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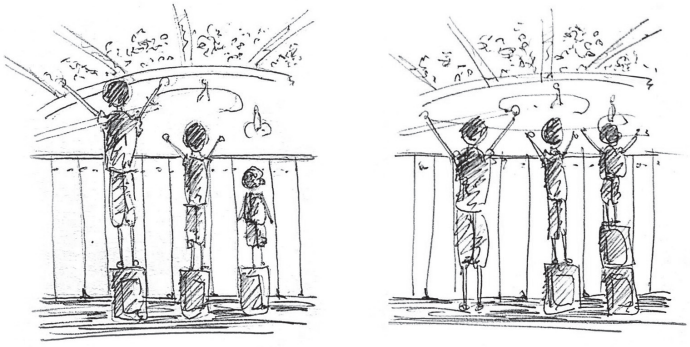
INEQUALITIES IN CORONARY HEART DISEASE MANAGEMENT AND OUTCOMES IN PORTUGAL



CARLA ALEXANDRA RODRIGUES ARAÚJO

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This thesis was developed at the *Unidade de Investigação em Epidemiologia - Instituto de Saúde Pública da Universidade do Porto* (EPIUnit), and at the *Departamento de Ciências da Saúde Pública e Forenses e Educação Médica*, *Faculdade de Medicina da Universidade do Porto*, under the supervision of Professor Ana Azevedo (University of Porto Medical School; Institute of Public Health, University of Porto).

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Araújo C, Laszczyńska O, Viana M, Dias P, Maciel MJ, Moreira I, Azevedo A. Quality of care and outcomes of women and men with acute myocardial infarction. [under review].

Araújo C, Laszczyńska O, Viana M, Melão F, Henriques A, Borges A, Severo M, Maciel MJ, Moreira I, Azevedo A. Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study. *BMJ Open* 2018; 8:e018798.

Araújo C, Laszczyńska O, Viana M, Dias P, Maciel MJ, Moreira I, Azevedo A. Missed opportunities in symptomatic patients before a first acute coronary syndrome: EPIHeart cohort study. *Cardiology* 2017; 139:71-82.

I have collaborated in the field work, data collection, training of medical record abstractors, classification and coding; in the definition of the study hypotheses of all papers, in the statistical analyses of the data; and I was responsible for the writing of the first draft of all papers and for preparing the final versions.

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ABBREVIATIONS AND ACRONYMS

ACC: American College of Cardiology

ACCA: Acute Cardiovascular Care Association

ACS: acute coronary syndrome

ACUITY: Acute Catheterization and Urgent Intervention Triage strategy

AHA: American Heart Association

AMI: acute myocardial infarction

APC: annual percent change

CABG: coronary artery bypass graft surgery

CHD: coronary heart disease

CI: confidence interval

CICD: Chronic Ischaemic Cardiovascular Disease

CPU: Chest Pain Unit

CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines

CTA: coronary computerized tomography angiography

CVD: cardiovascular disease

DALYs: disability-adjusted life years

ECG: electrocardiogram

ESC: European Society of Cardiology

EURHOBOP: EURopean Hospital Benchmarking by Outcomes in acute coronary syndrome Processes

EUROASPIRE: European Action on Secondary and Primary Prevention by Intervention to Reduce Events

EuroHeart: European Heart Health Strategy

GRACE: Global Registry of Acute Coronary Events

HDL: high density lipoprotein cholesterol

ICD: International Classification of Diseases

ICTUS: Invasive versus Conservative Treatment in Unstable coronary Syndromes

INEM: National Institute for Medical Emergencies

INOCA: Ischemia and No Obstructive Coronary Artery Disease

LBBB: left bundle branch block

LDL: low density lipoprotein cholesterol

MINAP: Myocardial Ischaemia National Audit Project

MINOCA: myocardial infarction with non-obstructed coronary arteries

NHS: National Health System

NICE: National Institute of Health and Care Excellence

NSTEACS: non-ST elevation acute coronary syndrome

NSTEMI: non-ST elevation acute myocardial infarction

NUTS: Nomenclature of Territorial Units for Statistics

OR: odds ratio

PCI: percutaneous coronary intervention

PROMIS: Patient Reported Outcomes Measurement Information System

QI: quality indicator

SCORE: Systemic COronary Risk Evaluation

SEP: socioeconomic position

STEMI: ST elevation myocardial infarction

TIMACS: Timing of Intervention in Acute Coronary Syndromes

YLL: years of life lost

ABSTRACT

The management and outcomes of patients with coronary heart disease (CHD) have improved considerably in Portugal in the last three decades. However, important challenges and opportunities remain to achieve the optimal delivery and assessment of care, particularly to vulnerable groups; namely women, patients with a lower socioeconomic position, and patients from the interior and rural regions. The lack of availability of disaggregated data, and complexity of their interpretation due to the interplay of multiple patient and/or health system level factors determining different CHD results, makes the task of assessing inequalities in CHD management and outcomes in Portugal a stimulating and useful challenge.

The specific objectives of this work were: 1) to describe time trends in death rates, absolute number of deaths and years of life lost from CHD among men and women in Portugal, by region, during the period 1981–2012; 2) to analyse sex differences in conservative versus invasive management of patients with acute coronary syndrome (ACS) in 10 hospitals with different characteristics; 3) to assess differences by sex in management and outcomes (30-day mortality) of patients with acute myocardial infarction (AMI), by the application of standard quality indicators (QIs); 4) to analyse sex differences in presenting symptoms of ACS; 5) to assess the proportion of patients with a first episode of ACS who reported chest pain, medical care seeking and performance of exams because of the pain; and to identify determinants of seeking medical advice and referral to electrocardiogram (ECG).

Different sources of data were used. We performed a secondary analysis of data of population at risk and number of deaths from CHD between 1981 and 2012, disaggregated by sex, age and region, which was provided by Statistics Portugal. To analyse the regional variation in CHD mortality trends, we used joinpoint regression analysis to calculate the annual percent change in age-standardised mortality rates, and the Global Burden of Disease method to obtain years of life lost (YLL) due to premature mortality for CHD.

The remaining data were provided by two cohort studies of patients consecutively discharged with a type 1 ACS: the EURHOBOP study, retrospective and multinational, performed in seven countries, and within Portugal, in 10 hospitals covering different regions, from North to South, and including both coastal and interior regions; and the EPIHeart study, prospective and performed in two northern Portuguese hospitals, one in the coast and one in the interior.

Within the EURHOBOP study, which included patients admitted between 2008 and 2010, we analysed, by review of medical records, performance of coronary angiography, reperfusion and revascularisation by sex in 2941 Portuguese patients with an ACS.

The EPIHeart study comprised 939 patients and was assembled between August 2013 and December 2014. Detailed information was collected through questionnaires and review of medical records. Within the

EPIHeart study, twenty QIs for the key aspects of the AMI care pathway were calculated for 771 patients; clinical presentation by sex was evaluated in 873 patients through a face-to-face interview; and reported chest pain within the preceding six months of the event and health system resources seeking behaviour and utilisation were analysed in 690 patients with a first episode of ACS.

In Portugal, between 1981 and 2012, relative declines of CHD mortality indicators were different by geographic region. Consistent decreases in mortality rates were only observed in the Centre, Lisbon and North, smaller declines were observed in Alentejo, and later declines, after 2003, in Algarve and Madeira. Across the country, the YLL from CHD decreased from 1981 to 2012 (mainly after 2000), with the lowest decreases in Alentejo and the highest in Madeira. Lisbon and the North were the two geographic regions with the lowest YLL. In most regions, greater declines in mortality rates were observed among women compared to men.

We found that women diagnosed with ST elevation myocardial infarction (STEMI) or ACS with left bundle branch block, but not with non-ST elevation acute coronary syndrome (NSTEACS), had a lower probability when compared with men to be submitted to coronary angiography (adjusted odds ratio [OR] 1.64, 95% confidence interval [95% CI] 1.11–2.44). There was no difference in the performance of reperfusion and revascularisation by sex among those managed invasively, for the whole spectrum of ACS presentation.

The application of QIs showed that specific evidence-based management strategies for AMI patients need increased implementation in clinical practice, namely the assessment of ischemic and bleeding risk using GRACE and CRUSADE prognostic tools, and the use of fondaparinux in eligible patients. Through the use of time dependent QIs, we found that fewer eligible women with AMI received timely reperfusion than men, corroborating previous findings. We also found differences in long term secondary prevention; fewer women with AMI were discharged on dual antiplatelet therapy, on high intensity statins and were referred to cardiac rehabilitation than men. Women received recommended interventions at a whole (59.6% vs 65.2%, $p<0.001$) less often compared with men, and also had a higher mean GRACE 2.0 risk score adjusted 30-day mortality (3.0% vs 1.7%, $p<0.001$), which was inversely associated with the composite QI (OR 0.08, 95% CI 0.01-0.64) for the highest performance tertile compared with the lowest).

A distinct clinical presentation between women and men suffering an ACS may contribute to differences in management and outcomes. Chest pain was reported by 82% of patients, with no differences in frequency or location between sexes. Women were more likely to feel pain with an intensity higher than 8/10, and this association was stronger for patients under 65 years old (interaction $p=0.028$), and referred pain particularly to typical and atypical locations simultaneously. The multiple symptoms cluster, which was characterized by a high probability of presenting with all symptoms, was almost four-fold more prevalent in women (OR 3.92, 95% CI 2.21–6.98) than in men, and was associated with a higher 30-day mortality rate adjusted for the GRACE 2.0 risk score (4.9% vs 0.9% for the two other clusters, $p<0.001$).

Chest pain in the six months preceding the index ACS was reported by 61% of patients, 43% sought the health care system, mainly the public sector, less than half of them had an ECG performed, and in nearly 40% the pain was attributed to a problem of the heart. Patients with hypertension were more likely (OR 2.13, 95% CI 1.29-3.51) to seek the health care system because of preceding chest pain, while former smokers (OR 0.52, 95% CI 0.28-0.99) and patients from the upper middle/upper social class (OR 0.16, 95% CI 0.05-0.48) were less likely to do so. Electrocardiogram was performed more frequently by men (OR 2.56, 95% CI 1.11-5.87), patients with a health subsystem (OR 3.88, 95% CI 1.11-13.53) and patients from the northeastern region (OR 9.07, 95% CI 4.07-20.24); and less frequently by patients with cognitive impairment (OR 0.37, 95% CI 0.15-0.92) and those who were employed (OR 0.36, 95% CI 0.14-0.97).

In conclusion, inequalities in CHD in Portugal are present at different levels, in acute and long term management and in outcomes; according to region, sex/gender and socioeconomic position. Opportunities and insights for intervention to improve diagnosis, management and outcomes throughout the CHD continuum in different vulnerable groups were identified. Policies, programmes and practices will only successfully reach the most vulnerable, if data are available to identify, not only where the inequalities are, but importantly what are their underlying mechanisms. Additionally, there is a complex interplay between patient and health system characteristics, present throughout the whole CHD pathway of care, from perception of need to benefiting from care.

RESUMO

Nas últimas três décadas houve uma melhoria significativa na abordagem e resultados da doença coronária em Portugal. Continuam, no entanto, a existir desafios e oportunidades para melhorar a qualidade do tratamento e da monitorização, particularmente de grupos vulneráveis como as mulheres, doentes de grupos socioeconómicos desfavorecidos e de regiões rurais ou do interior. A avaliação das desigualdades na abordagem e resultados da doença coronária em Portugal é um desafio estimulante e útil, em virtude de limitações relacionadas com a disponibilidade de dados desagregados e da complexidade de interpretação dos resultados, que são consequência da interação de múltiplos fatores ao nível do doente e/ou do sistema.

Os objetivos específicos deste trabalho foram: 1) descrever a evolução da taxa de mortalidade, número de óbitos e anos de vida perdidos por doença coronária em homens e mulheres em Portugal, por região, para o período compreendido entre 1981 e 2012; 2) analisar as diferenças por sexo na abordagem conservadora *versus* invasiva de doentes com síndrome coronária aguda (SCA) em 10 hospitais com distintas características; 3) avaliar as diferenças por sexo na abordagem e resultados (mortalidade aos 30 dias) de doentes com enfarte agudo do miocárdio (EAM), através da aplicação de indicadores de qualidade predefinidos; 4) analisar as diferenças por sexo na apresentação clínica da SCA; 5) avaliar a proporção de doentes com o primeiro episódio de SCA com dor torácica prévia ao evento, procura de cuidados médicos e realização de exames devido à dor; e identificar determinantes de procura de aconselhamento médico e de pedido de eletrocardiograma (ECG).

Foram usadas diferentes fontes de dados. Foi realizada uma análise secundária de dados da população em risco e número de óbitos por doença coronária entre 1981 e 2012, desagregados por sexo, idade e região, disponibilizados pelo Instituto Nacional de Estatística. Para analisar a variação regional na evolução da mortalidade por doença coronária, usámos análise de regressão *joinpoint* para calcular a variação percentual anual da taxa de mortalidade padronizada para a idade. O número de anos de vida perdidos por mortalidade precoce devido a doença coronária foi calculado através do método do estudo *Global Burden of Disease*.

Os restantes dados foram obtidos através de dois estudos de coorte que incluíram doentes consecutivos com o diagnóstico de alta de SCA tipo 1: o estudo EURHOBOP, retrospetivo e multinacional, realizado em sete países, e em Portugal em 10 hospitais em diferentes regiões, de Norte a Sul e incluindo regiões do litoral e do interior; e o estudo EPIHeart, prospetivo e realizado em 2 hospitais do norte de Portugal, um no litoral e um no interior.

Com dados do estudo EURHOBOP, que incluiu doentes internados entre 2008 e 2010, analisámos a realização de angiografia coronária, reperfusão e revascularização por sexo em 2941 doentes Portugueses com SCA, informação obtida através da revisão dos registos médicos.

O estudo EPIHeart incluiu 939 doentes entre agosto de 2013 e dezembro de 2014. Através de questionários e revisão de registos médicos foi recolhida informação detalhada. Com dados do estudo EPIHeart, foram calculados 20 indicadores de qualidade relativos aos principais componentes da abordagem do EAM para 771 doentes; a apresentação clínica por sexo foi avaliada em 873 doentes através de uma entrevista; a presença de dor torácica nos seis meses anteriores ao evento e o comportamento relacionado com a procura e utilização de recursos do sistema de saúde foram avaliados em 690 doentes com um primeiro episódio de SCA, através da aplicação de outro questionário.

Em Portugal, entre 1981 e 2012, a redução relativa dos indicadores de mortalidade por doença coronária foi diferente por região. As regiões do Centro, Lisboa e Norte foram as únicas com diminuição consistente das taxas de mortalidade; o Alentejo apresentou menores reduções das taxas e no Algarve e na Madeira, o declínio foi mais tardio, após 2003. Em todo o país, os anos de vida perdidos por doença coronária diminuíram entre 1981 e 2012 (sobretudo após 2000), o Alentejo teve as menores reduções e a Madeira as maiores. Os anos de vida perdidos foram menores nas regiões de Lisboa e do Norte. Na maioria das regiões, as mulheres apresentaram reduções maiores na mortalidade por doença coronária do que os homens.

A probabilidade de realizar angiografia coronária foi menor nas mulheres com EAM com supradesnivelamento de ST ou com SCA com bloqueio completo de ramo esquerdo, mas não nas com SCA sem supradesnivelamento de ST, em comparação com os homens (odds ratio [OR] ajustado 1,64 intervalo de confiança a 95% [IC 95%] 1,11-2,44). No subgrupo de doentes abordados de forma invasiva, não foi observada diferença na proporção de reperfusão e revascularização entre homens e mulheres, independentemente do tipo de SCA.

A aplicação dos indicadores de qualidade mostrou que há necessidade de promover a implementação na prática clínica de estratégias específicas de abordagem de doentes com EAM, nomeadamente a avaliação da estratificação do risco isquémico e hemorrágico usando as ferramentas prognósticas GRACE e CRUSADE e a utilização do fondaparinux nos doentes elegíveis. Através da utilização de indicadores de qualidade dependentes do tempo observámos que a reperfusão atempada nas mulheres com EAM elegíveis foi menos frequente do que nos homens, corroborando os resultados prévios. Também foram observadas diferenças na prevenção secundária de longo prazo; a proporção de mulheres com EAM que tiveram alta com dupla antiagregação e com estatinas de alta intensidade, e que foram referenciadas para reabilitação cardíaca foi menor em relação à observada para os homens. As mulheres receberam menos intervenções no global do que os homens (59,6% vs 65,2%, p<0,001) e apresentaram também uma maior mortalidade aos 30 dias ajustada para o score GRACE 2,0 (3,0% vs 1,7%, p<0,001), negativamente associada ao indicador de qualidade composto (OR 0,08 IC 95% 0,01-0,64 para o tercil de *performance* mais elevado comparado com o mais baixo).

Uma apresentação clínica distinta entre mulheres e homens com SCA pode contribuir para diferenças na abordagem e nos resultados. Do total de doentes, 82% referiu dor torácica, não se observaram diferenças na frequência ou localização da dor entre mulheres e homens. As mulheres apresentaram dor com intensidade superior a 8/10, esta associação foi mais forte em doentes com menos de 65 anos de idade (p de interação=0,028), e dor referida, particularmente para localizações típicas e atípicas simultaneamente, mais frequentemente do que os homens. O cluster de múltiplos sintomas, caracterizado por elevada probabilidade de apresentar todos os sintomas, foi quase 4 vezes mais prevalente em mulheres do que em homens (OR 3,92 IC 95% 2,21-6,98) e associou-se a uma maior mortalidade aos 30 dias ajustada para o score de risco GRACE 2,0 (4,9% vs 0,9% para os dois restantes clusters, p<0,001).

Do total de doentes, 61% declararam ter tido dor torácica nos seis meses anteriores ao SCA índice, 43% procuraram o sistema de saúde, principalmente o setor público, menos de metade destes realizaram ECG e em aproximadamente 40% a dor foi atribuída a um problema do coração. Os doentes hipertensos apresentaram maior probabilidade (OR 2,13 IC 95% 1,29-3,51) e os ex-fumadores (OR 0,52 IC 95% 0,28-0,99) e doentes de classes sociais média alta/alta (OR 0,16 IC 95% 0,05-0,48) menor de procurar o sistema de saúde devido à dor torácica prévia ao SCA. O ECG foi realizado mais frequentemente em homens (OR 2,56 IC 95% 1,11-5,87), em doentes com um subsistema de saúde (OR 3,88 IC 95% 1,11-13,53) e da região nordeste (OR 9,07 IC 95% 4,07-20,24); e menos frequentemente em doentes com deterioração cognitiva (OR 0,37 IC 95% 0,15-0,92) e com emprego (OR 0,36 IC 95% 0,14-0,97).

Concluindo, existem desigualdades na doença coronária em Portugal a diferentes níveis, na abordagem aguda e de longo prazo e nos resultados; por região, sexo/género e grupo socioeconómico. Foram identificadas oportunidades e dados para delinear estratégias para intervir no sentido de melhorar o diagnóstico, abordagem e resultados ao longo do *continuum* da doença coronária em diferentes grupos vulneráveis. Para que os grupos mais vulneráveis beneficiem de políticas, programas e práticas é fundamental existirem dados que permitam perceber onde estão as desigualdades e quais os mecanismos que lhe estão subjacentes. Há uma interface complexa entre as características do doente e do sistema de saúde, presente ao longo de todo o processo de abordagem da doença coronária, desde a perceção da necessidade até ao benefício do tratamento.

1. INTRODUCTION

1.1 Coronary heart disease

1.1.1 Cardiovascular risk factors

Epidemiological research on coronary heart disease (CHD) began with aetiological observational studies in the late 1940s; by the end of the 1960s, the concept of cardiovascular risk factors and the power of observational studies were well established [1,2]. Several modifiable variables associated with an increased risk of cardiovascular disease (CVD) were identified: elevated arterial blood pressure, elevated blood cholesterol, tobacco smoking, a sedentary lifestyle and diabetes [1,3-7]. The multifactorial origin of the disease tailored preventive research; the effect of multifactorial intervention strategies was studied at the population level and in high-risk people [8-10]. Controlled trials at the community level [11,12] and demonstration projects [13-15] were also important to understand that differences in incidence of CHD between intervention and control groups were the result of the extent of differences achieved in cardiovascular risk profile [16].

INTERHEART [17], a large international case-control study evaluated the association between various risk factors and acute myocardial infarction (AMI), by geographic region, ethnic origin, sex and age. Consistently in women and men, across all geographic regions and ethnic groups of the world, nine easily measured risk factors (smoking, raised Apolipoprotein B/Apolipoprotein A1 ratio, history of hypertension, diabetes, abdominal obesity, psychosocial factors, lack of daily consumption of fruits and vegetables, regular alcohol consumption, and a lack of regular physical activity) accounted for more than 90% of the risk of an AMI (population attributable risks: 90% in men and 94% in women).

Genetic factors contribute importantly to the risk of CHD, mostly in younger individuals [18], and in the past decade, there has been major progress in this area [19]. Results from the Framingham Offspring Study strengthened the role of heritability in the risk of CHD, by finding an age-specific incidence of CHD increase of more than two-fold after adjustment for conventional CHD risk factors in participants with a family history of premature disease [20]. The tools applied in genetic epidemiology, namely genome-wide association studies complemented by bioinformatic approaches have identified associations between several human traits and diseases; for CHD, 62 loci have been identified thus far, explaining 15% of the disease's heritability [19,21,22]. Several CHD loci show substantial pleiotropy, more than one-third of the CHD loci showed an association with traditional cardiovascular risk factors and almost one-half of the CHD loci showed a strong or suggestive association with other diseases or traits [22]. The genetic basis of CHD derives from the cumulative effect of multiple common and small effect size risk alleles rather

than from rare variants with large effects on CHD risk [19]. More research is needed to understand the mechanisms by which these loci affect CHD risk.

Primary prevention management is based on the assessment of total cardiovascular risk. Proposed risk charts to evaluate total cardiovascular risk, for example the Systemic COronary Risk Evaluation (SCORE) [23], take conventional major cardiovascular risk factors into account. Other risk factors may be relevant for assessing total cardiovascular risk, mainly when the individual's risk is close to a decisional threshold. Family history of premature CVD, socioeconomic position (SEP), social isolation or lack of social support, body mass index, or central obesity are among the modifiers considered to have reclassification potential [23]. Although genetic risk scores can improve CHD risk prediction beyond traditional risk factors, they are still not used in clinical practice [24-26].

The understanding of CHD causality is further complicated by the vast network of connections between characteristics of individuals, their lifestyles, and extrinsic social, economic and political context, which we will attempt to disentangle in this thesis.

1.1.2 Atherosclerosis

Coronary atherosclerosis is a complex, long lasting and continuously evolving inflammatory disease characterized by remodelling of the coronary arteries. In the 1980s, several insights of the pathogenesis of atherosclerosis were available [27]. During this time, the major components of atherosclerotic plaque considered were deposited lipids derived largely from the lower-density lipoproteins of the blood, and modified arterial smooth muscle cells with their synthesized connective tissue products. Endothelial dysfunction has been described, as was the role of other cells in addition to platelets to the progression of atherosclerotic plaque, including activated monocytes and monocyte-derived macrophages, injured endothelial cells and smooth muscle cells [27].

In the 1990s, the hypothesis that atherosclerosis lesions result from an excessive fibroproliferative response to various forms of insult to the endothelium and smooth muscle of the artery wall was advocated and evidence supported the idea that atherosclerosis could be reversed [28]. The endothelial cell, at this time, was considered a barrier gatekeeper and its important role in the vascular homeostasis had not yet been described. The following two decades were profitable to the study of mechanisms involved in the initiation and progression of atherosclerotic plaques. Evidence derived from cell biology and physiology, followed by biochemistry, pharmacology and bioengineering changed the understanding of the vital role of the vascular endothelium, and endothelial dysfunction is nowadays considered a pathogenic *sine qua non* for atherosclerotic CVD [29]. Endothelial dysfunction involves

impaired vasodilator capacity, mediated by nitric oxide [30] but also disturbances in antithrombotic, profibrinolytic, anti-inflammatory and antioxidant properties of the normal endothelium [31].

Life history of an atherosclerotic lesion

The earliest changes that are detectable in an atherosclerotic lesion are focal permeation, trapping and physicochemical modification of circulating lipoprotein particles in the subendothelial space [32]. This is the onset of the pathogenic sequence that originates foam cells (the hallmark of early fatty streak lesions), which involves the selective recruitment of circulating monocytes from the blood into the intima, its differentiation into macrophages and the internalization of modified lipoproteins [32,33]. Activated endothelium and macrophages elaborate multiple chemokines and growth factors that activate smooth muscle cells, promoting their proliferation and synthesis of extracellular matrix components within the intimal layer, creating a fibromuscular plaque. Progressive structural remodelling originates lesions with a fibrous cap, overlying a lipid-rich necrotic core. The edges of these complex plaques contain inflammatory cells, that intervene in the modulation of the endothelial pro-inflammatory phenotype, promoting the structural instability of the plaque [34]. These unstable or vulnerable plaques may trigger an acute clinical event, caused by atherothrombotic occlusion because of rupture, with luminal release of the highly thrombogenic contents of the necrotic core. Superficial intimal erosions without plaque rupture, a consequence of endothelial cell apoptosis and consequent localized endothelial denudation with thrombus formation [35], can also trigger an acute clinical event, namely an acute coronary syndrome (ACS) [36]. Characteristics of plaques prone to these superficial erosions have already been described. They contain abundant smooth muscle cells and proteoglycans, and few macrophages, and they are associated with regions of disturbed blood flow [35]. On the other hand, stable lesions have a thick fibrous cap, less lipid and inflammatory cell content, and typically do not precipitate atherothrombotic events, but can cause ischemic symptoms by reduction of the vessel lumen.

There are still several unknowns related to plaque progression and triggering of acute events. Findings from clinical, imaging and pathological studies have challenged commonly held notions of the pathophysiological features of atherosclerosis [36]. Evidence suggests the possibility of plaque rupture without forming an occlusive thrombus and provoking little consequences, and of mild erosions leading to occlusive thrombus [37]. Additionally, multiple atherosclerotic plaques, at different stages of pathobiologic evolution, can coexist in an individual [37].

1.1.3 Clinical presentation

In Europe, CVD is responsible for more than four million deaths each year, accounting for 45% of all deaths (49% and 40% of all deaths in women and men, respectively) [38]. CHD and cerebrovascular disease are the most common causes of CVD deaths. The proportional decreases in age-standardised death rates over 10 years (to the latest year available), varied between European countries, ranging in men from 25.2% in Austria to 49.7% in Luxembourg, and in women from 25.3% in Italy to 42.9% in Portugal [38]. This is the result of effective primary and secondary prevention measures implemented mainly in the management of AMI and stroke [39]. Consequently, the initial presentations of CVD in contemporary practice have changed in comparison with the latter part of the last century, and the majority are heart failure, angina, transient ischemic attack and peripheral artery disease [39].

In particular, CHD presentation is a continuum, characterized by transition from unstable to stable syndromes or vice-versa, without a clear boundary [40]. Even reversible myocardial demand/supply mismatch episodes, related to transient ischaemia or hypoxia that causes minute troponine release below the threshold for AMI, have prognostic implications [41,42]. Stable CHD is characterized by episodes of reversible myocardial demand/supply mismatch, related to ischaemia or hypoxia and commonly associated with transient chest pain (*angina pectoris*). Stable CHD is usually caused by exercise, emotion or other stress, but may also occur spontaneously. Stable CHD also includes the stabilized and often asymptomatic phases after an ACS [40]. A careful medical history remains the cornerstone of the diagnosis of stable CHD. Prediction tools have been developed to assist in the diagnosis of chest pain. In primary care, a validated prediction rule [43], containing five determinants [age/sex (male≥55 years, female≥65 years); known vascular disease; patient assumes pain is of cardiac origin; pain is worse during exercise and pain is not reproducible by palpation: one point for each determinant], has been proposed to be a useful tool for general practitioners to rule out CHD in patients presenting with chest pain [40]. More research is needed to validate its use in clinical practice.

Unstable angina is defined as myocardial ischaemia at rest or minimal exertion in the absence of cardiomyocyte necrosis. The application of the universal definition of myocardial infarction together with the use of contemporary troponin assays, reduced the proportion of patients with unstable angina to the benefit of patients with non-ST elevation AMI (NSTEMI) (4% absolute and 20% relative increase) [44,45]. Furthermore, the relative incidences of NSTEMI and ST elevation myocardial infarction (STEMI) are increasing and decreasing, respectively [46].

Patients with symptoms suggestive of ischemia and a left bundle branch block (LBBB) present an important diagnostic and therapeutic challenge. The three electrocardiographic criteria proposed by Sgarbossa and colleagues [47] are the most validated tool to assess the diagnosis of STEMI in

patients with LBBB. These criteria have high specificity but low sensitivity, compromising its utility in clinical practice [48]. Prompt and accurate identification of STEMI in the presence of LBBB remains difficult [49] and is of paramount importance because very proximal coronary occlusion is required to involve the septal perforating arteries that supply the proximal left bundle branch [50]. The key is to rapidly distinguish patients with LBBB without STEMI from those with STEMI, to avoid inappropriate management by emergent coronary angiography or fibrinolysis for the former group, and guarantee adequate and timely reperfusion therapy for the latter group [49]. To reduce false catheterization laboratory activation and inappropriate fibrinolytic therapy, and to avoid denying reperfusion therapy to patients who benefit, a group proposed a diagnosis and triage algorithm incorporating the Sgarbossa criteria to quickly and accurately identify, among patients presenting with chest pain and new or presumably new LBBB, those with acute coronary artery occlusion [49]. Further studies are needed to validate this approach.

With contemporary ACS assessment strategies, including the widespread use of coronary angiography in management of patients with ACS, a novel syndrome arose, termed myocardial infarction with non-obstructed coronary arteries (MINOCA), defined as obstructions below 50% on angiography [51,52]. MINOCA can account for about 10% of all AMI cases, according to data from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE) registry [53]. There are different aetiological entities leading to MINOCA [54], which can present as both myocardial infarction type 1 and type 2, according to the universal definition of myocardial infarction [55].

Increasingly recognized are also patients presenting with the syndrome of symptoms and signs suggesting ischemic heart disease, not AMI, but found to have no obstructed coronary arteries (less than 50% diameter stenosis) [56,57]. Ischemia and No Obstructive Coronary Artery Disease (INOCA) was the term proposed to describe these patients' presentation [58].

Considering these recent proposed syndromes, figure 1 depicts the biological and clinical progression features of CHD, adapted from the scheme proposed by Labarthe DR [59].

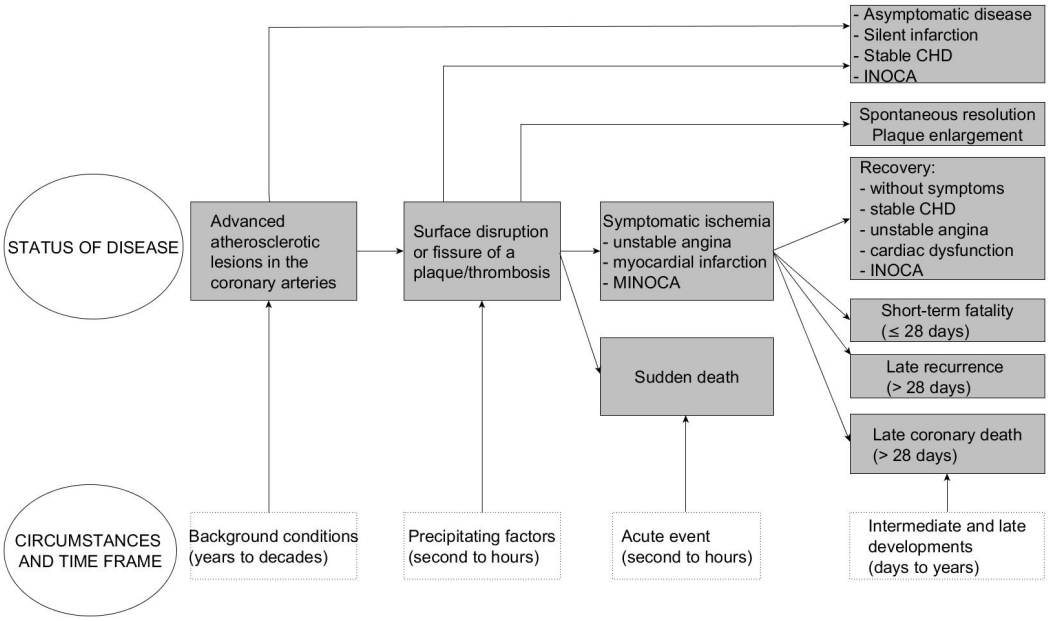

Figure 1. Biological and clinical progression features of CHD (adapted from Labarthe DR) [59].

1.1.4 Diagnostic approaches

Location and/or extent of atherosclerotic lesions and ischemia are amenable to investigation through several invasive and non-invasive methods, anatomical and/or functional. Indications for diagnosis strategy, particularly for suspected CHD will mainly depend on the evaluation of risk and clinical presentation.

The diagnosis and risk stratification of patients with ACS, both with non-ST elevation ACS (NSTEACS) or STEMI, is objectively proposed by cardiology societies and is relatively consensual, depending on risk predictors, presenting symptoms, electrocardiogram (ECG) and biomarkers measurement [45,46]. Yet, for the chronic stable phase of CHD, recommendations for diagnostic test indication and exam selection are not so consensual if we compare current practice guidelines on the management of stable CHD [40,60,61]. For stable CHD, the European Society of Cardiology (ESC) guidelines propose a Bayesian approach to the selection and interpretation of non-invasive cardiac tests. This approach uses clinicians' pre-test probability of disease along with results of diagnostic tests to generate individualized post-test disease probabilities for a given patient [40]. The pre-test probabilities of stable CHD proposed by these guidelines are based on the Diamond-Forrester score, and depend on the prevalence of the disease in the population studied, as well as on clinical features (including the presence of cardiovascular risk factors) of an individual, by age and gender; and on the nature of symptoms [62]. For patients with low pre-test

probability of stable CHD (<15%), no further investigation is needed to exclude the diagnosis; for those with an intermediate pre-test probability of disease (15-85%), non-invasive testing should be performed to establish the diagnosis. The diagnosis of CHD is established for patients with a high pre-test probability of disease (>85%), who should proceed directly to risk stratification [40].

Several anatomical or functional non-invasive tests for diagnosing (and stratifying) CHD are widely available, including exercise stress test, stress echocardiography, nuclear stress testing, coronary computerized tomography angiography (CTA), and stress cardiac magnetic resonance, each with varying accuracy, cost and availability [63]. Multi-detector CTA has good diagnostic accuracy in the detection of significant coronary artery stenosis in patients with low to intermediate risk, who present with acute chest pain [64]. On the other hand, CTA is sensitive to heart rate, body weight and the presence of calcification. A strategy of initial CTA, as compared with functional testing, did not improve clinical outcomes of patients with suspected CHD over a median follow-up of 2 years [56]. The best diagnostic approaches by non-invasive test for stable CHD remain largely a work in progress; however, globally, their performance for likelihood of diagnosis of CHD is good, and only rarely is a coronary angiography necessary for the sole purpose of diagnosing suspected CHD in stable patients [40].

1.1.5 Management (primary and secondary prevention)

A central principle in CHD management is that the first lifetime diagnosis signals the failure of primary prevention and the need to initiate secondary prevention of recurrent or related CHD events. Prevention strategies for CHD in the current generation of adults are in fact, at least in part, a postponement of events. Premature deaths and disability adjusted life years (DALYs) can be prevented and are accompanied by an increase in the prevalence of CHD in the elderly and in the very old, and in other manifestations of end-stage CVD, such as heart failure, chronic kidney disease, atrial fibrillation and vascular dementia. The prevention of the development of total cardiovascular risk may only be achieved by primordial prevention from childhood onwards [2].

Guidelines from recognized organisations, namely from the ESC [65], the American Heart Association (AHA) [66], the American College of Cardiology (ACC) [67], the National Institute of Health and Care Excellence (NICE) [68], among others, summarize evidence and expert opinion, and provide graded recommendations for evaluation and management of CHD patients.

In Europe, significant efforts have been made to develop and disseminate guidelines for the management of CHD, both for primary and secondary prevention settings (Figure 2).

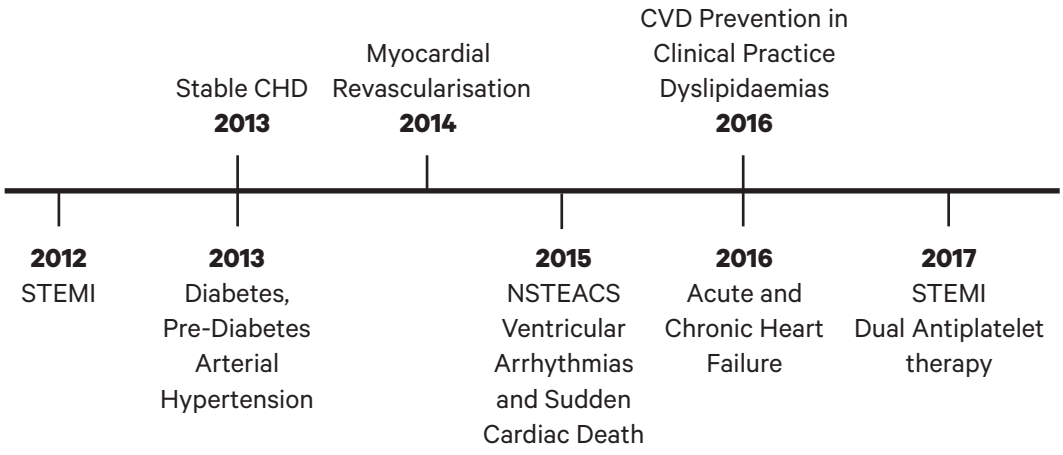

Figure 2. The most recent ESC Guidelines for management of patients with CHD (primary and secondary prevention settings).

a) Primary prevention

CHD prevention is defined as a coordinated set of actions, at the population or at individual level, aimed at eliminating or minimizing the impact of CHD and its related disabilities [69].

CVD primary prevention, through implementation of lifestyle changes or use of medication, is cost effective [23].

The SCORE system estimates the 10 year risk of a first fatal atherosclerotic event and because it is based on a large pooled dataset of 12 European prospective studies, it captures the heterogeneity across Europe in terms of baseline CVD risk [70]. The calculation of total cardiovascular risk, through the SCORE chart, should be systematic for individuals at increased cardiovascular risk, namely those with risk factors or comorbidities that increase CVD risk; and may be considered in men above 40 years of age and in women above 50 years of age or post-menopausal with no known cardiovascular risk factors [23]. Risk categories obtained through the application of risk scores assist physicians in decisions with individual people. However, and applying Rose's theory of distribution of risk in a population [71], although individuals at the highest levels of risk gain most from risk factor interventions, most deaths and morbidity in a population come from those at lower levels of risk, simply because they are more numerous compared to high-risk individuals. Management strategies of high-risk subgroups should be complemented by actions targeting low-risk populations, namely public health measures to encourage a healthy lifestyle and to reduce population levels of cardiovascular risk factors [71].

Current risk factor goals and target levels for important cardiovascular risk factors according to ESC guidelines are presented in table 1.

Risk factors	Goals and targets
Smoking	No exposure to tobacco in any form.
Diet	Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.
Physical activity	At least 150 minutes a week of moderate aerobic physical activity (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic physical activity (15 minutes for 5 days/week) or a combination thereof.
Body weight	Body mass index 20–25 kg/m^2. Waist circumference <94 cm (men) or <80 cm (women).
Blood pressure	<140/90 mmHg if <60 years old. Systolic blood pressure: 150 - 140 mmHg if >60 years old with initial values ≥160 mmHg
Lipids LDL (Low density lipoprotein cholesterol) is the primary target	*Very high-risk*: 70 mg/dL, or a reduction of at least 50% if the baseline is between 70 and 135 mg/dL. *High-risk*: <100 mg/dL, or a reduction of at least 50% if the baseline is between 100 and 200 mg/dL. *Low to moderate risk*: <115 mg/dL.
HDL (High density lipoprotein cholesterol)	No target, but >40mg/dL in men and >45 mg/dL in women indicate lower risk.
Triglycerides	No target but <150 mg/dL indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	Hemoglobin A1c <7%.

Table 1. Risk factor goals and target levels for important cardiovascular risk factors (adapted from ESC guidelines) [23].

Risk factor intervention at the individual level is defined for each major cardiovascular risk factor, and includes lifestyle interventions for all [23]. The benefit of risk factor-lowering therapy depends on the risk factor level itself and on the total cardiovascular risk.

For blood pressure, although several classes of drugs are available [thiazide and thiazide-like diuretics (chlorthalidone and indapamide), beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers], which can adequately lower blood pressure and reduce the risk of cardiovascular death and morbidity, benefits of treatment are mainly driven by blood pressure reduction *per se* and not by the type of drug, and most patients with indication for medication need combination treatment. Dyslipidaemic and diabetogenic effects of some beta-blockers and thiazides has questioned their role as first-choice blood pressure-lowering drugs, particularly in hypertensive patients with multiple

metabolic risk factors and conditions that increase the risk of new onset diabetes mellitus [72,73].

Low density lipoprotein cholesterol (LDL) reduction is the key point of treatment and, although several lipid-lowering drugs are available, statins are the first drugs of choice in patients with dyslipidaemia [23,72], due to its effectiveness in reducing cardiovascular morbidity and mortality, and the need for coronary artery interventions [74,75].

Although the use of antiplatelet therapy in primary prevention is still controversial, proved by changes in position of the ESC in the last decade [76], most recent European guidelines [23] do not support the use of this class of drugs in primary prevention. This is due to the conclusion that the number of primary serious cardiovascular events prevented is offset by the increased risk of major bleeding [77,78]. Ongoing primary prevention trials, in patients with diabetes mellitus [79,80], in individuals with advanced age [81] and in individuals with moderate risk [82], prove that the scientific community considers this is not yet a solved research question. Interestingly, data analysing current practice patterns of prophylactic aspirin utilisation showed that its use is in the opposite direction of current recommendations, with patients at low risk for CVD using aspirin more frequently than patients at high risk [83].

Several drugs for diabetes mellitus management have been introduced, but metformin is still recommended as the first-line therapy, if tolerated and not contra-indicated [23].

Globally, simplifying the treatment regimen of cardiovascular risk factors to the lowest acceptable level is recommended, as is continuous adherence monitoring [23].

b) Stable CHD

Prognostic assessment is an important part of the management of patients with stable CHD. The goal is to correctly identify patients with severe disease who may have outcome benefit with a more aggressive investigation and potentially with intervention, namely revascularisation; but also to avoid unnecessary invasive and non-invasive tests, and revascularisation procedures in patients with less severe disease and good prognosis [40]. And here stands the difficult task.

After establishing the diagnosis of stable CHD, optimal medical therapy should be instituted and stratification for risk of subsequent events should be performed. Risk stratification depends on clinical evaluation, on assessment of ventricular function by resting echocardiography and, in most patients, on non-invasive assessment of ischaemia/coronary anatomy; usually these variables of risk stratification are obtained during the process of stable CHD diagnosis [40].

Patients with a predicted annual mortality ≥3% are defined as high event risk patients [40] and may directly benefit from coronary angiography and eventually revascularisation. The remaining patients should be managed with optimal medical therapy, with those remaining symptomatic despite treatment eventually benefiting from referral to an invasive approach [40].

Optimal medical therapy of stable CHD encompasses lifestyle modification, control of cardiovascular risk factors, evidence-based pharmacological therapy and patient education. Pharmacological management has two main goals, relief of angina symptoms and prevention of the occurrence of cardiovascular events. Several classes of drugs are available for relief of angina symptoms [40]. Beta-blockers and/or calcium channel blockers are the first-line treatment; the addition of one of the second-line drugs (long-acting nitrates, ivabradine, nicorandil or ranolazine) is the next step. All patients should also be prescribed short-acting nitrates [40]. For event prevention, low-dose aspirin and statins are recommended in all stable CHD patients; clopidogrel is an alternative in the case of aspirin intolerance. For patients with stable CHD and concomitant heart failure, hypertension or diabetes, angiotensin converting enzyme inhibitors or angiotensin receptor blockers are recommended [40].

The decision to proceed to a revascularisation of a patient with stable CHD will depend on many clinical, anatomical, technical and environmental factors that should be discussed within a Heart Team. The large number of possible combinations of these factors is responsible for the lack of absolute revascularisation recommendations for patients with stable CHD. The severity of obstructive coronary artery stenosis, the amount of related ischaemia, left ventricular systolic function and the expected benefit for prognosis and/or symptom relief are factors to take into account in this decision [40]. Nevertheless, there is still a gap in evidence as to what is the real benefit from myocardial revascularisation of patients with stable CHD.

c) Acute coronary syndromes

Non-ST elevation acute coronary syndrome (NSTEACS)

The selection of the best acute management approach for patients with NSTEACS greatly depends on risk stratification. For prognosis estimation of patients with ACS, established ischaemic and bleeding risk scores are superior to clinical assessment alone [84], and should therefore be part of the initial management of patients with NSTEACS [45]. The Global Registry of Acute Coronary Events (GRACE) risk score provides accurate stratification of ischaemic risk both at admission and at discharge [85]. The updated GRACE risk score 2.0 has better discrimination and is easier to use than the previous score, and it performed equally well acutely and over the long term [86]. Age, systolic blood pressure, pulse rate, serum creatinine, Killip class at presentation, cardiac arrest at admission, elevated cardiac biomarkers and ST deviation are used for the GRACE 2.0 risk calculation. If the Killip class or serum creatinine values are not available, a modified score can be calculated by adding renal failure and use of diuretics, respectively [86]. Bleeding risk is another part of the risk assessment of NSTEACS. The CRUSADE bleeding risk score [87] is recommended for patients undergoing coronary angiography [45]. This score includes baseline patient characteristics (i.e. female gender, history of diabetes, history of peripheral vascular disease or stroke), admission clinical variables (i.e. heart rate, systolic blood pressure, signs of heart failure) and admission

laboratory values (i.e. haematocrit, calculated creatinine clearance) to estimate the patient's likelihood of an in-hospital major bleeding event [87].

The acute inpatient medical treatment of NSTEACS includes pharmacological treatment of ischaemia, antiplatelet inhibition, anticoagulation, initiation of secondary prevention drug therapy, and decision between conservative vs invasive treatment; and thereafter time and type of revascularisation [45].

The European guidelines updated the risk criteria to decide referral and time to coronary angiography among patients with NSTEACS. For patients with at least one very-high-risk criterion (recurrent or ongoing chest pain refractory to medical treatment; haemodynamic instability or cardiogenic shock; life-threatening arrhythmias or cardiac arrest; mechanical complications of AMI; acute heart failure; recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation), an **immediate**, within two hours from hospital admission, invasive strategy with intent to perform revascularisation is recommended, irrespective of ECG or biomarker findings [45]. An **early** invasive strategy (defined as coronary angiography within 24 hours of hospital admission) is recommended for patients with a high-risk profile, defined as at least one high-risk criterion (rise or fall in cardiac troponin compatible with AMI; dynamic ST- or T-wave changes, symptomatic or silent; GRACE score >140) [45]. This recommendation is based on two meta-analyses of randomised trials, a retrospective analysis of the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial, and on a beneficial effect of early intervention in a high-risk subgroup (GRACE >140) of patients, observed in The Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial [88-91]. Both meta-analyses concluded that there is insufficient evidence either in favour of or against an early invasive approach in the NSTEACS population, considering benefit for the hard endpoints of mortality, nonfatal AMI or major bleeding, but only a reduction in secondary outcomes, particularly refractory ischaemia. The **invasive** strategy (defined as coronary angiography within 72 hours of hospital admission) is recommended for patients with at least one intermediate risk criterion (diabetes mellitus, renal insufficiency defined as estimated glomerular filtration rate below 60 ml/min/1.73 m^2, left ventricular ejection fraction below 40% or congestive heart failure, early post-infarction angina, prior percutaneous coronary intervention (PCI), prior coronary artery bypass graft surgery (CABG), GRACE risk score >109 and <140); recurrent symptoms or known ischaemia on non-invasive testing [45]. Patients with no symptom recurrence and none of the very high, high or intermediate risk criteria are to be considered at low risk of ischaemic events, and a **non-invasive stress test** (preferably with imaging) for inducible ischaemia is recommended before deciding on an invasive strategy [45].

Considering these recommendations, coronary angiography followed, if indicated, by revascularisation is indicated for most patients with NSTEACS. The time and selection of the revascularisation modality depend on numerous factors, namely clinical presentation, comorbidities, risk stratification, presence of high-risk features specific for a revascularisation modality, frailty, cognitive status, estimated life

expectancy, and functional and anatomic severity as well as the pattern of coronary arteries lesions [45].

ST elevation myocardial infarction (STEMI)

The primary goal in treating patients with STEMI is rapid restoration of coronary arterial flow and reperfusion. In the 1980s, fibrinolysis was the only means to accomplish this. Over the last two decades, primary PCI has become the preferred reperfusion strategy if performed on time by skilled operators [46].

In STEMI patients, the main limitation to referral to reperfusion therapy is the time of presentation after symptom onset. For patients with the clinical presentation of STEMI within 12 hours of symptom onset and with persistent ST-segment elevation or LBBB, early mechanical or pharmacological reperfusion should be performed. Whether PCI is also beneficial in patients presenting more than 12 hours after symptom onset is more controversial. Patients with clinical and/or electrocardiographic evidence of ongoing ischaemia benefit more than asymptomatic patients. In patients who present more than 48 hours after symptom onset, and are stable and without signs of ischaemia, routine PCI is not recommended [46]. This timeframe recommendation was extended from 24 hours [92] to 48 hours in the 2017 guidelines [46], according to the results of a randomized clinical trial of approximately 350 patients, that showed improved myocardial salvage and 4 year survival in asymptomatic patients without persistent symptoms 12-48 hours after symptom onset treated with primary PCI, compared with those with conservative treatment [93,94].

International guidelines recommend primary PCI generally within 90 minutes of first medical contact, preferably within 60 minutes if patients present at a primary PCI capable hospital. Fibrinolysis is recommended if PCI cannot be performed within 120 minutes from first medical contact. After a successful fibrinolysis, a routine early PCI strategy, preferably within 2 to 24 hours, is indicated [46,95]. There still is a large debate on the time delay that is acceptable before deciding on fibrinolysis, or instead in a combination of the two reperfusion modalities, due to the lack of contemporaneous data to set the limit to choose PCI over fibrinolysis [46,96]. Significant delays may negate the benefit of primary PCI over fibrinolysis. The total ischaemic time, time from symptom onset until effective reperfusion, is influenced by patient and health care system delays. Preventing these delays in STEMI patients means reducing mortality and morbidity [97]. This involves identifying barriers to access, which may occur in many steps of this complex chain, in the perception of need and health system seeking behaviour of the patient, the pre-hospital logistics of care including pre-hospital triage, ambulance services and networks between non-PCI and PCI capable hospitals, and treatment strategies. To prevent delays, the process of monitoring of care is also important [98]. Several challenges and opportunities exist throughout this process of care to improve quality. Considering the monitoring phase, different definitions of STEMI delays used for evaluating performance limit benchmarking and interpretation of delay determinants [46,99].

Despite acknowledging the challenge and diagnostic uncertainty of LBBB, the 2012 ESC guidelines

recommended emergent reperfusion therapy for this subgroup of patients [92]. In the 2013 American STEMI guidelines, the recommendation to treat patients with new or presumably new LBBB as STEMI equivalent was removed [95]. This conceptual change was supported by arguments related with the subjective definition of "new LBBB" when no ECG is available for comparison, the low frequency of LBBB at AMI presentation, the possibility of other diagnosis besides STEMI, the increased risk of complications from inappropriate approaches, namely false catheterization laboratory activation or inappropriate fibrinolytic therapy [95]. The most recent European guidelines for management of patients with STEMI go in the opposite direction of the American guidelines, supporting that patients with LBBB, regardless of whether the LBBB is previously known, should be managed in a way similar to STEMI patients. This position is grounded on the lack of sufficient diagnosis acuity of the complex electrocardiographic algorithms to assist in the diagnosis of transmural AMI in patients with LBBB. These guidelines also support a primary PCI strategy to patients with right bundle branch block and persistent ischaemic symptoms, considering that it also may be difficult to detect transmural ischaemia in patients with chest pain and right bundle branch block [46]. The debate around these recommendations will continue.

MINOCA and INOCA

No clinical practice management guidelines exist for the management of the heterogeneous group of patients with MINOCA or INOCA, although working groups critically reviewed available literature and current practices, and suggested research directions to develop evidence-based therapies [58,100]. According to the position of these working groups, extrapolation from some studies support the role of some drug classes to target coronary microvascular dysfunction, namely statins, angiotensin converting enzyme inhibitors, aspirin and antianginal agents. However, there is a lack of appropriately designed clinical outcome trials to support evidence-based therapeutic strategies for these specific groups of patients [58,100].

d) Long-term management of patients with acute coronary syndromes

The long-term management of patients with NSTEACS and STEMI, according to the most recent European guidelines is summarised in table 2 [23,45,46]. Drug therapy and participation in a well-structured cardiac rehabilitation programme, classes and levels of recommendation are presented for patients with NSTEACS and STEMI, without contraindication for each specific class of drugs and for exercise-based cardiac rehabilitation.

		NSTEACS		STEMI		
	Recommendation	**Class**	**Level**	**Class**	**Level**	**Comment**
Drug class						
Low dose aspirin		I	A	I	A	Indefinitely
P2Y12 inhibitor		I	A	I	A	
Dual antiplatelet therapy						Duration depends on type of stent, concomitant oral anticoagulation and is not a solved research question
Aspirin+ticagrelor		I	B	I	A	
Aspirin+prasugrel		I	B	I	A	Prasugrel if PCI
Aspirin+clopidogrel		I	B	-	-	Clopidogrel if ticagrelor or prasugrel not feasible or if oral anticoagulation
High-intensity statin	All patients and as early as possible LDL target <70 mg/dl or a 50% reduction	I	A	I	A	If LDL cholesterol ≥70mg/dL despite a maximally tolerated dose of statin, **ezetimibe** should be added[101] (IIa)
ACEI	Patients with systolic dysfunction, or heart failure, or diabetes	I	A	I	A	LVEF≤40% specifically defined for NSTEACS For NSTEACS also hypertension For STEMI also anterior infarction
	All patients	-	-	IIa	A	
ARB	For those who are intolerant to ACEI	I	A	I	B	Preferably **valsartan** in STEMI
Beta-blockers	Heart failure or LVEF ≤40%	I	A	I	A	
	All patients	-	-	IIa	A	
Aldosterone antagonists	In patients with systolic dysfunction and either heart failure or diabetes	I	A	I	B	Preferably **eplerenone** For NSTEACS: LVEF≤35% For STEMI: LVEF≤40%
Exercise-based cardiac rehabilitation program		I	A	I	A	To improve patient outcomes

Table 2. Long-term management of patients with acute coronary syndromes (drug therapy and cardiac rehabilitation).

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NSTEACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

1.2 Health care quality assessment and improvement

Quality of care is difficult to define and implies the characterisation of several domains, which represent attributes or properties of the process of care itself, but also of goals or objectives of that process, defined by the medical care system and by the larger society of which it is a part [102]. The definition of health care quality proposed by the Institute of Medicine is widely accepted: "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [103]. Its specific aims are the following:

Effectiveness: relates to providing care processes and achieving outcomes as supported by scientific evidence to all who could benefit, and refraining from providing services to those not likely to benefit (avoiding underuse and overuse).

Efficiency: relates to maximizing the quality of a comparable unit of health care delivered or unit of health benefit achieved for a given unit of health care resource used.

Equity: relates to providing health care of equal quality to those who may differ in personal characteristics other than their clinical condition or preferences for care, such as gender, ethnicity, geographic location, and socioeconomic position.

Patient centeredness: relates to meeting patient needs and preferences, and providing education and support.

Safety: relates to avoiding actual or potential harm.

Timeliness: relates to obtaining needed care while minimising delays.

Quality of care is not a unitary concept, as relevant dimensions and values can be defined differently, according to time and setting. The selection of dimensions to define quality of health care will impact the approaches and methods employed in its assessment. Hence, although the sense of quality of care is intuitive, it is difficult to develop an operational definition, and valid and reliable measures.

Avedis Donabedian is widely recognised as one of the most important figures in health care quality research. He gave an important contribution to define and disseminate approaches and methods of assessment, and proposed, what are still today considered, the three types of indicators of quality of health care. Evaluating whether high quality care is provided can be performed by examining what the outcomes of care are, by measuring the actual process of care and/or by assessing the structure of the setting in which care is provided [102]. Advantages and limitations of these **outcome, process and structure indicators of quality of care** can be identified.

Outcome indicators

The outcome of medical care, in terms of recovery, restoration of function and survival, has been frequently used as an indicator of health services quality, because of its advantages: accepted validity, stability and objectivity. However, there are some limitations to take into account, one very relevant is the fact that outcomes will depend not only on the degree to which evidence based medicine has been applied in the instances under study, but also on the power of medical science itself to achieve certain results under any given set of conditions. Furthermore, other factors besides medical care may influence outcome, and have to be taken into account if valid conclusions are to be drawn. One of the major factors affecting post-treatment status is pre-treatment status [104]. Noteworthy is also the fact that long periods of time, sometimes decades, must elapse before relevant outcomes manifest after intervention, so this lag of time should be considered to appraise the results of care. Another limitation of outcome measures for quality improvement purposes is that they may not provide insights into why there were poor outcomes and what needs to be changed to yield better outcomes. Finally, not all outcome indicators are unmistakable and easy to measure as mortality, examples of outcome indicators more difficult to measure are patient attitudes and satisfactions, social restoration, and physical disability and rehabilitation [102]. The important role of these outcome indicators collectively referred as health-related quality of life measures [105] has been increasingly recognised, proved by the development of a repository of patient reported outcome measures, *The Patient Reported Outcomes Measurement Information System* (PROMIS) [106].

Process indicators

Process indicators are not interested in the power of medical technology to achieve results, but in whether what is known to be "good" medical care has been applied. These indicators pretend to answer whether medicine is properly practiced; such measures are used because research has demonstrated a link between those processes and important outcomes.

Disadvantages of process indicators include the fact that it is difficult to relate many processes of care with outcomes. Links between outcome and process are more likely when the patient group is well defined by a medical condition and/or demographic characteristics, when there is a well understood physiologic, biochemical, or psychological mechanism that links medical intervention with outcome, and when the outcomes are targeted for the medical condition. Another shortcoming is related to the complexity of the process of care for several conditions, a multitude of actions take place across the pathway of care, and it is difficult to develop and use enough measures to form a comprehensive assessment. Although it is increasingly recognised that it is not adequate to simply assess individual processes of care, but rather groups of processes that need to occur to lead to a better outcome [107], the interpretation of results in terms of what needs to be changed is more difficult.

Structure indicators

This third approach to quality assessment is related with studying the settings in which health care takes place and the instrumentalities of which it is the product [102]. Structure indicators include material resources (facilities, equipment), human resources (number of personnel and their qualifications) and organisational structure (medical staff organisation, level of reimbursement) [102]. Another important aspect of structure is organisational culture, including the priority given to quality and leadership, and policies and procedures for maximizing the quality of care [108]. One of the major allure of structure measures is that they are fairly concrete and usually accessible to evaluate. It is relatively easy to determine whether a hospital has a cardiac catheterization laboratory available 24 hours a day. However, the relationship between structure and process, or structure and outcome is often not well established, because it is very complex [109] and weak [110].

This framework developed by Avedis Donabedian, and providing a valuable conceptualisation of outcome, process and structure as essential domains for evaluating medical care quality, was determinant in directing the investments in health care quality measurement and improvement.

Questions related with sources of data, sampling, methods of analysis and interpretation of quality measures are a current topic. The recognition of the importance of availability; standardisation of measures for specific care settings and clinical conditions; of broad multistakeholder engagement in the development of measures were important to identify solutions to controversial issues, including adequacy of risk adjustment and strategies to link cost and quality, as well as set new directions of research.

The hierarchical structure evaluation criteria for the endorsement of standard measures for health care quality set by the National Quality Forum in the United States of America, which was established in 1999, is a good example of the relevance of the quality improvement goal to define quality measures. The National Quality Forum evaluation criteria measures include: importance to measure and report (first must-pass) are related with the level of evidence for the measures and the existence of an opportunity for improvement. Scientific acceptability of the measurement properties (second must-pass) are related with the reliability and validity of the measure. Usability and use are related with accountability and improvement. Feasibility is related with implementation of the measures without undue burden and captured with electronic data. Also included is the need to assess related and competing measures [111].

Accurate data collection for quality assessment implies identifying patients with the specified disease, evaluating the severity of their condition to determine whether they are appropriate candidates for the performance measure, doing appropriate risk adjustment and measuring the process or outcome of care to compare with accepted standards [112]. Risk adjustment is particularly a challenge; although a range of biostatistical techniques is available to account for variability due to patient factors, much

variability remains unexplained [112].

Measures are being developed to increasingly take advantage of the best data available for measurement, which include the use of clinical data registries, electronic health records (standardised data from laboratory results, imaging results and patient vital signs), and the ability to link these data and track patients using multiple registries. Denmark is a remarkable example. A 10-digit personal identification number is allocated to each Dane from birth to death and used in all medical databases, allowing unambiguous linkage between various registries [113] and therefore the creation of a network of more than 60 publicly financed nationwide clinical quality databases [114]. These registries contain systematically collected data related to clinical observations, diagnostic procedures, treatments and outcomes within the context of patient pathways of specific diseases or health-related interventions [115]. Clinical quality databases are required to fulfil a set of national criteria regarding organisation, functionality, data safety and reporting to be approved. Questions related with data validity, namely completeness and other issues related with quality of data are also objectively addressed [114]. Authors highlight the potentials of this approach to quality improvement, namely the following advantages: population-based studies on large cohorts of patients usually with fairly complete data and complete follow-up; collection of data independently of the research question, minimising risk of some types of bias such as recall bias and the impact of a decision on diagnosis and therapy through awareness of an ongoing study; unique data source in studies of long-term health; lower cost; more detailed clinical data than the central health registries and better control for confounding [114].

Currently, in Nordic countries, registry data can be used in legally approved research without obtaining informed consent. Concerns are being raised about the requirement for individual patient informed consent before data can be collected or used, considering positions advocated by the European Commission [116] and by the World Medical Association [117]. To maximise the potential of these clinical quality databases for research purposes, there are several technical, legal, educational and financial challenges [114].

1.2.1 Access to health care

Access is an important concept to the study of the organisation, financing and delivery of health care services. Access to health care is defined as access to a service, a provider or an institution, thus defined as the opportunity or ease with which consumers or communities are able to use appropriate services in proportion to their needs [118]. Access to health care has been the subject of much study and battle of frameworks; seen from the beginning as a multi-dimensional concept, still today, the definition of dimensions and operational measuring lacks consensus.

Andersen developed one of the most important and cited theory of access, “the behavioural model of health services use” [119]. The key item noticed by Andersen and colleagues was that earlier concepts of use of health care focused on 2 major alternative dimensions: the characteristics of the population vs. the characteristics of the delivery system. They also noted that access could be measured using service and outcomes of the use process. The biological imbalance of individuals was termed “need” and was also considered an important component of the core conceptualisation. The overall framework included causal links and pathways between and among the elements, labeled “predisposing” (generally characteristics of individuals) or “enabling” (system or structural characteristics) that led to an outcome.

The Penchansky conceptualisation of access focused on the interaction of key elements that determined use of services [120]. Penchansky suggested the concept of “fit” between the patient’s needs and the system’s ability to meet those needs. He suggested that this fit could be measured across five dimensions: availability, which is the volume of physician and other health care services; accessibility, the spatial or geographic relationship between the providers of health care and the users of care; accommodation, describes the organisation and content of the health care system as it relates to the ease with which people can use care (clinic hours, waiting time and length of time waiting for an appointment); affordability, the financial ability of the population to use the care provided by the system and the perception of value on the part of patients; and acceptability, which represents the attitudes of the users of health care toward the providers, and vice versa.

Frenk extended the work of Penchansky, to suggest that “fit” was a process of adjustment between the population and the health care delivery system [121]. Frenk also noted the internal problem of using terms which have not been clearly defined but are used interchangeably (access, accessibility, availability).

All these frameworks highlighted the central role of health system characteristics with regards to facilitating or impeding the use of services by potential users, and were in line and influenced by the conceptual framework for evaluating quality of medical care proposed by Donabedian [102].

More recently, the concept of access was revisited by Levesque and colleagues [122], who tried to draw the different steps in the sequence that a patient will experience through the process of care, which represent crucial transitions, where barriers or facilitators to access can be revealed. Levesque and colleagues defined access to health care as “the opportunity to identify health care needs, to seek health care services, to reach, to obtain or use health care services, and to actually have a need for services fulfilled”. These authors subdivided, at the system level, the dimension of accessibility into five sub-dimensions (approachability, acceptability, availability/accommodation, affordability and appropriateness) and identified, at the population level, five corresponding abilities of populations to interact with the dimensions of accessibility, to generate access (ability to perceive, ability to seek, ability to reach, ability to pay and ability to engage).

The ultimate goal of disaggregating access into broad dimensions and sub-dimensions, that is, to identify its specific determinants, is to obtain more operational measures for its evaluation. But this is still a difficult task that raises the question about if they are sufficiently distinct to be measured and studied separately. Independently of how these dimensions are labelled and defined, they surely represent closely related phenomena, and should be taken into account in the design, analysis and interpretation of health care research.

1.2.2 Quality indicators in acute coronary syndrome

Despite the advances in primary and secondary prevention, namely some revolutionary in technology with respect to ACS, important challenges and opportunities remain in the optimal delivery of care to this patient population. Adherence to recommended guidelines has been convincingly associated with significant improvement in survival [123], but is still suboptimal [124]. The use of evidence-based ACS treatments is less than ideal, particularly for certain high-risk populations, namely older and female patients [125], non-white patients [126], patients from lower SEP [127-129], and patients from certain geographic regions [130]. Opportunities to quality improvement exist, which imply the existence of operational indicators of quality assessment for ACS.

Quality indicators (QIs) are developed for each condition of interest in most instances by the use of general consensus statements or guidelines as a basis. However, guidelines are not quality of care indicators; guidelines suggest diagnostic or therapeutic interventions for most patients in most circumstances, its use is left to the discretion of the physician. In contrast, QIs in addition to stating an explicit diagnostic or therapeutic action to be performed, must also define how to identify patients for whom a specific action should be taken. Thus, health care providers, researchers and payers identified a need to link development of guidelines with development of QIs [112].

Considering the conceptual framework of quality of health care, it is not surprising that there is not a unique and universal standardised set of QIs for ACS. In 2015, the Spanish Society of Cardiology and the Spanish Society of Thoracic and Cardiovascular Surgery organized a task force to define outcome and process indicators of hospital cardiology practice [131,132]. More recently, the ESC/ Acute Cardiovascular Care Association (ACCA) proposed a set of QIs for the management of AMI [133], based on the ESC guidelines [45,92]. They comprise 7 domains across 20 QIs including the evaluation of key aspects of the AMI care pathway and include structure, process and outcome indicators. The relevance of time dependent QIs, of risk stratification assessment, of the need to gather appropriate clinical detail, for example the need to consider the specific type and doses for some drugs, and of composite QIs are strengthened in this

proposal. These indicators were validated using data from the National Health Service of England and Wales (Myocardial Ischaemia National Audit Project [MINAP]) and showed the potential to improve care and reduce unwarranted variation in death from AMI [134], serving as a conceivably useful tool to improve benchmarking and to study inequalities. The 2017 version of the ESC guidelines for the management of STEMI patients [46] recommend a set of QIs to measure and compare the quality of health service provision, based on the ESC/ACCA proposal [133].

A comprehensive approach to quality assessment and improvement should be made at four levels of analysis: national, regional, institutional and individual, as suggested by Leatherman [135].

There are several examples of quality of care assessment and improvement initiatives for CHD, performed at different levels. In the United States of America, the Guidelines Applied in Practice program from the ACC [136], and the Get With The Guidelines program from the AHA [137] were developed to increase the use of evidence-based medical therapies for patients with ACS in the acute phase of the illness, at hospital discharge and at long-term follow-up. In Europe, several initiatives were also developed to increase the use of CHD guidelines. The EURopean Hospital Benchmarking by Outcomes in acute coronary syndrome Processes (EURHOBOP) study intended to provide the European Community with valid standardised and adjusted benchmarking tools that allow European hospitals to monitor their outcomes in key procedures used in CHD [138]. The European Heart Health Strategy (EuroHeart) I [139], by strengthening cross-sector cooperation and determining areas of policies and public health interventions which can contribute to prevent avoidable deaths and disability across Europe, ultimately served the propose of increasing adherence to guidelines, and included one package specifically drawn to improve awareness, diagnosis and treatment of cardiovascular disease in women.

Several strategies for hospitals to encourage maximal utilisation of evidence-based interventions for ACS care have been described, including separate standardised order sheets [140], quality of care teams to do real time surveillance and ensure that guideline-based therapies are not omitted in patients unless specific contraindications [141], and evaluation and report of performance to quality metrics on a regular basis [142]. Patient information and discharge forms improve health literacy and are an opportunity for the patient and family to ask any questions they may have regarding the patient's diagnosis, prognosis, severity of disease, risks and benefits of the newly prescribed medications, and follow-up plans. Lifestyle modifications, such as healthy eating and smoking cessation, should be included in the patient discharge forms [124].

Despite being used within and across several health care systems, there is a lack of strong scientific evidence supporting the many different quality improvement and patient safety strategies, namely dissemination of clinical guidelines, auditing and accreditation [114].

1.2.3 Importance of registries to the evaluation of adherence to recommended guidelines

a) CRUSADE

The CRUSADE registry, developed in 2001, has been used to evaluate guideline adherence and to increase the practice of evidence-based medicine in NSTEACS (including unstable angina). In 2007, approximately 200,000 patients were enrolled [143]. The CRUSADE database provided important observations on guideline adherence. The database was used to evaluate the usage of early invasive and conservative approaches; recipients of the early invasive approach were younger, more frequently male and white, more likely to be under the care of a cardiologist, and less likely to have heart failure or impaired renal function [144].

b) GRACE

The GRACE registry was a multinational study conducted between 1999 and 2009 to assess patient characteristics, clinical outcomes, and derive predictive risk scores in patients with ACS. Main GRACE involved 123 hospitals in 14 countries in North and South America, Europe, Australia, and New Zealand. GRACE 2 (expanded GRACE) comprised 154 hospitals in Europe, North and South America, Asia, Australasia, and China [145].

By identifying missed opportunities, GRACE analyses were critical to improve the quality of care of ACS patients. One example was the observation that modern reperfusion strategies were not offered to nearly 30% of eligible patients with STEMI in 2002, particularly to the elderly, those with atypical presenting symptoms and those with previous coronary bypass surgery [146]. Rates of reperfusion of eligible STEMI patients in 2008 were clearly improved [147].

GRACE also provided strong evidence that adherence to performance measures in the use of medications, both in-hospital and at discharge, is associated with mortality reduction [148], and identified opportunities to improve quality of care in vulnerable populations of ACS, including those with diabetes, heart failure and women [149-151].

c) EUROASPIRE

In nine European countries in 1995 and 1996, a survey was developed to describe clinical practice, namely secondary prevention of CHD [152], the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) I. The EUROASPIRE II (1999 to 2000), III (2006 to 2007) and IV (2012 to 2013) surveys were conducted in the same geographical areas and selected hospitals in each country, and included consecutive patients (≤70 years) after CABG, PCI, or ACS. According to comparisons of results of these surveys, lifestyle habits have deteriorated over time with increases in

obesity, central obesity and diabetes, and stagnating rates of persistent smoking. Although blood pressure and lipid management improved, they were still not optimally controlled [153].

d) CICD

The Chronic Ischaemic Cardiovascular Disease (CICD) registry was created to characterize CICD in terms of demographic characteristics, clinical profiles management and outcomes, and to identify inter-regional differences and potential gaps between actual treatment and evidence-based recommendations in a European contemporary environment.

The CICD-Pilot survey, an international prospective observational longitudinal registry in CHD and/or peripheral artery disease patients with a 3-year follow-up, aimed to validate the structure, performance, feasibility and quality of the data set, with the intention of extending the survey to other participating European countries into a long-term registry. Portugal was one of the Southern European countries participating in the CICD-Pilot [154].

From April 2013 to December 2014, 2420 consecutive CICD patients with NSTEACS (n=755) and chronic stable CHD (n=1464), or with peripheral artery disease (n=201), were enrolled. According to the results of the CICD-Pilot registry, the implementation of guideline recommended therapies has improved since the previous surveys. However, important heterogeneity exists in the clinical profile and treatment modalities in the different cohorts of patients enrolled with a broad spectrum of CICDs.

e) Portuguese registries

The National Cardiology Data Collection Centre (*Centro Nacional de Coleção de Dados em Cardiologia*), was created in 2002 by the Portuguese Society of Cardiology, to provide logistic support for joint national studies, including technical, data management and human resources. This data centre gives support to two continuous registries, the National Registry of Acute Coronary Syndromes and the National Registry of Interventional Cardiology, which were established in January 2002; to periodic registries on metabolic syndrome (the VALSIM study, beginning in 2006) and on hypertension and dyslipidemia (beginning in 2005); and to the ESC's Euro Heart Surveys [155].

These registries showed that the implementation of guideline recommended therapies for ACS and outcomes have improved in Portugal in the last two decades and also identified issues requiring further interventions [156,157].

These observational data enabled the identification of an important gap between recommendations and clinical practice, and identified groups of patients with CHD deserving further investigation to assess and understand these inequalities in management, namely women, older patients, patients of

low SEP, patients of minority ethnic groups, patients from certain geographical regions, and those with comorbidities, including diabetes, heart failure and renal failure. Opportunities to improve quality of care of these vulnerable populations with CHD were identified.

1.3 Health inequalities, “the causes of the causes”

Health inequalities are systematic disparities in health or in the major determinants of health between distinct populations or groups, defined by a large variety of constructs, including age, gender, SEP, ethnicity and geographic region. Inequalities in health systematically put groups of people who are already socially disadvantaged at further disadvantage with respect to their health [158]. Inequalities have important impacts on the accessibility and effectiveness of cardiovascular disease preventive measures [159].

The Black Report [160] (Report of the Working Group on Inequalities in Health), published in 1980 by the United Kingdom Department of Health and Social Security, showed an unequal distribution of ill-health and death among the British population, and suggested that these inequalities have been widening rather than diminishing since the establishment of the National Health Service in 1948. The Report concluded that these inequalities were driven by social inequalities influencing health (income, education, housing, diet, employment, and conditions of work), increasing the interest of researches and public policy on health inequality. This report also showed that the provision of free services to all citizens at the time of need did not reduce differences in mortality risk between people in more and less advantaged social circumstances. Access to health care itself was not sufficient to reduce health inequality, mainly due to two main reasons, one is the relevant role of social environment and lifestyles in health, the other is the fact that most common causes of mortality and disability in developed societies, namely CHD, involves longstanding processes, diagnosed and treated late in the natural long period course of the disease [161].

A socioeconomic explanation of health inequalities is relevant to all countries in the world. The model of socioeconomic determinants of health [162], developed in 2007 by Solar and Irwin for the Commission on Social Determinants of Health, is a conceptual framework that goes beyond the immediate causes of disease. Applied to the study of inequalities in CHD, it serves to trace individual “agentic” level or the societal “structural” level determinants of cardiovascular health, which interplay between them. Understanding inequalities in management and outcomes is therefore a complex task, because it involves the quantification of different factors and at different levels. This socioeconomic model traces the roots of health and disease beyond health services to determinants at the macro level, namely public, social and economic politics, cultural and societal norms and values, which influence at the individual level gender, education, occupation, income, ethnicity/race and other SEP indicators. These individual socioeconomic characteristics have impact in health by determining health literacy, psychosocial factors and behaviours, which can favour or protect against disease risk factors and also influence attitudes toward health and health service interactions. The practical implication for this conceptual framework is that measures undertaken to reduce health inequalities should not only target the system level of access, but also the patient level, and the general population, with its several dimensions [162].

The concept of health inequality is sometimes used with ambiguity, we use the term as descriptive in nature, of variations in health by groups, without assuming a moral judgment of unfairness. By contrast the term "inequity" applies to health variations that being unnecessary and avoidable are judged to be unfair or unjust, and therefore unacceptable. The term 'inequity' has therefore a moral and ethical dimension [118]. Equity in health relates to allocating means unequally, based on the notion that different subpopulations have different needs and it is concerned with creating equal opportunities for health, bringing health differentials down to the lowest possible level. Equality means making the same offer accessible to all people regardless of potentially different needs level [118]. A long and complex debate exists about equality, equity and justice in health [163].

When health inequalities emerge, it is complex to conclude to which extent they are inequities [118,158]. The answer to the question of which inequalities are inequities varies according to place and time. Margaret Whitehead, by proposing seven main determinants of health differences and by identifying those that are unfair, gave a good contribution to this discussion (Table 3) [118].

Inequalities
Natural, biological variation.
Health-damaging behaviour if freely chosen, such as participation in certain sports and pastimes.
The transient health advantage of one group over another when that group is first to adopt a health-promoting behaviour (as long as other groups have the means to catch up fairly soon).
Inequities
Health-damaging behaviour, where the degree of choice of lifestyles is severely restricted.
Exposure to unhealthy, stressful living and working conditions.
Inadequate access to essential health and other public services.
Natural selection or health-related social mobility involving the tendency for sick people to move down the social scale.

Table 3. Seven main determinants of health differences proposed by Whitehead [118].

Monitoring inequality was considered an emerging priority for health post-2015 [164]. The World Health Organisation developed initiatives related to health inequality monitoring at the global and/or national level, which improved availability of disaggregated data [165]. Sustainable Development Goals cannot be accomplished without addressing inequality, and the goal is "leaving no-one behind" [166]. Health inequality monitoring entails collecting, analysing, interpreting and reporting health disaggregated data. With the World Health Organisation's Health Equity Monitor database, between 2014 and 2016, the Health Equity Assessment Toolkit software was developed [167]. This application allows for the assessment of inequalities within a country using over 30 reproductive, maternal, newborn and child health indicators,

and five dimensions of inequality (economic status, education, place of residence, subnational region and child's sex, where applicable).

1.3.1 Determinants of inequalities in coronary heart disease by vulnerable group

a) SEX AND GENDER

Both biological and social/cultural factors are important for women's and men's health status. A dichotomous view of the concepts of sex and gender pretended to capture separately those factors. Unlike one's biological sex, gender was considered the social and cultural construction of masculinity and femininity [168]. The American Psychological Association stated that "sex is biological; use it when the biological distinction is prominent", while "gender is cultural and is the term to use when referring to men and women as social groups" [169]. In 2001, the Institute of Medicine defined the concepts similarly: sex was classified according to reproductive organs and functions assigned by the chromosomal complement, and gender as a person's self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual's gender presentation [170].

The terms sex and gender employed in biomedical publications are frequently misused [171], it is not so simple to separate biology from social/cultural factors. More recently, the concepts of "sex" and "gender" meant for gender researchers within medicine were explored. They concluded that "sex is more than biology", concepts of "sex" and "gender" should be looked beyond a dichotomous view, because they are intertwined [172]. To compare differences between women and men in papers of this thesis, we used the term "sex", considering that "sex is more than biology".

Sex and gender gap in CVD research

The first inequality is the sex and gender gap in CVD research. Besides sex and gender differences across most areas of heart disease, women are still underrepresented in cardiovascular research, namely in the field of CHD. The EuroHeart project revealed a high underrepresentation of women in randomized clinical trials. Since 2006, the percentage of women enrolled in trials ranged between 15% and 60%, but only 50% (31 trials) reported an analysis of the results by sex/gender [173]. It is accepted that one priority of research is the need for more explanatory sex and gender specific cardiovascular research [174] to be able to adapt existing guidelines for better cardiovascular health in women.

Burden

CHD was perceived as a disease predominantly affecting males, which promoted a knowledge gap with

impact on physicians and also on patients, contributing for suboptimal care for at-risk women [175]. In fact, women and men are about equally affected by the still main cause of death across Europe, 20% of females and 19% of males dye from CHD in Europe [38]. To strengthen that sex-specific CVD research is a priority is the fact that, in some settings, the decline in mortality from CHD does not extend to younger women (49 and under), in whom the rate of change has reversed in the last 20 years, indicating a future plateau and possible reversal of previous improvement in CHD mortality rates [176].

Pathophysiology

One of the major sex differences in CHD is in the pathophysiology. Women have higher probability of non-obstructive CHD, and of coronary plaque erosion and distal embolization, microemboli and dysfunction of the microvascular coronary system [177], mainly women at younger ages [178]. In fact, the role of microvascular dysfunction leading to subendocardial ischaemia without coronary obstructive disease seems to be greater in women than in men [179]; MINOCA and INOCA are more frequent among women [52,58,180]. Inflammatory and thrombotic processes are involved in the progression of atherosclerotic disease in men and women, while the role of endogenous oestrogen status in delaying the onset of atherosclerosis in women is not definitively clarified [181]. Furthermore, inflammatory diseases, which may be more involved in the progression of atherosclerosis in females, are more prevalent in older women compared with men [182].

Cardiovascular risk factors

Although CVD risk factors are the same in women and men, once CHD has developed, women tend to have a higher burden of risk factors, when compared to age-matched male patients [183]. Additionally, although overall prevalences of traditional cardiovascular risk factors are higher in men, which largely explains the lower ACS prevalence among women at younger ages [184], there is substantial sex/gender related variability in their relative weighting and in the associated outcomes [185]. Elderly hypertensive women and young female smokers are particular at risk subsets [186-188]; as are female diabetic patients. According to a meta-analysis of prospective cohort studies, the relative risk for fatal CHD associated with diabetes is 50% higher in women than in men [189]. Although women with diabetes have more classical cardiovascular risk factors than men; excess risk factor clustering only partially explains how diabetes eliminates the “female advantage” of a predominately lower CHD prevalence and outcome risk [190]. The prevalence of hypercholesterolaemia is lower in women compared with men, but above 65 years of age, mean low-density lipoprotein-cholesterol is higher among women [191]. High-density lipoprotein cholesterol values in men are generally lower than those of women at all ages, but sex/gender differences in high-density lipoprotein values diminish with advancing age [175]. Hypertriglyceridaemia and low high-

density lipoprotein cholesterol seem to be more important risk factors of CVD for women than men [7].

Psychosocial factors strongly influence the development of CHD, particularly among women [192]. Besides traditional psychosocial factors (e.g. depression), factors associated with responsibilities at home or multiple roles have an important deleterious impact on CHD risk and prognosis in women [192,193]. Women have a lower SEP more often, and a lower social support is associated with worse health status and more depressive symptoms over the first year of AMI recovery, particularly for women [194]. Men and women experience different barriers to lifestyle change, display distinct dietary patterns and levels of physical exercise, and are subject to different psychosocial factors. Their different socio-cultural preferences impact sustained adherence to healthy behaviour [195]. A group-based psychosocial intervention program for women with CHD may prolong lives independently of other prognostic factors [196]. Behavioural factors have been addressed in guidelines for CVD prevention, but a more gender specific approach is still lacking [23].

Traditional risk factors underestimate the CHD risk in women, non-classic risk factors were proposed to improve risk stratification, namely C-reactive protein, whose mean levels are higher in women compared to men [197]. The hypothesis is that of a synergism between inflammation and other traditional risk factors to speed up the development of CHD in women (4).

The lower perceived risk of CVD despite a similar calculated risk for women versus men is one of the main factors associated with a lower adherence to CVD preventive recommendations [198]. According to the EUROASPIRE III results, women are less likely than men to achieve blood pressure, cholesterol and glycated haemoglobin targets after a coronary event, despite similarities in medication exposure. This gap did not narrow between 1994 and 2007 [199].

Clinical presentation and diagnoses approaches

Women have a similar or slightly higher prevalence of angina across countries that differ widely in AMI mortality, despite men having a universal excess of fatal AMI [200]. There is a widespread understanding that women with CHD present with symptoms that are different from those in men. However, current evidence supports that the same symptoms during an ACS episode occur, though available data are not consistent regarding the proportion presenting with different symptom combinations [201-203]. Sex/gender specific research of ACS presentation is therefore a priority [204].

Significant sex/gender bias has been identified in the use of investigations in stable CHD [205]. In women, the accuracy of most non-invasive diagnostic investigations for CHD is diminished compared with men [206], as is coronary angiography, which is considered the gold standard to detect CHD if obstructive, and therefore less suited for middle aged women [207]. The use of more advanced non-invasive imaging modalities such as resonance perfusion imaging or computed tomographic angiography, as well as intracoronary imaging

techniques, has the potential of being better suited to the detection of CHD in female patients [46,174].

Acute coronary syndrome

Differences in outcomes of therapeutic strategies in NSTEACS low-risk patients were observed between men and women, the benefit in mortality of an early invasive strategy was only observed for men [208,209]. Additionally, an increased risk of adverse clinical outcomes was observed for women with ACS undergoing an early invasive strategy and coronary revascularisation compared with men [210].

Analyses of sex/gender based differences in outcomes after ACS have revealed conflicting results. In STEMI, female sex (especially young women) is associated with higher in-hospital mortality but not with long-term mortality [211]. Other studies showed that in STEMI, 30-day mortality was higher among women, whereas in NSTEMI and unstable angina mortality was lower among women, but after additional adjustment for clinical differences at presentation and angiographic disease severity, 30-day mortality among women was not significantly different than among men, regardless of ACS type [212]. The increased mortality might be explained by the fact that women with ACS are generally older with more clustering of risk factors, differences in treatment and in vascular flow [174]. Furthermore, although rates of vascular complications in women have decreased in the last two decades with the development of less aggressive anticoagulation regimens, weight-adjusted heparin dosing, and the availability of smaller sheath sizes suitable for the smaller newer third and fourth-generation devices; women undergoing PCI (primarily through the femoral artery) continue to have a two-fold increased risk of bleeding and vascular complications compared with men, even after adjusting for differences in baseline and procedural characteristics [213]. Women with bleeding complications have a 75% increased risk of death, AMI, or stroke during their index hospitalisation after controlling for both clinical and procedural differences [213]. Thus, therapies that reduce bleeding complications after PCI may be particularly beneficial to female patients, and may help to narrow the mortality gap between men and women. One useful strategy, that has proved to reduce bleeding, is the use of radial instead of femoral access [214].

Furthermore, obstructive CHD has been the focus of therapeutic strategies [197], therefore benefiting more male patients.

But not all is biology, feminine roles and personality traits were associated with higher rates of recurrent ACS and major adverse cardiac compared with masculine characteristics, independently of female sex [215].

b) SOCIOECONOMIC POSITION

Socioeconomic position (social class, social stratification, social or socioeconomic status are often used interchangeably) is a common and intuitive concept in health research. However, there are several socioeconomic

indicators and ways to measure them, which indicate the complexity of the construct [216].

Krieger and colleagues [217] discussed in detail concepts and methodologies to measure socioeconomic inequalities in health. Socioeconomic position refers to the social and economic factors that influence what positions individuals or groups hold within the structure of a society, and is related to numerous exposures, resources and susceptibilities that may affect health [217]. Different socioeconomic indicators measure different, often related aspects of socioeconomic stratification. According to aims, settings and time frames, and also whether SEP is the exposure of interest or a potential confounding/mediating factor, one or another will be more or less suitable for research [216]. Several socioeconomic indicators besides gender exist: education, income, occupation based measures, subjective social class, housing characteristics and geographic region are examples of indicators measuring life course SEP of the individual, each having advantages and limitations [216,218]. Considering the complexity of the socioeconomic construct, particularly when SEP is a potential confounding factor, a single measure of SEP will not encompass the entirety of the effect of SEP on health. Multiple SEP indicators or composite measures will be needed to avoid residual confounding by unmeasured socioeconomic circumstances [219] and also to deal with the time varying exposure nature of SEP [220].

The inverse association between SEP and health status is particularly evident in the case of CHD. However, the underlying mechanisms by which social inequalities impair cardiovascular health are complex and not well understood [221].

There is an accepted association between SEP and CV risk factors, namely with hypertension [222], tobacco smoking [223], physical inactivity [224] and obesity [225]. The influence of SEP on cardiovascular risk factors is different between women and men [226]. To analyse results of studies on this subject, the setting, timeframe and the SEP indicators used should be taken into account.

Part, but not all SEP differences in CHD risk are accounted for by associated differences in risk factors prevalences; growing evidence supports a role for social cognitions for this association [221,227]. Differences in incidence of CHD between patients with different SEP are explained not only by cardiovascular risk factors, but also by psychosocial work environment and social support [228].

Even in settings with universal health care systems, SEP had effects on access to invasive cardiac procedures following an AMI [229], and this socioeconomic gradient is not explained by geography and service supply [230].

Patients from lower SEP are less likely to change risk behaviours (smoking cessation, cardiac rehabilitation, medication adherence, diet and physical activity) following an AMI [231]. The excess CHD mortality and morbidity rates among persons with low SEP were considerable in developed settings [232], and seem to have persisted over time [233]. The inverse relationship of SEP with CHD risk, management and outcomes probably lies in a complex interaction of genes, environment and behaviour.

1.4 The Portuguese context

According to the recently published health system review report [234], health inequalities remain a general problem in Portugal. As per this report, health inequalities in Portugal are mainly related to gender and geographic location [234].

Portugal (including the two archipelagos of Azores and Madeira) has a population of 10.3 million people, has a democratic regimen since 1974, and is a member of the European Community since 1986 and of the Euro Zone since 1999. Portugal is divided into municipalities and parishes, which have their own level of elected government. Mainland Portugal is conceptually divided in five regions (North, Centre, Lisbon, Alentejo and Algarve), but regional authorities have no real decisional power and the government nominates their leaders [234].

The average life expectancy at birth in Portugal was 81.3 years in 2014 (European Union in 2014: 80.9 years). According to data from 2014, Portuguese women are expected to live 6.4 years longer than men, whereas the EU average is 5.5 years. Increasing life expectancy, the decline in fertility rates and the decrease of those aged 15–64 years are causing a "double ageing" effect in Portugal, which will pose a huge nearby challenge to the health system [234].

1.4.1 The Portuguese health care system

In 1946, the first social security law was launched, health care was provided for the employed population and their dependents through social security and sickness funds. After 1974, a process of health services was progressively restructured and in 1979 the National Health Service (NHS) was established [235]. The NHS is a universal system, financed mainly through taxation. The Portuguese health system has three co-existing and overlapping systems: the NHS (with the aim of being "universal, comprehensive and almost free"); special health insurance schemes for particular professions or sectors called the health subsystems (covering approximately 16% of the population) [236]; and private voluntary health insurance (covering about 26% of the population) [237].

Regional health administrations were introduced in 1993 and are responsible for management at the regional level, although with financial responsibilities limited to primary care because hospital budgets are defined centrally. The autonomous Azores and Madeira have broad powers for their own health care planning and management. Public and private expenditure in the NHS account for approximately 66% and 35% of total health expenditure, respectively [234].

In May 2011, the economic crisis led Portugal to sign a Memorandum of Understanding with the

International Monetary Fund, the European Commission and the European Central Bank [238,239]. A set number of measures in the health sector were therefore implemented, aimed at increasing cost-containment, improving efficiency and increasing regulation [240].

Resources and provision of health services

In Portugal in 2014, there were 225 hospitals, 113 of which belonged to the NHS, with a total capacity of 34,522 beds. There were 442.6 physicians per 100,000 population (above the European Union average of 349.6) and 637.8 nurses per 100,000 population (below the European Union average of 864.3). Health workers and health equipment are concentrated in the major urban centres and along the coast, leaving the interior underserved. Despite the universal and comprehensive nature of the NHS, for example the lack of all medical specialties in hospitals located outside great metropolitan areas like Lisbon, Porto and Coimbra represents geographical gaps in provision. The distribution of health resources, including health workers, does not seem to take into consideration the characteristics of the population, for example municipalities with a higher ageing index, and therefore higher health needs, are not those concentrating more resources, in part because those municipalities are not very densely populated [241].

The NHS predominantly provides primary care and acute hospital care. Although with public funding to a considerable extent, dental consultations, diagnostic services, renal dialysis and rehabilitation are more commonly provided in the private sector. The reorganisation of Portuguese primary care was started in 2007, with the creation of Family Health Units. Hospitals provide secondary and tertiary care, and are grouped into Hospital Centres covering a given geographical area [234].

In Portugal, public hospitals provide treatment for the majority of acute coronary events [242]. According to the cardiology referral net that was updated in 2015 [243], there are 38 public hospitals with human and technical resources to provide structured care for patients with ACS, of which 16 have catheterisation laboratory facilities. A coronary fast track system was implemented at the national level, with the aim of increasing the proportion of STEMI patients submitted to reperfusion, namely through primary PCI. This fast track system is organized to diagnose ACS, to identify the subgroup of patients with STEMI by enabling the performance and analysis of ECG, to provide immediate care, and to assist in transport to the appropriate hospital. The National Institute for Medical Emergencies (INEM) is responsible for the coordination and functioning of an integrated medical emergency system in Portugal, and is crucial to the coronary fast track functioning. INEM provides medical aid at the scene; assists transportation of patients to the appropriate hospital; and ensures the coordination between various participants in the system [234].

Nevertheless, a description of the cardiology resources at the national level hides a heterogeneous geographic distribution. Cardiologists are concentrated in Lisbon and in the North, regions where 42.4% and 34.1% of the total number of Cardiologists work, respectively. Additionally, in 2013, the number of

catheterisation laboratory rooms per inhabitant varied from 1/743,306 in Alentejo to 1/311,947 in Lisbon. For example, in the northeastern region of Portugal, an interior and rural region, several subregions have only access within a maximum of 60 minutes to one basic emergency department, while the coastal regions have several emergency departments, basic, intermediate and with intensive care facilities accessible within the acceptable maximum distance, considering the importance of rapid access to the appropriate health service of patients with ACS [243].

1.4.2 Coronary heart disease in Portugal

Burden

In terms of CVD disease, Portugal is a low-risk country (the age-adjusted 2012 CVD mortality cut-offs in those 45 –74 years of age are less than 225/100,000 in men and less than 175/100,000 in women) [23].

According to the latest available data from Statistics Portugal [244], diseases of the circulatory system were the main cause of death in 2015. In 2015, CHD [International Classification of Diseases (ICD) 10: I20-I25] accounted for 6.7% of mortality in the whole country (7.5% for men and 6.0% for women), but with differences by region, ranging from 9.8% in Azores to 3.7% in *Viseu, Dão, Lafões* and *Coimbra* regions. The sex ratio for death due to CHD was 124.4 male deaths per 100 female deaths. For CHD, the age standardised mortality rate was 37.1 deaths per 100,000 inhabitants (52.6 for men and 24.4 for women); the adjusted rate of potential years of life lost (YLL) was 182.6 per 100,000 inhabitants (317.7 for men and 59.7 for women); and the average number of potential YLL 11.1 (11.6 for men and 9.2 for women) [244].

In Portugal, in recent decades a dramatic decrease in CVD mortality and YLL was observed, with a parallel transition towards cancer, with women having the highest burdens of disease from CVD until later than men [245].

In 2015, CHD was responsible for the loss of 1,272 DALYs per 100,000 males and of 571 DALYs per 100,000 females, being within the group of European countries with the lowest age-standardised DALYs rate for CHD [246]. Results of evaluation of the burden of CHD by region in Portugal in 2013, revealed that age-standardised DALYs rates per 1000 population ranged from 7.3 in the Northern and Central regions to 11.8 in the Algarve in men, and from 2.6 in the Northern region to 4.6 in Lisbon in women [247].

Inequalities in risk factors, management and treatment

Important insights about relative contributions of different primary and secondary prevention measures to the decline in CHD mortality in Portugal were given by Pereira and colleagues [248], with the application of the IMPACT CHD Policy Model. This model was able to explain 92% of the estimated decrease in number

of deaths. Approximately 42% of the decrease in CHD mortality explained by the model was attributable to population risk factor reductions, mainly blood pressure (27% in men and 60% in women) and total cholesterol (14% in men and 5% in women), and smoking in men (11%). However, these reductions were partially offset by adverse trends in diabetes (18% in men and 2% in women) and obesity (6% in men and 5% in women), and smoking in women (2%). In the last decades, there was a decrease in blood pressure levels, observed in middle-aged and older adults, while among young adults, the levels remained approximately constant [249]. Self-reported diabetes and overweight/obesity increased in both sexes; and smoking prevalence increased only among women [248,250-252].

No systematic and comprehensive information about trends in risk factors by Portuguese region or SEP is available. However, cross-sectional studies on some cardiovascular risk factors support inequalities in their distribution by Portuguese region [253,254] and SEP [255,256]. According to results of an ecological study, using aggregated statistics on hospital admissions and mortality from CHD between 2000 and 2007, and regional data on demography, economics and health care resources, an inner/coastal pattern in the geographic distribution of incidence and mortality from CHD was clear even after adjustment for age, gender, economic development and health resources distribution [257].

According to the IMPACT model, approximately 50% of the decrease in CHD mortality explained was attributable to increased uptake of treatments, including initial treatments after an AMI (10%) [248]. In recent decades, an improvement in secondary prevention of ACS was observed in Portugal. There was an increase in the use of recommended pharmacological therapy for secondary prevention, during hospitalisation and at hospital discharge, after an ACS [258]; the proportion of mixed ACS patients treated with fibrinolysis decreased and the use of PCI increased, while the use of CABG did not change [259]. Between 2002 and 2013, there was a three-fold increase in primary angioplasty rates per million population, with no statistically significant differences in age and sex distribution by year of analysis [260]. Between 2010 and 2015, a two-fold increase in primary angioplasty was observed at the national level, no information is given about trends by sex, age or region [156].

According to results obtained from the Portuguese interventional cardiology database, from the period between 2002 and 2012, women with STEMI treated by primary PCI had a greater risk factor burden, were less frequently revascularised within six hours of symptom onset, and had a 1.7 times higher risk of in-hospital death compared with men. After risk adjustment, in-hospital mortality was similar between women and men with STEMI treated by primary PCI [261].

There are also known differences in distribution of structure and process quality indicators for CHD at the geographic level, namely the number of patients submitted to primary PCI, the mean time delay to coronary angiography, and the number of patients admitted through the coronary fast track system [243,262].

No adequate systematic monitoring of disaggregated data by group prone to inequality is available in

what concerns trends in secondary prevention of CHD in Portugal.

Portuguese goals to deal with inequalities

The department of quality in health of the National Health System was created to promote and disseminate the improvement of the health institutions quality, proving efforts to develop this area in Portugal [263]. The current National Health Plan, which was extended until 2020, defines strategies for improving citizens' empowerment and tackling health inequalities, through involvement of social and private sectors, and the development of intersectoral and multidisciplinary approaches [264]. The current plan sets four main axes: health citizenship, equity and adequate access to health care, health quality, and health policies.

The National Strategy for Quality in Health 2015–2020, in line with the European Union Health Programme 2014–2020, defines several priorities, including improving organisational and clinical practice quality; increasing the adoption of practice guidelines in clinical practice; strengthening patient safety; strengthening clinical research; continuous monitoring of quality and safety; disseminating comparable performance data; improving quality and accreditation of health care providers; providing transparent information to citizens and citizens' empowerment [234]. However, the health policy-making process is not systematically evaluated; health impact assessments have not been institutionalised in Portugal, nor have specific guidelines on this subject been produced [234].

The information infrastructure of the health system in Portugal is extensive, with electronic platforms that store different kinds of health information, used for different purposes. Limitations related to effective connection of different platforms and challenges concerning patient privacy and the legal basis for connecting patient data exist in the monitoring and reporting of the health system performance, and in the use of these data for research purposes.

2. OBJECTIVES

Independently of differences in patient and system level determinants of health care between and within countries, tackling inequalities in health status is a worldwide target priority [165], and a task particularly important and challenging for Portugal [234]. Cardiovascular science advances over the past two centuries have been remarkable, and today, a huge focus is set to improve the implementation of well-established consensus in this field in routine clinical practice. The continuum of CHD presentation, the effective and safe diagnoses and therapeutic approaches available and the current organisation of health systems in developed countries create several opportunities to improve the quality of care of these patients, which encompasses reducing inequalities. To study inequalities in management and outcomes of patients with CHD in Portugal, we used two frameworks to address the complex process of care of this disease, particularly of ACS: the model of socioeconomic determinants of health proposed by Solar and Irwin [162], and the model of access to health care proposed by Levesque [122]. Departing from the clinical knowledge of the disease, the use of these conceptual frameworks was structural to guide the objectives, select data sources, groups of patients, variables of exposure, outcomes and confounding; and also to analyse and interpret results (Figure 3).

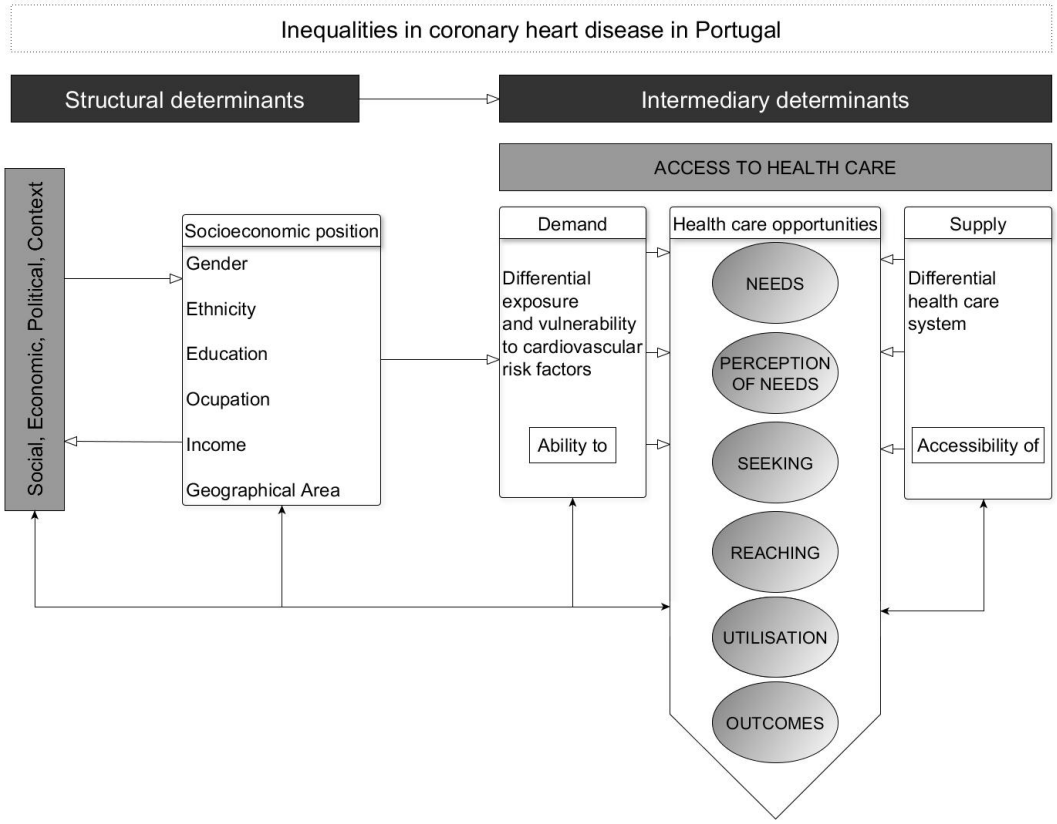

Figure 3. Conceptual framework to study inequalities in CHD in Portugal (adapted from the model of socioeconomic determinants of health proposed by Solar and Irwin [162], and from the model of access to health care proposed by Levesque [122]).

The specific objectives of this thesis are depicted in figure 4 and are the following:

1. To describe time trends in death rates, absolute number of deaths and years of life lost from coronary heart disease among men and women in Portugal, by region, during the period 1981–2012 (Paper 1).

2. To analyse sex differences in conservative vs invasive management of acute coronary syndrome in 10 hospitals with different characteristics (Paper 2).

3. To assess differences by sex in management and outcomes (30-day mortality) of patients with acute myocardial infarction, by the application of standard quality indicators (Paper 3).

4. To analyse sex differences in presenting symptoms of acute coronary syndrome (Paper 4).

5. To assess the proportion of patients with a first episode of acute coronary syndrome who reported chest pain, medical care seeking and performance of exams because of the pain; and to identify determinants of seeking medical advice and referral to electrocardiogram (Paper 5).

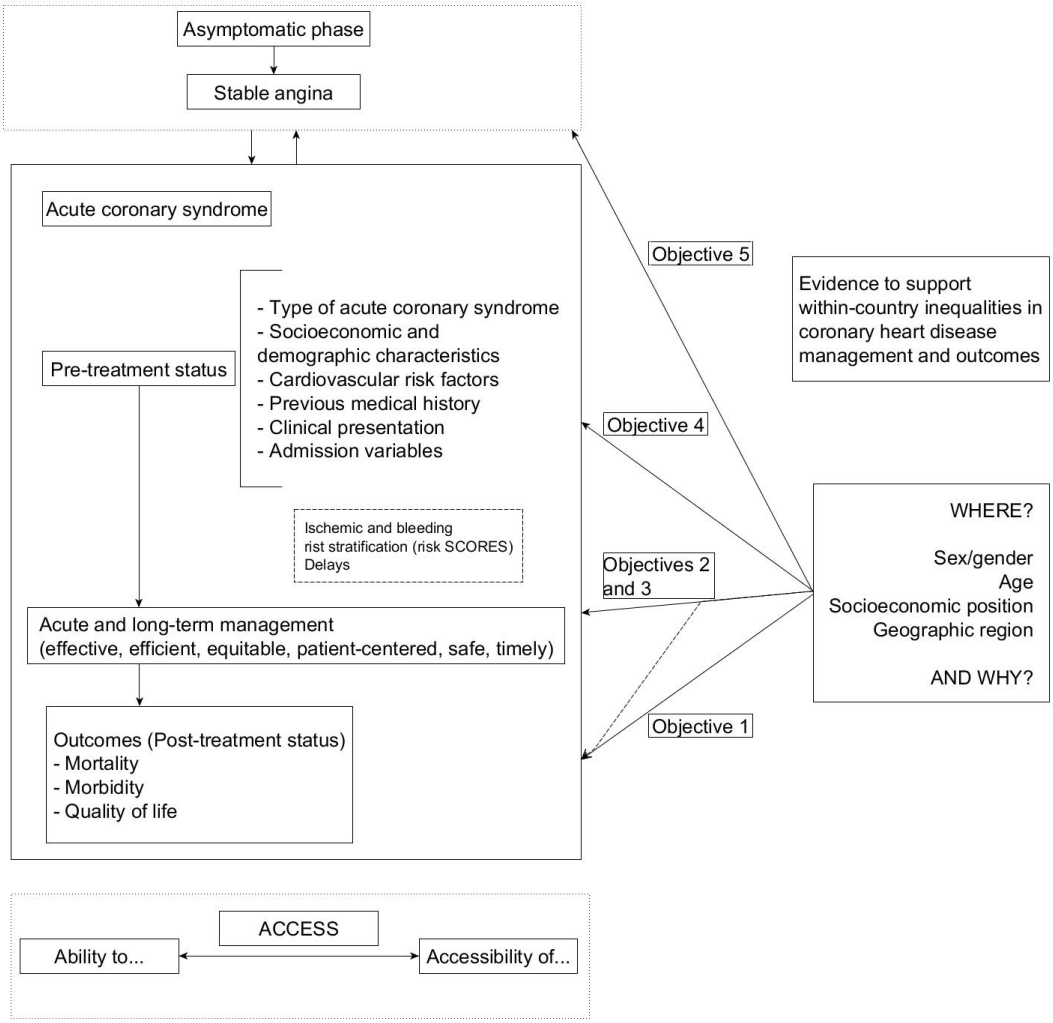

Figure 4. Schematic depiction of the specific objectives.

We started our research by assessing differences in outcomes from CHD at the geographical level and separately in men and women. Departing from assessing inequalities at the regional level, we then moved to the individual level, analysing differences in management and its relation with outcomes between women and men hospitalised with an ACS. Considering that different diagnostic accuracy of symptoms by sex may be one possible determinant of delayed diagnosis, of management and of attainment of the maximal benefit of treatment, we decided to characterise differences by sex in clinical presentation of ACS. We then moved backward, towards potential missed opportunities to intervene before the ACS phase.

3. PAPERS

3.1. PAPER 1

REGIONAL VARIATION IN CORONARY HEART DISEASE MORTALITY TRENDS IN PORTUGAL, 1981-2012

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Regional variation in coronary heart disease mortality trends in Portugal, 1981–2012

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ABSTRACT

Background: Information is scarce about the geographic variation in time trends of mortality from coronary heart disease (CHD). We aimed to describe trends in death rates, absolute number of deaths and years of life lost (YLL) due to CHD among men and women in Portugal, by region, from 1981 to 2012.
Methods: The age-standardized mortality rates from CHD were estimated by sex and region. We used joinpoint regression analysis to calculate the annual percent change (APC) in mortality and to identify points of significant change in the trend. The YLL due to premature mortality for CHD were computed using the Global Burden of Disease method.
Results: The age-adjusted mortality from CHD decreased between 1981 and 2012, both in men and women, but with significantly different APC by region. Smaller declines in rates were observed in Alentejo (men: APC 1993–2012: −2.4%; women: APC 1991–2012: −2.4%). The greatest decline was observed in Madeira between 2003 and 2012, in men (APC: −7.6%) and women (APC: −9.7%). The decline in rates in Algarve started only after 2003, whereas it was consistent from 1981 in the North and started in the 1990s in most other regions. A decrease in the number of deaths was only observed after 2000. The YLL from CHD decreased from 1981 to 2012, mainly after 2000.
Conclusions: In Portugal, between 1981 and 2012, relative declines of CHD mortality indicators were different by geographic region. Consistent decreases in mortality rates were only observed in the Centre, Lisbon and North, the most populated and urbanized regions.

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1. Introduction

Cardiovascular diseases (CVD) are the most common cause of death. In 2012, almost half of non-communicable disease deaths worldwide were caused by CVD (17.5 million deaths), more than double the number of deaths caused by cancers [1,2]. CVD are responsible for close to half of all deaths in Europe (over 4 million deaths per year), with coronary heart disease (CHD) accounting for 20% of all deaths in Europe annually (nearly 1.8 million deaths) [2]. The most up-to-date data on CVD still show disparities in the death rates between European countries, with Central and Eastern Europe having higher rates than Northern, Southern and Western Europe [2]. Within-country CVD mortality inequalities have been reported in several European countries, by region, socioeconomic characteristics and country of birth [3–5].

CVD and CHD death rates have been consistently falling across most but not all European countries; the timing and magnitude of this decrease also vary [2]. CHD mortality trends may also be different by demographic groups, with young adults, especially women, experiencing smaller decreases in CHD mortality rates in the two last decades [6]. Specific indicators such as years of life lost are needed to capture premature mortality due to CHD.

In Portugal, the age-adjusted mortality from CVD, in 2011, was 174.7/100,000 among men and 126.8/100,000 among women, and the age-adjusted mortality rates from CHD are among the lowest in Europe [2]. There was a decrease in the age-adjusted mortality from CVD between 1980 and 2010 [7], and also from CHD [2], but there is no information about the magnitude of these trends by region. Differences in health status by geographic region, namely in less populated and less urban regions, are among the sizeable inequalities identified

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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in the Portugal health system performance assessment in 2010, conducted by the World Health Organization [8]. This report states that it is difficult to assess and monitor the extent of the health inequalities in Portugal, due to the lack of a monitoring system of health indicators by target population groups, owing, at least in part, to a narrow interpretation of the data confidentiality law. A recent ecological study showed geographic variation in hospital admissions and in-hospital mortality of patients admitted with ischemic heart disease in Portugal from 2000 to 2007, with the interior regions showing higher rates, not fully explained by socio-demographic, economical and health resource factors [9]. It is of interest to expand this observation to a longer period and to consider total mortality, in addition to in-hospital mortality.

We aimed to describe time trends in death rates, absolute number of deaths and YLL from CHD among men and women in Portugal, by region, during the period 1981–2012.

2. Methods

2.1. Sources of data

Estimates of population at risk as well as the number of deaths from CHD [International Classification of Diseases 9th revision clinical modification, (ICD 9 CM) 410–414] were obtained from official statistics [10,11].

All data were obtained from 1981 to 2012 for each sex in age groups (<1, 1–4, 5-year age groups to 80–84 and ≥85 years), by region [Nomenclature of Territorial Units for Statistics (NUTS II): Alentejo, Algarve, Azores, Centre, Lisbon, Madeira and North].

2.2. Trends in mortality rates

We calculated age-standardized mortality rates per 100,000 by the direct method, using the European standard population (2013 revision) as reference [12].

To calculate the annual variation in mortality and to identify points of significant change in the log-linear slope of the trend (joinpoints) [13] we performed a joinpoint regression analysis, using Joinpoint® version 3.4 from the Surveillance Research Program of the US National Cancer Institute. The analysis starts with the minimum number of joinpoints, with no joinpoints corresponding to a straight line, testing if one or more joinpoints significantly improve model fit. We set the minimum number of years before the first, after the last and between consecutive joinpoints as five. The best fitting models for the trends are presented for men and women by region. The estimated annual percent change (APC) in mortality for each period was calculated taking the calendar year as the independent variable and assuming a Poisson distribution.

2.3. Years of life lost

The years of life lost (YLL) due to premature mortality for CHD, by sex and age group, in each geographic region, were computed using the Global Burden of Disease method [14], by multiplying the number of deaths at each age by the life expectancy at the age at which death occurs. We considered the recommended standard life expectancy at birth of 80 years for men and 82.5 years for women. The average age at death was set to the mid-point of each five-year age group, except for the oldest group in whom it was assumed to be 87.5 years [14]. We applied a 3% time discount rate to assign less weight to the YLL corresponding to the periods more distant from the time of death than to those referring to the first years after death, an age-weighting parameter to weight YLL in the very young and the older ages less than other ages (Global Burden of Disease standard value is 0.04) and an age weighting correction constant so that the introduction of age-weights did not alter the total number of YLL (Global Burden of Disease standard value is 0.1658) [14]. The total YLL for each gender and region was obtained by summing the YLL of all age groups. Moving averages (over 3 years) for YLL were calculated.

3. Results

3.1. Trends in mortality rates

In Portugal, the age-adjusted mortality rates from CHD decreased between 1981 and 2012, both in men and women, though with different patterns by geographic region, both in magnitude and year of decline onset.

In Portugal, among men, age-standardized mortality rates decreased from 195.6/100,000 in 1981 to 86.7/100,000 in 2012; and among women, from 108.0/100, 000 to 50.0/100,000, in the same period.

Among men, Azores and Alentejo were the two regions with the highest standardized mortality rates in 1981 (326.5/100,000 and 250.3/100,000), respectively and also in 2012 (174.9/100,000 and 157.6/100,000, respectively). In the remaining regions, the standardized mortality rates were similar among regions in 1981, ranging from 171.1/100,000 in Algarve to 186.4 in Lisbon, while in 2012 the North showed a lower standardized mortality rate than all other regions (66.4/100,000). Among women, Azores and Alentejo were also the two regions with the highest standardized mortality rates both in 1981 (148.4/100,000 and 164.6/100,000, respectively) and in 2012 (97.4/100,000 for both regions). In the remaining regions, the mortality rates in 1981 ranged from 87.1/100,000 in the Algarve to 139.7/100,000 in Madeira, while the North ranked again as the region with the lowest mortality rate in 2012 (32.6/100,000) (Fig. 1).

When analysing the decreases in standardized mortality rates over the study period, in the whole country 1993 and 2003 mark inflexion points for progressively steeper declines in rates among men, with APC ranging from −0.7% in 1981–1993 to −5.1% in 2003–2012. Among women, inflexion points were observed in 1992 and 2003, with APC ranging from −0.2% in 1981–1992 to −5.5% in 2003–2012 (Table 1).

Among men, the decline in rates in Algarve and Madeira started later, only after 2003, whereas it was consistent from 1981 in the North and started in the nineties in the other regions. Among women, Algarve also started to experience a decrease in rates only after 2004, whereas the North and Centre had consistent decreases in rates from 1981, and from the nineties in the remaining regions, except for Madeira where a fluctuating pattern was observed (Table 1, Fig. 1).

Among men, smaller relative declines in CHD mortality rates were observed in Alentejo and in the Centre region (APC 1993–2012: −2.4% and −3.3%, respectively), while among women the region with the smallest decline was Alentejo (APC 1991–2012: −2.4%) (Table 1, Fig. 1). The greatest relative decline was observed in Madeira for the period 2003 to 2012, both in men (APC: −7.6%) and in women (APC: −9.7%) (Table 1, Fig. 1).

The declines in mortality rates had similar magnitude over time between men and women, when analysing the country as a whole. However, in most regions, greater declines were observed among women compared to men, with larger sex differences in the Centre (APC: −5.7% vs −3.3%; women vs men), followed by Madeira (APC: −9.7% vs −7.6%) and the North (APC: −6.2% vs −4.3%) (Table 1).

3.2. Number of deaths and YLL

Although the decrease in the age-adjusted mortality rates from CHD started in the nineties in the majority of the Portuguese regions, the decrease in the number of deaths was only observed after 2000 (Fig. 2).

All over the country, the YLL from CHD were significantly higher in men. The YLL from CHD decreased from 1981 to 2012, both among men and women, ranging from a 23.9% decrease in Alentejo to a 64.5% decrease in Madeira, among men, and from a 4.8% decrease in Alentejo to a 57.8% decrease in Madeira, among women (Table 2). This decrease was mainly observed after the year 2000, and Lisbon and the North were the two geographic regions with lowest YLL, both in men and women, during the majority of the period studied (YLL in 2012, among men: 7.09/1000 population in Lisbon and 4.43/1000 population in the North; and among women: 4.91/1000 population in Lisbon and 2.70/1000 population in the North) (Table 2, Fig. 2).

4. Discussion

CHD mortality rates decreased in Portugal over the last 30 years, but with geographic disparities, meaning that cardiovascular health inequalities persisted in the country throughout this period. Azores and Alentejo started with the highest rates in 1981, and despite the decrease, still showed higher rates in 2012, although the difference from the other regions was attenuated. The North, on the other hand, had a mortality rate that was dissimilar to other regions, which began to diverge early in the nineties but maintaining the lowest rates until 2012.

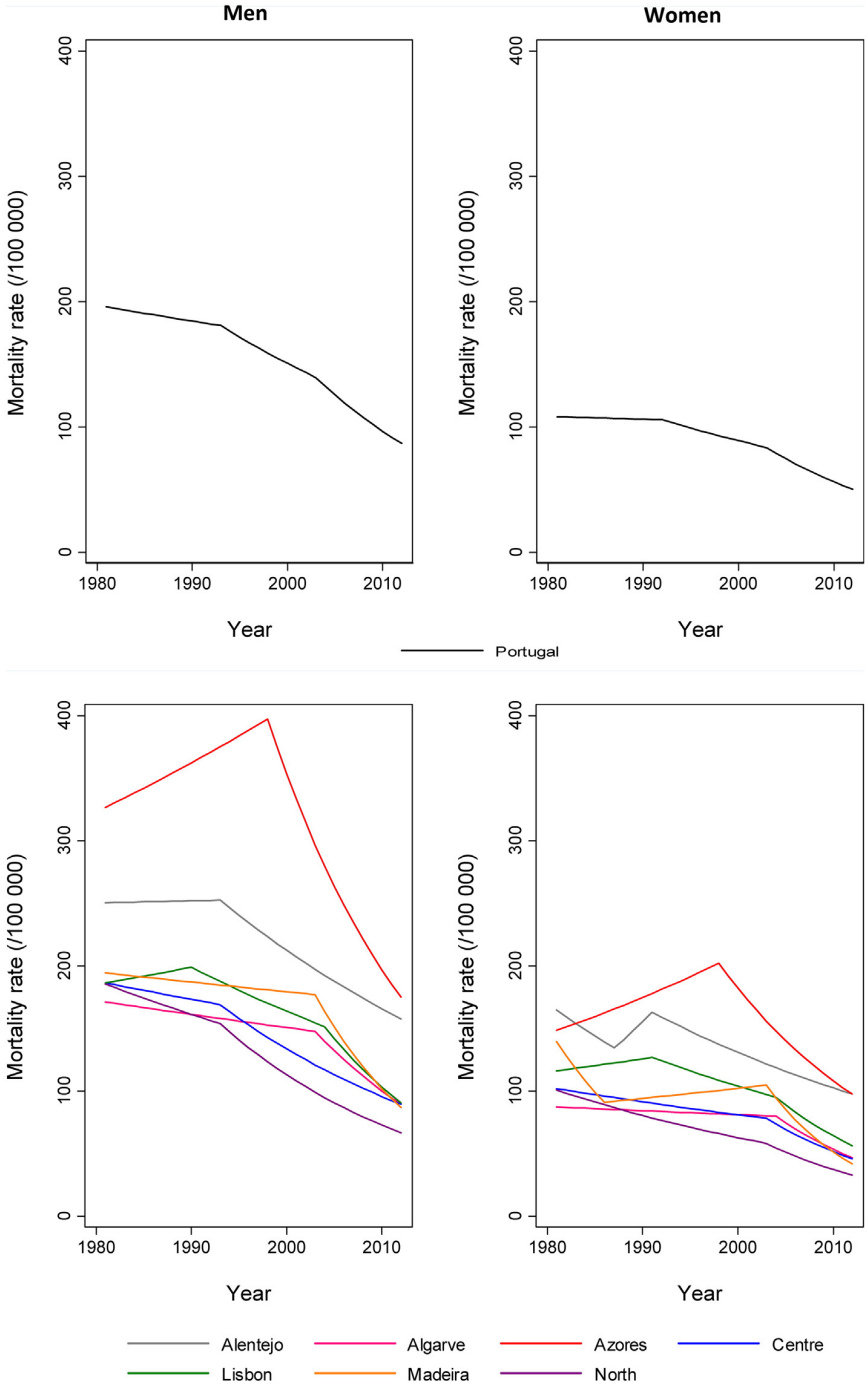

Fig. 1. Time trends in age standardized (European population) mortality rates for coronary heart disease, by sex and region, 1981–2012.

The YLL from CHD also decreased from 1981 to 2012 and the decrease in the number of deaths was only observed after 2000. The CHD mortality trends in Portugal are similar to those observed in other developed countries of the world, namely in Western Europe [15]. This decline has generally been described at the national level, which masks any existing differences between socioeconomic groups or geographic regions.

From 1981 to around 2000 the increase in the population size and the older age structure [11] exceeded the contribution of decrease in rates to a lower mortality burden, explaining an increase in the number of deaths due to CHD until 2000. The higher YLL from CHD in men is in accordance with the fact that the difference of CHD risk by sex is significantly larger in young people. Lisbon and the North are the two regions with the youngest population, explaining the lowest YLL observed [16].

The inequalities in CHD mortality trends by Portuguese region are dependent on two main domains, namely 1) the prevalence of cardiovascular risk factors and 2) health-care related factors, including the distribution and quality of health resources, access to the services and patterns of use of health care [17]. These factors are related not only with socioeconomic conditions, but also with lifestyle choices,

Table 1
Annual percent change (95% confidence intervals, CI) in coronary heart disease mortality rates, by sex and region, 1981–2012.

Men			Women		
Period[a]	Mortality rate[b]	APC, % (95% CI)[c]	Period[a]	Mortality rate[b]	APC, % (95% CI)[c]
Portugal					
1981–1993	195.6	−0.7 (−1.2 to −0.1)	1981–1992	108.0	−0.2 (−1.0 to 0.6)
1993–2003	180.7	−2.6 (−3.4 to −1.8)	1992–2003	105.6	−2.1 (−2.9 to −1.4)
2003–2012	139.2	−5.1 (−5.9 to −4.3)	2003–2012	83.3	−5.5 (−6.4 to −4.6)
Alentejo					
1981–1993	250.3	0.1 (−1.0 to 1.2)	1981–1987	164.6	−3.3 (−6.7 to 0.2)
1993–2012	252.4	−2.4 (−3.0 to −1.9)	1987–1991	134.4	4.9 (−4.5 to 15.3)
			1991–2012	163.0	−2.4 (−2.9 to −2.0)
Algarve					
1981–2003	171.1	−0.7 (−1.4 to 0.0)	1981–2004	87.1	−0.4 (−1.2 to 0.4)
2003–2012	148.0	−5.4 (−7.8 to −2.9)	2004–2012	79.8	−6.5 (−10 to −2.8)
Azores					
1981–1998	326.5	1.2 (0.4 to 1.9)	1981–1998	148.3	1.8 (0.7 to 3.0)
1998–2012	397.1	−5.7 (−6.7 to −4.7)	1998–2012	202.0	−5.1 (−6.5 to −3.7)
Centre					
1981–1993	186.3	−0.8 (−1.8 to 0.2)	1981–2003	101.8	−1.2 (−1.6 to −0.8)
1993–2012	168.9	−3.3 (−3.8 to −2.8)	2003–2012	78.0	−5.7 (−7.7 to −3.8)
Lisbon					
1981–1990	186.4	0.7 (−0.7 to 2.2)	1981–1991	116.0	0.9 (−0.2 to 2.0)
1990–2004	198.8	−1.9 (−2.6 to −1.3)	1991–2004	126.7	−2.2 (−2.9 to −1.5)
2004–2012	151.3	−6.2 (−7.5 to −4.9)	2004–2012	94.9	−6.3 (−7.7 to −5.0)
Madeira					
1981–2003	194.3	−0.4 (−1.4 to 0.6)	1981–1986	139.7	−8.2 (−15.2 to −0.7)
2003–2012	177.0	−7.6 (−11.6 to −3.4)	1986–2003	90.9	0.8 (−0.5 to 2.1)
			2003–2012	104.6	−9.7 (−12.8 to −6.5)
North					
1981–1993	185.5	−1.5 (−2.5 to −0.5)	1981–2003	100.7	−2.5 (−3.2 to −1.7)
1993–2012	153.8	−4.3 (−4.8 to −3.8)	2003–2012	58.1	−6.2 (−9.0 to −3.3)

[a] Periods with constant log-linear trend identified in the joinpoint analysis.
[b] Mortality rate (/100,000), estimated age-standardized mortality rate at the beginning of the respective period.
[c] APC, annual percent change; 95% CI, 95% confidence interval.

structured by cultural forces, often operating in opposite directions. For instance, in Portugal, those forces promote the Mediterranean diet and at the same time smoking among women [17].

The contribution of the reduction in risk factors to the decline of Portuguese CHD mortality from 1995 to 2008 was estimated to be 42% and the increase in the uptake of treatments contributed approximately 50% [17]. Previous studies have analysed trends in the prevalence or means of cardiovascular risk factors in Portugal [18–20]. In the last decades there was a decrease in blood pressure levels, observed in middle-aged and older adults, while among young adults the levels remained approximately constant [18]. Self-reported diabetes and overweight/obesity, on the other hand, increased in both sexes; while smoking prevalence increased only among women [17,19–21]. These estimates, very important to understand the main determinants of the CHD mortality decline in Portugal, certainly conceal different proportions across geographic regions.

There is no systematic and comprehensive information available about trends in risk factors by Portuguese regions, but cross-sectional studies on some cardiovascular risk factors distribution by Portuguese region convey relevant information. According to the AMALIA study [22], which included 38,893 individuals, with regional, gender and age-group distribution representative of the Portuguese population, between October 2006 and February 2007, Azores, one of the regions with the highest standardized mortality rate over the last three decades, was the region with the highest prevalence of self-reported hypertension (35.6%), hypercholesterolemia (25.6%), diabetes (15.4%) and overweight/obesity (77.7%). Algarve, Madeira and the North were the regions with the lowest prevalence of hypercholesterolemia (15.6, 15.8 and 15.9%, respectively); Algarve and the North had also the lowest prevalence of hypertension (18.3 and 19.3%, respectively) and diabetes (9.1 and 6.5%, respectively). The North had the lowest prevalence of overweight/obesity (41.3%). Algarve was the region with the highest self-reported prevalence of smoking (20.3%), and Madeira and the Centre region the lowest (11.9 and 12.8%, respectively). According to the VALSIM study [23], carried out between April 2006 and November 2007, there were significant regional variations in the prevalence of metabolic syndrome, adjusted for gender and age: residents in the Algarve or in Lisbon and Tagus Valley had lower prevalence [odds ratio (OR) (95% confidence interval): 0.78 (0.66–0.92) and 0.83 (0.77–0.91), respectively], while residents in the North or Centre regions had higher prevalence (OR (95% confidence interval): 1.11 (1.01–1.21) and 1.08 (1.002–1.16), respectively). After adjusting for gender and age, the higher prevalence in Alentejo residents was no longer observed, probably due to its elderly population. Considering a possible different individual's global risk of developing CHD profile by region and therefore a probable different need of risk-factor lowering treatment for CHD primary prevention within Portugal, data on time trends of different drugs utilization by region, namely statins and blood pressure lowering agents, would help to compare CHD risk level and risk-factor lowering treatment, analysing the importance of evidence based treatment in the reduction of CHD mortality by region. If regions with a faster reduction in CHD mortality showed a larger increase in risk-factor lowering treatment, a positive effect of these agents on CHD mortality and a risk-based prescription would be supported; however if a “discordant” relation (slower reduction in mortality accompanied by a larger increase in prescription) was observed, which was already observed with statins in other settings [24], other factors apart from the actual risk of the patients would emerge as an explanation. Available data do not allow the quantification of time trends in cardiovascular risk factors by region, which would help to better understand the determinants of

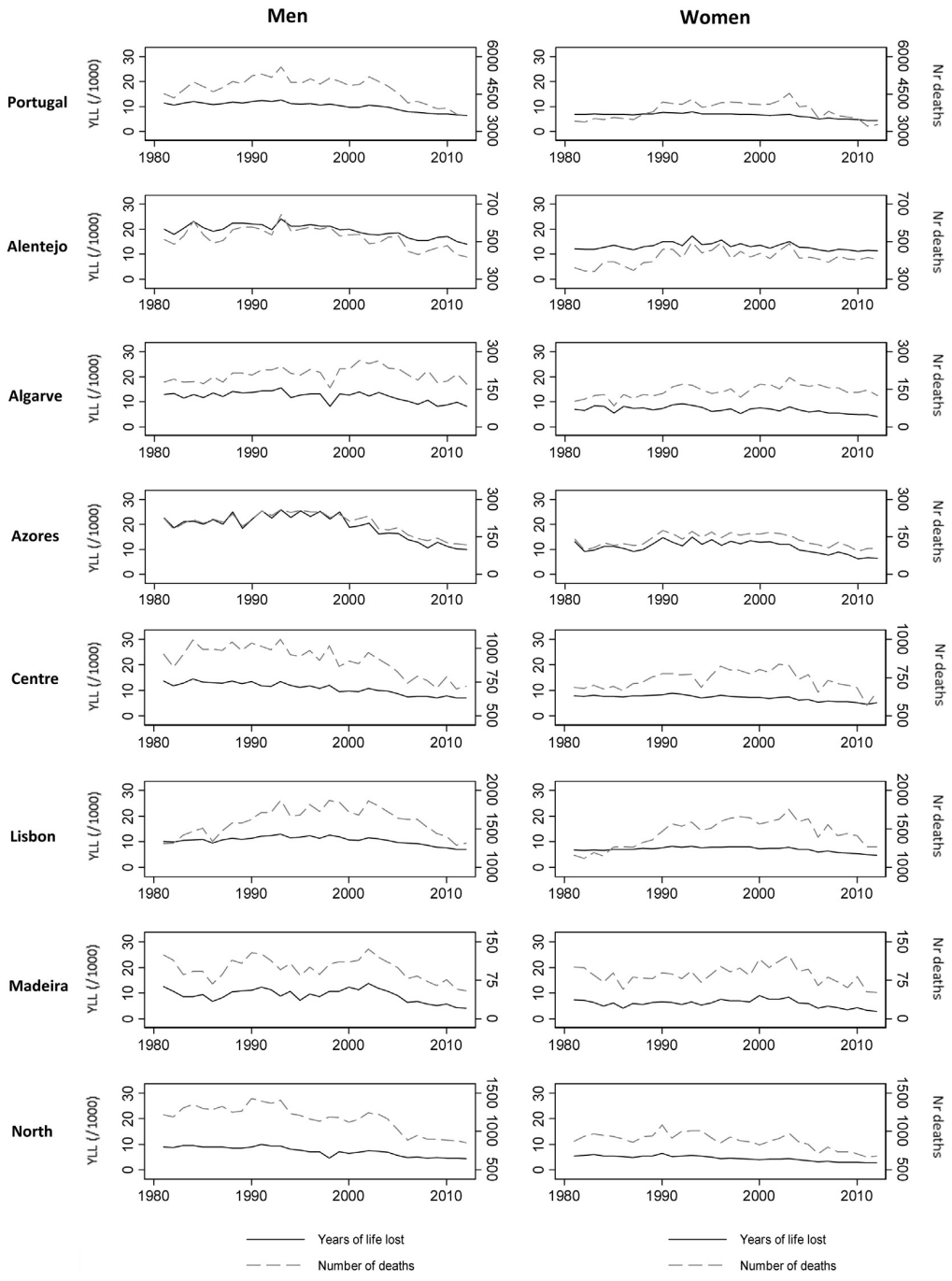

Fig. 2. Time trends in years of life lost and in number of deaths for coronary heart disease, by sex and region, 1981–2012.

the different patterns of coronary disease mortality declines observed, we expect that these differences are partly explained by an unequal prevention and control of risk factors per region.

The National Health Service (NHS) provides universal coverage, financed mainly through taxation, which should ensure avoidance of inequalities, at least in access to care. Treatment of CHD in Portugal should therefore be equitable and based on clinical need, and not dependent on age, sex, race, region of residence and other socio-economic factors. Indeed the majority of acute coronary events are treated in public hospitals, but long-term care of patients is also carried out by other providers, both public and private [25]. Besides the NHS, the Portuguese health care system has two other coexisting and overlapping players: special public and private insurance schemes for certain professions (health subsystems) and private voluntary health insurance. Public provision is particularly responsible for primary and hospital care. Specialist consultations and diagnostic services, among other treatments, are commonly provided also in the private sector, less accessible to the general population [26]. Despite the NHS' supposed universal coverage, the geographic distribution of health resources is heterogeneous [25]. Algarve and Alentejo are the regions with the lowest number of hospital beds (2.1 and 2.2 per 1000 inhabitants in 2010, respectively). Azores and Alentejo are the regions with the lowest physician workforce, approximately 2 doctors per 1000 inhabitants, about half the number at the national level [27]. Additionally there are several access indicators,

Table 2
Years of life lost from 1981 to 2012, by region and sex.

	Men			Women		
	YLL[a]		YLL[a] reduction (%)	YLL[a]		YLL[a] reduction (%)
	1981	2012	1981–2012	1981	2012	1981–2012
Portugal	11.05	6.60	40.3	6.9	4.4	36.2
Alentejo	18.99	14.46	23.9	12.06	11.48	4.8
Algarve	13.10	9.05	30.9	6.74	4.44	34.1
Azores	20.60	10.11	50.9	11.07	6.53	41.0
Centre	12.75	7.15	43.9	7.75	4.87	37.2
Lisbon	10.09	7.09	29.7	6.65	4.91	26.2
Madeira	11.58	4.11	64.5	7.25	3.06	57.8
North	8.82	4.43	49.8	5.52	2.70	51.1

[a] YLL, years of life lost in years. The YLL of each year was calculated as the moving average over 3 years.

directly related to CHD outcomes, with clear differences by region. Some of these indicators have improved in the last years at the national level, namely the number of patients submitted to primary percutaneous coronary intervention (primary PCI), that increased by 37.0% from 2009 to 2013, the mean delay time to coronary angiography, that decreased from 22.3 days in 2009 to 13.7 days in 2013, or the number of patients admitted through the coronary fast-track system that increased by 80.5% from 2009 to 2013. However, at the region level, these improvements were not of the same magnitude. Considering specific cardiac procedures, in 2013, Alentejo was the region with the lowest number of patients submitted to primary PCI (170.9 per million of inhabitants) and with the highest mean delay time after a coronary angiography is indicated (30 days). Lisbon and the Algarve were the regions with the highest number of patients submitted to primary PCI (506.4 and 429.5 per million of inhabitants, respectively); and Algarve and the North were the regions with the lowest mean delay time after a coronary angiography is indicated (2 and 8.2 days, respectively). Additionally the coronary fast-track system was not implemented at the same time in the different Portuguese regions, with Alentejo being the region with the latest implementation [25]. Despite the increase in the use of recommended pharmacological therapy for secondary prevention after an ACS during hospitalization and at hospital discharge over the last two decades in Portugal [28], there is no information on trends of utilization of these drugs in this group of patients by region. Treatment with invasive procedures may be dependent on access determinants, namely access to catheterization laboratories, but the prescription of pharmacological treatment during hospitalization and at discharge only depends on the medical decision. It would be important to evaluate variation in trends of utilization of pharmacological therapy for secondary prevention of ACS by region, and to understand their role in the different patterns of decrease in mortality observed. All these data suggest that the factors that determine the observed trends, even in regions with similar CHD mortality trends, play through different causality pathways. Understanding the specific pathways operating in each region has the potential to further reduce the burden of CHD.

Considering the five main patterns of CHD mortality trends at country level recently proposed, Portugal was included in a pattern characterized by the lowest age-standardized mortality rate and with a consistent decrease throughout the period of analysis [29]. The Centre, Lisbon and the North regions, where most of the population lives, a young and more educated population that lives predominantly in urban areas [16], were closest to this same pattern, while the remaining regions were more similar to a pattern characterized by higher rates observed until later, after 2000. This difference shows inequalities in cardiovascular health by region.

When analysing the CHD mortality trends by sex, we found greater declines among women. The most consistent sex differences in adult global mortality are attributed to CHD, which is the most common vascular condition with consistently greater age-adjusted mortality rates and risks in men than women, across different countries [2]. Lower CHD mortality rates among women are explained by a better risk factor profile, even though there is evidence of higher in-hospital mortality after a cardiovascular event and lower access to evidence-based secondary prevention [30]. The smaller sex difference in CVD mortality after midlife has traditionally been related to postmenopausal oestrogen deficiency in women [31], but it might also be explained by the deceleration of the age-related increase in male specific mortality in midlife, whereas women's mortality rates steadily increase with age, with no significant or particular change at menopause [32]. The fact that greater declines were observed among women might be the result of effective primary and/or secondary prevention measures implemented among this group. Despite the slight increase in the prevalence of smoking among women, changes in the major cardiovascular risk factors in Portugal contributed significantly more to the CHD decrease among women than among men (58% vs 29%), with greater differences by sex observed in the decrease in the mean population systolic blood pressure (6.5 mm Hg in men and 12.4 mm Hg in women), that were estimated to have prevented or postponed 40% of deaths in men and 72% in women [17]. Interestingly, the effect of antihypertensive treatment was small, similar in men and women, and therefore this difference was mainly attributable to lifestyle changes [17]. The greater declines in CHD mortality among women are also in accordance with a recent study showing improvements in sex-differences in discharge medications of patients admitted with acute coronary syndromes in Portugal, after adjusting for the potential confounding effect of age, co-morbidities, and contraindications [33].

5. Limitations

The key factor to correctly interpret these results is good-quality data on mortality, dependent on the coverage, accuracy of diagnosing causes of death and correct coding. Portuguese mortality data have high coverage and the underlying cause of death is certified by a medical practitioner. Nevertheless there is still a high proportion of deaths (17%) coded as ill-defined causes [34] and validation studies are needed to better measure the accuracy of causes of death diagnosis.

Although we used ICD-9, which has considerably less detail than ICD-10, we are measuring CHD as a large group, without needing specific codes, which minimizes errors, even considering changes in coding rules and revisions done during the period of the study.

6. Conclusion

Despite the large decrease in age-adjusted mortality and in the YLL from CHD observed in Portugal, between 1981 and 2012, relative declines and the respective periods were different by geographic region. Recognition of these inequalities clearly underlies the need to implement an objective and systematic approach to monitor cardiovascular risk factor prevalence and proportion of control, and uptake of evidence-based treatments, both during acute events and in more stable phases, by region. Good quality data on determinants of CHD incidence and mortality by region are essential to define specific targets for intervention.

Conflict of interest

The authors declare that they have no conflict of interest.
For this type of study formal consent is not required.

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3.2. PAPER 2

SEX-RELATED INEQUALITIES IN MANAGEMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME – RESULTS FROM THE EURHOBOP STUDY

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ORIGINAL PAPER

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Sex-related inequalities in management of patients with acute coronary syndrome—results from the EURHOBOP study

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Summary

Background: Real-world data from different levels of hospital specialisation would help to understand if differences in management between women and men with acute coronary syndrome (ACS) are still a priority target. We aimed to identify sex inequalities in management of patients with different types of ACS.

Methods: We analysed 1757 patients with a non-ST-elevation ACS (NSTEACS) and 1184 with ST elevation myocardial infarction (STEMI) or left bundle branch block (non-classifiable (NC) ACS (STEMI/NC ACS group), consecutively discharged from ten Portuguese hospitals with different specialisation levels, between 2008 and 2010. We estimated odds ratios (OR) and 95% confidence intervals (95% CI) for the association between sex and the performance of coronary angiography, reperfusion and revascularisation.

Results: Among STEMI/NC ACS, men had higher probability of performing coronary angiography than women (adjusted OR = 1.64, 95% CI: 1.11-2.44), while among NSTEACS patients there was no significant difference by sex (adjusted OR = 1.26, 95% CI: 0.99-1.62). In patients who underwent coronary angiography, there was no difference in proportion of women and men submitted to revascularisation, regardless of the ACS type. Although men with STEMI/NC ACS were more likely to undergo reperfusion (crude OR = 2.17, 95% CI: 1.68-2.81), the effect became not significant after multivariable adjustment (adjusted OR = 1.33, 95% CI: 0.96-1.84).

Conclusion: Women diagnosed with STEMI/NC, but not NSTEACS, had lower probability when compared with men to be submitted to coronary angiography. There was no difference in performance of reperfusion and revascularisation by sex.

1 | INTRODUCTION

In the last decades, one of the major determinants of the decrease in coronary heart disease (CHD) mortality in Europe, in women and men, was a more effective access to coronary angiography.[1] However, recent data show that men with an acute coronary syndrome (ACS) are still more likely to undergo an invasive approach.[2] In Portugal, between 2010 and 2013, 16.5% of patients with non-ST-elevation myocardial infarction, mostly women, were treated with a conservative strategy.[3] Although from 2002 to 2013 a three-fold increase in primary angioplasty was observed, the proportion of women remained approximately the same (24.5% and 26.2%, respectively).[4] These data were obtained from registries that included patients admitted to cardiology departments, but not to other departments, and to hospitals offering differentiated care, and therefore might not represent the national trends in the invasive diagnostic-therapeutic approach of women and men with ACS.

The decrease in CHD mortality in Portugal was found to be greater among women compared to men,[5] the result of effective primary and/or secondary prevention measures implemented in this group. Changes in the major cardiovascular risk factors in Portugal contributed significantly more to the CHD decrease among women than among men, mainly due to lifestyle changes, as the effect of risk factor lowering treatment was small and similar between sexes.[1] Improvements in sex

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differences in discharge medications after an ACS as well as in drug-eluting stents use might also have contributed to these results.[6,7]

Sex and gender differences concerning ACS are described in several categories, namely risk assessment, disease awareness, comorbidities, presentation, treatment and outcomes,[8] contributing to a potential different access to health care between women and men. Real-world data about sex differences in management of ACS patients, treated in hospitals with diverse characteristics, and considering possible relative contraindications to an invasive approach and to revascularisation, represent an operational measurement of effective access. We aimed to analyse sex differences in management of ACS, controlling for age, hospital characteristics, cardiovascular risk factors, previous medical history, complications at admission and coronary anatomy, within a sample of Portuguese hospitals serving both urban and rural populations and with different levels of specialisation.

What is known

- Several studies have suggested that women with acute coronary syndrome are more likely to be treated with a conservative strategy than men.
- Studies in different settings support that disparities in care and outcomes of women and men persisted over time.
- Whether this sex-gap in management is observed for diagnostic or also for invasive therapeutic coronary procedures; and for the whole spectrum of presentations of acute coronary syndrome, managed in hospitals with different levels of specialisation is controversial.

What is new

- Women with ST-elevation acute myocardial infarction/non-classifiable (left bundle branch block) acute coronary syndrome, but not with non-ST-elevation acute coronary syndrome, were less frequently submitted to coronary angiography than men.
- No differences in reperfusion or revascularisation among those managed invasively were observed between women and men for the whole spectrum of acute coronary syndrome presentations.

2 | METHODS

2.1 | Study design and sample selection

Data for this study were collected within the framework of the EURopean Hospital Benchmarking by Outcomes in acute coronary syndrome Processes (EURHOBOP) project, a collaborative, multicentre and multinational retrospective study of patients consecutively hospitalised with a discharge diagnosis of ACS from 70 hospitals in 7 European countries (Finland, France, Germany, Greece, Italy, Portugal, and Spain),[9,10] For the current analysis we used data from patients admitted to the 10 Portuguese hospitals, which were selected to cover different regions from the mainland country, from north to south and west to east and including both coastal and interior regions, urban and rural populations. Furthermore, these hospitals had different characteristics, regarding population served, facilities, technical and human resources, and specialisation levels. These diverse settings were selected with the purpose of seeking representativeness of the general ACS population. Overall five hospitals had a catheterisation laboratory, three had a cardiac surgery department, in one patients with ACS were admitted to the internal medicine department, as the hospital had no cardiology department or cardiologists, four were university hospitals, the number of beds ranged from 280 to 1124 and the populations served ranged from less than 300 000 to more than 700 000 people. Each hospital contributed with approximately 300 consecutive patients discharged between 2008 and 2010 with diagnosis of ACS (International Classification of Diseases 10th revision: I.21.0-I 21.9 and I.20.0). From 3009 ACS patients included, those with missing data on the type of ACS were excluded (n = 68).

2.2 | Procedures and data collection

With the use of standardised forms, trained investigators extracted data from discharge letters, emergency room records and laboratory systems. When necessary, different sources were cross-checked to ensure completeness and quality of the information. Information on type of ACS, demographic characteristics, previous medical history, admission data, procedures used during hospitalisation, severity indicators and complications during hospitalisation, including vital status and in-hospital medication (the main classes of recommended drugs for patients with ACS)[11,12] was extracted.

2.3 | Definition of variables and data analysis

Patients with left bundle branch block were defined as non-classifiable (NC) ACS (NC ACS) and analysed with STEMI patients (STEMI/NC ACS group).

The management was considered invasive if coronary angiography was performed. Reperfusion was defined as either thrombolysis or primary percutaneous coronary intervention; revascularisation, either as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Anaemia was defined as haemoglobin below 12 g/dL for females and below 13 g/dL for males[13] and renal impairment was subdivided in two groups: estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 and between 30 and 60 mL/min/1.73 m^2.[14] Angiographic coronary disease was defined as normal/mild if coronary arteries were normal or with stenosis <30%; moderate for stenosis between 30% and 70%; and severe for any obstruction >70% or >50% if the obstruction was in the left main coronary artery. Severe coronary disease was further divided into 1-, 2- and 3-vessels disease categories, according to the number of affected arteries. In-hospital complications were evaluated by sex and type of ACS through a composite endpoint of pulmonary oedema, shock, acute renal failure, re-infarction, stroke and a drop of haemoglobin of 3 or more g/dL. In-hospital death was also assessed separately by sex and type of ACS.

The proportions of prescription of main classes of drugs during hospitalisation were assessed for eligible patients, according to sex, type of ACS and management approach, namely invasive vs conservative (according to the performance or not of coronary angiography). We computed composite variables for drugs combinations: double antiplatelet therapy with aspirin and clopidogrel, 3-drug treatment [(aspirin or clopidogrel) and beta-blocker and statin] and 5-drug treatment [aspirin and clopidogrel and beta-blocker and (angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and statin]. For simple antiplatelet therapy (aspirin or clopidogrel), haemoglobin below 10 g/dL for females and below 11 g/dL for males at admission was considered a contraindication. For double antiplatelet therapy, besides a low value of haemoglobin at admission, previous atrial fibrillation or being on oral anticoagulation at admission were considered also contraindications. A systolic blood pressure lower than 100 mm Hg or severe renal failure (eGFR less than 30 ml/min/1.73 m^2) at admission were considered contraindications for ACEi or ARB. Contraindications for beta-blockers were systolic blood pressure lower than 100 mm Hg or heart rate below 50 bpm at admission.

Potential confounders of the association between sex and management were grouped as follows: hospital characteristics, cardiovascular risk factors, cardiovascular history, complications at admission and angiographic coronary disease (the latter for the revascularisation models only). In the univariate analysis, we identified which variables were associated with management (*P*-value<.15), using logistic regression. Within each group mentioned above, variables with a significant effect on the dependent variable were included in the multivariate model and a backward strategy was used to exclude the least significant variables, based on Wald test (*P*-value <.05). To fit the final model, we departed from all variables with significant effect on outcome derived from the intragroup multivariate modelling, repeated backward strategy to choose the significant variables and performed likelihood ratio test for boundary p value. In sensitivity analysis, we examined the sex differences in management for STEMI group excluding the NC ACS patients. Data were analysed, using STATA version 11 for Windows (Stata Corp LP, College Station, TX, USA).

2.4 | Ethics

The study was approved by the ethics committee of the University of Porto Medical School and the National Commission for Data Protection. These two entities agreed that it would not be necessary to ask for patients' informed consent, since the study was based on the collection of retrospective clinical data from the medical records during hospitalisation, and the confidentiality of patients' identification was assured.

3 | RESULTS

3.1 | Baseline characteristics

A total of 2941 patients were included, 1757 (59.7%) with NSTEACS diagnosis and 1184 (40.3%) with STEMI/NC ACS (Tables 1 and 2).

The proportions of women included by hospital varied between 27.5% and 39.2% and the mean age of the patients between 64.1 and 70.2 years old (Table 1). In the majority of the hospitals, the proportion of patients with STEMI/NC ACS was above 40%, however, in three hospitals lower proportions were observed; the lowest was 24.7% in a hospital without catheterisation laboratory and cardiology ward (Table 1). Only in one hospital, the proportion of patients with previous history of myocardial infarction, PCI or CABG was below 20%. The proportions of patients with complications at admission varied between 38.7% and 61.1% between hospitals. The two hospitals with the lowest and the highest proportions of complications at admission were similar in characteristics, namely were tertiary hospitals, with catheterisation laboratory, located in the coast and covering an urban predominantly population. In all hospitals, most patients had severe angiographic coronary disease of at least of one vessel. The proportion of patients who had at least one in-hospital complication varied between 7.3% in Hospital de Faro and 23.7% in Centro Hospitalar do Porto. The in-hospital mortality varied between 0.8% in Centro Hospitalar Alto Ave and 14.6% in Centro Hospitalar Cova da Beira, the latter is located in the interior, had no catheterisation laboratory and cardiology ward, therefore patients with ACS were admitted to the internal medicine department (Table 1).

Compared to men, women with either ACS type were older, had more frequently hypertension and diabetes and were less frequently current smokers. Women had more comorbidities than men, independently of the ACS type: they suffered more often from previous heart failure, atrial fibrillation and renal failure. In the NSTEACS population, previous myocardial infarction, PCI or CABG were more prevalent in men. Anaemia and renal impairment at admission were more prevalent in women, who presented less often with severe angiographic coronary disease (Table 2). Compared with men, the composite endpoint of in-hospital complications (pulmonary oedema, shock, acute renal failure, reinfarction, stroke, drop in haemoglobin of 3 g/dL or more) was more frequently observed among women with NSTEACS (15.3% vs 11.2%, *P* = .014) and with STEMI/NC ACS (19.7% vs 13.8%, *P* = .011). Of all patients included in this analysis, 5.1% of women and 3.7% of men with NSTEACS died during hospitalisation (*P* = .159), while among STEMI/NC ACS patients, in-hospital death was significantly higher among women than men (17.9% vs 8.3%, *P*<.001, respectively) (Table 2).

3.2 | Management

Compared with patients treated conservatively, women and men with NSTEACS or STEMI/NC ACS who were treated invasively more frequently had prescription of the several recommended classes of drugs during hospitalisation. Patients with STEMI/NC ACS, both women and men, managed conservatively were the subgroup who had the lowest prescription of recommended drugs during hospitalisation (Figure 1). Women with NSTEACS managed conservatively were significantly less likely to receive statins (54.2% vs 64.7%, *P* = .009) and 5-drug treatment (20.7% vs 34.3%, *P* = .002) than

TABLE 1 Baseline characteristics of patients with acute coronary syndrome admitted to the ten Portuguese hospitals

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Hospital 5	Hospital 6	Hospital 7	Hospital 8	Hospital 9	Hospital 10	*P*
Women	82 (27.5)	99 (33.6)	113 (39.2)	101 (34.5)	95 (31.7)	87 (29.0)	109 (36.1)	80 (29.9)	116 (38.7)	93 (31.3)	.025
Age (y), mean (SD)	64.1 (13.1)	66.9 (14.1)	70.2 (14.1)	67.2 (14.2)	67.6 (13.0)	65.1 (13.3)	70.1 (13.3)	65.9 (12.9)	68.3 (13.4)	68.8 (12.5)	<.001
STEMI/NC ACS	136 (45.6)	119 (40.3)	123 (42.7)	120 (41.0)	147 (49.0)	74 (24.7)	140 (46.4)	94 (35.1)	121 (40.3)	110 (37.0)	<.001
Previous MI, PCI or CABG	83 (27.9)	62 (21.0)	73 (25.4)	84 (28.7)	74 (24.7)	88 (29.3)	53 (17.6)	56 (20.9)	73 (24.3)	60 (20.2)	.006
Complications at admission											
Pulmonary oedema, shock, anaemia or renal impairment	115 (38.7)	132 (45.8)	126 (56.0)	169 (57.7)	152 (51.0)	125 (43.1)	170 (59.2)	106 (41.1)	182 (61.1)	123 (43.0)	<.001
Severe (1, 2 or 3 vessels) coronary disease	237 (89.1)	222 (92.7)	146 (83.9)	188 (88.7)	215 (92.3)	174 (92.1)	110 (83.3)	191 (91.0)	187 (87.0)	130 (84.4)	<.001
In-hospital complications											
Pulmonary oedema, shock, acute renal failure, re-infarction, stroke, drop in haemoglobin≥3 g/dL	46 (15.4)	70 (23.7)	52 (18.1)	54 (18.4)	22 (7.3)	50 (16.7)	34 (11.3)	27 (10.1)	29 (9.7)	22 (7.4)	<.001
In-hospital death	21 (7.1)	27 (9.2)	42 (14.6)	20 (6.8)	18 (6.0)	16 (5.3)	15 (5.0)	2 (0.8)	22 (7.3)	21 (7.1)	<.001

List of hospitals: hospital 1 – Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE (Unidade I); hospital 2 - Centro Hospitalar do Porto, EPE (Hospital de Santo António); hospital 3 - Centro Hospitalar Cova da Beira, EPE (Hospital Pêro da Covilhã); hospital 4 - Centro Hospitalar São João, EPE (Hospital São João); hospital 5 - Centro Hospitalar Universitário do Algarve, EPE (Hospital de Faro); hospital 6 - Unidade Local de Saúde de Matosinhos, EPE (Hospital Pedro Hispano); hospital 7 - Centro Hospitalar do Nordeste, EPE (Unidade Hospitalar de Bragança); hospital 8 - Centro Hospitalar Alto Ave, EPE (Hospital da Senhora da Oliveira); hospital 9 - Centro Hospitalar Lisboa Norte, EPE (Hospital de Santa Maria); hospital 10 - Centro Hospitalar de Leiria, EPE (Hospital de Santo André).

Total may not add to 2941 due to missing data.

Data are counts with percentages unless otherwise indicated.

CABG, coronary artery bypass surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI/NC ACS, ST-elevation myocardial infarction/Non-classifiable acute coronary syndrome.

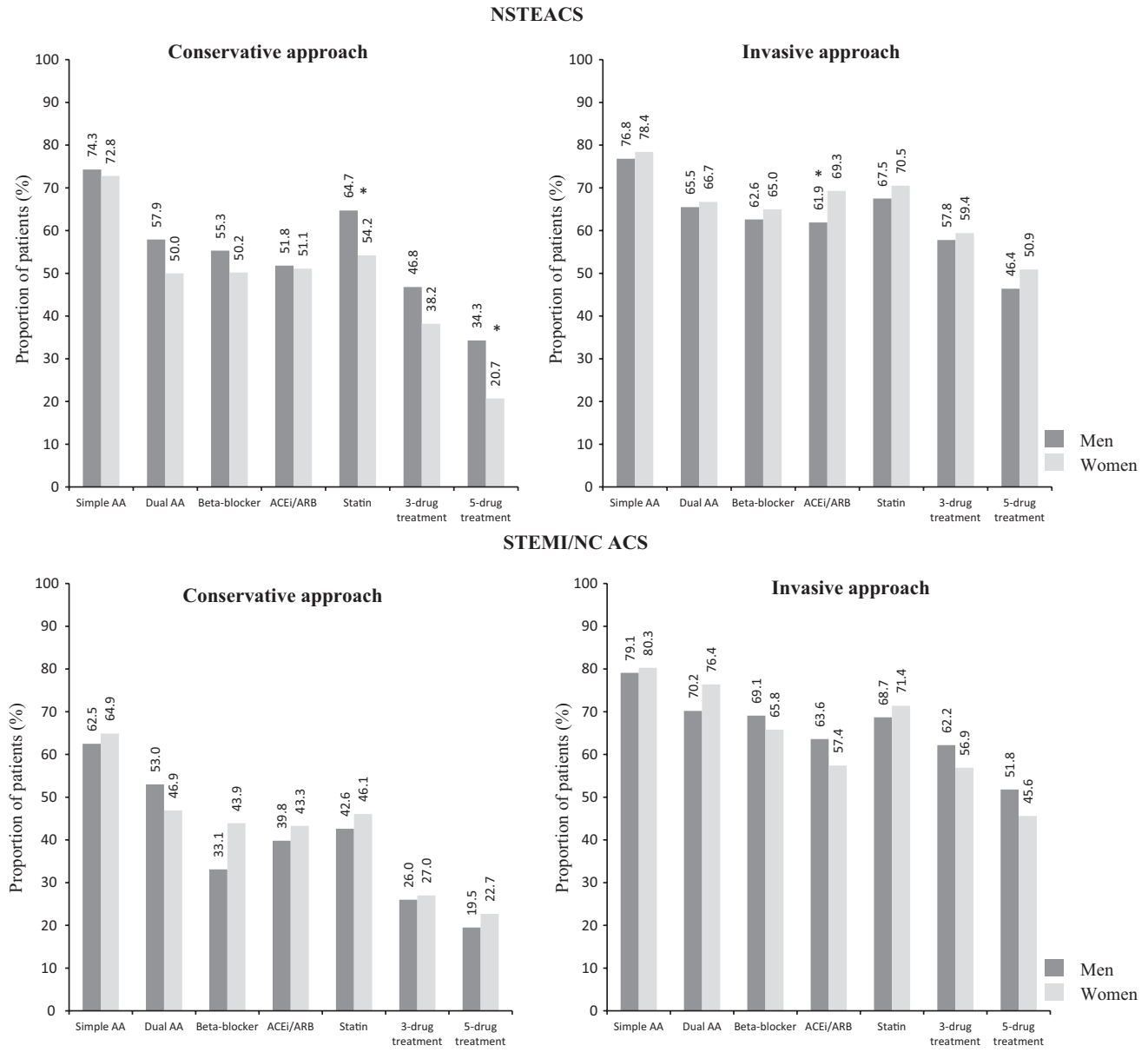
TABLE 2 Baseline characteristics of patients with different types of acute coronary syndrome, by sex

	NSTEACS			STEMI/NC ACS		
	Women	Men	*P*	Women	Men	*P*
	634 (36.1)	1123 (63.9)		341 (28.8)	843 (71.2)	
Age (y), mean (SD)	73.2 (11.8)	65.7 (12.7)	<.001	73.2 (13.6)	63.1 (13.5)	<.001
Cardiovascular risk factors						
Hypertension	500 (78.9)	751 (66.9)	<.001	246 (72.1)	461 (54.7)	<.001
Diabetes	275 (43.4)	351 (31.3)	<.001	104 (30.5)	206 (24.4)	.032
Dyslipidaemia	327 (51.6)	634 (56.5)	.049	146 (42.8)	384 (45.6)	.391
Current smoking	34 (5.4)	306 (27.3)	<.001	29 (8.5)	323 (38.3)	<.001
Cardiovascular history						
Previous MI, PCI or CABG	156 (24.6)	382 (34.0)	<.001	46 (13.5)	122 (14.5)	.661
Previous HF	87 (13.7)	101 (9.0)	.002	45 (13.2)	34 (4.0)	<.001
Previous AF	55 (8.7)	72 (6.4)	.078	29 (8.5)	35 (4.2)	.003
Chronic renal failure	214 (33.8)	236 (21.0)	<.001	97 (28.5)	136 (16.1)	<.001
Previous stroke	67 (10.6)	98 (8.7)	.204	31 (9.1)	52 (6.2)	.074
Peripheral artery disease	21 (3.3)	59 (5.3)	.061	4 (1.2)	20 (2.4)	.185
Complications at admission						
Pulmonary oedema or shock	9 (1.4)	8 (0.7)	.146	10 (2.9)	23 (2.7)	.847
Anaemia	238 (39.0)	300 (28.0)	<.001	115 (35.6)	156 (19.3)	<.001
Renal impairment (GFR)						
30 to <60 ml/min/1.73 m^2	264 (43.1)	257 (23.9)		136 (42.4)	182 (22.7)	
<30 ml/min/1.73 m^2	79 (12.9)	91 (8.5)	<.001	44 (13.7)	38 (4.7)	<0.001
Angiographic coronary disease						
Normal/Mild	67 (18.8)	59 (7.5)		15 (7.1)	19 (2.8)	
Moderate	15 (4.2)	34 (4.3)		5 (2.4)	11 (1.6)	
Severe—1 vessel	117 (32.9)	254 (32.2)		105 (50.0)	347 (51.3)	
Severe—2 vessels	78 (21.9)	227 (28.8)		48 (22.9)	180 (26.6)	
Severe—3 vessels	79 (22.2)	215 (27.3)	<.001	37 (17.6)	119 (17.6)	.054
In-hospital complications						
Pulmonary oedema, shock, acute renal failure, re-infarction, stroke, drop in haemoglobin ≥3 g/dL	97 (15.3)	126 (11.2)	.014	67 (19.7)	116 (13.8)	.011
In-hospital death	32 (5.1)	41 (3.7)	.159	61 (17.9)	70 (8.3)	<.001

Total may not add to 2941 due to missing data.
Data are counts with percentages unless otherwise indicated.
AF, atrial fibrillation; CABG, coronary artery bypass surgery; GFR, glomerular filtration rate; HF, heart failure; MI, myocardial infarction; NSTEACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI/NC ACS, ST-elevation myocardial infarction/Non-classifiable acute coronary syndrome.

men with NSTEACS managed conservatively; while women with NSTEACS managed invasively were more likely to receive an ACEi/ARB during hospitalisation than men with the same diagnosis and management approach (69.3% vs 61.9%, *P* = .037, respectively). The remaining sex differences in prescription of drugs during hospitalisation among patients without contraindications were not significant (Figure 1).

An invasive strategy was less frequent in women, regardless of the type of ACS (56.6% vs 71.8%, *P*<.001, and 62.5% vs 80.8%, *P*<.001 among patients with NSTEACS and STEMI/NC ACS, respectively). The difference in the odds of being managed invasively between sexes was observed in the STEMI/NC ACS group, after adjustment for patient and hospital characteristics (adjusted odds ratio [OR] 1.64, 95% confidence interval [95% CI] 1.11-2.44). Among patients performing coronary angiography, 52.7% and 76.5% of women and 58.3% and 81.6% of men with NSTEACS and STEMI/NC ACS, respectively, were submitted to revascularisation. There was no difference by sex in the odds of revascularisation in both



*P-value <.05
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSTEACS, non-ST elevation acute coronary syndrome; STEMI/NC ACS, ST-elevation myocardial infarction/non-classifiable acute coronary syndrome
3-drug treatment (aspirin or clopidogrel) and beta-blocker and statin
5-drug treatment aspirin and clopidogrel and beta-blocker and (ACEi or ARB) and statin

FIGURE 1 Proportion of patients treated with pharmacological treatment during hospitalisation for acute coronary syndrome with or without ST-elevation according to sex and management approach.

NSTEACS (0.84, 0.61-1.14) and STEMI/NC ACS (1.00, 0.62-1.62) after adjustment (Table 3). More men than women with STEMI/NC ACS had reperfusion therapy (67.9% vs 49.3%, respectively). However, this significant crude association between male sex and reperfusion (2.17, 1.68-2.84) was explained after multivariable adjustment (1.33, 0.96-1.84). In the sensitivity analysis, NC ACS patients (n = 163) were excluded and the results were comparable to primary results (Table 4).

4 | DISCUSSION

This study shows that women with STEMI/NC ACS, but not with NSTEACS, were less frequently submitted to coronary angiography than men, after controlling for age, characteristics of the hospitals, cardiovascular risk factors, previous medical history and complications at admission. No significant differences between sexes in the performance of reperfusion and revascularisation were observed.

TABLE 3 Sex differences in in-hospital management, by type of acute coronary syndrome (women are the reference class)

	Women n (%)	Men n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjustment variables
NSTEACS					
Diagnostic catheterisation	359 (56.6)	806 (71.8)	1.94 (1.59-2.39)	1.26 (0.99-1.62)	Patient characteristics: age, dyslipidaemia, history of heart failure, stroke, renal impairment at admission, anaemia at admission Hospital characteristics: number of beds
Revascularisation[a]	189 (52.7)	470 (58.3)	1.26 (0.98-1.62)	0.84 (0.61-1.14)	Patient characteristics: age, renal impairment at admission, angiographic coronary disease Hospital characteristics: presence of catheterisation laboratory, university hospital
STEMI/NC ACS					
Diagnostic catheterisation	214 (62.5)	681 (80.8)	2.53 (1.91-3.34)	1.64 (1.11-2.44)	Patient characteristics: age, dyslipidaemia, smoking, history of myocardial infarction, percutaneous intervention or coronary artery bypass surgery, of heart failure, of stroke, of renal failure, renal impairment at admission Hospital characteristics: presence of catheterisation laboratory, number of beds
Reperfusion[b]	168 (49.3)	572 (67.9)	2.17 (1.68-2.81)	1.33 (0.96-1.84)	Patient characteristics: age, dyslipidaemia, smoking, history of myocardial infarction, percutaneous intervention or coronary artery bypass surgery, of heart failure, renal impairment and anaemia at admission Hospital characteristics: presence of catheterisation laboratory, cardiothoracic surgery department
Revascularisation[a]	163 (76.5)	555 (81.6)	1.35 (0.93-1.96)	1.00 (0.62-1.62)	Patient characteristics: age, history of renal failure, anaemia at admission, angiographic coronary disease Hospital characteristics: presence of catheterisation laboratory

CI, confidence interval; NSTEACS, non-ST-elevation acute coronary syndrome; OR, odds ratio; STEMI/NC ACS, ST-elevation myocardial infarction/Non-classifiable acute coronary syndrome.
[a]Percutaneous coronary intervention and/or coronary artery bypass surgery among those submitted to coronary angiography.
[b]Thrombolysis or primary percutaneous coronary intervention.

We included 10 hospitals with different levels of specialisation, located in heterogeneous geographic areas. The analysis of the characteristics of the patients included by hospital identified differences in ACS epidemiology and outcomes. Between and within country differences in management and outcomes of patients with ACS have been described, but remain poorly understood.[10,15,16] In Portugal, between 1981 and 2012, relative declines of CHD mortality indicators were different by geographic region; consistent decreases in mortality rates were only observed in the most populated and urbanised regions.[5] Our finding of significant differences by hospital in in-hospital mortality of patients with ACS deserves further analysis.

Of patients hospitalised with NSTEACS and with STEMI/NC ACS 36.1% and 28.8%, respectively, were women, similar proportions to the observed in the whole EURHOBOP sample.[10] Approximately 40% of patients of our sample were diagnosed with STEMI/NC ACS; data from the Portuguese Registry of Acute Coronary Syndrome (ProACS) reported a similar proportion (41.2%).[17] The prevalence of cardiovascular risk factors in women and men with ACS, higher among patients with NSTEACS is also in line with other national and international data.[10,17] Particularly relevant is the high prevalence of diabetes in our sample, particularly among women with NSTEACS, higher than the observed in other countries.[10] For both types of ACS data from the overall EURHOBOP study showed that Portugal had one of the highest proportions of in-hospital events and mortality, even after exhaustive model adjustment.[10] Analysing data separately by sex and type of ACS, we were able to identify a subgroup of patients with particularly high risk of in-hospital death, women with STEMI/NC ACS (17.9%). Considering prescription of drugs during hospitalisation, higher differences were observed between patients with different management approaches, than between women and men. The decision to proceed or not to an invasive approach may influence the prescription of recommended drugs for patients with ACS, not only antiplatelet therapy, which is expected, but probably other classes of drugs. Our results are in line with previous findings

TABLE 4 Sex differences in in-hospital management of patients with ST-elevation myocardial infarction (women are the reference class)

	Women n (%)	Men n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjustment variables
STEMI					
Diagnostic catheterisation	189 (72.1)	636 (83.8)	2.00 (1.43-2.78)	1.99 (1.31-3.00)	Patient characteristics: age, dyslipidaemia, history of stroke, of renal failure Hospital characteristics: presence of catheterisation laboratory, number of beds
Reperfusion[a]	162 (61.8)	559 (73.7)	1.72 (1.28-2.32)	1.37 (0.97-1.94)	Patient characteristics: age, dyslipidaemia, renal impairment at admission Hospital characteristics: presence of catheterisation laboratory
Revascularisation[b]	152 (80.4)	529 (83.2)	1.20 (0.79-1.82	1.01 (0.60-1.70)	Patient characteristics: age, angiographic coronary disease Hospital characteristics: presence of catheterisation laboratory

CI, confidence interval; OR, odds ratio; STEMI, ST-elevation myocardial infarction.
[a]Thrombolysis or primary percutaneous coronary intervention.
[b]Percutaneous coronary intervention and/or coronary artery bypass surgery among those submitted to coronary angiography.

of very few sex differences in discharge medications of patients with ACS in Portugal, after adjusting for the potential confounding effect of age, comorbidities and contraindications.[6] Women and men differ in the pathophysiology and mechanisms of coronary heart disease. Women with ACS are on average older than men, suffer from more comorbidities, are more prone to atypical presentations, thrombus formation and plaque erosion, but less prone to suffer from severe obstructive coronary artery disease.[18,19] Women encounter longer delays between the onset of symptoms and first medical contact, arrival at a hospital and evidence-based treatment.[8] Additionally although lower cardiac catheterisation rates seen in women with ACS were considered to be partially due to women's own preferences,[20] recent data suggest that differences in catheterisation rates by sex may be driven largely by physicians, through different patterns of counselling and referral to cardiovascular testing between women and men, and not by differential attitudes, behaviours and decisions of female patients.[21]

Considering access to healthcare in a multilevel perspective, both factors related to health care systems and to patient[22] explain the difference in management of women and men with ACS. Several determinants, at both levels, that are not independent and influence each other and operate at different times during the process of illness and care, probably enable or hinder differently in women and men, the ability to perceive, seek, reach, pay and engage in health care and the ability of the system to fulfil the needs of the patient.[22]

Compared with data reported by the ProACS from 2010 to 2013, a lower proportion of NSTEACS patients in the EURHOBOP cohort were treated invasively (66.3% vs 84.8%).[3] Although part of this difference may be dependent on a true increase in the invasive treatment of patients with ACS, the results observed in the ProACS may be an overestimation of the true proportion, due to the fact that only hospitals with higher specialisation levels were included in this registry. In NSTEACS patients, only those with unstable angina, without risk criteria and no recurrent symptoms are recommended a non-invasive testing for ischaemia (preferably with imaging) before deciding on an invasive evaluation.[11] All the others should be treated invasively, unless some contraindication exists or the risks appear to outweigh the benefits. The factors that should be taken into account to weigh risks and benefits are related with clinical presentation, comorbidities, risk stratification, frailty, cognitive status and estimated life expectancy.[11] After adjusting for several of these factors, no difference in performance of coronary angiography between sexes was observed in the NSTEACS group, representing an improvement in the sex equality of access to evidence-based treatment.[2]

In STEMI patients, the main limitation to reperfusion therapy is the time of presentation after symptoms onset. Early mechanical or pharmacological reperfusion should be performed within the first 12 hours from symptoms onset; whether PCI is also beneficial in patients presenting more than 12 hours after symptoms onset is more controversial.[12] The use of reperfusion therapy in our sample is similar to the observed in ProACS covering years 2002-2008 (62.5% vs 61.9%, respectively),[23] but lower than the observed in the second phase of the ProACS (84.8%).[17] Implementation of a pre-hospital fast-track network in Portugal improved reperfusion rates in STEMI patients, through an increase in primary angioplasty.[4] Studies performed with data from the ProACS were not reported by sex, which limits further comparisons. Among STEMI/NC ACS patients, different probabilities of performing coronary angiography by sex might result from distinct patient and hospital delays.[8] In 2008, Portugal was among the countries performing less primary PCI in Europe.[24] One major factor contributing for this finding might be the high proportion (55%) of patients who were admitted more than 12 hours after symptom onset;[4] with higher delays being expected among women. The subjective experience of symptoms influences patients' attitudes in help seeking and professionals' interpretation of clinical presentations, thus affecting access to effective health care.[25]

In both types of ACS, no differences in revascularisation among those managed invasively were observed between women and men. This also represents a sex-gap improvement in access to care. When the decision to proceed to an invasive approach is made, risks and benefits of revascularisation have already been evaluated.[26] In our cohort, a significant proportion of patients of both sexes, especially in the NSTEACS group was not revascularised. Clinical and/or anatomic reasons such as non-obstructive coronary heart disease, or coronary lesions not amenable to intervention, as well as patient and system delays for STEMI/NC ACS, may explain these revascularisation proportions.

4.1 | Limitations

Given the retrospective nature of this study and the data sources, the validity of the conclusions relies on the accuracy and completeness of the original documentation. Although we considered the main confounding variables at the individual and hospital level, no detailed information on socioeconomic status, clinical presentation and time delays was available.

5 | CONCLUSIONS

In a real-life setting, women with STEMI/NC ACS are less likely than men to be managed invasively. No sex differences in reperfusion and revascularisation were observed in both types of ACS, which represents an important achievement, and help to understand the greater declines in CHD mortality observed among women compared to men in Portugal. Further improvements are still necessary, especially in the management of women with STEMI/NC ACS. To reduce inequalities in management of patients with ACS in Portugal, the sex-gap in analysis and report of results from national registries and other data sources must be improved, and patients admitted to hospitals with lower specialisation levels should be included.

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DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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AUTHOR CONTRIBUTIONS

Carla Araújo participated in data collection, collaborated in the field work, raised the hypotheses, analysed and interpreted the data and drafted the first version of the manuscript. Marta Pereira participated in data collection, collaborated in the field work, analysed and interpreted the data and revised the final version of the manuscript. Olga Laszczyńska analysed and interpreted the data, and revised the final version of the manuscript. Paula Dias interpreted the data and revised the final version of the manuscript. Ana Azevedo coordinated the Portuguese collaboration in EURHOBOP study, raised the hypotheses, interpreted the data and revised the final version of the manuscript. Each author participated sufficiently in the work to take public responsibility for its content and all authors approved the final version of the manuscript.

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3.3 PAPER 3

QUALITY OF CARE AND OUTCOMES OF WOMEN AND MEN WITH ACUTE MYOCARDIAL INFARCTION

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Quality of Care and 30-Day Mortality of Women and Men With Acute Myocardial Infarction

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Keywords:
Quality indicators
Acute myocardial infarction
Mortality
Women

ABSTRACT

Introduction and objectives: Despite greater awareness of disparities in care and outcomes of women and men with acute myocardial infarction (AMI), no consistent attenuation of these differences over last decade has been observed. We aimed to identify differences by sex in management and 30-day mortality using the European Society of Cardiology Acute Cardiovascular Care Association quality indicators (QI) for AMI.
Methods: The 20 QIs proportions and standard errors were calculated for 771 patients with AMI who were admitted to the cardiology department of two tertiary hospitals in Portugal between August 2013 and December 2014. The association between the composite QI and 30-day mortality was derived from logistic regression.
Results: Significantly fewer eligible women received timely reperfusion, were discharged on dual antiplatelet therapy, on high intensity statins and were referred to cardiac rehabilitation than men. Women less often received recommended interventions (59.6% vs 65.2%, p<0.001) and also had a higher mean GRACE 2.0 risk score adjusted 30-day mortality (3.0% vs 1.7%, p<0.001). An inverse association between the composite QI and crude 30-day mortality was observed for both sexes (odds ratio [OR] 0.08, 95% confidence interval [95% CI] 0.01-0.64 for the highest performance tertile compared to the lowest).
Conclusions: Performance in AMI management is lower in women compared to men and is associated with higher 30-day mortality, still worse for women. Objective and guideline supported QIs in constant assessment of practice´s quality have the potential to improve healthcare delivery and prognosis in overall AMI population and also to bridge the gap between women and men.

Calidad del cuidado y mortalidad a 30 dias en mujeres y hombres con infarto agudo de miocardio

Palabras clave:
Indicadores de calidad
Infarto agudo de miocardio
Mortalidad
Mujeres

RESUMEN

Introducción y objetivos: A pesar de una mayor conciencia de las disparidades en el tratamiento y resultados en mujeres y hombres con infarto agudo de miocardio (IAM), no se observó una atenuación consistente de estas diferencias en la última década. El objetivo del estudio fue identificar diferencias por sexo en el tratamiento y la mortalidad a 30 días utilizando los indicadores de calidad (IC) de la Asociación de Cuidados Cardiovasculares Agudos de la Sociedad Europea de Cardiología para el IAM.
Métodos: Las proporciones y los errores estándar de los 20 IC se calcularon para 771 pacientes con IAM que ingresaron en el departamento de cardiología de dos hospitales terciarios en Portugal, entre agosto de 2013 y diciembre de 2014. La asociación entre el IC compuesto y la mortalidad a 30 días se analizó por regresión logística.
Resultados: Significativamente menos mujeres elegibles recibieron una reperfusión oportuna, tuvieran alta con doble terapia antiplaquetaria, con estatinas de alta intensidad y fueron remitidas a rehabilitación cardíaca en comparación con los hombres. Las mujeres recibieron con menos frecuencia las intervenciones recomendadas (59,6% vs 65,2%, p <0,001) y también tuvieron un *score* de riesgo GRACE 2.0 más alto

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ajustado a la mortalidad a 30 días (3,0% vs 1,7%, p <0,001). Se observó una asociación inversa entre el IC compuesto y la mortalidad bruta a 30 días para ambos sexos (odds ratio [OR] 0,08, intervalo de confianza 95% [IC 95%] 0,01-0,64 para el tercil de mayor rendimiento en comparación con el menor).
Conclusiones: el rendimiento en el tratamiento del IAM es inferior en las mujeres que en los hombres y se asocia con una mayor mortalidad a los 30 días, aún peor para las mujeres. Los IC objetivos y basados en directrices, para la evaluación constante de la calidad de la práctica, tienen el potencial de mejorar la prestación y el pronóstico de la atención médica en los pacientes con IAM en general y también de reducir el gap entre mujeres y hombres.

Abbreviations

ACS: acute coronary syndrome
AMI: acute myocardial infarction
NSTEMI: Non-ST elevation myocardial infarction
QI: quality indicator
PCI: percutaneous coronary intervention
STEMI: ST elevation myocardial infarction

Abreviaturas:

IAM: infarto agudo de miocardio
IAMCEST: infarto agudo de miocardio con elevación del segmento ST
IAMSEST: infarto agudo de miocardio sin elevación del segmento ST
IC: indicador de calidad
ICP: intervención coronaria percutánea
SCA: síndrome coronario agudo

INTRODUCTION

In recent decades, basic and clinical investigation helped to better understand the multifactorial and multidimensional differences between women and men suffering from an acute coronary syndrome (ACS).[1] An emerging interest in coronary heart disease (CHD) in women revealed sex differences in the pathophysiology and clinical presentation, in preventive interventions and diagnostic strategies, in management of ACS, and in the response to therapies.[2] Despite these differences, evidence supports equal benefit of evidence-based treatment of ACS for women and men and the need to promote stringent guideline implementation in management of women with ACS.[3]

Comparing quality of care of ACS by sex is challenging because of the multiple dimensions of the process of care.[4] Based on the European Society of Cardiology (ESC) guidelines for the management of ACS,[3, 5] the ESC Acute Cardiovascular Care Association (ACCA) proposed a set of quality indicators (QI) for the management of AMI.[4] They comprise 7 domains across 20 QIs including the evaluation of the key aspects of the AMI care pathway. Recently these indicators were validated using data from the National Health Service of England and Wales (Myocardial Ischaemia National Audit Project [MINAP]) and showed potential to improve care and reduce unwarranted variation in death from AMI.[6] These indicators may also be a useful tool to study sex inequalities in the ACS process of care and outcomes in contemporary settings. Using a prospective cohort study, we aimed to assess differences by sex in quality of care and 30-day mortality, by the application of the ESC ACCA QIs for AMI.

METHODS

Study Design and Sample Selection

The EPIHeart cohort study was designed with the a priori working hypotheses of the presence of inequalities in management and outcomes of patients with CHD in Portugal. This study included all consecutive patients admitted between August 2013 and December 2014 to the cardiology departments of two tertiary hospitals in two regions in northern Portugal (Hospital de São João, Porto, covering part of the metropolitan area of Porto in the coast; and Hospital de São Pedro, Vila Real, covering the interior, northeastern region). These two centres are high volume units (more than 250 ACS hospitalisations annually). Eligible patients were 18 years old or older, living in the catchment area of these hospitals, not institutionalised before the event, expected to be hospitalised for at least 48 hours and who were diagnosed with type 1 (spontaneous) ACS. Of 1297 patients initially considered, in 164 the diagnosis of ACS was not confirmed, 60 were discharged or transferred and 18 died before being invited. Further 44 were unable to answer the questionnaire due to clinical instability, no understanding of Portuguese, hearing problems, or cognitive impairment. Seventy-two patients refused to participate. Enrolled patients who were discharge alive, had valid contact details and agreed to continue in the study were interviewed 6 months after discharge (n=890). For this analysis only patients with a discharge diagnosis of ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) were included, as ESC ACCA QIs were proposed for these types of ACS.[4] A total of 771 patients were analysed. The study protocol was in compliance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of both hospitals. All patients gave written informed consent.

Procedures, data collection and definition of variables

Data were collected by trained researchers through structured interviews with patients and extended review of medical records, including discharge notes and exams reports. Patients were also asked to complete the Mini-Mental Status Examination (MMSE)[7] and their self-care and mobility activities of daily living was assessed using the Modified Barthel Index (BI).[8] For patients who were discharged alive before 30th day after admission, vital status was obtained from the 6 months follow-up interview.

Marital status was considered partnered for married patients or living in civil union. Completed years of schooling were classified into four categories: less than 4 (little formal education), 4 (elementary school), less than 12 (high school), and 12 or more years (secondary education or more).

Cognitive impairment was defined based on the MMSE score, taking into account established cut-offs for individual education level.[9] Physical disability was assigned to patients scoring less than 90 in the BI.[8, 10]

ESC quality indicators

Each of 20 QIs[4] was calculated for patients eligible for the procedure/treatment (and without contra-indications) with complete data. For QIs of the "reperfusion/invasive strategy" domain we considered eligible: 1) STEMI patients with onset of symptoms to diagnosis (first medical contact) time less than 12 hours; 2) NSTEMI patients at intermediate or high risk (those presenting at least one of the following criteria: diabetes mellitus, renal dysfunction defined as Cockcroft-Gault estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73 m^2, left ventricular ejection fraction (LVEF) equal to or less than 0.40, heart failure, prior percutaneous coronary intervention (PCI), prior coronary artery bypass surgery (CABG), GRACE risk score higher than 140).[4] Major relative contra-indications to coronary angiography were severe anaemia (admission haemoglobin less than 8 mg/dl) and/or severe renal failure (eGFR less than 30 ml/min/1,73m^2 at admission).[11, 12]

Variables to calculate the QIs of the "reperfusion/invasive strategy" domain were derived directly from collected data, except door-in door-out time for STEMI transferred patients, ascertained indirectly. Using exact times of admission to the non-PCI and PCI capable hospitals, we estimated the time of transportation between these two hospitals by ambulance applying the ArcGIS version 10.4.1 Network Analysist and an updated street network dataset provided by Environmental Systems Research Institute (ESRI). For each street segment, the street network dataset includes information on the traffic, average speed, type of street (main, secondary, highway), allowing to accurately estimate the shortest time-distance (minutes) between the hospitals' point locations. Hospital locations were geocoded using Google Maps. We added 10 minutes to estimated time of transportation to take into account time delays related with preparation of the patient and staff in the ambulance.

To calculate individual GRACE 2.0 risk score[13] we used "diuretic usage" as a surrogate for Killip class II for 39 patients, and 19 patients had no information regarding ST segment deviation. For CRUSADE bleeding score,[14] haematocrit was obtained by formula: admission haemoglobin*2.94.[15]

For the anti-thrombotics QIs, patients at high bleeding risk (CRUSADE score higher than 50),[14] with previous haemorrhagic stroke or discharged on oral anticoagulation were considered non-eligible. Although clinical trials of secondary prevention treatment in MINOCA (Myocardial Infarction With Non-obstructive Coronary Artery Disease) patients are lacking, observational data showed a neutral effect of dual antiplatelet therapy on long-term outcomes and a trend toward an increased bleeding rate, therefore supporting that it is reasonable to treat this subgroup of patients with simple antiplatelet therapy.[16] We performed a sensitivity analysis, considering patients with MINOCA (absence of obstructive coronary artery disease ≥50% stenosis) non-eligible for the quality indicators that include dual antiplatelet therapy.

A systolic blood pressure lower than 100 mmHg or severe renal failure (eGFR less than 30 ml/min/1,73m^2) at discharge were contra-indications for angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Contra-indications for beta-blockers were systolic blood pressure lower than 100 mmHg at discharge, asthma and 2nd or 3rd degree atrioventricular block (Supplementary Table 1).

In the calculation of the opportunity-based main composite QI, the numerator was the sum of points of individual main indicators and the denominator the sum of points of applicable indicators, with all 12 indicators weighted equally (if fulfilled=1).

Data Analysis

To examine differences between women and men, the chi-square or Fisher's test was used for categorical variables and the t-test or Mann-Whitney test for continuous variables. For the QIs, proportions and standard errors (SE) were calculated for eligible patients and without missing data for the procedure or treatment.

The GRACE risk score adjusted 30-day mortality was estimated based on predicted probabilities derived from logistic regression. The association between the composite QI and crude 30-day mortality was assessed using a logistic regression model; independent variable of the performance was categorised into low, intermediate and high attainment according to tertiles distribution of the whole study sample.

All analyses were performed using STATA version 11.1 for Windows (Stata Corp LP, College Station, TX) and R version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria), with statistical significance determined at 5%.

RESULTS

Baseline characteristics

Women (n=202, 26.2%) were older (68.6 vs 61.4 years, p<0.001), were more likely to be unpartnered, less educated, were more often disabled, and had a lower income compared with men. Women more frequently had hypertension and diabetes, and were more often obese and never smokers, compared with men. Women were also more likely to have prior atrial fibrillation and cancer than men. There were no significant differences regarding a previous history of ischemic heart disease, heart failure, renal failure and stroke by sex. Women more frequently had cognitive impairment than men and disability for activities of daily living (Table 1).

Admission characteristics, risk stratification and management

NSTEMI was the final diagnosis in 412 patients (53.4%), 64% patients were firstly admitted to a PCI capable hospital and 24% were admitted through a fast track system, without differences by sex (Table 2).

Patient and system delays[5] were longer for women than men, for both types of AMI (Table 2). Among STEMI patients, women had significantly higher median times for symptoms onset to first medical contact (FMC) and for PCI capable hospital admission to arterial access. The median time between hospital admission and coronary angiography was significantly longer in women with NSTEMI than in men (Table 2).

Women were more often admitted with hemodynamic instability when compared with men, had lower mean eGFR, scored higher in GRACE and CRUSADE and were less likely to be submitted to invasive procedures regardless of myocardial infarction type (Table 2).

Quality indicators (Table 3)

Domain 1: *Centre Organisation.* These two centres do not routinely assess relevant times for the reperfusion process in STEMI patients and one centre participates in a regular registry for quality assessment.

Domain 2: *Reperfusion/invasive strategy.* Only 21.1% of

Table 1 Baseline demographic, socioeconomic and previous medical history characteristics of women and men with acute myocardial infarction*.

	Women (n=202)	Men (n=569)	p
Age (years), mean (SD)	68.6 (12.6)	61.4 (12.7)	<0.001
Socioeconomic			
Marital status			
Partnered	119 (59.2)	467 (82.7)	<0.001
Education			
Little formal education	87 (43.5)	58 (10.3)	
Elementary school	64 (32.0)	230 (40.9)	
High school	26 (13.0)	171 (30.4)	
Secondary education or more	23 (11.5)	104 (18.5)	<0.001
Employment status			
Employed/housewives	60 (29.9)	203 (35.9)	
Unemployed	16 (8.0)	85 (15.0)	
Retired	82 (40.8)	205 (36.3)	
Disabled	43 (21.4)	72 (12.7)	0.001
Household income (euros)			
<500	67 (33.2)	106 (18.6)	
501-1000	55 (27.2)	187 (32.9)	
1001 – 2000	19 (9.4)	122 (21.4)	
>2000	13 (6.4)	67 (11.8)	
No response	48 (23.8)	87 (15.3)	0.001
Region			
Porto	98 (21.7)	353 (78.3)	
Northeastern region of Portugal	104 (32.5)	216 (67.5)	0.001
Cardiovascular risk factors			
Smoking			
Never	162 (80.2)	155 (27.2)	
Current	31 (15.4)	236 (41.5)	
Former	9 (4.5)	178 (31.3)	<0.001
Hypertension	163 (80.7)	344 (60.5)	<0.001
Diabetes mellitus	78 (38.6)	159 (27.9)	0.005
Dyslipidaemia	124 (61.4)	342 (60.2)	0.769
BMI (kg/m^2)			
Mean (SD)	27.5 (5.0)	26.9 (4.2)	0.157
Under or normal weight	72 (37.3)	179 (33.7)	
Overweight	71 (36.8)	247 (46.5)	
Obese	50 (25.9)	105 (19.8)	0.048
Family history of CVD	87 (46.3)	205 (40.4)	0.160
Previous medical history			
Myocardial infarction, PCI and/or CABG	31 (15.4)	104 (18.4)	0.332
Heart failure	16 (7.9)	33 (5.8)	0.297
Renal failure	11 (5.5)	42 (7.4)	0.350
Atrial fibrillation	18 (8.9)	24 (4.2)	0.012
Stroke	25 (12.4)	48 (8.4)	0.100
Cancer	22 (10.9)	38 (6.7)	0.055
Cognitive impairment (MMSE score)	71 (37.2)	91 (17.6)	<0.001
Disability (BI score)	41 (21.4)	38 (7.2)	<0.001

*Values are number and percentage unless otherwise indicated.
Total may not add to 100% due to missing data.
BI, Barthel index; BMI, body mass index; CABG, coronary artery bypass surgery; CVD, cardiovascular diseases; MMSE, Mini-Mental State Examination; PCI, percutaneous coronary intervention; SD, standard deviation.

Table 2 Clinical presentation, patient and system delays, risk stratification and management of women and men with acute myocardial infarction*.

	Women (n=202)	Men (n=569)	p
NSTEMI (vs STEMI)	113 (55.9)	299 (52.6)	0.406
Admission to a PCI-capable hospital	126 (62.4)	367 (64.5)	0.589
Admission through fast track system	34 (20.6)	120 (25.0)	0.253
Patient and system delays, median (IQR)			
STEMI (min)			
Symptom onset – FMC	119 (60-300)	81 (45-190)	0.040
First medical contact – arterial access	197 (113-630)	183 (95-415)	0.411
Symptom onset – arterial access	460 (220-1096)	308 (190-779)	0.078
PCI-capable hospital admission- arterial access	96 (55-189)	66 (34-203)	0.028
First hospital admission- arterial access	124 (79-477)	107 (52-336)	0.133
Door-in door-out time for transferred patients	156 (96-378)	134 (73-248)	0.230
Onset of symptoms to diagnosis			
<12 hours	77 (89.5)	242 (92.0)	
12-24 hours	6 (7.0)	11 (4.2)	
>24h hours	3 (3.5)	10 (3.8)	0.582
NSTEMI			
Symptom onset – FMC (min)	185 (60-395)	120 (60-333)	0.119
Hospital admission- coronary angiography time (hours)	32 (20-70)	27 (17-55)	0.049
Admission variables/risk stratification			
Heart rate, mean (SD), bpm	81 (23)	77 (18)	0.003
Systolic blood pressure, mean (SD), mmHg	146 (63)	141 (42)	0.286
Cardiac arrest at admission	10 (5.0)	22 (3.9)	0.507
ST-segment deviation on admission	143 (72.6)	410 (73.9)	0.725
Hemodynamic instability at admission[a]	26 (12.9)	24 (4.2)	<0.001
Baseline haematocrit at admission, mean (SD), %	38.3 (4.7)	42.8 (5.4)	<0.001
GFR (CG) mean (SD)	79.0 (37.4)	95.8 (41.4)	<0.001
Calculated GRACE risk score			
NSTEMI mean (SD)	142 (3.8)	132 (2.0)	0.014
STEMI mean (SD)	168 (4.6)	141 (2.0)	<0.001
Calculated CRUSADE risk score			
NSTEMI mean (SD)	41 (17)	21 (16)	<0.001
STEMI mean (SD)	36 (15)	19 (13)	<0.001
Management approach			
STEMI			
Coronary angiography	86 (96.6)	269 (99.6)	0.019
Primary PCI	52 (74.3)	196 (86.3)	0.017
Thrombolysis	10 (11.2)	18 (6.7)	0.163
NSTEMI			
Coronary angiography	101 (89.4)	286 (95.7)	0.017
Revascularization	64 (56.6)	220 (73.6)	<0.001
PCI	54 (47.8)	158 (52.8)	0.036
CABG	11 (9.7)	65 (21.7)	0.005
Moderate or severe left ventricular systolic dysfunction	42 (20.9)	94 (16.8)	0.188

*Values are number and percentage unless otherwise indicated.
Total may not add to 100% due to missing data.
[a] Killip class III or IV; or shock at admission.
ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CABG, coronary artery bypass surgery; eGFR (CG), estimated glomerular filtration rate (Cockcroft-Gault); FMC, first medical contact; IQR, interquartile range; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST elevation myocardial infarction.

Table 3 Quality of care according to the European Society of Cardiology Acute Cardiovascular Care Association quality indicators for women and men with acute myocardial infarction.

Domain of care	Quality indicator	Women		Men		
		Eligible (n)	Proportion (SE)	Eligible (n)	Proportion (SE)	P
Centre organization	**Main QI**: Centre is part of a network organization	202	100	569	100	N/A
	Secondary QI (1): routine assessment of relevant times for the reperfusion process	202	0	569	0	N/A
	Secondary QI (2): participation in regular registry or program for quality assessment	202	51.5 (3.5)	569	38.0 (2.0)	0.001
Reperfusion-invasive strategy	**Main QI (STEMI 1):** proportion of STEMI patients reperfused	77	98.7(1.3)	242	99.6 (0.4)	0.425
	Main QI (STEMI 2): proportion of patients with timely reperfusion	76	21.1 (4.7)	236	33.5 (3.1)	0.041
	. Fibrinolysis: < 30 min from FMC to needle	10	30.0 (15.3)	18	26.7 (11.8)	1.0
	. Primary PCI in patients admitted to PCI-capable hospitals: door to arterial access <60 min	45	28.9 (6.8)	154	45.5 (4.0)	0.047
	. For transferred patients: door-in door-out time <30 min	22	0	68	7.5 (3.2)	0.332
	Secondary QI (STEMI): time from FMC to arterial access for primary PCI - median (IQR)	66	166 (83-335)	220	158 (93-283)	0.690
	Main QI (NSTEMI): proportion of patients with NSTEMI who receive coronary angiography within 72h after admission	63	73.0 (5.6)	167	83.8 (2.9)	0.063
In hospital risk assessment	**Main QI (1):** proportion of patients with NSTEMI who have GRACE risk score assessment	113	8.8 (2.7)	299	7.7 (1.5)	0.699
	Main QI (2): proportion of patients with STEMI and NSTEMI who have CRUSADE bleeding score assessment	202	5.4 (1.6)	569	3.7 (0.8)	0.283
	Main QI (3): proportion of patients with STEMI and NSTEMI who have LVEF numerical value recorded	202	78.7 (2.9)	569	82.1 (1.6)	0.294
Anti-thrombotics during hospitalization	**Main QI (1):** proportion of AMI patients with adequate $P2Y_{12}$ inhibition	132	94.7 (2.0)	461	97.4 (0.7)	0.120
	Main QI (2): proportion of patients with NSTEMI treated with fondaparinux, except candidate to immediate (≤2h) coronary angiography or with eGFR<20 ml/min	107	12.2 (3.2)	287	8.7 (1.7)	0.304
	Secondary QI: Proportion of AMI patients discharged on dual antiplatelet therapy	132	90.9 (2.5)	459	95.9 (0.9)	0.025
Secondary prevention discharge treatment	**Main QI (1):** Proportion of AMI patients discharged on high intensity statins (atorvastatin≥40 mg or rosuvastatin≥20 mg)	192	46.9 (3.6)	537	61.8 (2.1)	<0.001
	Secondary QI (1): Proportion of patients with AMI and clinical evidence of HF or LVEF≤0.40 discharged on ACEI/ARB	26	76.9 (8.4)	104	78.8 (4.0)	0.831
	Secondary QI (2): Proportion of patients with AMI and clinical evidence of HF or LVEF≤0.40 discharged on beta-blockers	27	85.2 (7.0)	102	80.4 (4.0)	0.569
Patient satisfaction	**Main QI:** patient experience					
	Pain control and explanations	N/A	0	N/A	0	N/A
	Cardiac rehabilitation referral	197	14.9 (2.6)	562	26.3(1.9)	0.001
	Smoking cessation advice	29	51.7 (9.4)	224	28.6 (3.0)	0.011
Composite and outcome QI	**Main composite QI (Main CQI)**: opportunity based	202	59.6 (1.1)	569	65.2 (0.6)	<0.001
	Coronary angiography in STEMI and NSTEMI patients at intermediate or high ischaemic risk	143	93.0 (2.1)	369	97.0 (0.9)	0.040
	Low-dose aspirin	132	95.5 (1.8)	461	98.1 (0.6)	0.094
	Main composite QI categories	202		569		
	Low (0-<57% attainment)		43.1 (3.5)		29.2 (1.9)	
	Intermediate (≥57-<73% attainment)		33.7 (3.3)		36.2 (2.0)	
	High (≥73)		23.3 (3.0)		24.6 (2.0)	0.001
	Secondary composite QI	124	54.0 /4.5)	421	60.9 (2.8)	0.174
	Patients without HF and LVEF>0.40 (low-dose aspirin, $P2Y_{12}$ inhibitor, high-intensity statins)	110	55.5 (4.8)	337	65.6 (2.6)	0.056
	Patients with HF or LVEF≤40 (low-dose aspirin, $P2Y_{12}$ inhibitor, high-intensity statins, ACEI/ARB, beta-blockers)	14	42.9 (13.7)	84	41.5 (4.5)	0.922
	Secondary outcome QI: 30-day mortality rate adjusted for the GRACE 2.0 risk score	190	3.0 (3.4)	533	1.7 (3.7)	<0.001

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate; FMC, first medical contact; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; QI, quality indicator; SE, standard error; STEMI, ST elevation myocardial infarction.

women and 33.5% of men received timely reperfusion (p=0.041). The median time from FMC to arterial access for primary PCI patients was similar between women and men. Among NSTEMI patients, eligible women less often received coronary angiography within 72 hours after admission than men (73.0% vs 83.8% p=0.063).

Domain 3: *In hospital risk assessment.* GRACE risk score was only assessed in 8% of NSTEMI patients, and CRUSADE bleeding score in 4.2% of all AMI patients; with no differences by sex. LVEF was similarly recorded in women and men (78.7% vs 82.1%, p=0.294).

Domain 4: *Anti-thrombotics during hospitalisation.* Above 90% of patients received $P2Y_{12}$ inhibitors, and a similar proportion was treated with fondaparinux or low molecular weight heparin (94.4% vs 91.6%, p=0.359, for women and men respectively). Fondaparinux alone was prescribed to only about 10% of patients. There was a significant difference in proportion of eligible women discharged on dual antiplatelet therapy compared with men (90.9% vs 95.9%, p=0.025). After excluding patients with MINOCA [20 (9.9%) women and 26 (4.6%) men], this difference was still observed (89.7% vs 96.1%, for women and men respectively, p=0.006).

Domain 5: *Secondary prevention discharge treatment.* Significantly fewer women than men were discharged on high intensity statins (atorvastatin≥40 mg or rosuvastatin≥20 mg) (46.9% vs 61.8%, p<0.001), but no differences between sexes were observed in prescriptions of ACEI/ARB and of beta blockers at discharge.

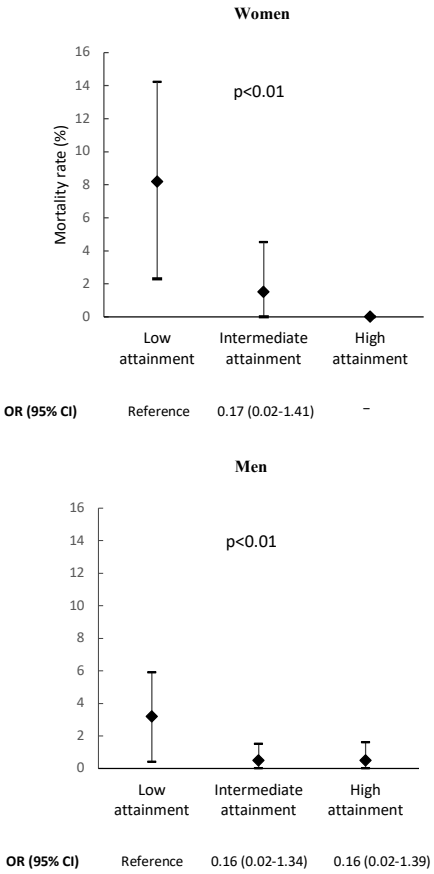
Domain 6: *Patient satisfaction.* In contrast to cardiac rehabilitation referral, eligible women received smoking cessation advice more often than men (14.9% vs 26.3%, p=0.001 and 51.7% vs 28.6%, p=0.011, respectively).

Domain 7: *Composite quality indicators.* About 60% of women and 65% of men received the interventions they were eligible for (p<0.001). For the secondary composite QI, 54.0% of women and 60.9% of men with AMI received all the secondary prevention drugs for which they were eligible for (p=0.174). The results were similar after excluding patients with MINOCA (54.1% vs. 60.8%, p=0.212). *Outcome quality indicator*. There were 15 deaths within 30 days after admission, 8 in women and 7 in men. The mean GRACE 2.0 risk score adjusted 30-day mortality was 3.0% in women and 1.7% in men (p<0.001).

Quality indicators and mortality

An inverse association between the composite opportunity based QI (by tertiles of attainment) and crude 30-day mortality was observed, both for women and men (Figure 1). Patients with higher attainment of recommended care were less likely to die in comparison with patients in category of low (odds ratio [OR] 0.15, 95% confidence interval [95% CI] 0.03-0.66 and OR 0.08, 95% CI 0.01-0.64 for patients in intermediate and high attainment, respectively).

Figure 1. Association between the composite opportunity-based quality indicator tertiles of attainment and crude 30-day mortality for women and men with acute myocardial infarction.



DISCUSSION

Using the EPIHeart prospective cohort study and the ESC ACCA QIs for AMI, performance for women was lower than for men in 6 domains. Fewer women than men received timely reperfusion, were discharged on dual antiplatelet therapy and on high intensity statins, were referred for cardiac rehabilitation and scored lower in the main composite QI for advisable interventions. An inverse association between the attainment of composite QI and mortality was observed for both sexes. Without differences by sex, we found low levels of ischemic and bleeding risk stratification assessment using GRACE and CRUSADE prognostic tools and of use of fondaparinux in NSTEMI eligible patients.

The ACS care pathway is complex to evaluate, patient and system factors have competing effects on patient flow through the health care system, often influence each other and act at different times during an episode of illness and care.[17] Disparities in health care provided to women and men and in outcomes are multifactorial and occur at different levels of the ACS pathway process of care.[18, 19] The differences in demographic, socioeconomic and cardiovascular risk factors, comorbidities and severity presentation found between women and men of our cohort are in accordance with updated data focused on the multifactorial determinants of sex disparities in CHD management and outcomes.[2]

The results on QIs in the reperfusion/invasive strategy strengthens the importance of timeliness of care delivery in the evaluation of care.[20] Time-based QIs are significantly influenced by hospital system factors adjusted for patient factors, namely patient delay times.[21] In fact, the high level of reperfusion distracts

attention from a low level of timely reperfusion for both sexes, significantly lower for women; and for patients admitted to both PCI and non-PCI capable hospitals. The very low proportion of patients transferred from non-PCI capable hospitals for primary PCI, particularly women, within the target 30 minutes door-in door-out time is particularly relevant in terms of health policy and planning. According to the Codi Infart registry of Catalonia, first medical contact to artery opening time above 120 minutes was strongly associated with first medical contact in a centre without a catheterization laboratory.[22] Implementation of the national coronary fast track system in Portugal largely contributed to a twofold increase in primary angioplasty from 2010 to 2015,[23] but no data exist about the parallel achievement and improvement of timely reperfusion. The implementation of these networks, which favour primary angioplasty rather than thrombolysis, might result in time delays that outweigh the benefits of mechanical reperfusion.[22] The non-significantly different proportion of women submitted to coronary angiography within 72 hours from admission, when compared to men, may indicate an improvement in timely invasive strategy for NSTEMI patients. Among patients with NSTEMI, indication for an invasive approach depends on numerous factors, including clinical presentation, comorbidities, risk stratification, frailty, cognitive status, estimated life expectancy, among others.[3] Frailty, worse cognitive status, other comorbidities, a lower estimated life expectancy increases with age, and women of our cohort were significantly older than men. Not all these factors were considered in the QI assessment, however the main NSTEMI QI of the invasive strategy is a time-based QI, measures delay times and not the decision to proceed to an invasive approach.

The very low level of performance of GRACE and CRUSADE assessment among both women and men should be addressed, as objective risk assessment using risk scores provides superior risk discrimination when compared with physician estimated risk.[24]

Use of incomplete drugs combinations after an ACS is associated with a higher risk of cardiovascular morbidity and all-cause mortality.[25] Results from a retrospective cohort study revealed that in Portugal women with STEMI were less likely to be discharged on aspirin and clopidogrel.[26] These results are in line with our finding of a lower proportion of eligible women discharged on dual antiplatelet therapy. High-intensity statins are recommended in all patients with AMI, irrespective of cholesterol concentration at presentation.[27] Previous studies reporting equally very high prescription of statins for secondary prevention after an ACS among women and men do not inform about the specific type of statins.[6, 26] However, poorer compliance with recommendation for high-intensity dose statins has been already reported[28] and results from EPIHeart study enlarge the knowledge about existing sex differences in prescription of this evidence based treatment. The use of lower-intensity statin therapy may be considered in patients at increased risk of side effects from statins (e.g. elderly, hepatic or renal impairment, previous side effects, or a potential for interaction with essential concomitant therapy).[27] In real-world practice, patients who besides this frail condition have very low baseline low-density lipoprotein cholesterol (LDL-C), are more probably candidates to be discharged on lower-intensity statin therapy, which is not necessary a wrong practice. We do not have the LDL-C levels at presentation, nor were able to identify this subgroup of patients with increased risk of side effects from statins. In anti-thrombotics and secondary prevention discharge treatment no differences by sex were observed, with high levels of performance for all treatments, except for fondaparinux. Treatment with fondaparinux was also the QI with the widest hospital variation in the MINAP register.[6] Not all possible relative contra-indications to prescription of different classes of drugs were taken into account, however the most relevant variables were considered to achieve our objectives.

Increasing referral to cardiac rehabilitation, especially among women can further reduce differences in mortality after an ACS between women and men, considering that referral to and attendance at cardiac rehabilitation is associated with a significant mortality reduction in women, comparatively better than that in men.[29] The higher smoking cessation advice observed for eligible women compared to men may be explained by evidence of higher appropriateness of this particular care for women, since women who smoke have a greater risk of developing cardiovascular disease than male smokers.[1]

Women had twice the 30-day mortality rate of men, adjusted for GRACE score. However, other factors not captured by the GRACE risk score that may have impact on outcomes, namely patient's adherence to secondary prevention, frailty, among others, were not addressed, which limits definitive conclusions on the association between sex and 30-day mortality rate.[30, 31]

Considering the low number of deaths in our cohort and the difficulty to demonstrate the relation between a single QI and clinical outcome,[32] we used the composite QI to measure the relation between process and outcome indicators. We found an inverse relation between attainment of this QI covering the spectrum of AMI care pathway and crude mortality; however this finding has to be considered with caution, since the small number of deaths within the tertiles of attainment of the composite QI precluded adjustment for possible confounders. Guideline recommended management and treatment performance indicators have already been associated with outcomes for patients with AMI.[20, 33] Our results are in line with findings that despite more than a decade since gender disparities in management and outcomes were described for the first time in a large-scale observation study[34] sex-related differences have not been eliminated.[35, 36] Further studies are needed to explore the reasons behind our findings, particularly to explore potential causal pathways to the associations between sex and management and outcomes, among patients with ACS.

Quality indicators in addition to stating an explicit diagnostic or therapeutic action to be performed, define how to identify patients for whom a specific action should be taken. It is not surprising that there is not a unique and universal standardised set of QIs for ACS; in 2015, the Spanish Society of Cardiology and the Spanish Society of Thoracic and Cardiovascular Surgery organized a task force to define outcome and process indicators of hospital cardiology practice.[37] Measuring and reporting variations by sex using validated QIs has the potential to further reduce sex inequalities in quality of care, with the ultimate goal of decreasing the still higher short term mortality of women with AMI.

Study limitations

These results report to two centres and do not represent the national scenario for ACS quality of care and outcomes. Because of eligibility criteria, for some QI small samples were used, but sampling was consecutive and the two hospitals contributed with 320 and 451 patients each. Although door-in door-out time for STEMI transferred patients was ascertained indirectly, we do not expect systematic errors in calculation with the methodology used.

Patients who died before the interview were older (81.5±11.8 vs 64.0±13.0 years, p<0.001), were more often women (66.7% vs 26.0%, p<0.001), and more frequently had a diagnosis of STEMI (81.3% vs 43.4%, p=0.003) than did participants. Patients who were not enrolled because of clinical instability or inability to understand the questionnaire because of cognitive impairment were older (75.2±10.1 vs 64.0±13.0 years, p<0.001), but there were no differences in sex proportion (male 68.2% vs. 74.1%, p=0.389) and ACS type (STEMI 37.2% vs. 46.6%, p=0.257). Patients who refused to participate were older (72.7±11.0 vs 64.0±13.0 years, p<0.001), were less often partnered (65.7% vs 76.8%, p=0.036), and had little formal education (43.1% vs 19.7%, p<0.001) compared with participants. Refusals were equally often male

(65.3% vs. 73.8%, p=0.119) and diagnosed with STEMI (37.1% vs. 46.6%, p=0.130) as participants. The higher risk of non-inclusion of women due to death in the early hours of admission means that a greater difference by sex in mortality would be expected. We have no further information on other characteristics and outcomes of these high risk patients.

CONCLUSIONS

Applying the ESC ACCA QIs, we observed differences in quality of care at different levels of the care pathway between women and men with AMI. These findings and the association of the composite QI with 30-day mortality, which is still higher in women, (and despite the fact that we cannot conclude that this difference in outcome is explained by the sex *per se*) provide evidence to support the measuring of these validated QIs separately by sex, to improve guideline recommended management and reduce mortality from AMI in women.

What is known about the topic?

Differences in management and outcomes in acute myocardial infarction patients were observed between women and men. Suboptimal care of women with acute myocardial infarction persisted through time. Use of the European Society of Cardiology Acute Cardiovascular Care Association quality indicators, which capture the key aspects of the acute myocardial infarction care pathway, has potential to improve care and reduce unwarranted variation in death.

What does this study add?

Adherence to validated performance measures for acute myocardial infarction is still lower in women compared to men and is associated with higher 30-day mortality. Timely reperfusion, discharge on dual antiplatelet therapy and on high intensity statins, and referral to cardiac rehabilitation were identified as targets to reduce sex inequalities in management of these patients. Use of the European Society of Cardiology Acute Cardiovascular Care Association quality indicators for management of acute myocardial infarction has also potential to bridge the gap between women and men.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Supplementary Table 1 Description of the ESC ACCA QIs for AMI domains.

Domain of care	Type of QI	Description	Components/eligibility
1.Centre organization	1.1 Main	Centre is part of a network organisation.	Single emergency phone number; pre-hospital ECG; pre-hospital activation of the catheterisation laboratory.
	1.2 Secondary 1	Centre routinely assess relevant times for the reperfusion process in STEMI patients.	Times from 'call to first medical contact', 'first medical contact to door', 'door to arterial access'; and 'door-in-door-out' for centres without a catheterisation laboratory on site.
	1.3 Secondary 2	Centre participates in a regular programme for quality assessment.	
2.Reperfusion-invasive strategy	2.1 Main (STEMI 1)	Proportion of STEMI patients eligible reperfused.	Onset of symptoms to diagnosis <12 h.
	2.2 Main (STEMI 2)	Proportion of STEMI patients eligible with timely reperfusion.	For fibrinolysis: <30 mins from diagnosis (FMC) to needle; for primary PCI and admission to PCI capable centres: <60 mins from door to arterial access; for transferred patients: door-in door-out time of <30 mins.
	2.3 Main NSTEMI	Proportion of high-intermediate risk NSTEMI patients who receive coronary angiography within 72 h after admission.	High-intermediate risk: at least one: diabetes mellitus, renal dysfunction (eGFR<30 ml/min/1.73 m²), LVEF⩽0.40, heart failure, recent PCI, prior CABG, GRACE risk score >140 or recurrent symptoms or ischaemia on non-invasive testing.
	2.3 Secondary (STEMI)	Time between the FMC and arterial access for primary PCI.	
3.In hospital risk assessment	3.1 Main (1)	Proportion of NSTEMI patients with GRACE risk score assessment.	GRACE risk score numerical value assessed and recorded in the discharge letter.
	3.2 Main (2)	Proportion of AMI patients with CRUSADE bleeding score assessment.	CRUSADE bleeding score numerical value assessed and recorded in the discharge letter.
	3.3 Main (3)	Proportion of AMI patients with LVEF assessment.	LVEF numerical value assessed and recorded in the report of the last echocardiography during hospital stay.
4. Anti-thrombotics during hospitalisation	4.1 Main (1)	Proportion of patients with 'adequate P2Y12 inhibition' on discharge.	For ticagrelor: AMI patients without previous haemorrhagic stroke, high bleeding risk, fibrinolysis or oral anticoagulation; prasugrel was not prescribed, for clopidogrel: no indication for prasugrel or ticagrelor and no high bleeding risk.
	4.2 Main (2)	Proportion of patients with NSTEMI treated with fondaparinux.	Exclusion of candidates for immediate (⩽2 h) invasive strategy or with eGFR<20 ml/min.
	4.3 Secondary	Proportion of eligible patients discharged on dual antiplatelet therapy.	Eligible: patients with CRUSADE risk score <50 and without oral anticoagulation on discharge.
5. Secondary prevention-discharge treatment	5.1 Main	Proportion of patients with AMI discharged on statins at high intensity.	Atorvastatin ⩾40 mg or rosuvastatin ⩾20 mg.
	5.2 Secondary (1)	Proportion of patients with AMI and clinical evidence of HF/LVEF ⩽0.40 discharged on ACEI/ARB.	Contra-indications: systolic blood pressure of less than 100 mmHg or severe renal failure (eGFR <30 ml/min).
	5.3 Secondary (2)	Proportion of patients with AMI and clinical evidence of HF/LVEF ⩽0.40 discharged on beta-blockers.	Contra-indications: systolic blood pressure of less than 100 mmHg at discharge, asthma and 2nd or 3rd degree atrioventricular block.
6. Patient satisfaction	6.1 Main	Feedback regarding the patient's experience systematically collected.	Recommendation to attend a cardiac rehabilitation programme used as surrogate.
7. Composite and outcome QI	7.1 Main composite (CQI)	Opportunity-based CQI.	Centre is part of a network organisation; STEMI patients reperfused; coronary angiography in high ischaemic risk AMI patients; GRACE in NSTEMI; CRUSADE in AMI patients; LVEF before discharge; low dose aspirin; adequate $P2Y_{12}$ inhibition; ACEI/ARB in patients with HF/LVEF⩽0.40; beta-blockers in HF/LVEF⩽0.40; high intensity statins; cardiac rehabilitation referral.
	7.2 Secondary CQI	All-or-none CQI based on 3 or 5 components, according to the LVEF.	For patients without HF/with LVEF>0.40: low-dose aspirin, $P2Y_{12}$ inhibitor, high-intensity statins. For patients with HF/with LVEF⩽0.40: low-dose aspirin, P2Y12 inhibitor, high-intensity statins, ACEI/ARB, beta-blockers.
	7.3 Secondary outcome	30-day mortality rate adjusted for the GRACE 2.0 risk score.	No information about follow-up was available for 29 patients and GRACE 2.0 risk score was not possible to calculate for 19 patients.

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; AMI, acute myocardial infarction; CABG, coronary artery bypass surgery; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FMC, first medical contact; HF, heart failure; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; QI, quality indicator; STEMI, ST elevation myocardial infarction.

3.4 PAPER 4

SEX DIFFERENCES IN PRESENTING SYMPTOMS OF ACUTE CORONARY SYNDROME: THE EPIHEART COHORT STUDY

Carla Araújo, Olga Laszczyńska, Marta Viana, Filipa Melão, Ana Henriques, Andreia Borges, Milton Severo, Maria Júlia Maciel, Ilídio Moreira, Ana Azevedo

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Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study

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ABSTRACT

Objectives Prompt diagnosis of acute coronary syndrome (ACS) remains a challenge, with presenting symptoms affecting the diagnosis algorithm and, consequently, management and outcomes. This study aimed to identify sex differences in presenting symptoms of ACS.

Design Data were collected within a prospective cohort study (EPIHeart).

Setting Patients with confirmed diagnosis of type 1 (primary spontaneous) ACS who were consecutively admitted to the Cardiology Department of two tertiary hospitals in Portugal between August 2013 and December 2014.

Participants Presenting symptoms of 873 patients (227 women) were obtained through a face-to-face interview. Outcome measures: Typical pain was defined according to the definition of cardiology societies. Clusters of symptoms other than pain were identified by latent class analysis. Logistic regression was used to quantify differences in presentation of ACS symptoms by sex.

Results Chest pain was reported by 82% of patients, with no differences in frequency or location between sexes. Women were more likely to feel pain with an intensity higher than 8/10 and this association was stronger for patients aged under 65 years (interaction P=0.028). Referred pain was also more likely in women, particularly pain referred to typical and atypical locations simultaneously. The multiple symptoms cluster, which was characterised by a high probability of presenting with all symptoms, was almost fourfold more prevalent in women (3.92, 95% CI 2.21 to 6.98). Presentation with this cluster was associated with a higher 30-day mortality rate adjusted for the GRACE V.2.0 risk score (4.9% vs 0.9% for the two other clusters, P<0.001).

Conclusions While there are no significant differences in the frequency or location of pain between sexes, women are more likely to feel pain of higher intensity and to present with referred pain and symptoms other than pain. Knowledge of these ACS presentation profiles is important for health policy decisions and clinical practice.

Strengths and limitations of this study

- ► Within a prospective cohort study, presenting symptoms of acute coronary syndrome were obtained through a structured questionnaire applied within the first 48 hours after admission.
- ► Consecutive sampling, the detailed clinical information obtained through the questionnaire and adjustment for several confounding variables strengthens our results.
- ► The results of this study are valid for stable patients admitted to the hospital and who were able to answer the questionnaire in the acute phase of the acute coronary syndrome.
- ► Some of the sex differences in presenting symptoms may be influenced by selection bias because of a higher risk of non-inclusion of women due to misdiagnosis or death in the early hours of admission.

INTRODUCTION

Acute coronary syndrome (ACS) is still one of the main causes of death worldwide and in Europe.[1 2] Coronary heart disease mortality has decreased in the last decades in high-income countries because of primary prevention and improvement in treatment of patients with ACS.[2] Attainment of the maximal benefit of treatment of these patients is threatened by delayed diagnosis, partly dependent on clinical suspicion of ACS. The subjective experience of symptoms influences patients' attitudes in seeking help and professionals' interpretation of clinical presentations.[3] Early recognition of ACS may be challenging because while patients with presumed ACS have contact with healthcare providers,[4] many patients do not have an electrocardiogram (ECG) before hospitalisation.[5] Therefore, physicians frequently have to make decisions that are only clinically based.

The population of patients with atypical ACS presentation is still not well characterised.[6] Women and men generally have the same type of symptoms during an ACS episode, although the proportion presenting with different combinations of symptoms varies.[7] This conflicting evidence can be partly explained by the diverse methodology used,

with few prospective studies, usually without a specific questionnaire. In prospective studies, small convenience samples were used and confounding was not always adequately addressed.[8 9] Therefore, sex-specific research on ACS presentation is a challenge and priority.[10]

This study aimed to analyse sex differences in presenting symptoms of ACS within a prospective cohort study, taking into account the contribution of age, socioeconomic data, previous history of coronary heart disease, risk factors, comorbidities, type of ACS and coronary anatomy to the presenting symptoms.

METHODS

Study design and sample selection

The EPIHeart cohort study was designed to identify inequalities in management and outcomes of patients with ACS. This study included all consecutive patients who were admitted between August 2013 and December 2014 to the Cardiology Department of two tertiary hospitals in two regions in northern Portugal (Hospital de São João, Porto, covering the metropolitan area of Porto in the coast; and Hospital de São Pedro, Vila Real, covering the interior, northeastern region). Eligible patients were aged 18 years or older who lived in the catchment area of these hospitals (districts: Porto, Vila Real, Bragança, and Viseu), with confirmed diagnosis of type 1 (primary spontaneous) ACS. The diagnosis of type 1 ACS and the classification in different subtypes was determined by the treating cardiologist, based on symptoms and signs at presentation, ECG findings and the increase in cardiac enzyme levels (high-sensitivity troponin I or T were used), according to the third universal definition of myocardial infarction.[11] The patients were also expected to be hospitalised for at least 48 hours and not institutionalised before the event. Of 1297 patients initially considered, in 164 the diagnosis of type 1 ACS was not confirmed, 60 were excluded due to discharge or transfer before the interview, 18 died before being invited and 44 were unable to answer the questionnaire because of clinical instability, no understanding of Portuguese, hearing problems or cognitive impairment. Seventy-two patients refused to participate. For this analysis, we excluded 61 patients who were not admitted because of a symptom (patients referred by a doctor, after a scheduled appointment or diagnostic exam), 4 with vasospastic angina and 1 illicit drug user. A total of 873 patients were included (figure 1). The study protocol was in compliance with the principles of the Declaration of Helsinki. All patients gave written informed consent.

Procedures and data collection

Presenting symptoms were obtained face-to-face using a structured questionnaire applied by trained interviewers, within the first 48 hours after admission, whenever possible. Over the following days, a second interview was conducted to collect data on sociodemographic characteristics and risk factors. Medical records were reviewed to extract data regarding previous medical history, admission information and clinical data during hospitalisation.

Pain, referred pain and symptoms other than pain were measured dichotomously (yes/no). For the location of pain (direct and referred), patients were asked to point out where pain was occurring. To measure the intensity of pain, a 10-point scale (0, no pain; 10, pain of maximal intensity) was used. Symptoms other than pain included dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness and an open-ended question of 'other' (12 items). Answers to the last item enabled identification of two other relatively frequent symptoms, other digestive symptoms and discomfort. Activity at the onset of the episode was measured dichotomously, including sleeping, rest, and any exertion. A stress trigger was assigned if the patient answered 'yes' for at least one of following events within 24 hours preceding the episode: accident, recent diagnosis of disease, financial problems and news of death/disease of a relative/friend.

Marital status was considered partnered for married patients or living in civil union. Education was recorded as completed years of schooling and classified into four categories: <4 (little formal education), 4 (elementary school), <12 (high school) and 12 or more years (secondary education or more). Occupations were classified into major professional groups, according to the Portuguese Classification of Occupations 2010,[12] integrated in the International Standard Classification of Occupations (ISCO/2008).

Definition of variables

Although symptoms of ACS have been widely described, their value for diagnosis of ACS is not unanimously recognised.[13–15] After discussion with clinical cardiologists of our team, we opted to use Cardiology Societies' position papers to define direct and referred pain locations and to select symptoms to evaluate.[16 17] Direct pain location was classified as follows: 1) typical for retrosternal, precordial, right thoracic or bilateral thoracic pain (chest pain); 2) atypical for epigastric pain or located in the back, left arm or shoulder, right arm or shoulder, neck or jaw and 3) a mixture when both typical and atypical locations were present. Referred pain location was considered as follows: 1) typical if pain referred to the left arm or shoulder, right arm or shoulder, neck or jaw; 2) atypical if pain referred to retrosternal, precordial, right thoracic, bilateral thoracic, epigastric or back regions and 3) a mixture for referred pain in typical and atypical locations.

Patients rarely present with a single symptom during an episode of ACS, and present with multiple symptoms instead that do not occur in isolation and may cluster.[18] There has been increasing interest in symptom cluster analysis in cardiovascular disease because it aids in assessment by enhancing recognition of patients with similar symptom profiles.[19] Groups of symptoms other than pain were obtained by latent class analysis.

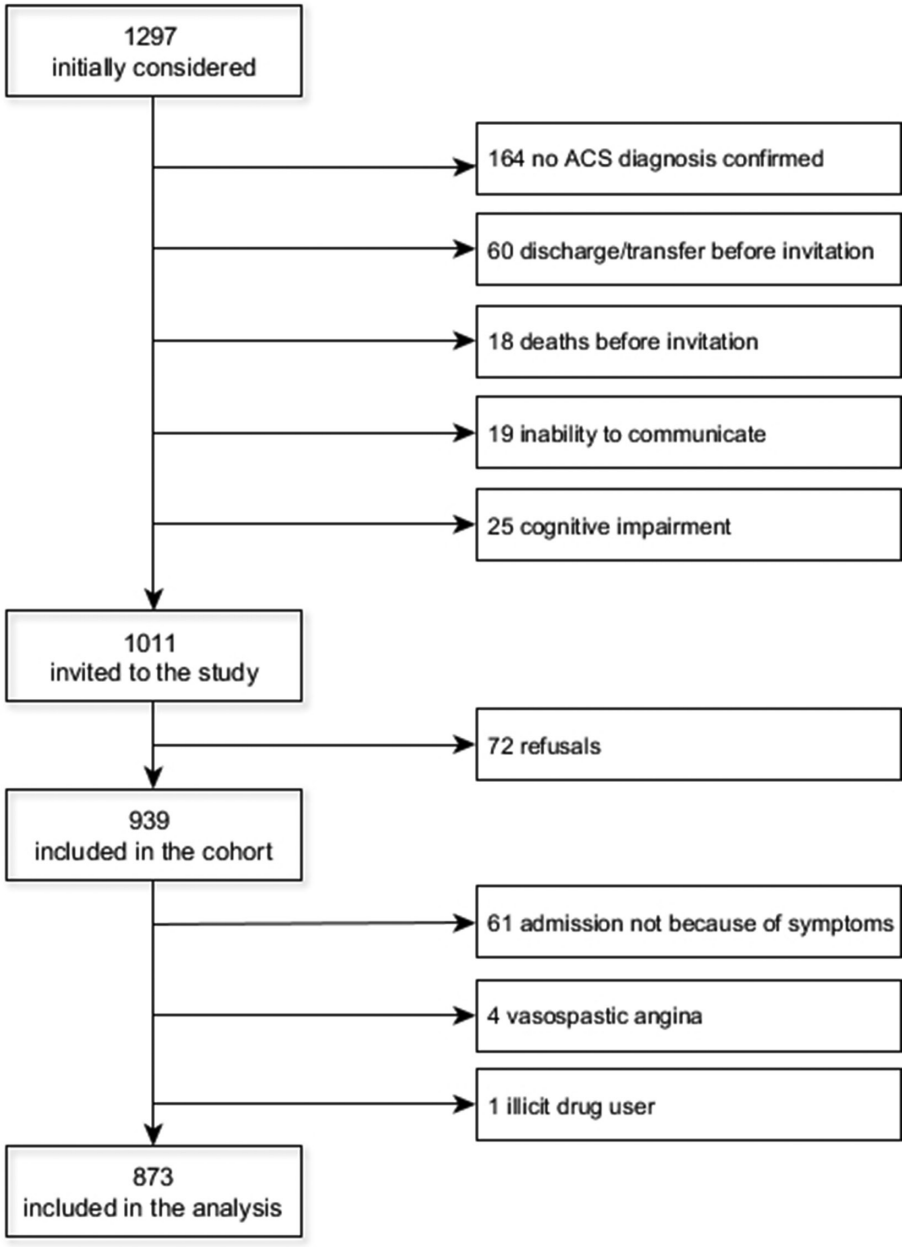

Figure 1 Flow chart of the study population. ACS, acute coronary syndrome.

The small group of non-classified (NC) patients with ACS (patients with left bundle branch block) was grouped with patients with ST-elevation myocardial infarction (STEMI) (STEMI/NC ACS group). Non-ST-elevation ACS (NSTEACS) included unstable angina and non-ST-elevation acute myocardial infarction or subacute myocardial infarction.

Considering the possible association between coronary anatomy and clinical presentation, we grouped patients according to coronary angiography into five groups: managed conservatively; non-obstructive coronary artery disease; lesions exclusively in the anterior descending artery; lesions in the right and/or circumflex artery and lesions in the left main coronary artery, three-vessel disease or disease both in the anterior descending artery and the right or circumflex artery.

Data analysis

Continuous variables are expressed as mean and standard deviation (SD) or as median and interquartile range (IQR). Categorical variables are shown as number and percentage. To compare differences between women and men, and by age groups, the χ^2 test or Fisher's exact test was used for categorical variables and the t-test, Mann-Whitney U test or Kruskal-Wallis test for continuous variables. Latent class analysis was used to identify distinct groups of individuals from a sample (clusters) who were homogeneous within the group. This was based on the

fact that performance of an individual in a set of items is explained by a categorical latent variable with K classes (clusters), commonly called latent classes. The number of latent clusters was defined according to the Akaike information criterion (AIC). Starting from one single cluster and increasing one cluster at each step, the best solution was identified when an increase in the number of clusters did not lead to a decrease in the AIC.

Patient and system delays, severity indicators, risk stratification using calculated GRACE and CRUSADE risk scores, left ventricular systolic dysfunction and 30-day mortality rate adjusted for the Global Registry of Acute Coronary Events (GRACE) V.2.0 risk score,[20] were assessed according to the presence of typical (chest) pain and cluster of symptoms other than pain. The 30-day mortality adjusted for the GRACE V.2.0 risk score was estimated based on predicted probabilities derived from logistic regression. Logistic regression was used to identify variables associated with clinical presentation. Variables with P<0.15 for a crude association with the end point were entered in the initial model and a backward strategy was used to exclude the least significant variables, based on Wald tests. We were then able to obtain the most parsimonious model with all the important determinants. Previous data support significant interaction between age and sex with clinical presentation, attenuated with advancing age, mainly in those aged 65 years or older.[3] We assessed for effect measure modification by stratifying adjusted analyses based on two age groups (under 65 and 65 years or older). Considering the relevance of analysing sex differences in ACS clinical presentation in younger patients, we also performed the age-stratified multivariate models using 55 years as cut-off age. Sex, age (continuous) and type of ACS were forced to remain in the models.

All analyses were performed using STATA V.11.1 for Windows (StataCorp, College Station, Texas, USA) and R V.2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Women (n=227, 26.0%) were older (69.1 vs 62.2 years, P<0.001) and more frequently lived in the interior region (52.4% vs 38.7%, P<0.001) than men. Women were more often treated conservatively and had non-obstructive coronary artery disease more frequently than men. In this sample, no difference by sex was observed in the type of ACS, where 56.6% of the patients had a discharge diagnosis of NSTEACS (table 1).

Women more frequently had hypertension (81.5% vs 62.7%, P<0.001) and diabetes (38.8% vs 29.9%, P=0.014), and were more frequently obese (25.5% vs 18.5%, P=0.020) and never smokers compared with men (P<0.001, table 1). Men were submitted to percutaneous coronary intervention more often than women. There were no significant differences in a previous history of renal failure, prior myocardial infarction, prior coronary artery bypass surgery, prior heart failure and dementia by sex (table 1).

Women were more likely to be unpartnered, disabled, less educated and had a lower income compared with men. The median time that elapsed between admission and application of the symptom questionnaire was slightly longer in women than in men (table 1).

Symptom characteristics by sex and age

Because differences in symptoms by sex and age were similar in direction and magnitude in STEMI/NC ACS and NSTEACS (see online supplementary table 1 and 2), both types of ACS were analysed together.

Although pain was present in most patients, men presented with pain more frequently than did women (97.4% vs 94.3%, P=0.028), with a higher sex difference among patients aged 80 or more years (88.0% vs 93.5%). Older patients presented less often pain, but the difference by age group in both sexes was not significant (table 2). No difference was found in the location of pain by sex. Approximately 80% of patients felt chest pain (typical pain). Older women presented less frequently with chest pain and had chest pain and pain in other locations (mixture group) more often than did younger women (P=0.014). Referred pain was observed more frequently in women and in younger patients (only significant for men, P=0.024); again in the older age group, the difference between women and men was notorious (56.8% vs 39.7%, respectively). Atypical and mixture referred pain were more frequent in women than in men (P<0.001), mainly in women aged≥65 years (P=0.009). Women felt pain with higher intensity than did men (median (IQR): 9 (8–10) vs 8 (6–9), P<0.001), without a difference by age (table 2). Women presented with symptoms other than pain more frequently than did men (82.8% vs 68.9%, P<0.001), with no difference by age group in both sexes (table 2).

Considering symptoms other than pain, the AIC optimum value supported a preference for a three-cluster solution (AIC 7207.508, 6869.390, 6862.476 and 6870.372 for one, two, three and four clusters, respectively). Cluster 1 had low endorsement probabilities for all items (no symptoms cluster). Cluster 2 had a high probability for dyspnoea at rest and sweating, and a low probability for the remaining items (dyspnoea and sweating cluster). Cluster 3 had high probabilities for all items (multiple symptoms cluster). This three-cluster model made sense conceptually to cardiologists of our team. Clusters counts and probabilities of occurrence of symptoms in established clusters are shown in online supplementary table 3. Differences in proportions of women and men in the three clusters were observed (P<0.001, table 2). Cluster 1 was the most prevalent, in which men presented with the no symptoms cluster more frequently (76.9% vs 62.6%) and the multiple symptoms cluster less frequently (4.8% vs 15.9%) than did women. Higher differences of multiple symptoms cluster proportions between women

Table 1 Baseline demographic, socioeconomic and clinical characteristics in the whole sample and by sex*

	Total (n = 873)	Women (n = 227)	Men (n = 646)	P value
Age (years), mean (SD)	64.0 (13.0)	69.1 (12.7)	62.2 (12.7)	<0.001
Socioeconomic status				
Marital status				
Partnered	667 (76.8)	133 (58.9)	534 (83.2)	<0.001
Education				
Little formal education	172 (19.9)	95 (42.4)	77 (12.0)	
Elementary school	337 (39.1)	73 (32.6)	264 (41.3)	
High school	213 (24.7)	32 (14.3)	181 (28.3)	
Secondary education or more	141 (16.3)	24 (10.7)	117 (18.3)	<0.001
Employment status				
Employed/looking after home	282 (32.6)	64 (28.3)	218 (34.1)	
Unemployed	107 (12.4)	16 (7.1)	91 (14.2)	
Retired	334 (38.6)	93 (41.2)	241 (37.7)	
Disabled	143 (16.5)	53 (23.5)	90 (14.1)	<0.001
Subjective social class				
Low	281 (32.2)	81 (35.7)	200 (31.0)	
Lower-middle	281 (32.2)	58 (25.6)	223 (34.5)	
Higher-middle/high	60 (6.9)	16 (7.1)	44 (6.8)	
No response	251 (28.8)	72 (31.7)	179 (27.7)	0.097
Household income (€)				
<500	204 (23.4)	77 (33.9)	127 (19.7)	
501–1000	276 (31.6)	60 (26.4)	216 (33.4)	
1001–2000	146 (16.7)	22 (9.7)	124 (19.2)	
>2000	88 (10.1)	14 (6.2)	74 (11.5)	
No response	159 (18.2)	54 (23.8)	105 (16.3)	<0.001
Region				
Metropolitan area of Porto	504 (57.7)	108 (47.6)	396 (61.3)	
Northeastern region of Portugal	369 (42.3)	119 (52.4)	250 (38.7)	<0.001
Cardiovascular risk factors				
Smoking habit				
Never	369 (42.3)	184 (81.0)	185 (28.6)	
Current	283 (32.4)	34 (15.0)	249 (38.5)	
Former	221 (25.3)	9 (4.0)	212 (32.8)	<0.001
Hypertension	590 (67.6)	185 (81.5)	405 (62.7)	<0.001
Diabetes mellitus	281 (32.2)	88 (38.8)	193 (29.9)	0.014
Dyslipidaemia	535 (61.4)	144 (63.4)	391 (60.6)	0.454
BMI (kg/m^2)				
Median (IQR)	26.5 (18.0–44.6)	26.7 (19.5–37.9)	26.4 (18.2–39.2)	0.531
Underweight	11 (1.4)	2 (0.9)	9 (1.5)	
Normal weight	272 (33.4)	80 (37.0)	192 (32.1)	
Overweight	366 (44.9)	79 (36.6)	287 (47.9)	
Obese	166 (20.4)	55 (25.5)	111 (18.5)	0.020
Family history of CVD	303 (34.7)	73 (32.2)	230 (35.6)	0.105

Continued

Table 1 Continued

	Total (n = 873)	Women (n = 227)	Men (n = 646)	P value
Previous medical history				
Renal failure	64 (7.3)	14 (6.1)	50 (7.7)	0.434
Myocardial infarction	156 (17.9)	34 (15.0)	122 (18.9)	0.186
PCI	100 (12.4)	18 (8.4)	82 (13.8)	0.041
CABG	34 (4.2)	5 (2.3)	29 (4.9)	0.111
Heart failure	63 (7.5)	21 (9.6)	42 (6.8)	0.172
Dementia	7 (0.8)	4 (1.8)	3 (0.5)	0.060
ACS type				
STEMI/NC ACS	379 (43.4)	101 (44.5)	278 (43.0)	
NSTEACS	494 (56.6)	126 (55.5)	368 (57.0)	0.703
Coronary anatomy				
Non-obstructive disease	57 (6.9)	22 (10.6)	35 (5.61)	
Left anterior descending artery only	162 (19.5)	38 (18.3)	124 (19.9)	
Right and/or circumflex artery only	196 (23.6)	46 (22.1)	150 (24.0)	
Mixture	417 (50.1)	102 (49.0)	315 (50.5)	
Not submitted to coronary angiography	41 (4.7)	19 (8.4)	22 (3.4)	0.004
Symptom questionnaire application				
Time from admission (hours), median (IQR)	42.1 (25.0-68.0)	45.4 (28.5-72.3)	40.0 (24.0-67.4)	0.052

*Values are number and percentage unless otherwise indicated.
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass surgery; CVD, cardiovascular diseases; IQR, interquartile range; NSTEACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI/NC ACS, ST-elevation myocardial infarction/non-classifiable acute coronary syndrome.

and men were observed among patients in the older age group. The proportion of dyspnoea and sweating cluster was similar in men and women (table 2).

Approximately 45% of patients were at rest and 35% were under physical effort at the beginning of the episode. Older women were more frequently at rest at the beginning of the episode and younger women were more frequently under effort (p=0.011). Less than 10% of patients identified a stressful event in the previous 24 hours, with no difference by sex, but among men, a younger age was slightly associated with this trigger (P=0.045, table 2).

Multivariate models

Despite the higher probability of women below or above 65 years to present without pain than men, no differences were observed in the adjusted pain frequency and location between men and women. Referred pain was more likely to be experienced by women (<65 years: adjusted OR 2.90, 95% CI 1.47 to 5.72; ≥65 years: 1.60 (95% CI 0.99 to 2.60), interaction P=0.528). Moreover, women below or above 65 years had a higher probability of having pain radiating to typical and atypical locations and of feeling pain with an intensity higher than 8 (table 3). The association between intensity of pain and female sex was stronger for patients below 65 years (interaction P=0.028) (table 3).

The presence of at least one symptom other than pain occurred almost two times more often in women than in men. With cluster 1 as the reference, clusters 2 and 3 were positively associated with female sex, with the latter being statistically significant. The multiple symptoms cluster was almost fourfold more likely in women than in men (3.92, 95% CI 2.21 to 6.98 in the whole sample, interaction P=0.501) (table 3).

No difference in the type of patients' activities at the beginning of the episode by sex was observed (table 3).

Performance of age-stratified multivariate models using the 55 years cut-off revealed similar results to the observed using the 65 years cut-off, with some differences mainly in the strength of association of some clinical presentation variables with sex among the younger age group (see online supplementary table 4). Although still not significant, among patients below 55 years, women were less likely to present with typical chest pain (0.65, 95% CI 0.23 to 1.86). A stronger association between female sex and referred pain, and intensity of pain higher than 8/10, among patients in the younger age groups was observed using the 55 instead of the 65 years cut-off. The remaining results were similar in direction and strength of association (table 3 and online supplementary table 4). The precision of the estimates is lower using the 55 cut-off, due to the small sample of patients below 55 years.

Table 2 Clinical presentation of patients with acute coronary syndrome, by sex and age*

	Women					P	Men						
	≤45	46–64	65–79	≥80	Total	value†	≤45	46–64	65–79	≥80	Total	P value‡	P value‡
Total	14 (6.2)	54 (23.8)	109 (48.0)	50 (22.0)	227 (100.0)		61 (9.4)	303 (46.9)	220 (34.1)	62 (9.6)	646 (100)		
Pain	14 (100.0)	52 (96.3)	104 (95.4)	44 (88.0)	214 (94.3)	0.229	60 (98.4)	297 (98.0)	214 (97.3)	58 (93.5)	629 (97.4)	0.228	0.028
Pain location§													
Typical	12 (85.7)	43 (82.7)	88 (85.4)	32 (72.7)	175 (82.2)		53 (89.8)	246 (83.7)	175 (82.2)	44 (75.9)	518 (83.0)		
Atypical	1 (7.1)	9 (17.3)	5 (4.9)	6 (13.6)	175 (9.9)		3 (5.1)	33 (11.2)	30 (14.1)	10 (17.2)	76 (12.2)		
Mixture	1 (7.1)	0 (0.0)	10 (9.7)	6 (13.6)	17 (8.0)	0.014	3 (5.1)	15 (5.1)	8 (3.8)	4 (6.9)	30 (4.8)	0.327	0.165
Referred pain	9 (64.3)	41 (78.8)	72 (69.2)	25 (56.8)	147 (68.7)	0.129	38 (63.3)	179 (60.3)	126 (58.9)	23 (39.7)	366 (58.2)	0.024	0.007
Radiation type¶													
Typical	8 (88.9)	20 (48.8)	28 (38.9)	7 (28.0)	63 (42.9)		28 (73.7)	114 (64.4)	67 (53.2)	10 (43.5)	219 (60.2)		
Atypical	0 (0.0)	13 (31.7)	18 (25.0)	13 (52.0)	44 (29.9)		7 (18.4)	37 (20.9)	39 (31.0)	8 (34.8)	91 (25.0)		
Mixture	1 (11.1)	8 (19.5)	26 (36.1)	5 (20.0)	40 (27.2)	0.009	3 (7.9)	26 (14.7)	20 (15.9)	5 (21.7)	54 (14.8)	0.104	<0.001
Pain intensity**	9.5 (8-10)	9 (8-10)	9 (8-9)	8 (8-9)	9 (8-10)	0.170	8 (7-10)	8 (6-9)	8 (6-9)	8 (7-9)	8 (6-9)	0.095	<0.001
Symptom	11 (78.6)	45 (83.3)	91 (83.5)	41 (82.0)	188 (82.8)	0.947	43 (70.5)	209 (69.0)	151 (68.6)	42 (67.7)	445 (68.9)	0.989	<0.001
Symptom clusters††													
Cluster 1	7 (50.0)	41 (75.9)	62 (56.9)	32 (64.0)	142 (62.6)		43 (70.5)	232 (76.6)	170 (77.3)	52 (83.9)	497 (76.9)		
Cluster 2	5 (35.7)	8 (14.8)	28 (25.7)	8 (16.0)	49 (21.6)		15 (25.6)	59 (19.5)	35 (15.9)	9 (14.5)	118 (18.3)		
Cluster 3	2 (14.3)	5 (9.3)	19 (17.4)	10 (20.0)	36 (15.9)	0.183	3 (4.9)	12 (4.0)	15 (6.8)	1 (1.61)	31 (4.80)	0.345	<0.001
Activity													
Sleep	2 (15.4)	16 (32.0)	11 (10.4)	7 (14.9)	36 (16.7)		6 (9.8)	65 (21.7)	35 (16.1)	13 (21.3)	119 (18.6)		
Rest	5 (38.5)	18 (36.0)	50 (47.2)	29 (61.7)	102 (47.2)		34 (55.7)	124 (41.3)	105 (48.2)	33 (54.1)	296 (46.3)		
Exertion	6 (46.2)	16 (32.0)	45 (42.5)	11 (23.4)	78 (36.1)	0.011	21 (34.4)	111 (37.0)	78 (35.8)	15 (24.6)	225 (35.2)	0.087	0.816
Stress trigger	2 (14.3)	6 (11.1)	11 (10.2)	3 (6.1)	22 (9.8)	0.700	11 (18.0)	23 (7.7)	15 (6.9)	6 (9.8)	55 (8.6)	0.045	0.605

*Values are number and percentage unless otherwise indicated.
†P for age differences within each sex.
‡P for differences between sexes.
§Pain location: typical—retrosternal, precordial, right thoracic or bilateral thoracic; atypical—epigastric, back, left arm or shoulder, right arm or shoulder, neck or jaw; mixture—typical and atypical location.
¶Radiation type: typical—left arm or shoulder, right arm or shoulder, neck or jaw; atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric or back regions; mixture—typical and atypical irradiation.
**Median (IQR).
††Symptom clusters: cluster 1 (no symptom cluster)—low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster)—high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster)—high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).

Table 3 Differences between women and men in clinical presentation of acute coronary syndrome, by age group (men are the reference class)

Symptoms	<65 years OR	<65 years 95% CI	≥65 years OR	≥65 years 95% CI	Interaction P value	Adjusted for
Pain	0.76	0.14 to 4.0	0.52	0.19 to 1.47	0.777	Age, type of ACS, marital status, dyslipidaemia, CABG
Typical (chest) pain (vs atypical or mixture)*	0.97	0.44 to 2.14	1.71	0.90 to 3.23	0.973	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Referred pain	2.90	1.47 to 5.72	1.60	0.99 to 2.60	0.528	Age, type of ACS, coronary anatomy, region, income, social class, previous renal failure
Radiation type†						
Typical	1	Reference	1	Reference		Age, type of ACS, employment status, region
Atypical	1.49	0.70 to 3.20	1.38	0.72 to 2.66	0.415	
Mixture	1.77	0.73 to 4.29	2.75	1.36 to 5.57	0.606	
Pain intensity (higher than 8/10)	3.81	2.04 to 7.13	2.03	1.22 to 3.37	0.028	Age, type of ACS, coronary anatomy, education, professional group, previous AMI
Symptoms	1.98	1.00 to 3.91	1.85	1.10 to 3.12	0.799	Age, type of ACS, region, previous AMI, previous heart failure
Symptom clusters‡						
Cluster 1	1	Reference	1	Reference		Age, type of ACS, professional group, region, previous AMI
Cluster 2	1.07	0.53 to 2.15	1.67	0.97 to 2.87	0.246	
Cluster 3	3.14	1.15 to 8.62	4.23	2.03 to 8.81	0.501	
Activity group						
Sleeping	1	Reference	1	(Reference)		Age, type of ACS, previous heart failure
Rest	0.68	0.33 to 1.38	1.38	0.74 to 2.57	0.284	
Exertion	0.77	0.37 to 1.59	1.70	0.89 to 3.25	0.408	

*Pain location: typical—retrosternal, precordial, right thoracic or bilateral thoracic; atypical—epigastric, back, left arm or shoulder, right arm or shoulder, neck or jaw; mixture—typical and atypical location.
†Radiation type: typical—left arm or shoulder, right arm or shoulder, neck or jaw; atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric or back regions; mixture— typical and atypical irradiation.
‡Symptom clusters: cluster 1 (no symptom cluster)—low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster)—high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster)—high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).
ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass surgery.

Clinical presentation and outcomes

Patients with a diagnosis of STEMI/NC ACS who presented with atypical or mixture pain took longer to seek medical care (135 vs 85 min, P=0.012) and had longer total ischaemic times (414 vs 328 min, P=0.080) than patients with chest pain (table 4). Among patients with NSTEACS, differences in time delays according to pain location were not significant. Patients with atypical or mixture pain presented more frequently with haemodynamic instability at admission (9.7% vs 4.6%, P=0.014) and had also more often moderate-to-severe left ventricular systolic dysfunction (32.9% vs 24.9%, P=0.052) than patients with chest pain. The 30-day mortality adjusted for GRACE V.2.0 was not significantly different between patients with chest pain and those with atypical or mixture pain (table 4).

Among patients with STEMI/NC ACS, the total ischaemic time was longer for patients with the multiple symptoms cluster compared with patients who presented with the two other symptoms clusters (533 vs 321 and 384 min, P=0.111). Patients with the multiple symptom cluster presented more often with haemodynamic instability at admission than patients with the other symptoms clusters (13.4% vs 6.4% and 4.2%, P=0.034). The mean 30-day mortality rate adjusted for the GRACE V.2.0 risk score was significantly higher for patients presenting with the multiple symptom cluster (4.9% vs 0.9% for the two other clusters, P<0.001) (table 4).

Table 4 Patient and system delays, severity indicators, risk stratification and 30-day mortality according to clinical presentation*

	Typical (chest) pain†	Atypical or mixture pain	P value	No symptom cluster‡	Dyspnoea and sweating cluster	Multiple symptoms cluster	P value
Patient and system delays, median (IQR)							
STEMI/NC ACS							
Symptom onset—FMC (min)	85 (45–210)	135 (65–325)	0.012	90 (46–240)	90 (50–185)	83 (45–430)	0.872
Symptom onset—arterial access (min)	328 (192–1075)	414 (246–1335)	0.080	321 (194–1011)	384 (201–1440)	533 (323–1428)	0.111
NSTEACS							
Symptom onset—FMC (min)	130 (60–393)	139 (60–335)	0.633	135 (60–390)	150 (60–390)	113 (45–393)	0.795
Hospital admission—coronary angiography time (hours)	30 (18–57)	29 (20–48)	0.884	30 (18–56)	35 (18–70)	28 (20–72)	0.385
Admission variables							
Heart rate, mean (SD), bpm	77 (18)	80 (24)	0.117	78 (19)	77 (19)	78 (28)	0.923
Systolic blood pressure, mean (SD), mm Hg	144 (49)	139 (30)	0.212	145 (59)	141 (30)	136 (33)	0.364
Haemodynamic instability at admission§	32 (4.6)	14 (9.7)	0.014	41 (6.4)	7 (4.2)	9 (13.4)	0.034
Risk stratification							
Calculated GRACE risk score, mean (SD)	134 (36)	147 (39)	<0.001	137 (37)	138 (35)	149 (44)	0.041
Calculated CRUSADE risk score, median (IQR)	21 (11–34)	25 (14–41)	0.012	22 (12–36)	23 (10–36)	30 (16–47)	0.019
Moderate or severe left ventricular systolic dysfunction	169 (24.9)	46 (32.9)	0.052	164 (26.4)	55 (33.3)	17 (25.4)	0.187
30-Day mortality rate adjusted for the GRACE V.2.0 risk score, mean (SD)	2.0 (4.0)	1.3 (1.4)	0.521	0.9 (2.0)	0.9 (2.0)	4.9 (5.5)	<0.001

*Values are number and percentage unless otherwise indicated. Total may not add to 100% due to missing data.
†Chest pain: retrosternal, precordial, right thoracic or bilateral thoracic.
‡No symptom cluster: low endorsement probabilities for all items; dyspnoea and sweating cluster: high probability for dyspnoea atrest and sweating; multiple symptoms cluster: high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).
§Killip class III or IV; or shock at admission.
CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes; FMC: first medical contact; GRACE: Global Registry of Acute Coronary Events; NSTEACS, non-ST- elevation acute coronary syndrome; STEMI/NC ACS, ST- elevation myocardial infarction/ non-classifiable acute coronary syndrome.

Patients with atypical or mixture chest pain and patients with the multiple symptom cluster had higher mean GRACE and median Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes (CRUSADE) risk scores (table 4).

DISCUSSION

In our study, after adjustment, no differences in the frequency and location of pain by sex were observed. Referred pain, pain radiating to typical and atypical locations and pain of higher intensity were more likely to occur among women. Women were also more likely than men to present with symptoms other than pain. Three clusters of symptoms other than pain were identified. Women were more likely to present with the multiple symptoms cluster. Presenting with the multiple symptoms cluster was associated with a higher mean 30-day mortality rate adjusted for the GRACE V.2.0 risk score.

Differences between women and men in perception of symptoms of ACS might be explained by anatomical, physiological, biological and psychosocial differences that influence each other.[9 21] We measured several variables of these different domains. Differences in symptom presentation by sex might be the result of differences in response to history-taking,[10] differences in neural receptors and pathways involved in pain and subtle differences in the location and type of atherosclerotic lesions.[22 23] Our findings of similar ACS symptoms between women and men are consistent with previous studies,[7 24] as well as our finding that women are more likely to have atypical presentations.[9] We observed that women have a higher likelihood of atypical referred pain and of several concomitant symptoms other than pain, common to other cardiac and non-cardiac diagnoses.

In our study, chest pain was the most frequent symptom in both sexes, consistent with previous studies.[25–27] Among those with pain, typical chest pain was observed in 82% of patients, regardless of sex. The remaining patients had pain in less typical locations and were thus prone to misdiagnosis and undertreatment and, consequently, to worse outcomes.[28] Considering differences in characteristics of pain by sex, studies suggested that women, in particular older women, were less likely to have the chief complaint of chest pain associated with acute myocardial infarction, while after adjustment, among patients aged 65 years or under, female sex was no longer a significant predictor.[29] Studies reported that chest pain did not differ between women and men,[9] others that women have pain in the neck and back more often than men,[30 31] without distinguishing between direct and referred pain. In our study, referred pain was observed in 61% of patients, was more frequent in women and typical referred pain was only observed in 33%. Notably, a study on diagnostic acuity of ACS symptoms showed that shoulder and arm pain was predictive of the diagnosis of ACS for women only.[24] Another study Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome (GENESIS PRAXY) on sex differences in ACS symptom presentation in patients aged 55 years or younger showed that being a woman was independently associated with ACS presentation without chest pain.[27] Although the association was not significant, and relied on a small sample of patients, our finding that women aged 55 years or younger were less likely to present with typical chest pain is in line with the GENESIS PRAXY study result.[27] We were also able to find a stronger association between female sex and presence of referred pain, and of pain with intensity higher than 8 among the younger subgroups of patients (aged below 55 and 65 years). These findings stress the relevance of taking into account age for studying the association between sex and clinical presentation. However, further conclusions on the role of age to this relation are limited by the small number of women below 55 years included in our study. Differences in age distribution, in clinical presentation measuring, in selection and definition of confounder variables limit conclusive comparisons of studies evaluating differences in frequency and location of pain between women and men.

According to previous studies, with regard to other symptoms, a higher proportion of women have less typical symptoms than men.[8 31] Women have also reported other symptoms, such as indigestion, palpitations, nausea, numbness in the hands and unusual fatigue, more frequently than men.[9] In our cohort, three symptom clusters were identified. Women had the multiple symptoms cluster more frequently than did men, characterised by high probabilities for all symptoms. Age did not change the association between female sex and presentation with symptoms other than pain and with the multiple symptoms cluster. According to Rosenfeld *et al*, women are more likely to cluster in a similar class, called the heavy symptom burden class.[32] With regard to ACS symptom clustering, there are contradictory findings on identified clusters, the proportion of patients per cluster and differences between clusters regarding demographic factors. In our study, clusters 1 and 3 (low and high probabilities for all symptoms, respectively) are in line with observations of other settings.[18 33] A recent systematic review of symptom clusters in cardiovascular disease[34] identified clusters with the most symptoms and clusters with the lowest number of symptoms. Our dyspnoea and sweating cluster has two common symptoms similar to the Riegel *et al*[26] stress symptoms cluster, which includes shortness of breath, sweating, nausea, indigestion, dread and anxiety.

Methodological differences related to sampling and measuring might explain these different results. Strengths of our study include consecutive sampling, a questionnaire with detailed clinical information was systematically applied and we adjusted for several confounding variables.

The value of symptoms for diagnosis of ACS varies across studies.[13 14 35] Overall, the diagnostic performance of chest pain characteristics for diagnosis is limited, with likelihood ratios close to 1.[36] Sensitivity for individual

symptoms of ACS, using the 13-Item ACS Checklist, ranges from 27% to 67% for women and 14% to 72% for men. Additionally, specificity ranges from 33% to 78% for women and 34% to 78% for men, with different associations between some symptoms and diagnosis of ACS by sex.[24] However, physicians still base the likelihood of ACS mainly on symptoms and use the ECG to rule in the diagnosis.[37] Evaluation of these patients is mostly unchanged, without implementation of evidence-based assessment tools in clinical practice to improve diagnostic accuracy. Public health messages should take into account the complexity of presenting symptoms of ACS, particularly the significant proportion of women and men with ACS without typical chest pain. Additionally, there is a higher likelihood of atypical referred pain and multiple concomitant symptoms in women. These factors should be accounted for to encourage timely and appropriate care of patients with ACS.

Presenting without chest pain and with the multiple symptoms cluster was associated with several markers of higher ACS severity and longer time delays, particularly significant among patients with STEMI/NC ACS. In our study, presenting with the multiple symptoms cluster, but not with atypical or mixture location of pain, was associated with a higher mean 30-day mortality adjusted for GRACE risk score. These results are consistent with data from the GRACE registry, which showed that patients with symptoms other than pain experienced greater morbidity and higher in-hospital mortality across the spectrum of ACS.[28] Other registry showed that the higher in-hospital mortality observed among women and men without chest pain, decreased or even reversed with advanced age.[38] Mortality is adjusted for GRACE risk score; however, we cannot conclude that the difference in outcome observed is explained by symptoms other than pain per se. Previous studies showed that the higher in-hospital mortality of patients with ACS who presented without chest pain was mostly due to late hospital arrival, comorbidities and underuse of medications and invasive procedures.[3 6 38] These studies focused mainly on presence of chest pain to define atypical presentation and used medical record reviews to characterise clinical presentation. More studies are needed to further explore the association between symptoms other than pain and outcomes.

Limitations

Participants were interviewed as soon as possible after admission, but this does not obviate the retrospective nature of data collection and the possibility of recall bias. Furthermore, preceding interviews by physicians may have influenced answers to the questionnaire; however, different consequences in women and men are not expected. The results of this study are valid for stable patients, who were admitted to the hospital and were able to answer the questionnaire in the acute phase of ACS. This type of study misses patients who die before reaching the hospital, patients who do not seek medical care, patients who are mistakenly discharged or misdiagnosed and admitted to non-cardiology departments. This sample selection process may contribute to underestimate the true prevalence of ACS atypical presentation in women and men.[27] For patients who were eligible but not enrolled, only information on sex, age and type of ACS was available. Patients who died before the interview were older (81.5±11.8 vs 64.6±13.1 years, P<0.001), were more often women (66.7% vs 26.0%, P<0.001) and more frequently had a diagnosis of STEMI (81.3% vs 43.4%, P=0.003) than did participants. Patients who were discharged or transferred to another hospital before the interview had STEMI less often (25.0% vs 43.4%, P=0.005) and patients who were not enrolled because of clinical instability or inability to understand the questionnaire were older. Patients who refused to participate were older (72.7±11.0 vs 64.0±13.0 years, P<0.001), were less often partnered (65.7% vs 76.8%, P=0.036) and had little formal education (43.1% vs 19.7%, P<0.001) compared with participants. Except for deceased patients, no difference in sex proportion was observed between participants and non-participants. We cannot exclude that some of the sex differences were caused by selection bias because of a higher risk of non-inclusion of women due to death in the early hours of admission, or due to a possible higher probability of misdiagnosis in women, particularly those with unstable angina.[39] Considering that atypical presentation is associated with a worse prognosis and with a higher probability of misdiagnosis, the proportion of patients with ACS presenting without typical chest pain or that of women with an atypical presentation could be even higher.[28]

CONCLUSION

This study shows no significant differences in the frequency and location of pain by sex, but approximately 20% of patients do not present with chest pain, regardless of sex. Women are more likely to report referred pain and multiple symptoms simultaneously. Presentation with the multiple symptoms cluster pain is associated with higher 30-day mortality adjusted for GRACE score. Health education messages should take into account the complexity of presentation of ACS and emphasise the possible non-chest location of pain in both sexes and the higher probability of concomitant symptoms other than pain in women. Further sex-stratified analysis of ACS presentation, also addressing the role of age for the relation between sex and clinical presentation, is required to determine the diagnostic accuracy of symptoms by sex.

Contributors CA and AA had the original idea to develop the EPIHeart cohort study and were responsible for acquiring the study grant. CA raised the hypotheses, participated in data collection and field work, analysed and interpreted the data and drafted the first version of the manuscript. OL analysed and interpreted the data, participated in drafting and revising the first draft of the manuscript. MV and AB participated in data collection, field work and interpretation of the data. FM and AH interpreted data. MS analysed and interpreted the data. MJM and IM were

involved in the conception of the study and in field work. AA was the responsible for the conception and development of the study, analysed and interpreted the data, participated in drafting and revising the first draft of the manuscript. All authors were involved in writing the paper, in revising it critically and approved the final version of the submitted manuscript.

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Supplementary Table 1. Clinical presentation of patients with ST elevation myocardial infarction/non-classifiable acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	6 (5.9)	22 (21.8)	53 (52.5)	20 (19.8)	101 (100.0)		37 (13.3)	144 (51.8)	77 (27.7)	20 (7.2)	278 (100)		
Pain	6 (100.0)	21 (95.5)	52 (98.1)	16 (80.0)	95 (94.1)	0.039	36 (97.3)	142 (98.6)	73 (94.8)	20 (100.0)	271 (97.5)	0.338	0.106
Pain location†													
Typical	5 (83.3)	17 (81.0)	44 (84.6)	9 (56.3)	75 (78.9)		31 (88.6)	120 (85.1)	55 (76.4)	13 (65.0)	219 (81.7)		
Atypical	1 (16.7)	4 (19.0)	2 (3.8)	5 (31.3)	12 (12.6)		1 (2.9)	17 (12.1)	14 (19.4)	5 (25.0)	37 (13.8)		
Mixture	0 (0.0)	0 (0.0)	6 (11.5)	2 (12.5)	8 (8.4)	0.021	3 (8.6)	4 (2.8)	3 (4.2)	2 (10.2)	12 (4.5)	0.032	0.347
Referred pain	4 (66.7)	18 (85.7)	38 (73.1)	8 (50.0)	68 (71.6)	0.114	24 (66.7)	90 (63.4)	51 (69.9)	7 (35.0)	172 (63.5)	0.038	0.152
Radiation type‡													
Typical	3 (75.0)	8 (44.4)	17 (44.7)	1 (12.5)	29 (42.6)		19 (79.2)	53 (59.6)	26 (51.0)	3 (42.9)	101 (59.1)		
Atypical	0 (0.0)	5 (27.8)	10 (26.3)	4 (50.0)	19 (27.9)		5 (20.8)	21 (23.6)	9 (17.6)	3 (42.9)	38 (22.2)		
Mixture	1 (25.0)	5 (27.8)	11 (28.9)	3 (37.5)	20 (29.4)	0.504	0 (0.0)	15 (16.9)	16 (31.4)	1 (14.3)	32 (18.7)	0.018	0.060
Pain intensity§	9.5 (8-10)	9 (8-10)	9 (8-10)	8.5 (8-9)	9 (8-10)	0.784	9 (7.5-10)	8 (7-10)	8 (6.5-9)	7.5 (6.5-9)	8 (7-10)	0.064	<0.001
Symptom	5 (83.3)	20 (90.9)	47 (88.7)	17 (85.0)	89 (88.1)	0.794	23 (62.2)	105 (72.9)	61 (79.2)	14 (70.0)	203 (73.0)	0.283	0.002
Symptom clusters‖													
Cluster 1	2 (33.3)	18 (81.8)	27 (50.9)	11 (55.0)	58 (57.4)		26 (70.3)	102 (70.8)	54 (70.1)	16 (80.0)	198 (71.2)		
Cluster 2	3 (50.0)	2 (9.1)	16 (30.2)	4 (20.0)	25 (24.8)		9 (24.3)	36 (25.0)	19 (24.7)	3 (15.0)	67 (24.1)		
Cluster 3	1 (16.7)	2 (9.1)	10 (18.9)	5 (25.0)	18 (17.8)	0.132	2 (5.4)	6 (4.2)	4 (5.2)	1 (5.0)	13 (4.7)	0.967	<0.001
Activity													
Sleep	1 (16.7)	3 (14.3)	4 (7.8)	3 (15.8)	11 (11.3)		5 (13.5)	29 (20.1)	10 (13.0)	4 (20.0)	48 (17.3)		
Rest	3 (50.0)	9 (42.9)	22 (43.1)	14 (73.7)	48 (49.5)		19 (51.4)	65 (45.1)	43 (55.8)	13 (65.0)	140 (50.4)		
Exertion	2 (33.3)	9 (42.9)	25 (49.0)	2 (10.5)	38 (39.2)	0.069	13 (35.1)	50 (34.7)	24 (31.2)	3 (15.0)	90 (32.4)	0.393	0.274
Stress trigger	1 (16.7)	2 (9.1)	4 (7.5)	3 (15.8)	10 (10.0)	0.519	5 (13.5)	11 (7.7)	6 (7.9)	2 (10.0)	24 (8.7)	0.669	0.697

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ||Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 2. Clinical presentation of patients with non-ST elevation acute coronary syndrome, by sex and age*

	Women						Men						
	<=45	46-64	65-79	>=80	Total	P¶	<=45	46-64	65-79	>=80	Total	P¶	P#
Total	8 (6.3)	32 (25.4)	56 (44.4)	30 (23.8)	126 (100)		24 (6.5)	159 (43.2)	143 (38.9)	42 (11.4)	368 (100)		
Pain	8 (100.0)	31 (96.9)	52 (92.9)	28 (93.3)	119 (94.4)	0.864	24 (100.0)	155 (97.5)	141 (98.6)	38 (90.5)	358 (97.3)	0.073	0.131
Pain location†													
Typical	7 (87.5)	26 (83.9)	44 (86.3)	23 (82.1)	100 (84.7)		22 (91.7)	126 (82.4)	120 (85.1)	31 (81.6)	299 (84.0)		
Atypical	0 (0.0)	5 (16.1)	3 (5.9)	1 (3.6)	9 (7.6)		2 (8.3)	16 (10.5)	16 (11.3)	5 (13.2)	39 (11.0)		
Mixture	1 (12.5)	0 (0.0)	4 (7.8)	4 (14.3)	9 (7.6)	0.172	0 (0.0)	11 (7.2)	5 (3.5)	2 (5.3)	18 (5.1)	0.778	0.367
Referred pain	5 (62.5)	23 (74.2)	34 (65.4)	17 (60.7)	79 (66.4)	0.728	14 (58.3)	89 (57.4)	75 (53.2)	16 (42.1)	194 (54.2)	0.350	0.020
Radiation type‡													
Typical	5 (100.0)	12 (52.2)	11 (32.4)	6 (35.3)	34 (43.0)		9 (64.3)	61 (69.3)	41 (54.7)	7 (43.8)	118 (61.1)		
Atypical	0 (0.0)	8 (34.8)	8 (23.5)	9 (52.9)	25 (31.6)		2 (14.3)	16 (18.2)	30 (40.0)	5 (31.3)	53 (27.5)		
Mixture	0 (0.0)	3 (13.0)	15 (44.1)	2 (11.8)	20 (25.3)	0.008	3 (21.4)	11 (12.5)	4 (5.3)	4 (25.0)	22 (11.4)	0.007	0.005
Pain intensity§	9.5 (8.5-10)	9.5 (8-10)	8 (8-10)	8 (7-9)	9 (8-10)	0.224	8 (6-9)	8 (6-9)	8 (6-9)	8 (7.5-9)	8 (6-9)	0.200	<0.001
Symptom	6 (75.0)	25 (78.1)	44 (78.6)	24 (80.0)	99 (78.6)	0.992	20 (83.3)	104 (65.4)	90 (62.9)	28 (66.7)	242 (65.8)	0.278	0.007
Symptom clusters‖													
Cluster 1	5 (62.5)	23 (71.9)	35 (62.5)	21 (70.0)	84 (66.7)		17 (70.8)	130 (81.8)	116 (81.1)	36 (85.7)	299 (81.3)		
Cluster 2	2 (25.0)	6 (18.8)	12 (21.4)	4 (13.3)	24 (19.1)		6 (25.0)	23 (14.5)	16 (11.2)	6 (14.3)	51 (13.9)		
Cluster 3	1 (12.5)	3 (9.4)	9 (16.1)	5 (16.7)	18 (14.3)	0.919	1 (4.2)	6 (3.8)	11 (7.7)	0 (0.0)	18 (4.9)	0.231	<0.001
Activity													
Sleep	1 (14.3)	13 (44.8)	7 (12.7)	4 (14.3)	25 (21.0)		1 (4.2)	36 (23.1)	25 (17.7)	9 (22.0)	71 (19.6)		
Rest	2 (28.6)	9 (31.0)	28 (50.9)	15 (53.6)	54 (45.4)		15 (62.5)	59 (37.8)	62 (44.0)	20 (48.8)	156 (43.1)		
Exertion	4 (57.1)	7 (24.1)	20 (36.4)	9 (32.1)	40 (33.6)	0.032	8 (33.3)	61 (39.1)	54 (38.3)	12 (29.3)	135 (37.3)	0.180	0.768
Stress trigger	1 (12.5)	4 (12.5)	7 (12.7)	0 (0.0)	12 (9.6)	0.140	6 (25.0)	12 (7.7)	9 (6.4)	4 (9.8)	31 (8.6)	0.044	0.731

*Values are number and percentage unless otherwise indicated. †Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location. ‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation. §Median (interquartile range). ‖Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort). ¶p for age differences within each sex; #p for differences between sexes.

Supplementary Table 3. Marginal percentage of subjects with each symptom in each assigned cluster*

	Symptom clusters		
	Cluster 1* n=639	**Cluster 2†** n=167	**Cluster 3‡** n=67
Dyspnoea at rest	17.4	34.2	37.3
Exertional dyspnoea	6.0	2.1	14.5
Sweating	22.2	89.6	71.7
Nausea and vomiting	6.5	9.7	41.4
Dizziness	2.6	18.0	74.1
Blurry vision	0.6	4.4	27.5
Presyncope	1.3	11.4	42.7
Syncope	1.6	3.6	10.5
Palpitations	0.3	5.4	19.5
Weakness	7.5	17.8	64.4
"Other symptoms"	4.5	5.5	12.8
Other digestive symptoms	1.0	1.0	1.4
Discomfort	1.3	1.1	4.2

*Values are percentages.
*Cluster 1: no symptom cluster; † Cluster 2: dyspnoea and sweating cluster; ‡Cluster 3: multiple symptoms cluster.

Supplementary Table 4. Differences between women and men in clinical presentation of acute coronary syndrome, by age group (< 55 vs ≥55 years old)
(men are the reference class).

	<55 years		>=55 years			
Symptoms	**OR**	**95% CI**	**OR**	**95% CI**	**Interaction p-value**	**Adjusted for**
Pain	--*	--*	0.46	0.18-1.18	0.777	Age, type of ACS, marital status, dyslipidaemia, CABG
Typical (chest) pain (vs atypical or mixture)†	0.65	0.23-1.86	1.55	0.88-2.71	0.973	Age, type of ACS, coronary anatomy, region, smoking, dyslipidaemia, previous heart failure
Referred pain	3.81	1.41-10.3	1.73	1.14-2.61	0.528	Age, type of ACS, coronary anatomy, region, income, social class, previous renal failure.
Radiation type‡						
Typical	1	Reference	1	Reference		Age, type of ACS, employment status, region
Atypical	1.19	0.41-3.45	1.34	0.77-2.35	0.415	
Mixture	1.43	0.40-5.16	2.56	1.39-4.71	0.606	
Pain intensity (higher than 8/10)	5.23	2.17-12.60	2.09	1.35-3.24	0.028	Age, type of ACS, coronary anatomy, education, professional group, previous AMI
Symptoms	1.88	0.76-.4.66	1.91	1.21-3.04	0.799	Age, type of ACS, region, previous AMI, previous heart failure
Symptom clusters§						
Cluster 1	1	Reference	1	Reference		Age, type of ACS, professional group, region, previous AMI
Cluster 2	0.88	0.31-2.50	1.49	0.93-2.38	0.246	
Cluster 3	3.30	0.99-10.97	4.08	2.07-8.05	0.501	
Activity group						
Sleeping	1	Reference	1	(Reference)		Age, type of ACS, previous heart failure
Rest	0.74	0.25-2.19	1.08	0.64-1.81	0.284	
Exertion	0.89	0.29-2.67	1.27	0.74-2.16	0.408	

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG: coronary artery bypass surgery; CI, confidence interval; OR, odds ratio.
*All women below 55 years old presented with pain.
†Pain location: Typical - retrosternal, precordial, right thoracic, or bilateral thoracic; Atypical - epigastric, back, left arm or shoulder, right arm or shoulder, neck, or jaw; Mixture - typical and atypical location.
‡Radiation type: Typical - left arm or shoulder, right arm or shoulder, neck, or jaw; Atypical: retrosternal, precordial, right thoracic, bilateral thoracic, epigastric, or back regions; Mixture: typical and atypical irradiation.
§Symptom clusters: cluster 1 (no symptom cluster) - low endorsement probabilities for all items; cluster 2 (dyspnoea and sweating cluster) - high probability for dyspnoea at rest and sweating; cluster 3 (multiple symptoms cluster) - high probabilities for all items (dyspnoea at rest, exertional dyspnoea, sweating, nausea, vomiting, dizziness, blurry vision, presyncope, syncope, palpitation, weakness, other symptoms, other digestive symptoms and discomfort).

3.5 PAPER 5

MISSED OPPORTUNITIES IN SYMPTOMATIC PATIENTS BEFORE A FIRST ACUTE CORONARY SYNDROME: EPIHEART COHORT STUDY

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Missed Opportunities in Symptomatic Patients before a First Acute Coronary Syndrome: The EPIHeart Cohort Study

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Keywords
Chest pain · Diagnosis · Delivery of health care · Acute coronary syndrome

Abstract
Objectives: The aim of this study was to assess the proportion of patients with a first episode of acute coronary syndrome (ACS) reporting preceding chest pain, having previously sought medical care and undergone the performance of exams, and to identify the determinants of seeking medical advice and undergoing electrocardiogram (ECG). ***Methods:*** Within a cohort study, 690 patients with a first episode of ACS were evaluated. A questionnaire was applied to assess chest pain within the preceding 6 months of the event and health system resources utilization. Determinants were identified by logistic regression. ***Results:*** Preceding chest pain was reported by 61% of patients, 43% of these sought medical help, of whom less than half underwent ECG, and in 39% pain was attributed to a problem of the heart. Patients with hypertension were more likely to seek medical care (adjusted odds ratio, OR, 2.13, 95% CI 1.29–3.51), and former smokers (OR 0.52, 95% CI 0.28–0.99) and patients of a higher social class (OR 0.16, 95% CI 0.05–0.48) were less likely to seek medical care. The performance of ECG was associated with male sex (OR 2.56, 95% CI 1.11–5.87), health subsystem coverage (OR 3.88, 95% CI 1.11–13.53), and living in the northeastern region (OR 9.07, 95% CI 4.07–20.24), whereas cognitive impairment (OR 0.37, 95% CI 0.15–0.92) and being employed (OR 0.36, 95% CI 0.14–0.97) were inversely associated. ***Conclusions:*** These results suggest there are opportunities to improve the diagnosis of myocardial ischemia before acute coronary events.
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Introduction

The triage of patients with possible myocardial ischemia is often difficult, and failure to recognize ischemia as a cause of acute chest pain has serious implications [1]. Prodromal symptoms and signs occurring before unstable angina and myocardial infarction and precipitating physician visits have been reported for over 4 decades [2].

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Of several prodromal symptoms, chest pain was considered the best single predictor of a subsequent cardiac event [2].

Most patients with first-onset chest pain still do not have a diagnosis at presentation or in the subsequent 6 months, including those who undergo cardiac investigations [3]. Potential missed opportunities of diagnosis and the management of coronary heart disease (CHD) have been described in primary care and in emergency department settings, based on medical record review, and have proved to be dependent on patient and health care system determinants [4, 5]. Furthermore, only about 25% of those with chest pain, either cardiac or noncardiac, actually seek medical advice from a family physician or by presenting to a hospital emergency department [6].

The "symptom iceberg" [7], defined as the prevalence of significant symptoms in the community that are not referred for professional advice, was assessed for several symptoms commonly evaluated in primary care. From a public health perspective, exploring the "symptom iceberg" in patients with a first episode of acute coronary syndrome (ACS), by evaluating reported chest pain before the ACS, may unveil a window of opportunity to improve the diagnosis and treatment of patients with CHD and eventually to prevent the cardiac event. Furthermore, the management of patients with chest pain who seek medical help is challenging, and myocardial ischemia can be misdiagnosed for different reasons [8]. Several testing modalities were developed to assist the diagnosis and risk stratification of patients with chest pain; however, clinical judgment continues to be paramount to the management of these patients. Clinical history, physical examination, and a resting electrocardiogram (ECG) remain the cornerstone for the initial evaluation of suspected CHD, in both inpatient and outpatient settings [9–11]. In this study, we aimed to assess the proportion of ACS patients who reported preceding chest pain, having sought medical care and the performance of exams because of the pain, and to identify determinants of seeking medical advice and referral to ECG.

Methods

Study Design and Sample Selection

EPIHeart is a prospective cohort study designed to assess inequalities in the management and outcomes of patients with CHD in Portugal. The cohort consists of all consecutive patients discharged between August 2013 and December 2014 from the cardiology departments of 2 tertiary hospitals in 2 regions in northern Portugal (Hospital de São João, Porto, covering part of the metropolitan area of Porto on the coast, and Hospital de São Pedro, Vila Real, covering the interior, northeastern region). The inclusion criteria were as follows: being discharged with a diagnosis of ACS type 1, aged 18 years or older, living in the catchment area of these hospitals, not having been institutionalized before the event, and expected to be hospitalized for at least 48 h. Initially, 1,297 patients were considered; the diagnosis was not confirmed in 164, 60 were discharged or transferred, and 18 died before the invitation to participate. A further 44 patients were excluded due to inability to complete the questionnaire (clinical instability, poor understanding of the Portuguese language, hearing problems, or cognitive impairment). Seventy-two patients refused to participate. For this analysis, patients with previous ACS, percutaneous coronary intervention, or coronary artery bypass graft (n = 198) documented in medical records, and patients with incomplete data on chest pain episodes preceding the index ACS (n = 51) were excluded. Only the first hospital admission was considered if a patient had more than 1 hospitalization for ACS during the study period. A total of 690 patients were analyzed. The study protocol was in compliance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of both hospitals. All patients gave their written informed consent for inclusion.

Procedures and Data Collection

Detailed information about sociodemographic characteristics, risk factors, comorbidities, previous medical history, and presenting symptoms was obtained by trained researchers through structured interviews with the patients during their hospitalization. Patients were asked if they had experienced acute and recurrent chest pain within the past 6 months, beside the episode of the index event. Patients who reported 1 or more episodes of preceding chest pain were interviewed about the date of the occurrence, their health-seeking attitudes and health system resources utilization, i.e., health system unit/units sought, complementary exams performed, and cause attributed to the pain ("problem of the heart" [including "myocardial infarction" and "angina pectoris"], "problem not of the heart," "nothing important," "not informed about the suspected cause" [from the open-ended question of "Other, what?"], and "do not know"). This questionnaire is presented in the Appendix. Regardless of reporting pain in the previous 6 months or not, additional data on previous (within the preceding year) medical appointments in the public or private sectors, of which specialty (primary care physician, cardiologist, internal medicine specialist, psychiatrist, other), and medication used at the time of the index event were collected. Additional information regarding patients' cardiovascular risk factors and comorbidities, as well as data on the type of ACS for index hospitalization, was extracted from clinical records. The Mini-Mental Status Examination (MMSE) [12] was used do assess the cognitive status and disability was measured using the modified Barthel Index [13].

Definition of Variables

Education was categorized as nonelementary and elementary according to the mandatory years of schooling in Portugal, which varies by age of birth. Elementary education corresponds to 4 or more years of schooling if born before 1967, 6 or more years if born between 1967 and 1980, and 9 or more years if born thereafter. The subjective social class was considered according to self-report as: lower class, lower middle class, upper middle class, and upper class. Occupations were classified into major professional groups, according to the Portuguese Classification of Occupations 2010,

Table 1. Baseline characteristics of patients with and without chest pain prior to the ACS

	No chest pain (n = 272)	Chest pain in the previous 6 months (n = 418)	p
Mean age ± SD, years	62.9±13.7	63.2±13.2	0.755
Male	201 (73.9)	302 (72.3)	0.634
Cognitive impairment (MMSE)	70 (26.2)	83 (20.2)	0.069
Disability (BI score)	27 (9.9)	28 (6.7)	0.128
Socioeconomic position			
Region			
Metropolitan area of Porto	139 (51.1)	235 (56.2)	
Northeastern region	133 (48.9)	183 (43.8)	0.187
Living alone	31 (11.5)	59 (14.4)	0.287
Elementary education	203 (74.6)	314 (75.5)	0.801
Employed	92 (34.0)	126 (30.2)	0.304
Occupation			
Upper white collar	50 (20.3)	60 (15.8)	
Lower white collar	48 (19.5)	97 (25.5)	
Blue collar	148 (60.2)	223 (58.7)	0.126
Subjective social class			
Lower/lower middle class	159 (59.3)	274 (65.9)	
Upper middle/upper class	23 (8.6)	31 (7.5)	
Refused to answer	48 (17.9)	49 (11.8)	0.059
Private health insurance coverage	39 (14.4)	47 (11.4)	0.255
Health subsystem coverage	50 (18.5)	63 (15.2)	0.259
Cardiovascular risk factors			
Hypertension	174 (64.0)	269 (64.4)	0.918
Smoking			
Never	116 (42.7)	179 (42.8)	
Current	94 (34.6)	141 (33.7)	
Former	62 (22.8)	98 (23.4)	0.968
Diabetes mellitus	73 (26.8)	139 (33.3)	0.074
Dyslipidemia	149 (55.0)	246 (58.9)	0.316
Overweight/obese	175 (64.6)	276 (66.8)	0.543
Family history of CVD	106 (40.8)	172 (42.7)	0.626
Previous medical history			
Heart failure	12 (4.4)	19 (4.6)	0.934
Renal failure	15 (5.5)	23 (5.5)	0.994
Atrial fibrillation	11 (4.0)	21 (5.0)	0.550
Stroke	29 (10.7)	31 (7.4)	0.139
Cancer	18 (6.6)	29 (6.9)	0.870
Medical visits in the previous year			
Primary care	204 (75.6)	330 (79.0)	0.297
Public hospital	76 (28.0)	136 (32.6)	0.205
Cardiologist in the hospital	12 (15.8)	20 (14.7)	0.833
Private sector	94 (34.7)	124 (29.9)	0.186
Cardiologist in the private sector	18 (19.4)	41 (33.1)	**0.025**

Table 1 (continued)

	No chest pain (n = 272)	Chest pain in the previous 6 months (n = 418)	p
Drug treatment prior to index episode			
Antiplatelet drug	50 (18.4)	94 (22.5)	0.189
ACEI/ARB	106 (39.0)	178 (42.7)	0.333
Beta-blockers	33 (12.1)	60 (14.4)	0.397
Calcium channel blockers	55 (20.2)	80 (19.2)	0.738
Nitrates	8 (2.9)	27 (6.5)	**0.039**
Statins	77 (28.3)	137 (32.9)	0.208
Oral anticoagulation	8 (2.9)	10 (2.4)	0.662
Clinical presentation during index episode			
NSTEACS	113 (41.7)	245 (58.9)	**<0.001**
Chest pain	214 (82.6)	330 (81.5)	0.709
Typical referred pain	84 (55.6)	133 (53.6)	0.697
Cluster of symptoms other than pain[1]			
Cluster 1	185 (69.6)	260 (68.8)	
Cluster 2	57 (21.4)	83 (22.0)	
Cluster 3	24 (9.0)	35 (9.3)	0.979

Values are n (%) unless otherwise indicated. Totals may not add to 100% due to missing data. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BI, Barthel Index; CVD, cardiovascular disease; SD, standard deviation; MMSE, Mini-Mental Status Examination; NSTEACS, non-ST elevation acute coronary syndrome. Bold represents significant p values ($p < 0.05$).

[1] Cluster 1 (no symptom cluster): low endorsement probabilities for all items; cluster 2 (dyspnea and sweating cluster): high probability for dyspnea at rest and sweating; cluster 3 (multiple symptoms cluster): high probabilities for all items.

integrated in the International Standard Classification of Occupations [14], and grouped into 3 categories: upper white collar (executive civil servants, industrial directors and executives, professionals and scientists, and middle management and technicians), lower white collar (administrative and related workers, and service and sales workers), and blue collar (farmers and skilled agricultural workers, fisheries workers, skilled workers, craftsmen and similar, machine operators and assembly workers, and unskilled workers). Retired and disabled subjects and housewives were classified considering their previous main occupation.

Cognitive impairment was defined based on the MMSE score, taking into account established cut-offs for individual education level [15]. Physical disability was assigned to patients scoring less than 90 in the Barthel Index [13, 16].

Direct pain was considered typical if located in the chest; referred pain was considered typical if referred to the left arm or shoulder, right arm or shoulder, neck, or jaw [10]. Clusters of symptoms other than pain were obtained by latent class analysis [17].

We defined 3 groups of patients according to report of preceding chest pain: no chest pain, at least 1 episode of chest pain in the previous 6 months, at least 1 episode of chest pain in the previous week. Patients with preceding chest pain were further categorized according to their health system-seeking attitude (yes/no) and to the performance of ECG (yes/no) for those who sought health care system assistance.

Data Analysis

Groups of patients were compared using the χ^2 or Fisher test for categorical variables, and the t test for continuous variables. Logistic regression was used to identify variables associated with health service-seeking behavior and with the performance of ECG. Variables with univariate association ($p < 0.15$) with the endpoint were used to build multivariable models with a backward strategy based on the Wald test to select relevant variables ($p < 0.05$). All analyses were performed using STATA version 11.1 for Windows (Stata Corp LP, College Station, TX, USA) and R version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Baseline characteristics of patients who reported chest pain within the 6 months preceding the index episode of ACS (n = 418, 61%), compared to those who did not, are shown in Table 1. In this predominantly male cohort (73.1%) with a mean age of 63.0 ± 13.5 years, more similarities than differences were observed in the baseline characteristics of patients who did not and did report pre-

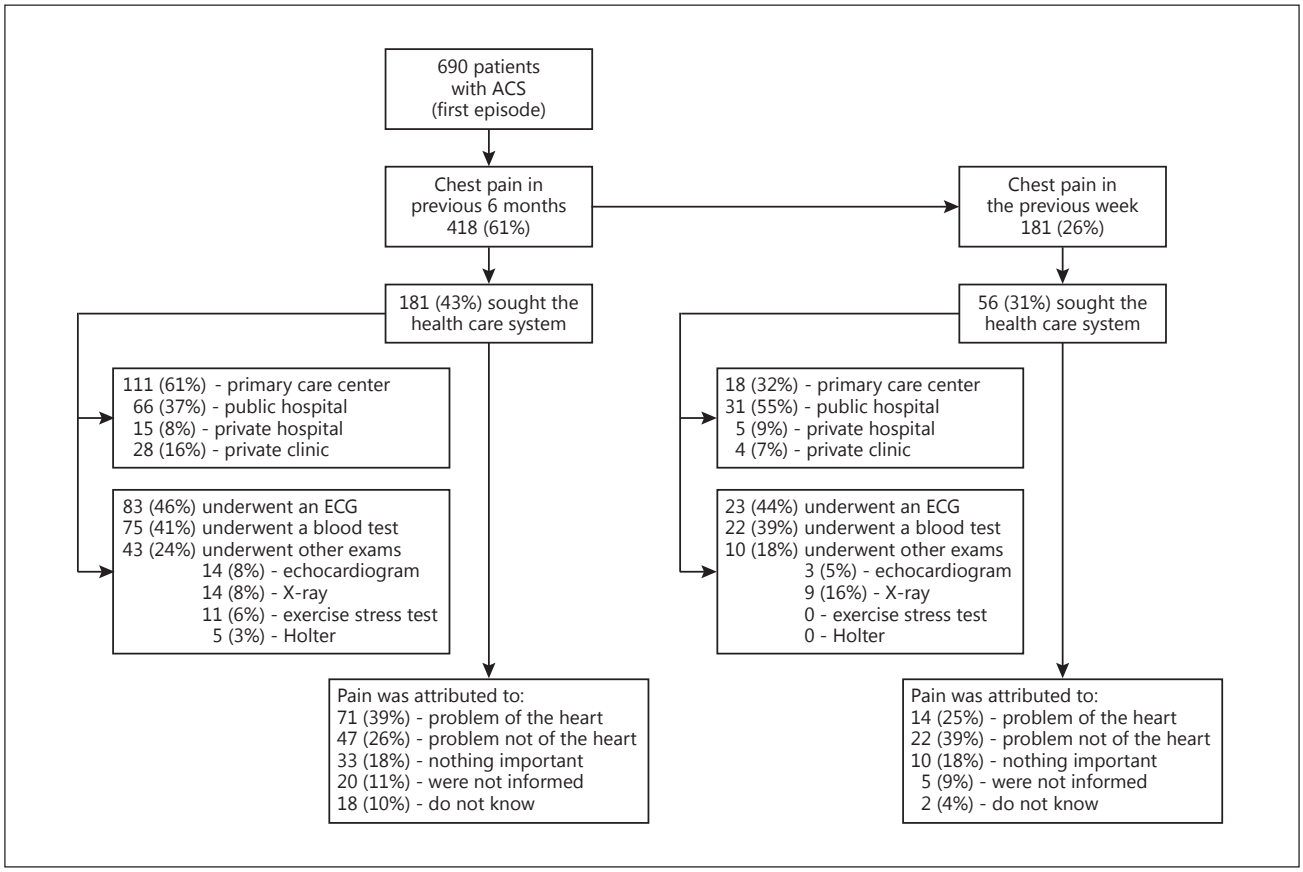

Fig. 1. Diagram of the flow of patients with previous chest pain through the health care system.

ceding chest pain. At least 1 primary care physician visit within the previous year was reported by 78% of patients, and a physician visit at the public hospital was reported by 31%, of whom 15% were seen by a cardiologist. Use of the private sector was reported by 32% of the patients, of whom about a quarter had a cardiology appointment, which was more often reported by patients with chest pain in the preceding 6 months of the acute event compared with patients without preceding pain (33.1 vs. 19.4%, p = 0.025). At admission for the index ACS, 20.9% of patients were on antiplatelet drugs and 31.1% on statins. Nitrates were the only drugs more often used prior to the index event by patients who reported preceding chest pain (6.5 vs. 2.9%, p = 0.039). We were not able to define the clinical indications and the exact time of these prescriptions, particularly whether these drugs were started before or after the episode(s) of preceding chest pain. The first ACS episode of patients who had reported chest pain prior to the index event was more frequently a non-ST elevation ACS.

Flow of Patients with Previous Chest Pain through the Health Care System

Of the 418 patients who reported chest pain within the 6 months preceding the first ACS, 43% reported having sought assistance from the health care system, the majority in the public sector, namely a primary care center (61%) or a public hospital (37%). An ECG was performed in less than half of the subgroup of patients who sought the health care system, 41% had a blood test and less than a quarter underwent other exams, including echocardiogram and an exercise stress test. Neither performance of myocardial perfusion scintigraphy nor coronary angiography was reported. Pain was attributed to a problem of the heart in 39% of these patients and to a problem not of the heart in 26%. A total of 21% of patients were not informed or did not know the suspected cause of the chest pain (Fig. 1). Among the subgroup of patients who reported that chest pain was cardiac in origin, 51% underwent an ECG, 41% a blood test, and 30% other exams

Table 2. Characteristics of patients with chest pain within the 6 months preceding the ACS according to their health system-seeking behavior and the performance of an ECG

	Health system seeking			Performance of electrocardiogram		
	no (n = 237)	yes (n = 181)	p	no (n = 98)	yes (n = 83)	p
Mean age ± SD, years	62.0±13.1	64.9±13.2	**0.030**	66.1±12.8	63.5±13.8	0.197
Male	173 (73.0)	129 (71.3)	0.696	63 (64.3)	66 (79.5)	**0.024**
Cognitive impairment (MMSE)	45 (19.3)	38 (21.5)	0.591	27 (27.8)	11 (13.8)	**0.023**
Disability (BI score)	18 (7.6)	10 (5.5)	0.395	7 (7.1)	3 (3.6)	0.301
Socioeconomic position						
Region						
Metropolitan area of Porto	135 (57.0	100 (55.3)		70 (71.4)	30 (36.1)	
Northeastern region	102 (43.0)	81 (44.8)	0.726	28 (28.6)	53 (63.9)	**0.001**
Living alone	30 (13.0)	25 (13.9)	0.790	13 (13.3)	12 (14.6)	0.791
Elementary education	179 (76.8)	130 (73.5)	0.432	67 (69.1)	63 (78.8)	0.147
Employed	83 (35.2)	43 (23.8)	**0.012**	18 (18.4)	25 (30.1)	0.064
Occupation						
Upper white collar	40 (18.2)	20 (12.5)		9 (10.3)	11 (15.1)	
Lower white collar	56 (25.5)	41 (25.6)		24 (27.6)	17 (23.3)	
Blue collar	124 (56.4)	99 (61.9)	0.305	54 (62.1)	45 (61.6)	0.608
Subjective social class						
Lower/lower middle class	141 (70.9)	133 (85.8)		66 (84.6)	67 (87.0)	
Upper middle/upper class	27 (13.6)	4 (2.6)		2 (2.6)	2 (2.6)	
Refused to answer	31 (15.6)	18 (11.6)	**<0.001**	10 (12.8)	8 (10.4)	0.894
Private insurance coverage	31 (13.4)	16 (8.9)	0.152	5 (5.1)	11 (13.4)	
Health subsystem coverage	43 (18.4)	20 (11.1)	**0.039**	7 (7.1)	13 (15.7)	0.068
Cardiovascular risk factors						
Hypertension	137 (57.8)	132 (72.9)	**0.001**	73 (74.5)	59 (71.1)	0.607
Smoking						
Never	89 (37.6)	90 (49.7)		51 (52.0)	39 (47.0)	
Current	88 (37.1)	53 (29.3)		26 (26.5)	27 (32.5)	
Former	60 (25.3)	38 (21.0)	**0.044**	21 (21.4)	17 (20.5)	0.670
Diabetes mellitus	68 (28.7)	71 (39.2)	**0.024**	35 (35.7)	36 (43.4)	0.293
Dyslipidemia	130 (54.9)	116 (64.1)	0.057	62 (63.3)	54 (65.1)	0.802
Overweight/Obese	155 (66.5)	121 (67.2)	0.881	64 (66.0)	57 (68.7)	0.701
Family history of CVD	98 (43.6)	74 (41.6)	0.689	41 (42.7)	33 (40.2)	0.739
Previous medical history						
Heart failure	8 (3.4)	11 (6.1)	0.189	1 (1.0)	10 (12.1)	**0.002**
Renal failure	11 (4.6)	12 (6.6)	0.377	4 (4.1)	8 (9.6)	0.134
Atrial fibrillation	7 (3.0)	14 (7.7)	**0.027**	8 (8.2)	6 (7.2)	0.815
Stroke	21 (8.9)	10 (5.5)	0.197	6 (6.1)	4 (4.8)	0.702
Cancer	20 (8.4)	9 (5.0)	0.167	4 (4.1)	5 (6.0)	0.549
Clinical presentation during index episode						
NSTEACS	128 (54.0)	117 (65.4)	**0.020**	40 (52.0)	33 (56.9)	0.567
Chest pain	190 (81.6)	140 (81.4)	0.969	76 (80.0)	64 (83.1)	
Typical referred pain	81 (58.3)	52 (47.7)	0.098	30 (49.2)	22 (45.8)	0.728
Cluster of symptoms other than pain[1]						
Cluster 1	156 (68.1)	104 (69.8)		59 (70.2)	45 (69.2)	
Cluster 2	51 (22.3)	32 (21.5)		17 (20.2)	15 (23.1)	
Cluster 3	22 (9.6)	13 (8.7)	0.933	8 (9.5)	5 (7.7)	0.868

Values are n (%) unless otherwise indicated. Totals may not add to 100% due to missing data. BI, Barthel Index; CVD, cardiovascular disease; SD, standard deviation; MMSE, Mini-Mental Status Examination; NSTEACS, non-ST elevation acute coronary syndrome. Bold represents significant p values ($p < 0.05$).

[1] Cluster 1 (no symptom cluster): low endorsement probabilities for all items; cluster 2 (dyspnea and sweating cluster): high probability for dyspnea at rest and sweating; cluster 3 (multiple symptoms cluster): high probabilities for all items.

Table 3. Determinants of health system-seeking behavior among patients with preceding chest pain and performance of ECG among patients with pain who sought medical care

	Adjusted OR (95% CI)
Health system-seeking behavior[1]	
Sex	
Female	1
Male	1.20 (0.66–2.17)
Age (per year)	1.00 (0.98–1.02)
Subjective social class	
Lower/lower middle class	1
Upper middle/upper class	0.16 (0.05–0.48)
Refused to answer	0.56 (0.29–1.06)
Hypertension	
No	1
Yes	2.13 (1.29–3.51)
Smoking	
Never	1
Current	0.60 (0.31–1.14)
Former	0.52 (0.28–0.99)
Performance of ECG[2]	
Sex	
Female	1
Male	2.56 (1.11–5.87)
Age (per year)	0.99 (0.95–1.02)
Cognitive impairment	
No	1
Yes	0.37 (0.15–0.92)
Region	
Metropolitan area of Porto	1
Northeastern region	9.07 (4.07–20.24)
Employed	
No	1
Yes	0.36 (0.14–0.97)
Health subsystem coverage	
No	1
Yes	3.88 (1.11–13.53)

[1] Models adjusted for sex, age, subjective social class, hypertension, and smoking.

[2] Models adjusted for sex, age, cognitive impairment, region, employment status, and health subsystem coverage. All independent variables were included in the model as categorical, except age (continuous).

(13% echocardiogram, 10% X-ray, 7% exercise stress test, and 6% Holter monitoring).

Chest pain in the week before hospitalization was reported by 181 patients. Of the 31% of patients who sought the health care system, 55% used the public hospital and 32% the primary care center. ECG was performed in 41%, a blood test in 39%, and other exams in 18% of these patients. Pain was attributed less often to a heart problem (25%) compared with the group of patients with pain in the preceding 6 months (Fig. 1).

Predictors of Health Care System-Seeking Behavior and of Performance of an ECG

Health care-seeking behavior and the performance of an ECG because of preceding chest pain were associated with different sociodemographic characteristics, risk factors, comorbidities, previous medical history, and clinical presentation during the index episode (Table 2).

Predictors independently associated with entering the health care system because of chest pain within 6 months of the ACS are presented in Table 3. Patients with hypertension (adjusted odds ratio, OR, 2.13, 95% CI 1.29–3.51) were more likely to seek health care assistance, while former smokers (OR 0.52, 95% CI 0.28–0.99) and patients who considered themselves to belong to an upper middle or upper class (OR 0.16, 95% CI 0.05–0.48) were less likely to seek the health care system.

Men were twice as likely to be referred to ECG as women (OR 2.56, 95% CI 1.11–5.87). ECG performance was also strongly associated with living in the northeastern region (9-fold more likely than among Porto residents) and being covered by a health subsystem (almost 4-fold more likely when compared with patients without such coverage). Cognitive impairment and being employed were inversely associated with the performance of an ECG (Table 3).

Discussion

Of patients admitted with a first ACS, 61% reported chest pain within the previous 6 months, of whom less than half reported seeking care and undergoing an ECG. In the week preceding the acute event, approximately a quarter reported chest pain, and less than a third of symptomatic patients sought the health care system, mainly a public emergency department. Different demographic, socioeconomic – including geographic residence and health subsystem coverage – and cardiovascular risk factors were found to be associated with health care system-seeking behavior and with referral to ECG.

In Portugal, the national health system (NHS) is "universal, comprehensive and almost free" [18]. Besides the NHS, the Portuguese health system has 2 other coexisting and overlapping systems: special health insurance schemes for particular professions or sectors called the health subsystems, and private voluntary health insurance [18]. In contrast with other settings, there are no

specific units for chest pain evaluation in Portugal. Patients with new-onset chest pain who seek emergency care, either public or private, are evaluated by physicians of interdisciplinary emergency departments who may ask for an evaluation by a cardiologist. Among noninvasive imaging modalities for ischemia, the Portuguese NHS currently reimburses only exercise stress tests and myocardial perfusion scintigraphy if referral is from the primary care. Furthermore, other noninvasive imaging modalities for ischemia are only available in some private and public hospitals. The private sector has protocols with health subsystems or private health insurance for medical consultations and for the performance of these noninvasive imaging modalities [18].

Depending on the time span before the ACS to define preceding chest pain, on the setting (outpatient vs. inpatient), and on the methodology used in other studies, the prevalence of chest pain before ACS varied [4, 5, 19] and was higher for patients with non-ST elevation acute myocardial infarction, in accordance with our results [20]. A proportion of 61% for chest pain in the previous 6 months is similar to previous findings from the 1970s [2]. As far as we know, no recent similar evidence is available to compare with our results.

Information on the reasons why people seek medical advice when symptoms of chest pain emerge is scarce [21], except in the context of myocardial infarction. Sociodemographic, symptom onset context, cognitive, affective/psychological, behavioral, and clinical factors influenced prehospital delay among patients with myocardial infarction [22]. Furthermore, decisions regarding actions in response to the ischemic symptoms depend on patients' preexisting ideas about coronary disease and the extent to which their symptom experience matches their expectations [23].

Almost 60% of patients reporting chest pain did not seek medical help. The perception of having a high social status, probably because of associated feelings of security, hope, and health [24], was associated with a lower probability of seeking help in our cohort. A possible explanation for patients with hypertension being more likely to seek help for chest pain is the patient's recognition of the role of hypertension as a cardiovascular risk factor due to health promotion activities, for example the "Portuguese Action against Salt and Hypertension." Additionally, primary care centers have an organized management approach to patients with hypertension and the correct surveillance of patients with high blood pressure can lead to 1 of the family doctors' financial incentives [18]. The fact that current/former smokers of our cohort were less likely to seek help due to chest pain may be at least in part related to a lower awareness of cardiovascular risk among smokers compared with hypertensive patients. Although Portugal introduced partial smoking-free legislation in bars and restaurants in 2008, the lack of funding for tobacco control limits media campaigns [25]. Additionally, compared with hypertension, smoking cessation consultations are not so well organized and are not a performance indicator with financial incentive in the primary care sector [18].

Most patients who reported preceding chest pain and sought medical help used the public sector, namely the general practitioner or the emergency department of a public hospital, the latter more often by patients with chest pain within the preceding week of the acute event. The fact that more than 75% of patients with an ACS, independently of reporting chest pain previously to the ACS or not, visited a primary care doctor in the preceding year further strengthens the potential role of the primary care sector to improve recognition of myocardial ischemia and the management of risk factors. The type of health care professional seen appears to be moderated by the frequency and severity of acute chest pain [26]. The low agreement in the risk stratification of patients presenting to the emergency department with chest pain between emergency department physicians and cardiologists, even with the application of objective risk scores [27], contributes to illustrate the difficulties in diagnosis.

Pain was attributed to a problem of the heart in 39% of patients who reported chest pain over the previous 6 months and sought medical help, and in a quarter of the subgroup who reported symptoms in the preceding week. Considering the high prevalence of noncardiac chest pain in the population [28], chest pain prior to an ACS might be nonischemic in some patients. However, for the subgroup of patients with symptoms occurring closer to the index event, the probability that chest pain was cardiac in origin was higher and, strikingly, these patients less frequently reported that chest pain was attributed to a problem of the heart.

The diagnosis of angina is challenging, mainly because it relies on clinical judgement [9]. Depending on clinical and epidemiological characteristics, the probability of a patient with chest pain having CHD can vary from less than 10% to more than 90%. We evaluated reported chest pain in a cohort of patients with a high cardiovascular risk profile, therefore even if physicians considered chest pain to be atypical angina or noncardiac pain, a large proportion, if not most, would not score low for pretest probabil-

ity of CHD. Only for patients with a low pretest probability (<15%) of stable CHD, no further investigation is needed to exclude the diagnosis [9]. Referral to ECG was used as a surrogate for the intention of further investigation of possible cardiac chest pain, as this exam is the cornerstone of the initial evaluation of patients whatever the type of health institution sought and is easily identified by patients. The low rates of performance of an ECG or other testing modalities, including exercise stress test (which was also low for the subgroup of patients who reported that pain was cardiac in origin), and the absence of performance of myocardial perfusion scintigraphy and coronary angiography, favor that inaccurate noninvasive coronary ischemia testing may be one of the factors contributing to the misdiagnosis of symptoms of myocardial ischemia [4]. Furthermore, the type of noninvasive test performed for diagnosing CHD suggests that the choice of the exam largely depended on physician preference and/or local availability [29]. The fact that ECG is an exam with a wide availability and acceptability, with low costs and lack of contraindications, strengthens the hypothesis that inaccurate clinical judgment and the pretest probability evaluation are other important determinants of misdiagnosis.

In our cohort, fewer women than men reported the performance of an ECG because of chest pain. The subjective experience of symptoms influences professionals' interpretation of clinical presentations [30]. Atypical presentations among women [31], the perception of a lower risk of CHD compared with men [32], and gender bias in the use of investigations for patients with stable angina have been observed [33]. Cognitive impairment was independently associated with a lower referral for ECG; poor communication is a factor contributing to the misdiagnosis of symptoms of myocardial ischemia [4].

Lower levels of psychological distress and health disorder observed in employed compared with not employed people have been attributed to employment status itself, rather than to demographic attributes and other socioeconomic variables [34]. This favorable profile of employed subjects may determine differences in perception and/or the communication of symptoms by patients and in the perception of CHD risk by physicians, and result in a lower probability for the performance of an ECG.

In Portugal, relative declines of CHD mortality indicators between 1981 and 2012 varied by geographic region, with consistent decreases in mortality rates observed only in the most populated and urbanized regions [35]. Despite the universal coverage of the NHS, resources and health professionals are concentrated in the major urban centers and along the coast, leaving the inland, specifically the northeastern region, underserved [18]. Patients from the metropolitan area of Porto less often reported the investigation of chest pain by ECG. In contrast with referral for other diagnostic exams, for example coronary angiography which is highly related to accessibility to cardiac catheterization laboratories [36], referral for ECG, an exam that is widely available, may depend more on physician attitudes. Meeting the expectations of patients or peers, as well as malpractice concerns, were some of the reasons found to explain the variation in physicians' propensity to test and treat [37].

Finally, the health subsystem coverage increased the probability of the performance of an ECG. Cardiac testing is more accessible and less expensive for patients with health subsystems, probably resulting in inequalities in diagnostic test performance between covered and not covered patients [38].

Limitations

Information on preceding chest pain and having sought health care was self-reported by patients during the first days of hospitalization and therefore may be prone to recall bias. However, the decision to use a questionnaire instead of a medical record review was grounded on 2 main limitations of the latter method: no information about previous chest pain for patients with symptoms who did not seek health care system assistance, and for those who seek help but for whom no information is recorded (the physician might not register the case). The second limitation would be a lack of detailed information about health service utilization related with the pain.

Correct identification of patients without previous ACS, percutaneous coronary intervention, or coronary artery bypass graft depends on high-quality data records. However, we assumed a high accuracy and completeness of reports, as these are variables systematically registered in discharge letters and electronic records of patients with ACS.

Selection bias due to patient refusal to participate and losses during recruitment are other potential limitations. For these patients, there is no information about the history of chest pain or of characteristics influencing the decision-making process regarding seeking health care assistance. Among the patients enrolled, the proportion of participation was high – only 6.9% did not answer the questionnaire about reported chest pain and heath care utilization.

Conclusions

Preceding chest pain was reported by most patients with a first ACS; however, less than half of them sought medical care or underwent an ECG due to those symptoms. There are potential broad opportunities to improve the diagnosis of myocardial ischemia before a first acute coronary event. Our results reinforce the need to explore patient and system barriers to access to appropriate care for patients with chest pain, and support the need of effective health education strategies for improving myocardial ischemia symptom awareness and appropriate health care system-seeking behaviors.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Appendix

Questionnaire

1. Besides this **chest pain** episode, have you had any other episodes?
   □ (0) No □ (1) Yes □ (88) Do not know
   1.1 Have you felt **recurrent chest pain** in the last six months?
   □ (0) No □ (1) Yes □ (88) Do not know
   1.1.1. Date of pain onset (dd/mm/yyyy) __/__/____
   1.1.2. Have you sought any health institution?
   □ (0) No □ (1) Yes □ (88) Do not know
   1.1.2.1. If yes, which health institution did you seek? *[point out several options]*
   □ (1) Primary care center □ (2) Public hospital
   □ (3) Private hospital □ (4) Private clinic
   □ (5) Other. Which one? _____ □ (88) Do not know
   1.1.2.1.1. Have any ECG been performed? □ (0) No □ (1) Yes □ (88) Do not know
   If yes, how many? __ __
   1.1.2.1.2. Have any blood tests been performed? □ (0) No □ (1) Yes □ (88) Do not know
   If yes, how many? __ __
   1.1.2.1.3. Have other complementary diagnostic exams been performed? □ (88) Do not know
   □ (0) No □ (1) Yes If yes, which one/s? _____
   1.1.2.1.4. What did they say it was attributable to? *[point out several options]*
   □ (1) Myocardial infarction
   □ (2) Angina pectoris
   □ (3) One problem of the heart
   □ (4) One problem not of the heart
   □ (5) Nothing important
   □ (6) Other. What? _____
   □ (88) Do not know
   1.2. Have you had any **acute episodes of chest pain** in the last six months?
   □ (0) No □ (1) Yes □ (88) Do not know
   1.2.1. If yes, how many episodes? __ __ □ (88) Do not know

Episode 1

1.3. Date (dd/mm/yyyy) __/__/____

1.3.1 Have you sought any health institution?

□ (0) No □ (1) Yes □ (88) Do not know

1.3.1.1. If yes, which health institution did you seek? *[point out several options]*

□ (1) Primary care center □ (2) Public hospital

□ (3) Private hospital □ (4) Private clinic

□ (5) Other. Which one? _____ □ (88) Do not know

1.3.1.1.1. Have any ECG been performed? □ (0) No □ (1) Yes □ (88) Do not know

If yes, how many? __ __

1.3.1.1.2. Have any blood tests been performed? □ (0) No □ (1) Yes □ (88) Do not know

If yes, how many? __ __

1.3.1.1.3. Have other complementary diagnostic exams been performed? □ (88) Do not know

□ (0) No □ (1) Yes If yes, which one/s? _____

1.3.1.1.4. What did they say it was attributable to? *[point out several options]*

□ (1) Myocardial infarction

□ (2) Angina pectoris

□ (3) One problem of the heart

□ (4) One problem not of the heart

□ (5) Nothing important

□ (6) Other. What? _____

□ (88) Do not know

Episode 2

1.4. Date (dd/mm/yyyy) __/__/____

1.4.1. Have you sought any health institution?

□ (0) No □ (1) Yes □ (88) Do not know

1.4.1.1. If yes, which health institution did you seek? *[point out several options]*

□ (1) Primary care center □ (2) Public hospital

□ (3) Private hospital □ (4) Private clinic

□ (5) Other. Which one? _____ □ (88) Do not know

1.4.1.1.1. Have any ECG been performed? □ (0) No □ (1) Yes □ (88) Do not know

If yes, how many? __ __

1.4.1.1.2. Have any blood tests been performed? □ (0) No □ (1) Yes □ (88) Do not know

If yes, how many? __ __

1.4.1.1.3. Have other complementary diagnostic exams been performed? □ (88) Do not know

□ (0) No □ (1) Yes If yes, which one/s? _____

1.4.1.1.4. What did they say it was attributable to? *[point out several options]*

□ (1) Myocardial infarction

□ (2) Angina pectoris

□ (3) One problem of the heart

□ (4) One problem not of the heart

□ (5) Nothing important

□ (6) Other. What? _____

□ (88) Do not know

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4. DISCUSSION

In this thesis, we evaluated inequalities in CHD in Portugal using process and outcome indicators, and focusing on sex/gender and region. We were able to identify specific targets for future research and improvement in the CHD equity and quality of care. We dismantled several of the steps of the complex CHD process of care; starting from outcomes, we moved backward until the symptomatic stage before an ACS, considering each step as an opportunity to promote CHD prevention. Selection of patient samples and sources of data, definition of variables, and analysis and interpretation of data implied judgment and choices, driven by the conceptual models of socioeconomic determinants of health and of access to health care and by the clinical knowledge of CHD care perceived by our team, a perspective that clinicians uniquely possess [112].

Data sources and methodology

Our objectives were pursued through different sources of data, each with different strengths and limitations, functioning as complementary between them.

Mortality data from CHD provided from Statistics Portugal was easy to obtain and in Portugal has universal coverage. Data availability by Nomenclature of Territorial Units for Statistics (NUTS) was set up by Eurostat at the beginning of the 1970s when dividing the European Union´s territories to produce regional statistics [265]. The last change in the classification of the Portuguese NUTS II territorial units was made in 2002 [266]. Stability of this classification is particularly relevant to the analysis of time-series [267]. Quality of death certification, namely accuracy of causes of death and correct coding are also crucial to correctly interpret our results. One index of the quality of reporting causes of death is the proportion of deaths coded as ill-defined causes, which has decreased in Portugal [268]. Universal coverage and standardisation of procedures for the whole country reduces the probability of geographic differences in the quality of cause-of-death information, therefore ensuring a high level of comparability in mortality statistics by Portuguese region. Furthermore, changing or revising coding rules would have a greater impact if we were considering specific codes of diseases, but we studied the whole group of CHD.

Patient level data were obtained from two other sources, both cohort studies performed on a subgroup of CHD patients, those with an ACS. The EURHOBOP project's main goal was the development of a tool to benchmark European hospitals in AMI and PCI, based on predicted in-hospital mortality. In 10 Portuguese hospitals, a comparison of ACS management between women and men was assessed by evaluating the performance of coronary angiography, and of reperfusion and revascularisation among patients treated invasively. Strengths of this database were consecutiveness, standardisation in the definition of variables

and process of collecting, and also the criteria used to select the Portuguese hospitals. The population studied was managed in hospitals that cover different regions, from North to South, including both coastal and interior regions, different human and material resources, and levels of specialisation. Limitations derive mainly from potential missing variables that could impact pre-treatment status and influence decisions on management, and a lack of information about timeliness of the procedures which would also be relevant. This is related with the fact that the variables were collected to the main goal of the European project, which was to provide a simple and precise benchmarking model, balancing parsimony and performance [138].

The EPIHeart study was the third data source, driven by the a priori hypothesis of inequalities in CHD in Portugal. Sample size, selection bias and losses to follow-up are potential limitations of the cohort, which were considered when analysing our results. The inclusion of two hospitals, that are both tertiary, cover two distinct populations in the northern region of Portugal, was relevant to the main objectives. The major strength is availability of detailed and standardised information on exposure, confounding and outcome variables that were very useful to further disentangle the complex ACS process of care. We ensured relevant aspects related with quality of data, namely correct identification of the type of ACS, appropriate evaluation of severity of the patient condition to determine whether they were appropriate candidates for performance measures, correct characterisation of the process of care to be able to compare it with the performance standard, data to perform risk adjustment of outcomes, to ensure that differences are attributable to care and not to underlying patient characteristics.

Inequalities in CHD management and outcomes in Portugal

The goal of reducing within country variations in CHD burden is considered a worldwide target [269]. By revealing that the CHD mortality decrease observed at the national level in the last three decades conceal different mortality trends by region **(Paper 1)**, we have strengthened the relevance of this goal for Portugal, and we have further objectively identified what regions need special attention, namely Alentejo and Azores. Similar geographic CHD mortality disparities persisting over time were observed in other settings [270].

Available information by Portuguese region on sociodemographic characteristics of the population, allocation of health system resources, prevalence of risk factors, and on process indicators for CHD was used to provide insights into possible differences in outcomes by region. However, we were not able to objectively explain why those differences were observed to guide changes within each region and improve equity. This is one of the limitations of outcome process indicators pointed out by Donabedian [102].

Greater relative declines in CHD mortality observed for women compared to men were found in most Portuguese regions, the result of effective primary and secondary prevention strategies directed to women. Considering evidence of stagnation in the decrease in CHD mortality in young adults, especially

women observed in other settings [271], our results are encouraging but do not obviate the relevance of continuously monitoring.

Moving toward to the patient level and to management of ACS, we found differences in the conservative/ invasive approach between women and men with STEMI and ACS with LBBB, but not with NSTEACS. Women with STEMI/NC ACS were the subgroup of patients who had the highest in-hospital mortality **(Paper 2)**.

The first and noteworthy factor limiting the comparison of our results with available data gathered from national registries, namely with data from the Portuguese Registry of Acute Coronary Syndromes and with the Portuguese National Registry of Interventional Cardiology, is related with the lack of report of results of the registries by sex [157,260]. Furthermore, these registries only cover cardiology departments, participation is voluntary and consecutiveness of patients within participating centers is not assured. Nevertheless, some remarks can be made.

According to results of the national registry from the 2002-2008 period, coronary angiography was performed in 62% of the whole sample [157], slightly lower than the observed in our sample. Compared with the same results, the proportion of patients undergoing revascularisation was higher in our cohort (66.9% vs 38%) [157]. Data from the registry reported to the 2010-2013 period showed a higher proportion of patients managed invasively (84.8%), probably an overestimation of the true proportion, due to the overrepresentation of patients admitted to hospitals with high level of specialisation. The differences in ACS epidemiology and outcomes observed between the ten Portuguese hospitals included in EURHOBOP, although deserving further research, strengthen the importance of including patients admitted to hospitals with different levels of specialisation, to better represent the whole ACS population of patients.

According to data from 2008, Portugal was among the countries performing less primary PCI in Europe [272]. Authors who participated and analysed these results considered that the main factor explaining this finding was the high proportion (55%) of patients admitted more than 12 hours after symptom onset [157,260]. Although our results are in line with the increasing proportion of reperfusion, and by primary angioplasty relative to fibrinolysis observed in Portugal (from 2002 to 2013, there was a three-fold increase in primary angioplasty rates per million population) [260], the significant difference of management between women and men with STEMI/ non-classifiable (LBBB) ACS of our cohort deserves attention. Our large consecutive sample, the inclusion of hospitals with different characteristics and the possibility of taking several potentially important confounders into account strengthens this finding.

For our third objective, which was drawn with the intention of further analysing differences in management and outcomes between women and men with CHD, we opted to use QIs for the management of AMI developed by ESC/ACCA [133] **(Paper 3)**. The decision to use this tool to investigate potential sex

inequalities was supported by several reasons. They link evidence and quality assessment; were proposed by the ESC, taking into account recent European guidelines; include different domains across several indicators for evaluating the key aspects of the complex AMI care pathway; they include an outcome indicator, 30 day mortality adjusted for the GRACE 2.0 risk score and the possibility of evaluating its association with management.

STEMI patients were considered eligible for reperfusion if admitted within 12 hours from symptom onset. The very high proportion of reperfusion observed for this subgroup of STEMI patients supports the previous hypothesis of delayed presentation in Portugal to be one main factor explaining low proportions of reperfusion, compared with other European countries. But this encouraging result became disappointing when we looked to the indicator related with timeliness of reperfusion. A low level of timely reperfusion was observed, significantly lower for women than for men (21.1% vs 33.5%, p=0.041). Although primary PCI remains the optimal reperfusion strategy for patients with STEMI, recommended timelines seem to be not met in Portugal. Not all the closest hospitals have the capability to perform primary PCI, therefore a significant number of patients will need to have an ambulance bypass the closest hospital or be transferred from non-PCI hospitals (in our cohort 36.1% of AMI patients). According to our results, looking to timely reperfusion of patients admitted to non-PCI capable hospitals is particularly relevant. In other developed countries, also with an organized transfer system for STEMI such as Denmark, 65% of transferred STEMI patients experienced a system-related delay (time from first contact with the health care system to the initiation of reperfusion therapy) of greater than 120 minutes, which was independently associated with increased mortality [273]. If the step forward in Portugal should target patient and health system barriers to achieve the target time windows for primary PCI for all patients or should identify settings where timely primary PCI is accepted as not being achievable, and where a formal proposal of the pharmacoinvasive strategy (fibrinolysis followed by coronary angiography) as standard of care would be more effective and safer should be evaluated [96].

We observed similar proportions of pharmacological therapy for secondary prevention prescription, when comparing with previous results from our team [274]. The lower proportion of eligible women discharged on dual antiplatelet therapy was previously observed for women with STEMI in the Portuguese sample of EURHOBOP [274]. With the analysis of statins type and doses, we uncovered a poorer compliance for high intensity dose statins following AMI, and also another sex gap in management. Referral to cardiac rehabilitation was significantly lower for women, compared to men. Recently published results from the 2013-14 national survey on cardiac rehabilitation in Portugal were not reported by sex. According to these data, 8% of patients with AMI were admitted to phase II cardiac rehabilitation program in 2013, while in 2007 the correspondent number was 3% [275].

The very low level of performance of the GRACE and the CRUSADE risk assessment among women and

men is particularly relevant. Besides its better risk discrimination when compared with physician estimated risk [84], decisions on place, type and time of acute management should be made according to its calculation [45]. Considering the low level of the GRACE risk assessment for NSTEACS patients of our cohort, time of coronary angiography most often was not based on its calculation. These QIs propose the timeline of 72 hours from admission as a standard performance measure for NSTEMI coronary angiography, although guidelines advise procedures within two hours and 24 hours from admission for very-high and high risk patients, respectively [45]. This is a very objective example of the difference between guidelines and QIs statements. This decision about considering the 72 hours timeframe for all NSTEMI patients is in accordance with the Dutch position [276]. The Dutch ACS working group appointed several reasons to not consider referral within 24 hours to be a necessity for their situation: the lack of strong support to an early invasive approach from available meta-analysis; the argument that the TIMACs trial results were only a hypothesis-generating result in a trial which did not show a significant reduction of the primary endpoint of death or myocardial infarction; results of the Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial showing good results with a more conservative (selective invasive) treatment of NSTEACS patients [277]; and reasons related with the Dutch specific organisation of the health care system [276].

Despite the low number of deaths, women had almost twice the GRACE 2.0 risk score 30-day mortality rate compared with men. Mortality was inversely associated with the composite QI, which captures several steps from the AMI care pathway. This association is conceptually relevant, favouring the future use of this composite QI to improve quality of care of AMI patients. Obviously, not all determinants influencing outcomes are included in this composite QI. For example, besides timely invasive strategy, the intensity (dosage, combination, and duration) of periprocedural antithrombotic treatment largely varies and can also influence outcomes [278].

Presenting symptoms of ACS, by impacting health care seeking/reaching, and also diagnosis, are critical for ACS management, and particularly may impact eligibility for reperfusion of STEMI patients. The decision to analyse differences by sex in clinical presentation of ACS was strengthened by results of previous papers and supported by the conceptual frameworks of our research hypothesis **(Paper 4)**.

With the application of a structured questionnaire within the first 48 hours after admission, we distinguished direct and referred pain, we evaluated symptoms other than pain and their clustering, activity at the onset of the episode and stress triggers. This detailed information, and the adjustment for several confounding variables strengthens our results. Previously, it has been reported that 63% of patients admitted to a tertiary Portuguese hospital with an ACS were not able to correctly interpret their symptoms, namely to attribute them to a problem of the heart, and that women were less likely to correctly interpret the clinical presentation of ACS compared with men [279]. Several factors can contribute to this

lower illness perception of women, clinical presentation itself is probably one, namely the more frequent occurrence of multiple symptoms other than pain, common to other cardiac and non-cardiac diagnoses, among women. The possible impact on outcomes of presenting with the multiple symptoms cluster, considering that these patients had a higher mean 30-day mortality adjusted for GRACE, deserves further research. Patients` interpretation of ACS symptoms is a known cause of delay in reaching the hospital [280], directly influencing the seeking health care decision and behaviour, but also, correct interpretation of symptoms by professionals. We did not find significant differences between clinical presentation by type of ACS, namely STEMI/non-classifiable ACS and NSTEACS, therefore the decision to analyse them together. However, and considering women with STEMI have a lower probability of performing coronary angiography and timely reperfusion, the association between clinical presentation and patient and system delays may have a stronger impact for women with STEMI.

A first ACS already signals the failure of primary prevention, thus the relevance to CHD prevention to study chest pain, health resource seeking and utilisation before the acute event **(Paper 5)**. Patients with a first episode of ACS very frequently reported preceding chest pain, which triggered health seeking behaviours and medical investigation in less than half. Demographic, socioeconomic characteristics, region, health subsystem coverage and risk factors accounted for differences in seeking medical care and performance of investigation through ECG. In a context of universal coverage health system, we were able to identify barriers in access both in the demand and supply determinants, and therefore opportunities for CHD prevention.

Chest pain is a common presentation to primary care and emergency departments worldwide. The care of these patients is challenging and has a high impact, both because timely diagnosis of several of its causes, namely of CHD, is of paramount importance for patient well-being and survival; but also because ruling out serious causes of chest pain, and diagnosing non-cardiac causes is determinant to avoid unnecessary occupation of health services, exams and to reduce costs. This task is difficult, diagnostic tools have not shown appropriate acuity to rule out ACS in patients with chest pain [281]. The model of Chest Pain Centres was initiated in 1981 in one hospital in Baltimore, while in 1998, the Society of Chest Pain Centres was created to improve evaluation of patients with symptoms suggestive of ischemia [282]. Some European countries, including the United Kingdom and Germany adopted this model, and created chest pain units (CPUs) to manage patients with acute chest pain. The German Cardiac Society runs a nation-wide certification campaign for specialised CPUs. According to data which reports to October 2015, 228 CPUs have been successfully certified in Germany and 300 CPUs were needed for full coverage and to close gaps in rural regions [283]. Between December 2008 and June 2014, about two-thirds of the patients admitted to CPUs in Germany received transthoracic evaluation [284], while for the period between January 2010 and April 2011, only 5.4% underwent cardiac computed tomography during the index CPU

stay [285]. The authors concluded that the use of cardiac computed tomography should be reconsidered during the next update of the CPU certification criteria [285]. Evidence supports the association between implementation of CPUs and prognosis of patients with ischemic origin of the symptoms, with additional cost-saving [286,287].

Public health implications

Our results support that tackling CHD inequalities in Portugal requires policies and investment at the population, patient and health system levels. The Commission on Social Determinants of Health recommended three aims of intervention to reduce health inequalities, namely to improve daily living conditions; to address inequitable distribution of power, money, and resources; and to measure and understand the problem and assess the impact of action.

We gave important insights to select targets and operational tools for the latter aim of intervention. First, we identified the need to improve the availability of high quality, timely and reliable disaggregated data by age, sex/gender, socioeconomic position and geographic location, including determinants of incidence and outcomes of CHD. Mortality data from Statistics Portugal should be analysed and reported by region and sex; the sex-gap in analysis and report of results from the National Registries of ACS and of Interventional Cardiology should also be improved. There is a need to further study differential barriers to access to effective and timeliness reperfusion and secondary long term management between women and men with an ACS in Portugal and to monitor trends; these two data sources should be used for this purpose.

Given the dynamic nature of populations, of patients, of the health care system and of medical sciences; adaptable quality assessment and improvement programs are increasingly considered the foundation to reduce inequalities in cardiovascular health, Portugal is not an exception. Working groups in Portugal need to link the adjustment of international guidelines on the management of CHD to our national context, with quality assessment. The introduction of standardised quality indicators for management of ACS would improve quality of care and enable hospital benchmarking. Our results support that time dependent QIs for ACS should be selected and that appropriate risk adjustment is of particular relevance to study inequalities; the ESC/ACCA QIs for management of AMI proposal would be a good tool to start this work.

Health promotion strategies, at the population and individual levels, with focus on symptom awareness as well as on prompt and adequate health system seeking behaviours of patients with symptoms suggestive of ischemia should be evaluated through epidemiological research [288]. Eventually, it would also be useful to study the cost-effectiveness of implementing other models of organisation for evaluating patients with chest pain, namely the CPUs model, in Portugal.

5. CONCLUSION

This thesis gave valuable insights about inequalities in CHD management and outcomes in Portugal. Focusing on sex/gender and region, we identified vulnerable groups of patients warranting intervention in Portugal, and also explored the dependence and interactions of factors that make the overall process of CHD management and outcomes complex to understand.

In Portugal, between 1981 and 2012, relative declines of CHD mortality indicators were different by geographic region, and greater declines in mortality rates were observed among women compared with men. Despite this encouraging result on mortality from CHD as a whole among women, we were able to identify targets to intervene to further reduce the sex/gender gap in management and outcomes from CHD, namely among women with STEMI, specifically in the reperfusion-invasive strategy; but also differences in the long term secondary prevention of AMI in general. The complexity of measuring clinical presentation of ACS is relevant, as our research underlined, and poses methodological challenges to include this variable in risk adjustment models. It is particularly relevant to understand inequalities in CHD management and outcomes by sex, considering the potential role of atypical ACS presentation in patient and system delays, and its impact on management, and consequently on outcomes. We identified opportunities to an earlier diagnosis and treatment of patients with CHD. Furthermore, we have found several determinants of the flow through the health system of patients with chest pain before the first ACS. Risk factors and subjective social class were associated with health care seeking behaviour; while gender, cognitive status, region, employment status and health subsystem coverage were associated with performance of ECG.

These findings strengthen that interpretation of health inequalities research results implies a profound clinical knowledge of the specific clinical condition, and also understanding of controversial issues related with measuring and analysis methodology. This thesis supports that CHD should be included as one of the target diseases in the “equity and adequate access to health care” goal, set by the Portuguese National Strategy for Quality in Health 2015–2020. Furthermore, our results support that interventions to promote equity and quality of CHD care should be directed not only to the health care system, but also to patients and to the general population.

"The landmarks of political, economic and social history are the moments when some condition passed from the category of the given into the category of the intolerable. I believe that the history of public health might well be written as a record of successive re-definings of the unacceptable."

Sir Geoffrey Vickers, 1958

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