, 1999). The final version of the BMQ consists of two sections - the General section (BMQ-General), which assesses more general beliefs about medicines and includes the General-Harm and the General-Overuse subscales - and the Specific section (BMQ-Specific), which explores beliefs about particular medication and

comprises the Specific-Necessity and Specific-Concerns subscales (Horne et al., 1999). The BMQ-Specific questionnaire was cross-culturally adapted into Portuguese for the general population of medicine users and applied to evaluate the beliefs about medicine. The adapted Portuguese version of the BMQ questionnaire presented good internal consistency and component structure identical to the original English version (Salgado et al., 2013). The BMQ-Specific comprises two 5-item factors assessing beliefs about the necessity of prescribed medication (Specific-Necessity) and concerns about prescribed medication based on beliefs about the danger of dependence and long-term toxicity and the disruptive effects of medication (Specific-Concerns). Each item is scored on a five-point Likert scale ranging from "strongly disagree" (1 point) to "strongly agree" (5 points). A necessity concerns differential was calculated by subtracting the concerns subscale scores from the necessity subscale scores. The BMQ score is the result of the difference between the two domains (Σ Necessity - Σ Concern). Thus, higher differential scores indicated higher perceived necessity or lower concerns, thereby representing a lower likelihood of intentional non-adherence. It was proven that many patients engage in an implicit cost-benefit analysis in which beliefs about the necessity of their medication are weighed against concerns about the potential adverse effects of taking it and that these beliefs are related to medication adherence (Horne & Weinman, 1999).

The global mean BMQ-Specific score was 4.21 and increases, as the CVD risk category increases - 3.63 for participants at low risk, 3.82 for participants at moderate risk, 4.83 for participants at high risk, and 4.34 for participants at very high risk for CVD. As shown in Table 27, the results in the present study showed that the BMQ scores were higher in the controlled group for the risk factors blood pressure and LDL-cholesterol, but no statistically significant difference was found. Furthermore, the BMQ score was higher in the patients who stated having no difficulty in buying the medicines (p=0.029).

Table 27 - Results of the BMQ-Specific score.

Risk factor	Status - group	n	Mean BMQ - Specific	p
Blood pressure	Controlled	126	4.27 (SD 6.58)	0.148
	Non-controlled	207	3.99 (SD 4.88)	
LDL-cholesterol	Controlled	108	4.43 (SD 5.14)	0.918
	Non-controlled	217	3.97 (SD 5.78)	
HbA1c	Controlled	50	4.94 (SD 4.99)	0.427
	Non-controlled	17	4.97 (SD 5.77)	

LDL-C - low-density lipoprotein; HbA1c - glycated hemoglobin.

Another considered subject was the patients' reported pattern of adherence to pharmacotherapy, as shown in Table 28. While analyzing the medicines that the participants brought to the assigned interview, the pharmacist registered the pattern of adherence, by inquiring the patients and verifying the medication with the prescriptions.

Table 28 - Patients' reported pattern of adherence to pharmacotherapy (n=588).

Pharmacotherapy	**n (%)**
Take medication	418 (71.1)
Take some medication, due to partial non-adherence	52 (8.8)
Take only contraceptive	34 (5.8)
Take no medication, due to total non-adherence	12 (2.0)
Take no medication	72 (12.3)

Taking some medication, due to voluntary partial non-adherence, was observed in 8.8% (n=52) participants and taking no medicine at all due to voluntary total non-adherence was observed in 2.0% (n=12) participants. From the 52 participants that reported not taking at least one of the prescribed medicines, 15 were statins, 8 antihypertensive medication, 9 nervous system medication (anxiolytics and antidepressants), 7 for the gastrointestinal system (mostly proton pump inhibitors), 6 for asthma, 2 blood glucose lowering medication, 2 for osteoporosis, 4 antiplatelet agents, 1 for benign prostatic hyperplasia, 1 for peripheral venous disease, and 1 for thyroid disorder.

For the voluntary non-adherent participants to cardiovascular pharmacotherapy a relationship between their non adherence and the modifiable cardiovascular factors or cardiovascular risk was established. All 15 participants, who were not taking their lipid lowering therapy, had uncontrolled lipid levels; from the 8 participants who were not taking their antihypertensive medication, 5 had uncontrolled blood pressure and the 2 patients not taking their oral antidiabetic medication, both had an HbA1c >7.5%. These results show that reported low adherence patterns have a negative impact on the control of cardiovascular risk factors. Twelve patients reported that they did not take any of the prescribed medications, including 5 statins, 2 uric acid, 1 antidepressant, 1 anxiolytic, 1 benign prostatic hyperplasia, 1 hypertension, 1 osteoporosis, 1 proton pump inhibitor, 1 hormone replacement.

The participants who stated to take only some medication, due to partial non-adherence, had a BMQ-Specific of 2.77, and the participants who stated to take no medication, due to total non-adherence, had a mean BMQ-Specific of zero. When analyzing

the BMQ score (Σ Necessity - Σ Concern) and the self-reported adherence pattern "Not taking some medication" (n=52) and the adherence pattern "Taking all medication" (n=418), a BMQ score of 2.77 and 3.33 respectively was found.

3. The cardiovascular pharmacotherapy in the analyzed patients

For the calendar year 2017, in the distribution of the Portuguese national health service expenditures of medicine costs by pharmacotherapeutic group, the cardiovascular system group appears in third place, with 20.14% of the total expenditure for the center region of the country (INFARMED, 2018). Thus, the furtherance of the rational use of cardiovascular pharmacotherapy will have cost-effective outcomes, in both safety and effectiveness. In the present study, the prescribed cardiovascular pharmacotherapy is summarized in Table 29.

As shown in Table 29, the lipid modifying agents - hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitors plain or in association with other lipid modifying agents, were the most prescribed medicines.

Table 29 - Cardiovascular medicines prescribed to patients (n=333).

ATC code	INN name	n
A10A	Insulins	14
A10BA	Metformin	40
A10BB	Sulfonylureas	12
A10BD	Combinations of metformin and other oral blood glucose lowering drug	20
A10BF	Alpha glucosidase inhibitors (Acarbose)	8
A10BG	Thiazolidinediones	1
A10BH	Dipeptidyl peptidase-4 inhibitors	5
A10BJ	Glucagon-like peptide-1 receptor agonist	1
A10BK	Sodium-glucose cotransporter-2 inhibitors	3
B01AA	Vitamin K antagonists (warfarin/acenocoumarol)	9/1
B01AC	Platelet aggregation inhibitors, excluding heparin (clopidogrel/ ticlopidine/ acetylsalicylic acid/ dipyridamole/ indobufen/ triflusal)	14/2/63/2/1/6
B01AE07	Direct thrombin inhibitors (dabigatran etexilate	5
B01AF	Direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)	6
C01A	Cardiac glycosides (digitalis glycosides)	5
C01B	Antiarrhythmics, class i and iii (amiodarone/propafenone)	12
C01DA	Vasodilators used in cardiac diseases (organic nitrates)	8
C01EB17	Other cardiac preparations (ivabradine)	2
C02A	Antihypertensives antiadrenergic agents, centrally acting (clonidine)	1
C03A	Low-ceiling Diuretics thiazides	9
C03B	Low-ceiling Diuretics excluding thiazides (indapamide)	18
C03C	High-ceiling diuretics (furosemide)	26
C03DB	Diuretics potassium-sparing agents (amiloride + HCTZ)	13
C03E	Diuretics and potassium-sparing agents in combination (espironolactona+altizida)	1
C04A	Peripheral vasodilators (pentoxifylline)	4

C07A	Beta blocking agents, selective and non-selective (atenolol/carvedilol/propranolol/metoprolol)	69
C07B	Beta blocking agents and thiazides (nebivolol + HCTZ /atenolol+ chlortalidone)	5
C08C	CCBs (amlodipine/lercanidipine/nifedipine)	33
C09A	Agents acting on the renin-angiotensin system, ACE inhibitors	38
C09BA	ACE inhibitors + diuretics	17
C09BB	ACE inhibitors + CCBs	17
C09BX	ACE inhibitors, other combinations (beta blocking agents) Perindopril+Amlodipine+Indapamide	6
C09C	Angiotensin II receptor blockers, plain	30
C09DA	Angiotensin II receptor blockers (ARBs) and diuretics	53
C09DB	Angiotensin II receptor blockers (ARBs) and CCBs	28
C10AA	Lipid modifying agents, plain-HMG CoA reductase inhibitors	173
C10AB	Lipid modifying agents, plain-Fibrates	8
C10BA	Lipid modifying agents-HMG CoA reductase inhibitors + other lipid modifying agents (Pravastatin + fenofibrate/ Atorvastatin+ ezetimibe)	13

WHO Collaborating Center for Drug Statistics Methodology

ACE - angiotensin-converting enzyme; ARBs - angiotensin receptor blockers; CCBs - calcium channel blockers; HCTZ - hydrochlorothiazide; HMG CoA - hydroxymethylglutaryl-coenzyme A.

The distribution of the prescribed HMG CoA reductase inhibitors in the analyzed patients are represented in Table 30.

Table 30 - Distribution of the prescribed HMG CoA reductase inhibitors in the analyzed patients.

Dosage						
Statin	**Low-intensity**	**n**	**Moderate-intensity**	**n**	**High-intensity**	**n**
Fluvastatin	20/40 mg	0/0	40 mg bid/ XL 80 mg	0/1	NA	NA
Atorvastatin	NA	NA	10/20 mg	45/23	40/80 mg	3/0
Lovastatin	20 mg	1	40 mg	0	NA	NA
Pitavastatin	1 mg	1	2/4 mg	0	NA	NA
Pravastatin	10/20 mg	2/3	40/80 mg	6/0	NA	NA
Rosuvastatin	NA	NA	5/10 mg	4/16	20/40 mg	1/-
Simvastatin	10 mg	3	20/40 mg	65/2	NA	NA
Ezetimibe*/atorvastatin	NA	NA	10/20 mg	-/3	40/80 mg	1/-
Ezetimibe*/simvastatin	10 mg	2	20/40 mg	3/-	NA	NA
Fenofibrate	n=17					

Statin Dosing and ACC/AHA Classification of Intensity (Stone et al., 2014a)
NA - not applicable; *Ezetimibe 10 mg

In 2013, the Portuguese national health service's charges with statins were 59 million euros. In the analysis by active substance, there was a sharp drop in expenditure on

Simvastatin due to the 35% administrative reduction in the price of generic medicines. Atorvastatin, with the entry into the reference price system in April 2011, also showed a decrease in charges for the Portuguese national health service. The increased use of lipid lowering therapy in the Portuguese population, in particular statins, is an important result of the strategy to prevent CVD. This increase in use was due to a decrease in the cost of day-to-day treatment of these medicines. In fact, the marketing of generic medicines of Simvastatin and, more recently of atorvastatin, have boosted their use.

As in the present study, the recent DISGEN-LIPID study showed that lipid abnormalities were highly prevalent in statin-treated patients. In fact, these observational data show that, despite their high-risk profile, more than half of the patients under lipid-lowering therapy, both men and women did not achieve the recommended target levels for LDL-C, and a large proportion also had abnormal HDL-C and TG (da Silva et al., 2019). The DISGEN-LIPID study was conducted in 24 centers and analyzed 368 patients, and the prescribed lipid-lowering therapy is shown and compared to the results of the present study in Table 31. The results of the DISGEN-LIPID study are similar to the ones found in the present study.

Table 31 - Prescribed lipid-lowering therapy.

	Present study	**DISGEN-LIPID study** (da Silva et al., 2019)
Simvastatin	75 (36.9%)	34.5%
Atorvastatin	75 (36.9%)	19.9%
Rosuvastatin	21 (10.3%)	17.8%
Pitavastatin	1 (0.5%)	13.1%
Pravastatin	11 (5.4%)	8.0%
Fluvastatin	1 (0.5%)	1.9%
Lovastatin	1 (0.5%)	0.5%
Non-statin lipid-lowering therapy		
Ezetimibe	9 (4.4%)	8.7%
Fibrate	17 (8.4%)	11.1%

As stated by the Portuguese Directorate-General of Health, the best cost-effective moderate-intensity statin is 20 or 40 mg simvastatin and 10 or 20 mg atorvastatin. In fact, in the present study, 135 patients were treated with the most cost-effective moderate-intensity statins. However, the 33 remaining patients were treated with less cost-effective statins. As stated by the same national guidelines, the best cost-effective low-intensity statin is 10 mg simvastatin. In the present study, 3 patients were treated with the most cost-effective low-intensity statin, the other 9 patients were treated with less cost-effective low-intensity statins. From the 3 patients on simvastatin, 2 reached normal LDL-c levels, from

the other 9 patients, only 3 showed normal LDL-c levels. Moreover, 5 patients in this group, treated with low-intensity statin, were high (n=1) and very high (n=4) cardiovascular risk patients, which should have been treated with the most potent moderate intensity and high-intensity statin. The best cost-effective high-intensity statins are 40 or 80 mg atorvastatin. None of the patients were taking 80 mg atorvastatin and only 3 patients were taking 40 mg atorvastatin, one showing high LDL-C levels and the other not being at very high risk of cardiovascular disease. One patient was treated with a less cost-effective high-intensity statins, being at very high cardiovascular risk, and showing uncontrolled LDL-C levels.

4. Type 2 diabetes risk assessment

The Portuguese Ministry of Health and the Directorate General of Health, through its National Program for the Prevention and Control of Diabetes, promotes the use of the type 2 diabetes risk assessment questionnaire to screen asymptomatic individuals. The diabetes risk score is a practical tool to predict type 2 diabetes risk and to intervene among individuals at increased risk, and ultimately to prevent the onset of type 2 diabetes. The applied diabetes risk score was derived from the Finnish Diabetes Risk Score (FINDRISC) and in 2008 it was adopted by the National Program for the Prevention and Control of Diabetes to determine the 10-year risk of developing type 2 diabetes, as a strategy to identify groups at increased risk of developing diabetes, although the type 2 diabetes risk assessment questionnaire has not yet been validated for the Portuguese population. The International Diabetes Federation, the European Society for the Study of Diabetes and the ESC also recommend the use of simple, practical, non-invasive and inexpensive surveys to identify individuals at increased risk of developing diabetes, in need of closer surveillance, and to limit the proportion of the population in need of diagnostic glucose tolerance tests (Cosentino et al., 2020).

The diabetes risk score was applied to all the participants except for patients with type 1 and type 2 diabetes, which were withdrawn from this analysis (n=70), and the results were compared with the effective measured HbA1c and fasting blood glucose levels.

Table 32 - Risk score of having type 2 diabetes within 10 years (n=518).

Risk category, points	n	Mean score	Mean FBG levels	n 110-126 mg/dL	n ≥126 mg/dL	Mean HbA1c	n HbA1c ≥6.5%
Low risk, < 7	118	3.77	92.55	0	0	5.43	1
Light risk, 7-11	164	9.03	95.67	6	0	5.55	0

Moderated risk, 12-14	116	12.95	96.91	7	0	5.69	1
High risk, 15-20	100	16.99	103.33	25	5	5.86	5
Very high risk, > 20	20	22.25	120.95	16	4	6.49	6

FBG - fasting blood glucose in mg/dL; HbA1c - glycated hemoglobin.

Nine patients with fasting glucose ≥26 mg/dl, 13 patients with HbA1c ≥6.5%, and 4 patients with fasting glucose ≥126 mg/dl and with HbA1c ≥6.5% simultaneously were found. The aforementioned patients were classified as very high-risk patients. As shown in Table 32 and in Table 33, both mean fasting blood glucose levels and HbA1c increase with increased risk category, with a significant increase in the very high-risk category. In fact, the use of a simple, practical, non-invasive and inexpensive questionnaire helps to identify individuals at increased risk of developing diabetes and in need of closer surveillance. The results show that the patients classified at high and very-high risk were actually showing high fasting blood glucose and HbA1c levels. Thus, a simple, practical, non-invasive and inexpensive questionnaire to identify individuals at increased risk of developing diabetes, in need of closer surveillance, and to limit the proportion of the population in need of diagnostic glucose tolerance tests should be routinely used in community pharmacies.

Table 33 - FINDRISC - 10-year risk of developing type 2 diabetes (n=518).

Risk category, points	**n**	**Mean score**	**Mean FBG levels**	**n 110-126 mg/dL**	**n ≥126 mg/dL**	**Mean HbA1c**	**n HbA1c ≥6.5%**
Very low risk, 0-3	45	1.53	90.93	0	0	5.40	1
Low risk, 4-8	139	6.26	94.61	1	0	5.50	0
Moderate risk, 9-12	141	10.66	95.55	6	0	5.59	0
High risk, 13-20	173	15.52	100.98	31	5	5.79	6
Very high risk, ≥21	20	22.25	120.95	16	4	6.49	6

FBG - fasting blood glucose in mg/dL; HbA1c - glycated hemoglobin.

Regarding the risk of developing diabetes, it was found that 78.4% participants were at-risk patients. In fact, 10 patients were screened as non-diagnosed diabetics, as in accordance with the standard No. 002/2011 of the Directorate General Health, which states the levels for fasting glucose ≥126 mg/dl and HbA1c ≥6.5% are criteria for DM diagnosis. The same patients had all presented a "High" or a "Very high risk" score of developing diabetes, in the screening process, showing the good predictive value of the type 2 diabetes risk questionnaire. All the 10 patients visited the pharmacy only to acquire medication, all of them had gone to the physician in the last year (mean visits=4.89), all had made laboratory analysis in the past year (mean=4.33) and had a mean age of 70.88 (SD 8.7). Moreover, it

was found that 28.0% (n=145) non-diabetic participants showed abnormal fasting glucose levels (102-125 mg/dL) and 1.7% (n=9) non-diabetic participants showed abnormal fasting glucose levels (>126 mg/dL).

It was demonstrated that the Type 2 Diabetes Risk Assessment or FINDRISC questionnaire, alone or simultaneously with the determination of capillary blood glucose and HbA1c, can be an important tool in diabetes screening actions, allowing the case-finding and selection of patients at higher risk.

5. Medication review - drug related problems and interventions

The Pharmaceutical Care Network Europe (PCNE) defines Medication Review as a "structured evaluation of patients' medicines with the aim of optimizing medicines use and improving health outcomes. This entails detecting DRPs and recommending interventions" (Griese-Mammen et al., 2018b). The same definition was recognized by the WHO *Medication Without Harm Global Patient Safety Challenge Campaign*. The PCNE classifies Medication Review in three basic types (type 1, 2, and 3) and subtypes (2a and 2b), as shown in Table 34.

Table 34 - PCNE types of medication review.

Medication review		Reveals
Type 1 Simple	Based on the available medication history in the pharmacy.	Drug interactions, some side effects, unusual dosages and some adherence issues.
Type 2a Intermediate	Based on medication history and patient information. Performed when the patient can be approached for information.	Drug interactions, some side effects, unusual dosages, adherence issues, drug-food interactions, effectiveness issues, and problems with OTC.
Type 2b Intermediate	An intermediate medication review can be performed if general practitioner information is also available. Such a review is based on medication history and medical information.	Drug interactions, some side effects, unusual dosages, adherence issues, drug-food interactions, effectiveness issues, indication without a drug and drugs without indication.
Type 3 Advanced	An advanced medication review is based on medication history, patient information and clinical information.	Drug interactions, some side effects, unusual dosage adherence issues, drug-food interactions, effectiveness issues, problems with OTC, indication without a drug and drugs without indication, dosage issues.

OTC - over-the-counter

In the three types of medication review, it is implicit that the information about the medicines that a patient takes or has taken in the recent past is available to the pharmacists. In the present study, a type 2a medication review was conducted.

Due to the complexity of resolving DRPs, Strand's research group at the University of Minnesota developed the first classification system with eight categories of DRPs. In 1998, the research group in Pharmaceutical Care of the University of Granada held a meeting for professionals and groups working on the identification and resolution of DRPs, where a reduction to six categories of DRPs was agreed, on what has come to be known as the Consensus of Granada (Santos et al., 2004). In 1999, the PCNE constructed a classification scheme for DRPs, during the working conference. The classification system is validated and adapted regularly. The current version of the PCNE classification for DRP is the V 9.1 and was used in the present study. DRP is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes".

The domains of the PCNE Classification for Drug-Related Problems V9.1 used in this study are presented in Table 35.

Table 35 - PCNE Classification for Drug-Related Problems V9.1.

	Code	Primary domains	Code	
Problems	P1	Treatment effectiveness - there is a problem with the (lack of) effect of the pharmacotherapy.	P1.2	Effect of drug treatment not optimal
			P1.3	Untreated symptoms or indication
Causes	C1	Drug selection - the cause of the DRP is related to the selection of the drug.	C1.1	Inappropriate drug according to guidelines
			C1.2	No indication for drug
			C1.5	No, or incomplete drug treatment in spite of existing indication
	C3	Dose selection - the cause of the DRP can be related to the selection of the dosage schedule.	C3.1	Drug dose too low
	C7	Patient related - the cause of the DRP can be related to the patient and his behavior (intentional or non-intentional) .	C7.1	Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason
Planned intervention	I0	No intervention.		
	I2	At patient level.	I2.1	Patient (drug) counseling
			I2.2	Written information provided (only)
			I2.3	Patient referred to prescriber

DRP - drug related problem

The found primary domains of the DRPs, causes, and the provided interventions are summarized in Table 36.

Table 36 - Drug-Related Problems found in the participants (n=588).

	Code	Primary domains	Code	
Problems	P1	↑HbA1c (n=28) ↑BP (n=259) ↑LDL-C (n=284) QI- 3 Metformin (n=8) QI-6 Smoking habits (n=73) QI-7/8 ASA (n=11) QI-9 ASA without indication (n=9) QI-4 Type 2 diabetes GLP-1RA or SGLT2i recommended (n=63)	P1.2	↑HbA1c (n=16) ↑BP (n=176) ↑LDL-C (n=120) QI- 3 Metformin (n=8) QI-4 Type 2 diabetes GLP-1RA or SGLT2i recommended (n=63) QI-9 ASA without indication (n=9)
			P1.3	↑HbA1c (n=12) ↑BP (n=83) ↑LDL-C (n=164) Smoking habits (n=73) QI-7/8 ASA (n=11)
Causes	C1	The cause of the DRP is related to the selection of the drug	C1.1	QI-4 type 2 diabetes GLP-1RA or SGLT2i recommended (n=63) QI-1 high BP no ACE inhibitors or ARBs (n=35) Fenofibrate LDL-C (n=4) QI- 3 Metformin (n=8)
			C1.2	ASA without indication(n=9)
			C1.5	↑HbA1c (n=12) No drug treatment for ↑BP (n=80) Incomplete drug treatment for ↑BP (n=141) No drug treatment for ↑LDL-C (n=149) Smoking habits (n=73) QI-7/8 ASA (n=11)
	C3	The cause of the DRP can be the selection of the dosage schedule	C3.1	QI-5 high-intensity statin up to the highest tolerated dose for LDL-C goals (n=114)
	C7	The cause of the DRP can be the patient and his behavior (intentional or non-intentional)	C7.1	Patient intentionally does not take the drug for: ↑HbA1c (n=2) ↑BP (n=3) ↑LDL-C (n=17)
Planned intervention	I0	No intervention		Not applicable
	I2	At patient level	I2.1	Smoking habits (n=73) HbA1c (n=2) BP (n=3) LDL-C (n=17)
			I2.2	Written information provided (only) (n=171)
			I2.3	QI-4 Type 2 diabetes suggest GLP-1RA or SGLT2i (n=63) Refer to prescribe drug treatment for ↑BP (n=80) Add drug treatment for ↑BP (n=141) Prescribe ACE inhibitors or ARBs (n=35) Replace fenofribate with statin (n=4) Prescribe statin (n=149) Intensify lipid lowering therapy (n=114) Prescribe ASA for indication (n=11) Deprescribe ASA (n=9) Prescribe Metformin (n=8)

ASA - acetylsalicylic acid; ACE - angiotensin-converting enzyme; ARBs - angiotensin receptor blockers; BP - blood pressure; DRP - drug related problem; GLP-1RA - glucagon-like peptide-1 receptor agonist; HbA1c - glycated hemoglobin; LDL-C - low-density lipoprotein cholesterol; QI - quality indicator; SGLT2 - sodium-glucose cotransporter-2.

From the 588 patients, only 171 patients showed no DRP, and the interventions were on promoting healthy lifestyle and highlighting the presented modifiable risk factors, which only 7 patients did not show. The remaining 164 showed modifiable risk factors, such as obesity or increased waist circumference (n=90), increased fasting glucose levels (n=29), and sedentarism (n=96).

All the patients were provided with support material to facilitate behavioral changes and with written information derived from the assessments performed as part of the service. Pharmacist and patients discussed the results and agreed on goals of the assessments included by the service. The CVD risk results card was completed by the pharmacist at the appointment and given to the patients. Whenever prescribing, deprescribing or changes of medicines was required, the information was registered on the card, and then given to the patient.

Often the same patient was the subject of different interventions, while presenting several DRPs simultaneously. In fact, only 187 patients needed just one intervention, 222 patients needed two or three interventions, and eight patients needed even four interventions. A total of 712 interventions were performed on 417 patients.

As demonstrated, most interventions would require the collaboration of a prescribing physician. The interventions that did not require the collaboration of a prescribing physician were those where the pharmacist had to improve the medication adherence, for the reason that the patient intentionally did not take the medicine for type 2 diabetes (n=2), for BP (n=3), and for LDL-C (n=17), and promote smoking cessation (n=73). Although the latter intervention might need the combination of prescription only medicines further on.

6. Cardiovascular risk evaluation with the new risk prediction algorithms SCORE2 and SCORE2-OP

Evidence-based science is undoubtedly constantly evolving, and health professionals need to update their knowledge and practice in order to provide updated quality health care to patients.

As mentioned before, the ESC guidelines were updated in September 2021, with the release of the 2021 ESC Guidelines on CVD prevention in clinical practice (Visseren et al., 2021). The current guidelines recommend the use of the new SCORE2 and SCORE2-OP

risk charts to calculate CVD risk (Visseren et al., 2021). A relevant difference is that the new charts predict the 10-year risk of fatal and non-fatal cardiovascular events, whereas the previous charts predicted the 10-year risk of fatal cardiovascular events. Based on updated mortality rates, Portugal was considered a moderate risk region for CVD, with the respective chart to be used. In the new charts, non-HDL cholesterol is applied instead of total cholesterol to evaluate the CVD risk.

The sample was reassessed with the new SCORE2 and SCORE2-OP risk charts and the differences between the SCORE and SCORE2 risk category results obtained are shown in Figure 30.

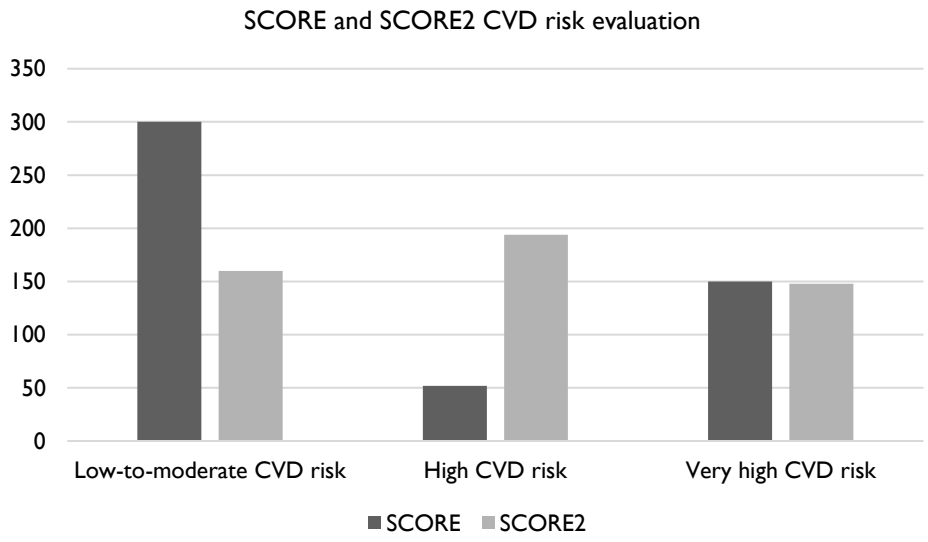

Figure 30 - SCORE and SCORE2 CVD risk evaluation.

The results for the very high CVD risk category overlap for both SCORE and SCORE2 evaluations. The main difference was found in the categories of low-to-moderate CVD risk, where most patients fit when evaluated with SCORE, moving into the high-risk category when assessed with SCORE2. These results were expected, as SCORE assesses the 10-year risk of fatal cardiovascular events, while SCORE2 assesses the 10-year risk of fatal and non-fatal cardiovascular events, hence there being a higher risk of these events.

Concluding remarks

The research reported in this thesis contributes with insights into the Portuguese community pharmacist intervention in CVD management, across its multidimensional scope.

Firstly, through the assessment of the feasibility of CVD risk screening services in community pharmacies. In this dimension, this work showed the community pharmacy users' profile of utilization, ascertaining that pharmacies are a healthcare setting with a high number of users, who visit the pharmacy approximately four times more often than their physicians. The users present a wide range of ages and reasons for visiting pharmacies. Thus, many opportunities exist for public health initiatives to be provided in community pharmacies - a setting that provides facilitated access to a trained health professional.

This work also showed that the acceptability of CVD risk factor screening by community pharmacy users is high. This result was strengthened by the fact that we adopted a total population sampling approach. Moreover, the assessed reasons for nonattendance revealed that there is room for improvement in the attendance rate, by increasing the awareness of the public towards pharmacy health services. In our study, it was found that pharmacy customers who were more likely to accept the risk evaluation were those who entered the pharmacy for the acquisition of medicines, elderly customers, and regular customers.

With the screening study, we found high-risk and very-high-risk SCORE statuses that corroborate the high mortality rates of CVD in Portugal, due to the high prevalence of risk factors. The prevalence of CVD risk factors, such as dyslipidemia, hypertension, overweight and sedentary lifestyle, was very high, and obesity, smoking, and abnormal fasting glucose levels were concerningly prevalent. Thus, community pharmacies can be a valuable venue for population screening and early detection of patients at risk of CVD, and for referring screened patients to the physician, even reaching patients who do not visit their physician or have not been included in routine health examinations.

The Kruskal-Wallis H test showed a significant difference in sex, age, and hypertension between the different CVD risk SCORE categories, as these are the major determinants of CVD risk included in the SCORE algorithm, and corroborate the assumption that the presence of an individual CVD risk factor predicts the clustering of CVD risk factors, rendering the screening process even more effective.

The realized umbrella review provided information on effective evidence-based services for CVD management to reduce the burden of CVD and highlighted community-pharmacist-based medication review as a beneficial intervention resulting in a significant reduction in cardiovascular risk factors.

In the next dimension, precisely through a type 2a medication review, we found that the cardiovascular pharmacotherapy guideline adherence in treated patients is low and we identified a lack of treatment intensification. For the evaluation of cardiovascular pharmacotherapy guideline adherence, we established quality indicators, supported by evidence-based clinical recommendations and based on A-level treatment evidence, which enabled the quantification of adherence to guideline recommendations and the degree of control of the risk factors in each group using chi-squared. The analysis of the QI identified many opportunities for intervention to increase adherence to the guidelines, manage cardiovascular therapy, improve outcomes, and reduce CVD risk. Although guideline adherence per se did not show improved risk factor control, proving that cardiovascular disease management requires a multifactorial approach, pharmacists can identify opportunities for intervention to optimize cardiovascular pharmacotherapy.

Through cardiovascular risk and risk factor assessment, this part of the work showed that risk factor control of patients already on cardiovascular pharmacotherapy is suboptimal and highly prevalent in Portuguese patients visiting the community pharmacy. In this scope, the important role that the pharmacist assumes when referring patients who do not reach their therapeutic and risk factor targets has been demonstrated.

With the remaining outcomes, we found that the type 2 diabetes risk assessment alone, or simultaneously with the determination of capillary blood glucose and HbA1c, was revealed to be an important tool in diabetes screening actions and allowed us to case-find and select patients at higher risk, who were referred to the physician. The BMQ scores were higher in the controlled group for the risk factors blood pressure and LDL-cholesterol, but revealed no statistically significant difference, yet was found to be higher in the patients who stated having no difficulty in buying the medicines. The evaluation of the sample in light of the new SCORE2 and SCORE2-OP charts shows us that many patients who were previously considered low-to-moderate risk patients are currently considered high-risk patients, demanding a stepwise intervention or treatment intensification of the CVD risk factors.

Portuguese community pharmacists do not have access to the patient's medical records. Therefore, the pharmacist depended on point-of-care testing performed in the pharmacy and the medication history provided by the patients. Access to the patient's

medical records would optimize the intervention of the pharmacist as a member of the interprofessional health care team and facilitate communication between pharmacists and physicians. Furthermore, the patient's medication adherence was not evaluated with a systematic and validated method, and the study was conducted in a single pharmacy, which limits the generalizability. Future research and follow-up studies are needed to describe clinical improvements in enrolled patients after the pharmacist's interventions, and evaluate the perceptions of primary care physicians regarding such a program and the response and collaboration regarding pharmacists referring patients.

There is no doubt that CVD is the leading cause of death worldwide. Likewise, in Portugal CVD has been the leading cause of death. The decline over the last three decades was due to risk factor control. Thus, assessing the global CVD risk in individuals and controlling their CVD risk factors, such as dyslipidemia, hypertension, diabetes, tobacco use, obesity, physical inactivity, harmful alcohol use, and unhealthy diet, is important to adequately manage patients and cardiovascular events. Cardiovascular pharmacotherapy plays a major role in the management of CVD and CVD risk factors and has proven to be the most beneficial intervention. However, although being on cardiovascular pharmacotherapy, many patients do not achieve their risk factor goals, showing that CVD risk is not adequately addressed. Adherence to cardiovascular pharmacotherapy guidelines is associated with improved outcomes.

This thesis contributes to the affirmation of the role of community pharmacists in the management of CVD, which can be extended to other chronic diseases. The increasing prevalence of chronic conditions in Portugal has profound consequences on the national healthcare service, requiring a shift in the current healthcare model. The Portuguese community pharmacist's scope of practice has to expand to include needed services, as pharmacists are clearly underutilized in the Portuguese health service. We have demonstrated that community pharmacists play a relevant role in providing cardiovascular risk screening and detecting CVD risk factors and at-risk customers, as well as in detecting non-adherence to cardiovascular pharmacotherapy guidelines and uncontrolled risk factors in patients already on cardiovascular pharmacotherapy. Pharmacists are able to improve the quality of care through the optimization of cardiovascular pharmacotherapy.

Effective CVD management requires a systematic, multifactorial, and multidisciplinary approach in the community. The presented results support the greater involvement of community pharmacists in the management of CVD, showing that community pharmacies are health settings of interest to cardiovascular health improvement planners. Pharmacists

can be included to maximize cardiovascular health coverage, due to having the required qualifications as well as pharmacies having an optimal wide geographical coverage.

In this scope, the disclosed findings of this work may contribute as an incentive to broaden the scope of professional practice of Portuguese community pharmacists and can be applied to plan and allocate CVD services in community pharmacies. This study may also provide the groundwork for further, larger, multicentric studies to corroborate the positive impact of pharmacist-led medication review on CVD.

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