Quality of health care in coronary heart disease in Portugal: an international comparative analysis

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Table of Contents

ACKNOWLEDGEMENTS ..... **VI**

LIST OF PUBLICATIONS ..... **VII**

ABBREVIATIONS ..... **IX**

LIST OF TABLES ..... **X**

ABSTRACT ..... **XI**

RESUMO ..... **XIII**

1 RATIONALE **1**
1.1 CORONARY HEART DISEASE – HEALTH STATUS AND VARIATIONS ACROSS AND WITHIN COUNTRIES 1
1.2 CORONARY HEART DISEASE IN PORTUGAL 2

2 OBJECTIVES **3**

3 BACKGROUND **4**
3.1 HEALTH SERVICES RESEARCH 4
3.1.1 Quality of health care *5*
3.1.2 International studies, benchmarking and hospital profiling *7*
3.2 THE CUTEHEART PROJECT 9
3.3 MATERIALS AND METHODS 10
3.3.1 Data sources (considerations about comparability across countries) *10*
3.3.2 Rate standardization for comparisons between groups *12*
3.3.3 Generalized linear mixed models for clustered data *13*

4 RESULTS **17**
4.1 PAPER 1 17
4.2 PAPER 2 29
4.3 PAPER 3 40

5 DISCUSSION AND RECOMMENDATIONS **69**
5.1 IMPLICATION OF MAIN FINDINGS 69
5.2 RECOMMENDATIONS AND FUTURE INVESTIGATION 73
5.2.1 Considerations about data quality - issues and strengths *73*
5.2.2 Recommendations and future investigation *74*

6 REFERENCES **77**

7 SUPPLEMENTARY MATERIAL **86**
7.1 COMPATIBILITY OF VARIABLES IN ADMINISTRATIVE DATA ACROSS COUNTRIES 86
7.2 SUMMARY DESCRIPTION OF DATA SOURCES WITH POTENTIAL USE FOR COMPARATIVE HEALTH CARE QUALITY ASSESSMENT 90
7.3 STANDARDIZATION AND RISK-ADJUSTMENT FORMULAS 93
Rate standardization *93*
Generalization of indirect standardization using regression models *94*
7.4 PAPER 1 SUPPLEMENTARY DATA 95
7.5 PAPER 2 SUPPLEMENTARY DATA 109
7.6 PAPER 3 SUPPLEMENTARY DATA 122

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This thesis was based in several publications.

Research Papers

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Abbreviations

ACS – Acute Coronary Syndrome
ACSS – Administração Central do Sistema de Saúde, IP
AHA – American Heart Association
AMI – Acute Myocardial Infarction
BMS – Bare-metal Stent
CABG – Coronary Artery Bypass Graft
CDC – Centers for Disease Control and Prevention
CHD – Coronary Heart Disease
CUTEheart – Comparative Use of Technologies for Coronary Heart Disease project
CVD – Cardiovascular Disease
DES – Drug-eluting Stent
EMR – Electronic Medical Records
ESC – European Society of Cardiology
EU – European Union
EUDAMED – European Database on Medical Devices
EURHOBOP – EURopean HOspital Benchmarking by Outcomes in acute coronary syndrome Processes Project
EUROSTAT – European Statistics
GBD – Global Burden of Disease
GLMM – Generalized Linear Mixed Models
HGLM – Hierarchical Generalized Linear Models
HSR – Health Services Research
ICC – Intraclass Correlation Coefficient
ICD-9-CM – International Classification of Diseases, 9th Revision, Clinical Modification
INE – Instituto Nacional de Estatística/Portugal Statistics
IOR – Interval Odds Ratio
LOS – Length of Stay
MOR – Median Odds Ratio
NAM – National Academy of Medicine
NHS – National Health Service
NIS – Nationwide Inpatient Sample
NSTEMI – Non ST-Elevated Myocardial Infarction
OECD – Organisation for Economic Co-operation and Development
OR – Odds Ratio
PC – Primary Care
PCI – Percutaneous Coronary Intervention
PCV – Proportional Change in Variance
POOR – Proportion of Opposed Odds Ratios
PT – Portugal
RCT – Randomized-controlled Clinical Trials
RSMR – Risk-Standardized Mortality Rate
RSRR – Risk-Standardized Readmission Rate
SD – Standard Deviation
SPC – Sociedade Portuguesa de Cardiologia/Portuguese Society of Cardiology
STEMI – ST-Elevated Myocardial Infarction
TAVR – Transcatheter Aortic Valve Replacement
US – United States of America
WHO – World Health Organization

List of Tables

Table 3.1 Health care quality domains.
Table 3.2. Common metrics used to assess contextual effects within the context of clustered data.
Table 7.1. Selection of variables in the inpatient hospital administrative data in Portugal and US.
Table 7.2. List, description and availability status of datasets in Portugal and the United States.

Abstract

Despite significant declines, coronary heart disease (CHD) remains a great burden to the Portuguese and worldwide health care systems, accounting for substantial morbidity and mortality, and with significant costs. Behavioral factors such as sedentary life style, high-sodium food intake, and population ageing significantly contributed to increased morbidity. The ever-growing understanding of the pathophysiology of these diseases and proliferation of health technologies on one side and better organization of health services on the other, promoted improvements in the survival and quality of life of these patients. However, health care quality variations across geographical regions and health care providers continue to be reported in the scientific literature. Some variation may be explained by fundamental differences in socio-political structures, personal values, organizational structures and processes as well as economic constraints. On the other hand, geographical or health care provider variation may be the result of underperformance in some health care systems due to overuse or underuse of treatments which in turn leads to intrinsic concerns regarding waste of resources that could be needed elsewhere.

This thesis builds on the opportunity that comparative studies afford to contrast different healthcare systems, with different practice patterns and needs, to gain insights into factors impacting health care quality. Specifically, this thesis aims at comparing the health care systems of Portugal and the United States in the context of CHD patient management. We selected CHD because it is a highly prevalent and fatal disease, for which health technologies have advanced substantially in past decades, thus investigating into questions associated with their adoption and diffusion is important . We compare access to and use of health technologies, their corresponding relationships to clinical outcomes of CHD patients, and contrast these relationships between the two countries.

We first sought to characterize the two health care systems in terms of their organization, epidemiological profiles, resource availability, including ability to access new health care technologies, and population health status. Briefly, our results indicate that relative to the United States, Portugal exhibits lower population risk profiles, has fewer CHD-related hospitalizations, and a smaller number of hospitals that provide advanced heart procedures. In addition, new health technologies enter the market using different regulatory pathways, which frequently result in faster diffusion in the United States. Despite the access differences, CHD mortality is numerically lower in Portugal but not statistically different than in the US when acute myocardial infarction (AMI) mortality is compared.

We next sought to characterize and compare care of patients hospitalized with an AMI in Portugal and the United States during 2000-2010. We selected AMI because this represents an acute condition within CHD requiring expensive care treatment. Also, restricting the scope of our analysis improved cross-country comparability. Concurrent with previous findings, hospitalizations in the United States presented more comorbid conditions, yet more hospitalizations in Portugal presented with ST-segment elevated myocardial infarction. Coronary revascularization procedures – coronary artery bypass graft and percutaneous coronary intervention – were less frequent in Portugal. Its utilization was associated with survival at discharge in both countries, but the probability of survival was larger in Portugal. Age-sex-adjusted in-hospital mortality rates in Portugal was twice that for the United States. Furthermore, significant declines in risk-adjusted mortality were observed in both countries over our eleven-year period. However, after adjusting for risk factors at presentation, we observed larger between-hospital variability in patient survival in Portugal relative to the United States – the risk of dying in a high relative to a low mortality hospital was 2.65 in Portugal compared to 1.03 in the United States.

Motivated by the variation results, we further investigated whether hospital characteristics could explain hospital heterogeneity in health care quality in Portugal.

We studied between-hospital variation in in-hospital mortality and 30-day unplanned readmission in AMI patients during 2012-2015. All else equal, health systems should provide high quality of care regardless of the hospital in which patients are treated. Our new findings confirmed that hospital represents a contextual effect – some hospitals perform consistently better than others, and these variations remain even after adjusting for hospital case-mix and hospital characteristics. Moreover, among the hospital characteristics examined, higher AMI caseload and larger hospitals were associated with lower mortality and readmission rates. Geographical location of the hospital was also related to quality of care with an AMI patient hospitalized in Alentejo/Algarve and Lisbon regions more than 20% more likely to be readmitted within 30-days of discharge compared to a patient treated in the North region.

This thesis provides significant information for improving the quality of CHD health care, and in particular, AMI patient management in Portugal. Limited data are available on marketing approval of new health technologies and further investigation will be needed to understand their diffusion. In line with the United State, Canada, and other countries that boast a strong tradition of monitoring the quality of care delivered to its citizens, Portugal could benefit from regular hospital measurement and monitoring of expensive, and frequent conditions such as AMI. Furthermore, health policies seem more sensible if addressed to specific hospitals depending on their risk level, while particular attention should be given to hospital caseload and practices across different geographical regions.

Resumo

Não obstante melhorias significativas, as doenças coronárias (DC) continuam a representar um peso substancial no sistema de saúde Português e sistemas de saúde um pouco por todo o mundo, contribuindo com uma elevada morbilidade e mortalidade bem como custos significativos. Fatores comportamentais, tais como um estilo de vida sedentário e uma alimentação rica em teor de sódio, bem como o envelhecimento da população contribuíram significativamente para o aumento da morbilidade. A crescente compreensão da pato-fisiologia dessas doenças e a proliferação de tecnologias de saúde, por um lado, e avanços na organização dos serviços de saúde, por outro, promoveram melhorias na sobrevida e qualidade de vida desses pacientes. No entanto, variações na qualidade dos cuidados de saúde entre regiões geográficas e entre prestadores de cuidados de saúde continuam a ser relatadas na literatura científica. Parte destas variações podem ser explicadas por diferenças fundamentais ao nível das estruturas sociopolíticas, valores pessoais, estruturas e processos organizacionais, bem como restrições económicas. Por outro lado, variações entre regiões geográficas ou entre prestadores de cuidados de saúde podem decorrer de um desempenho insuficiente de alguns sistemas de saúde devido à sub- ou sobre-utilização de tratamentos, o que, por sua vez, suscita preocupações relativas ao desperdício de recursos que podem ser necessários para outro fim.

Esta tese desenvolve-se sobre a oportunidade de estudos comparativos encerrarem a possibilidade de extrair conhecimento sobre a qualidade de cuidados de saúde ao contrastar diferentes sistemas de saúde, com diferentes necessidades e padrões de tratamentos. Especificamente, esta tese tem como objetivo comparar os sistemas de saúde de Portugal e dos Estados Unidos no âmbito do tratamento de pacientes com DC. Selecionámos a DC porque ser uma doença muito prevalente e fatal, para a qual tecnologias de saúde viram um avanço substancial nas décadas passadas, pelo que a investigação de questões relacionadas com a sua adopção e difusão são importantes. Comparámos o acesso e utilização de tecnologias de saúde, o seu impacto no desfecho desses pacientes, e comparam-se estas relações entre países.

Em primeiro lugar procurámos caracterizar os dois sistemas de saúde em termos de organização, perfis epidemiológicos, recursos disponíveis incluindo a capacidade de acesso a novas tecnologias de saúde, e estado de saúde das populações. Sumariamente, os nossos resultados indicam que a população de Portugal apresenta um perfil de risco menor, com menos internamentos relacionadas a DC, e os centros que oferecem procedimentos cardíacos avançados são também em menor número quando comparados com os Estados Unidos. Além disso, novas tecnologias da saúde estão sujeitas a diferentes regulamentações seguindo diferentes vias de aprovação, que favorecem frequentemente uma difusão mais rápida nos Estados Unidos. Apesar de diferenças no acesso, a mortalidade por DC é menor em Portugal, mas as diferenças entre os países não são estatisticamente significativas em relação à mortalidade por enfarte agudo do miocárdio (EAM).

Procurou-se de seguida caracterizar e comparar a prestação de cuidados hospitalares em pacientes com EAM em Portugal e nos Estados Unidos durante o período de 2000-2010. Selecionámos o EAM porque esta doença representar uma condição agudizada dentro da DC, requerendo tratamentos caros. Além disso, a restrição do âmbito da análise melhorou a comparabilidade entre países.

Apoiado pelos resultados anteriores, hospitalizações nos Estados Unidos apresentaram mais doenças concomitantes, mas mais hospitalizações em Portugal exibiram um enfarte do miocárdio com o segmento ST elevado. Os procedimentos de revascularização coronária – bypass coronário e intervenção coronária percutânea – foram menos frequentes em Portugal. A sua utilização estava

associado à sobrevivência do paciente à data da alta em ambos os países, contudo a probabilidade de sobrevivência era maior em Portugal. A mortalidade intra-hospitalar ajustada ao sexo e idade em Portugal foi o dobro da observada nos Estados Unidos. Além disso, observou-se uma diminuição anual significativa no risco de morte para ambos os países durante período de onze anos. Contudo, após controlar para factores de risco, observámos uma maior variabilidade intra-hospitalar na sobrevivência do paciente em Portugal, em comparação aos Estados Unidos – o risco de morte de um paciente num hospital de mortalidade elevada relativamente a um hospital de mortalidade baixa foi de 2,65 em Portugal, quando nos Estados Unidos era apenas de 1,03.

Motivado pelos resultados sobre a variabilidade, investigámos se características dos hospitais poderiam explicar a heterogeneidade entre hospitais. Nesse sentido, estudámos variações na mortalidade intra-hospitalar e readmissão urgentes ocorridas até 30 dias após alta de pacientes com EAM durante 2012-2015. Um sistema de saúde deve prestar cuidados de saúde de elevada qualidade independentemente do hospital em que os pacientes sejam tratados, assumindo que tudo o resto é igual. Os nossos resultados confirmaram que o hospital representa um efeito contextual – alguns hospitais têm desempenhos consistentemente melhores do que em outros hospitais, e essas variações permanecem mesmo depois de ajustar para *case-mix* de pacientes e características dos hospitais. Além disso, entre as características ao nível do hospital examinadas, verificou-se que o número de casos de EAM tratados e o tamanho do hospital estavam associados com taxas de mortalidade e readmissão mais baixas. A localização geográfica do hospital também exibiu uma relação com a qualidade dos cuidados prestados, tendo um paciente com EAM hospitalizado nas regiões do Alentejo/Algarve ou Lisboa um risco de readmissão urgente de mais de 20% quando comparado com um paciente tratado na região Norte.

Esta tese fornece informação vital para melhorar a qualidade dos cuidados de saúde na DC, e em particular, no tratamento de pacientes com EAM em Portugal. Os dados disponíveis sobre a autorização para comercialização de tecnologias de saúde são limitados e mais investigação será necessária para compreender a sua difusão. Em linha com os Estados Unidos, Canadá, e outros países que mostram uma forte tradição na monitorização da qualidade de cuidados de saúde prestada aos seus cidadãos, Portugal poderia beneficiar de atividades regulares de medição e monitorização de condições frequentes e dispendiosas como o EAM. Além disso, parece ser mais sensato que as políticas de saúde sejam dirigidas a hospitais específicos, dependendo do seu nível de risco, devendo ser dada especial atenção ao número de casos praticados por hospital e às práticas hospitalares em diferentes regiões geográficas.

1 Rationale

1.1 Coronary heart disease – health status and variations across and within countries

Cardiovascular diseases (CVD) are responsible for approximately one third of deaths worldwide.(World Health Organisation, 2017) Among these, coronary heart diseases (CHD), comprising disorders of the blood vessels (coronary arteries) that supply the myocardium (heart muscle), stand out for their substantial burden on health care systems and their high morbidity and mortality. According to the World Health Organisation (WHO), most of CVD-related deaths are due to CHD (41%) or stroke (39%).(World Health Organisation, 2017) The latter comprising disorders of the blood vessels that supply the brain. CHD accounts for approximately 1.8 million deaths per year, representing 20% of all deaths in European countries.(Nichols et al., 2014) In addition to being highly fatal, CHD also represents a major economic burden, representing an estimated 28% (€59 billion a year) of the overall direct and indirect costs attributed to CVD in the European Union (EU). Of costs directly supported by health care systems associated with CHD (€19 billion in 2015), inpatient hospital care accounted for €10 billion (55%) while drugs accounted for €4 billion (20%).(Wilkins E et al., 2017)

Among the CHD, acute myocardial infarction (AMI) (or heart attack) constitutes the highest risk condition to patients. This is a life-threatening acute event that occurs when a sudden blockade of the coronaries occurs resulting in an insufficient oxygenated blood supply to the myocardium, which if not timely reverted may result in the death of the patient.(Thygesen et al., 2007) The American Heart Association (AHA) estimates an annual incidence of 580 000 new attacks (approximately 190 attacks per 100 000 population) and 210 000 recurrent attacks (approximately 80 per 100 000 population) in the United States alone (US).(Benjamin et al., 2017) Population aging, increasingly sedentary life style, obesity rates, and high-sodium food greatly contributed for increased morbidity in most countries.(Moran et al., 2014, Nichols et al., 2014) Whereas, the understanding of the pathophysiology of AMI, new diagnostic and therapeutic technologies, and improved organization of health services (e.g pre-hospital care, coronary intensive care units, cardiac rehabilitation), vastly contributed to improvements in survival and quality of life of these patients.(Braunwald, 1998, Teixeira et al., 2013)

Although general declines in mortality rates among CHD patients have been observed worldwide, variations across health systems in CHD morbidity, patient management, and mortality persist.(André et al., 2014, Moran et al., 2014, Nichols et al., 2014, Puymirat et al., 2013, Wilkins E et al., 2017) Variations are also observable within randomized controlled clinical trials (RCT), which in principle are less likely to depend on epidemiological profiles of populations and treatments are more likely provided in a standardized manner.(Chang et al., 2005, Gupta et al., 2003, Simes et al., 2010) These studies thus suggest that fundamental differences in socio-political structures, personal values, organizational structures and processes and economic constraints may overwhelm the pathophysiological similarities of the

underlying disease process being treated. Consequently, the accurate evaluation of healthcare systems performance and quality of healthcare provided requires an understanding of many local factors: disease epidemiology, institutional resources, specialized professional training, and political planning, surveillance, and evaluation instruments.(Bradley et al., 2006, Brook and McGlynn, 1996, Chang et al., 2005, Peiró and Maynard, 2015)

As new health technologies, particularly those proven to be cost-effective, hold the potential for improving the health and well-being of patients, different healthcare systems adopt new health technologies at varying speeds and use rates. Despite the increasing rates of scientific and technological development, clear guidelines and recommendations for prioritizing, implementing, and disseminating technologies are currently lacking. These inefficiencies likely have a negative impact on the ability of physicians and health systems to deliver high quality cost-effective care.(Gonçalves and Seabra-Gomes, 2012, Pinto et al., 2015) Importantly, such inefficiencies further contribute to heterogeneity in health care quality across healthcare systems, centers, and medical providers.

While variations across health systems raise concerns for sub-optimal care in some geographic regions or in particular sub-populations, these differences also represent opportunities for a better understanding of determinants of health care improvement. This thesis exploits variations within and between countries through comparative analyses of CHD patient management. Findings from such comparisons would provide concrete measures of variations in treatments and outcomes, and identify factors that may improve health care quality of these patients.

1.2 Coronary heart disease in Portugal

Similar to what is generally observed in most high-income countries, CVD also represents the leading cause of death in Portugal. Despite significant declines in past decades, declines in mortality rates have slowed recently. According to age-standardized rates from the Portuguese Health Ministry and the Organisation for Economic Co-operation and Development (OECD), CHD mortality has in fact increased during 2011-2015.(Wilkins E et al., 2017, Direcção Geral da Saúde, 2018)

When compared to other European countries, Portugal is among those with lowest CHD mortality rates for both sexes.(Wilkins E et al., 2017) Yet, less favorable figures characterize in-hospital mortality in Portugal relative to other countries. André et al. (2014) observed that Portugal was among the countries with highest rates of in-hospital mortality in patients admitted with ST-segment elevated myocardial infarction (STEMI) and non-ST-segment elevated myocardial infarction (NSTEMI) (9.7% and 6.9% respectively). While the latter study was based on data collected prospectively during 2008-2010, it covered only 6 western European countries and each country contributed with data from 8-10 centers. Moreover, OCED reports show that mortality within 30 days after admission in AMI patients in EU countries ranged between 7.5% of admissions of adults aged 45 years and over in Italy to 19.1% in Latvia, and ranked Portugal (10.4 %) just above the EU average (9.9%) in 2013.(Organisation for Economic Co-operation and Development,

2016) Data collected under the auspices of the Portuguese Society of Cardiology (SPC) based on voluntary participation of centers provide another perspective of health care provided to CHD patients in Portugal. The SPC data indicate that health care improved substantially over the past few decades, with noticeable improvements in the use of the coronary fast-track emergency system, compliance with drug therapies, and adherence to coronary revascularization procedures as recommended in the European Society of Cardiology (ESC). A significant reduction in in-hospital mortality marked the period between 2002 and 2008, from approximately 9% to 6% in STEMI patients.(Gonçalves and Seabra-Gomes, 2012, Santos et al., 2009)

In the United States, several studies report on variations regarding in-hospital patient management (Arnold et al., 2015, Jernberg et al., 2011, Mathews et al., 2018) and outcomes (Bradley et al., 2010, Bradley et al., 2006, Krumholz et al., 2011, Krumholz et al., 2009, Krumholz et al., 2006, Rasmussen et al., 2008, Stukel et al., 2010, Wakeam et al., 2015, Xian et al., 2014) for patients having an AMI. These studies highlight that substantial hospital heterogeneity exists, and only partially explained by differences in patient case-mix. While the contextual effect of hospitals remains relatively poorly understood, the association of hospital characteristics (e.g. AMI volume, teaching status, size, cardiac facilities available, geographic location, profile of socio-economic status of patients) with outcomes suggest that hospital characteristics may play a meaningful role in explaining between-hospital variability. In Portugal, no such studies have been undertaken for CHD, and only limited information is available on inter-hospital variations in CHD health care quality. For example, Portugal's Health Ministry reported variations in treatment use such as volume of advanced hospital procedures (Administração Central do Sistema de Saúde, 2003, Direcção Geral da Saúde, 2018) and drug prescription practices (Dores et al., 2014, Ferreira et al., 2004). In response, a tool developed by the *Administração Central do Sistema de Saúde* (ACSS) for hospital benchmarking within the Portuguese National Health Service (NHS) was developed and public reports of several health care quality indicators commenced. While this tool provides an important step to fostering transparency and public accountability in quality of hospital care, only two indicators are specific to CHD hospital care: absolute frequency of coronary bypass surgery volume and angioplasty volume per hospital. While these metrics are important, they do not permit an assessment of the appropriateness of the procedures nor how they may impact on the health status of these patients.

With few metrics to quantify and identify factors that impact treatment use and outcomes, it is clear that health services research (HSR) in Portugal is still somewhat insipient with regard to certain domains of health care quality, such as accessibility and equity, despite a growing interest in the field and priority given to health programs in CVD. Important insights may be obtained by investing in this field of research, which are invaluable to guide health policies and ultimately to improve health care quality in Portugal.

2 Objectives

The goal of this thesis is to provide insights regarding quality of care for CHD, examining factors associated with access, effectiveness and equity of CHD

patient care. Taking advantage of a partnership between academic institutions in Portugal and the US, we compare the different health care systems in terms of access to and use of health technologies in CHD patient management, and their impact on the outcomes of these patients. We identify and quantify factors that may explain differences between countries and heterogeneity of outcomes across hospitals within countries. With this in mind we established three specific aims:

Aim 1: Comparison of healthcare systems (*Paper 1*)
To characterize two contrasting health care systems in terms of their organization, epidemiological profiles, resources available, and health status emphasizing the systems abilities to access new health care technologies (medical devices and drugs).

Aim 2: Assessment of AMI health care quality (*Paper 2*)
To characterize and compare AMI in-patient management and hospital health care quality in Portugal and the United States for hospitalizations during 2000-2010.

Aim 3: Explaining hospital heterogeneity in health care quality (*Paper 3*)
To assess between-hospital variation in treatment use and outcomes, accounting for patient-level and hospital-level characteristics.

3 Background

3.1 Health services research

The main concern of HSR is to produce scientific evidence that contributes to the development of more effective, more equitable and more efficient health care services.(Phillips, 2006) According to the AcademyHealth, the American professional organization for HSR, *"Put simply, HSR is the science of study that determines what works, for whom, at what cost, and under what circumstances. It studies how our health system works, how to support patients and providers in choosing the right care, and how to improve health through care delivery.*"(AcademyHealth, 2017)
Entailing a broad scope beyond assessing efficacy of health care, which is usually achieved under very controlled settings (e.g. RCT), HSR focus on whether health care works in real world settings, both under conditions similar to RCT or under different circumstances if practice differs from trial.(Ebinger, 2017, Scott and Campbell, 2002, Steinwachs and Hughes, 2008) The breadth of this study field is also reflected by the relevance attributed to taking into perspective what quality of care represents to patients, health systems, and organizations, while acknowledging the challenges of such multidimensional and multifactorial systems in which quality of care depends on the efficacy of interventions, on the effectiveness of structures and processes, and on contextual factors such as practice patterns, personal beliefs and economic constraints.(Chen et al., 2010, Da Costa et al., 2015, Enno et al., 2000, Nichols et al., 2017, Peiró and Maynard, 2015) Particularly when guidelines/consensus documents fail to provide strong evidence to guide

practitioners onto which procedures to adopt, personal interpretations are more likely to arise, eventually leading to different practice patterns.(Appleby et al., 2011, Chiang et al., 2014) Considering the multidimensional context of HSR, experimental studies are often difficult or inadequate to implement. For example, many decisions involve changes in organizational structures, modes of practice, and personnel skills and are often not readily amenable to randomization or blinding.(Scott and Campbell, 2002) Furthermore, randomization becomes unethical for enquiry of effectiveness after proven or judged efficacy of interventions.(Steinwachs and Hughes, 2008) Thus, quasi-experimental and observational studies take on an important role. Accordingly, electronic medical records (EMR), prospective registry data, administrative data, and survey data become crucial data sources in the field of HSR.(Ebinger, 2017, Pittman, 2010, Scott and Campbell, 2002) These data sources consist of systematic and standardized collection of information on patients characteristics, treatment, and outcomes. Although different data sources have varying levels of clinical detail and quality, they hold important advantages in HSR. First, they constitute real-world samples characterized by a large number of people, population coverage, and heterogeneity. Second, they usually allow for trend analysis, hence are adequate for investigating both cross sectional and longitudinal variations in health status and practice patterns (e.g. guideline adherence). Finally, the data sources are often linkable, e.g. interoperability between data sources (e.g. vital statistics, prescription data), and thus reduce lost-to-follow-up information and provide longer follow-up period than is possible in RCTs.(Brown et al., 2010)

3.1.1 Quality of health care

HSR aims to assess the quality of health care in order to derive insights that may improve it.(Blumenthal, 1996a, Blumenthal, 1996b, Brook and McGlynn, 1996) According to the National Academy of Medicine (NAM)(former Institute of Medicine) (Harris-Wehling and Morris, 1991), quality of care is "*the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge*". Dating back to the early 90s, this definition calls for the importance of evidence-based medical care as a mean to provide high-quality health care, which remains the paradigm of ideal health care practice today.(Heneghan, 2018) Evidence-based medicine is not just paramount to help providers to decide over the most appropriate/effective care, but also it is crucial to build more equitable and efficient health systems through standardized health care and services that are less permeable to personal preferences, and waste.(Appleby et al., 2011, Peiró and Maynard, 2015) Furthermore, quality of health care should also be synonymous of timely provision of services that are responsive to individual patient needs, preferences and values, regardless of their location and social-economic status and that protect patients from injuries during the care perceived. A systematization of aims around which health care should be built in order to achieve high-quality health care see Institute of Medicine (2001) (Table 3.1). This list of aims further helps the former definition to provide a structured concept and guidance on how to assess quality of health care. Variations of this list of aims have been proposed by others (Campbell et al., 2000) both more compact and extended versions of it. However, for the purpose of this

thesis, this section aims at establishing a broad definition of quality of care so that then emphasis is put on two crucial elements of quality of care - effectiveness and access (as conveyed through timely and equitable health care).

Table 3.1 Health care quality domains.(Institute of Medicine, 2001)

Safe: avoiding injuries to patients from the care that is intended to help them. **Effective**: providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and overuse, respectively). **Patient-centered**: providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions. **Timely**: reducing waits and sometimes harmful delays for both those who receive and those who give care. **Efficient**: avoiding waste, including waste of equipment, supplies, ideas, and energy. **Equitable**: providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status.

Measurement of health care quality is essential. It allows ascertaining weaknesses and strengths of health care services and hence identifying opportunities for improvement; it provides public accountability and hence more transparent health systems; and it makes information available to delineate health policies as well to evaluate ongoing reforms.(Papanicolas and Jha, 2017) Paraphrasing Porter et al. "*what is not measured cannot be managed or improved*".(Kaplan and Porter, 2011) However, because health care systems are multidimensional and involve a variety of players and stakeholder, assessing quality of health care is a hard task to accomplish in a meaningful way.

Seminal work from Avedis Donabedian prompted awareness both for the need and difficulties of quality of care appraisal.(Ayanian and Markel, 2016, Campbell et al., 2000, Donabedian, 1988, Donabedian, 2005, Normand and Shahian, 2007) His conceptual framework for assessment of quality of care based on measures of structure, process, and outcome remains a valid and important framework nowadays. Structure measures characterize the resources available to provide health services, including material and human resources and organizational structures. (e.g. number of CT scan machines, physician-nurse ratios, availability of cardiac surgery services). Structure measures are relatively easy to compute yet the extent of their association with health outcomes is difficult to establish. (Donabedian, 1988, Normand and Shahian, 2007)

Interactions between patients and providers are conveyed in process measures (e.g. number of appointments, admission through the emergency, prescription adherence). Its best use is to evaluate the compliance of health services against recommended care given that this is more likely to be associated with the final outcome. For instance, the percentage of patients admitted with an AMI with documented administration of acetylsalicylic acid at admission, or with a timely primary percutaneous coronary intervention

(PCI).(Entidade Reguladora da Saúde, 2017) Process measures are often straightforward to operationalize, may be the only measures available when outcome measures are not available, and may readily elucidate on which actions improve quality of health care, yet these measures are limited to a segment of the overall care provided for a particular medical condition, which may be applicable to only a small percentage of patients with a given condition.(Bradley et al., 2006, Donabedian, 1988, Harbaugh, 2006, Krumholz et al., 2007, Normand and Shahian, 2007)

Outcomes are arguably the ultimate validators of quality of health care because these represent the final effect of the health care delivered in the patient's health status (e.g. survival, satisfaction).(Donabedian, 2005) However, outcome measures are usually more complicated to operationalize when compared with process and structure measures because assessment of outcomes usually requires large samples, controlling for confounding effects and more sophisticated statistical methods to be implemented.(Krumholz et al., 2007, Normand and Shahian, 2007) Moreover, relative to other measures, outcomes may not render immediate actions to improve those outcomes, therefore its use should be done with discrimination.(Donabedian, 2005)

Quality indicators based on Donabedian's triad are increasingly used to measure, monitor and incentivize performance of health care systems and health organizations worldwide.(Bradley et al., 2006) The number of pay-for-performance programs, which stipulate financial penalties or incentives based on performance according to expected/contracted quality indicators, has grown over the last decade (e.g. Hospital Compare, Value-Based Purchasing programs in the US). In Portugal, pay-for-performance is being applied within primary care (PC) services, with 6% of the budget in contract agreements between PC units and the Ministry of Health associated with compliance of quality indicators goals. At a lesser extent, quality of hospital care is also stimulated through pay-for-performance measures, specifically resorting to outcome measures regarding adequate and timely access to clinical appointments, surgery and biologic medicines.(Administração Central do Sistema de Saúde, 2016)

This thesis aims to provide insights regarding quality of health services in Portugal within CHD patient management, emphasizing aspects about variability of quality of health care primarily through the analysis of outcomes measures. The term variability is used to refer both variability of health care quality when compared to other countries (between-country variations) as well as between-hospitals variations within two different countries.

With this in mind the next section motivates the use of comparative studies to draw insights of national health care performance. Further details on main methodological aspect of the approach adopted are given in section 3.3.

3.1.2 International studies, benchmarking and hospital profiling

Despite the publication of international and national updated guidelines, variations in CHD patient management, morbidity and mortality across countries, regions and institutions persist.(Institute for Health Metrics and Evaluation, 2018, Organisation for Economic Co-operation and Development, 2018) Even among high-income countries staggering differences in rates and trends exist.(André et al., 2014, Puymirat et al., 2013, Wilkins E et al., 2017) Comparative studies represent an opportunity to contrast different healthcare

systems, with different practice patterns and needs, and learn from the different realities. These comparisons may be used to evaluate the performance of national health systems, shape national health policies and to promote public accountability, which ultimately aim at improving health care quality, health and the well-being of populations.

The research conducted by international organization such as the WHO, the Organisation for Economic Co-operation and Development (OECD), and the Global Burden of Disease (GBD), are examples of international comparisons. These type of organizations work as central curators of health data from several countries, publishing regular influential reports at the national level, (Organisation for Economic Co-operation and Development, 2013, Wilkins E et al., 2017) and thus constitute valuable data sources in public health and health services research.(Steel, 2017)

International comparisons are common within the context of coronary heart disease health care.(André et al., 2014, European Society of Cardiology, 2018, McGovern et al., 1997, McNamara et al., 2014, Puymirat et al., 2013, Smith et al., 2013, Vargas et al., 2001, Zheng et al., 2017) For example, the EURopean HOspital Benchmarking by Outcomes in acute coronary syndrome Processes (EURHOBOP) project (http://www.eurhobop.eu) described characteristics of patients admitted for acute coronary syndrome (ACS) in Western Europe and analyzed international variations of patient management and in-hospital mortality.(André et al., 2014) Within the European Society of Cardiology, in collaboration with its national congeners, several surveys and prospective data registries have been developed to provide a better understanding of medical practice and assessment of adherence to guidelines and variations across regions or countries.(Gitt et al., 2010, Puymirat et al., 2013, Zeymer et al., 2017)

Notwithstanding the opportunities that international comparisons may yield, several challenges may undermine these comparisons.(Papanicolas and Jha, 2017) First, comparability of data sources and what differences represent is of crucial importance.(Bottle et al., 2013, Papanicolas and Jha, 2017) For example, Bottle et al. (2013) observed that a number of important variables in administrative data from several countries contained differing levels of detail depending on the country and required reconciliation prior to analysis. These authors also observe that different countries used different definitions of inpatient hospitalization, which may affect the identification of populations. Joseph et al. (2012) suggested that international variations in registration of extremely low birth weight and early gestation birth may lead to spurious rankings of perinatal and infant mortality rates across countries. Second, the association between interventions and observed cross-countries differences is difficult to establish and interpretations should be made in light of health systems scope, expectations of patients they serve, and national policies, values and priorities.(Papanicolas and Jha, 2017) For example, in an OECD's annual report Health a Glance, a 3-fold difference in cesarean section rates across countries was observed. Some of this variation may be justified by clinical need, but it could also mean that women are either having unnecessary operations, or being denied care they should be getting.(Organisation for Economic Co-operation and Development, 2013)

At a national level, comparisons are also common. Benchmarking and profiling activities became commonplace for purposes of transparency and

public accountability in high-income countries.(Administração Central do Sistema de Saúde, 2003, Medicare.gov, 2018) Geographical, social-economic, inter-hospital, inter-physician variations in health care quality are continuously subject of investigation (Maynou et al., 2015, Sinha et al., 2012), with several studies indicating that a substantial part of this variation remains unexplained even after accounting for the patients underlying risk effect.(Bradley et al., 2010, Bradley et al., 2006, Chen et al., 2010, Chung et al., 2015, Herrin et al., 2015, Krumholz et al., 2007, Stukel et al., 2010, Xian et al., 2014) A concern of access inequalities may provide some rationale for the unexplained variation - different care is given to patients with similar conditions, undermining the belief that health systems, in general, and health professionals, in particular, apply uniformly an unequivocally appropriate treatment for each health problem.(Peiró and Maynard, 2015) Moreover, large variations may suggest that some providers may produce suboptimal care and that potential savings could be allocated in resources needed elsewhere.(Appleby et al., 2011) As relevant as studying variations in quality of care may be, identifying sources of variations may require for sophisticated statistical analysis, especially if targeted at outcome measures.(Ash et al., 2012, Harbaugh, 2006, Normand and Shahian, 2007, Teixeira-Pinto and Normand, 2009) These analyses rely on the quality of data and of the choice of risk adjustment models, and consequently on the ability to separate sampling variability and case-mix effects from provider effects on outcomes. Section 3.3 provides additional information on methods used to tackle some of the challenges encountered within this context.

This thesis explores on the ability of international comparisons to extract information with potential impact on healthcare, health policy and health research. We compared the health systems of Portugal and the US. These health systems represent an interesting contrast, with the Portuguese health system relying on a National Health Service (NHS) structure, characterized by universal coverage and access that is tangentially free at the point of use and that is mainly financed through general taxation (Barros et al., 2011); and the US health system, having developed largely through the private sector where health coverage is mostly delivered through private insurance, mainly through an employer. Of note, by 2010, 16% of Americans were still uninsured (Rice et al., 2013). Comparable and comprehensive information on the two health care systems is available as supplementary data section 7.4.

3.2 The CUTEheart project

This thesis was developed under CUTEheart – Comparative use of technologies for heart disease project (http://cuteheart.med.up.pt), a grant aimed at comparing the use of health technologies between the health systems of the US and Portugal focusing on CHD treatment. The project encompassed five specific aims: 1) to compare the diffusion rates of new technologies for treating CHD, and identify patient, hospital, and environmental determinants of use in US and in Portugal; 2) to assess the impact of health technology diffusion in high risk patient cohorts; 3) to compare clinical effectiveness of the use of procedures to treat CHD; 4) to calculate cost-effectiveness of treating CHD in the US and in Portugal; 5) to leverage the international collaboration to develop a framework for designing

and implementing health services research between two health care systems. This thesis contributed mainly to aims 1, 3 and 5.

3.3 Materials and Methods

The main methodological elements of this thesis include information regarding data sources, standardization methods of rates between different populations, and multilevel models for analysis of clustered data. Further detailed information can be found in the papers that compose the results of this thesis under the Results section.

3.3.1 Data sources (considerations about comparability across countries)

The first objective of this thesis (Paper 1) was accomplished through published information or public databases with information at the country level (e.g. Eurostat, CDC, OECD, INE). For the reminder of the aims we mainly used administrative hospital inpatient data available by request/order. Administrative data refers to data collected by health-care providers and insurers with the intention of facilitating hospital financing or reimbursement.(Iezzoni, 1997) Summary information of all data sources considered for the CUTEheart project is available as supplementary material (Table 7.2 in Supplementary data 7.2). In this section we focus on aspects related with administrative data and its comparability across countries.

We obtained access to datasets of inpatient hospital administrative billing data in the US and Portugal. We opted for these sources of data because they represent the only feasible solution for comparison between the US and Portugal with nationwide representativeness capturing the natural hospital heterogeneity at the population level and with compatible information and reconcilable coding schemes variables (Table 7.1 in Supplementary data 7.1). Briefly, considering the reporting period spanned between 2000 and 2010, information available in these datasets consists of similar diagnosis and procedure codes (based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)), including primary and secondary diagnoses, type of admission and discharge status, patient demographic characteristics, length of stay (LOS), severity metrics and comorbidity measures. The majority of these variables have equivalent definitions and coding levels between the two countries with some minor differences. The number of potential diagnosis or procedure codes is 15 in the US and 20 in Portugal, no race/ethnicity information is available for Portugal, ‘urgent’ and ‘emergency’ are different types of admissions in the US but used interchangeably in Portugal, and inpatient hospitalization is defined as an over-night or longer stay in the US while in Portugal is defined as a 24-h or longer stay.

We created AMI cohorts using the principal diagnosis variable having an AMI diagnosis code (ICD-9-CM 410.xx excluding 410.x2). This approach assumes that the two countries have equivalent AMI definitions as well as similar practices of coding. Narrowing down the scope of our analysis to AMI within CHD was motivated to increase the reliability of cross-country comparability. First, given that AMI is an acute condition requiring expensive care treatment, it is less likely to be under-coded and more likely to be identified as a principal diagnosis variable (i.e. the condition “established after study to be chiefly responsible for occasioning the admission of the patient to the hospital for

care”).(Centers for Disease Control and Prevention, 2011) Second, even though variations in AMI definitions between countries may exist, one would expect that these would have been minimized after acknowledgement of the role of, less subjective, troponin biomarkers for diagnosis of AMI as conveyed in the universal definition of AMI proposed by the European Society of Cardiology and the American College of Cardiology collaborative effort that began in 2000.(Antman et al., 2000, Thygesen et al., 2012, Thygesen et al., 2007) Nevertheless, while new universal definitions have likely improved objectivity of AMI diagnosis, several authors have reported an apparent increase in the incidence of AMI as a result of the new definition. Highly sensitive and specific biomarkers facilitate the identification of less-extensive necrosis myocardial infarction that would not been classified as AMI according to prior definitions. Awareness of this distortion (or correction) factor is essential in interpreting results, even though this will likely affect both countries proportionally.

Secondary diagnoses codes were used to identify comorbid conditions and risk factors. Again, this implicitly assumes that documentation of comorbid conditions is correct or that the degree of under/over recording is proportionally equal in every hospital in the two countries.(Bottle et al., 2013) While data audits are regularly implemented in both countries, which should contribute for more leveled comparisons, it is possible that countries are exposed to different levels of coding artifacts motivated by different hospital financing systems.

During 2000-2010 procedural information collected into administrative data was operationalized with use of the ICD-9-CM system both in Portugal and the US. These codes permitted the identification of relevant interventional or surgical cardiac procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery (Table S1 in Supplementary data 7.5). However, identification of drugs through the ICD-9-CM is limited and investigation on practice patterns regarding drug use could not be compared with this type of data. In a preliminary study based on comparisons between administrative data for Portugal and data available at the SPC, we observed significant coding inaccuracies of procedures regarding the implantation of coronary drug-eluting stents (DES) and bare-metal stents (BMS) in Portugal. Therefore, overall PCI (including DES, BMS, and balloon angioplasty) or stenting (including DES or BMS) use was considered for analysis of cross-country comparisons. In the US, because of different payments initially for DES and BMS, coding for the two procedures was acceptable.

Patient identification became fully available since 2011 for Portugal, and prior to that date, patients were only partially available providing patient traceability within a hospital and a year. In the US, our data source was random sample each year and thus patients could not be linked if they had multiple admissions within and between years. Therefore, our unit of observation is the hospitalization. This approach has also been used by Bottle et al. (2013) when comparing administrative hospital data between the US, England, Europe and Canada. However, this may have an impact in the size of denominators defined and revascularization procedures documented for Portugal, given that fewer hospitals have capacity to provide revascularization procedures hence rendering multiple hospitalizations per patient.

Several factors limited our choice of outcome measures for comparisons between Portugal and US. Specifically, because vital statistics data was not linkable to the administrative data in Portugal, 30-day or any other time frame mortality was not possible to ascertain; comprehensive identification of all hospitalizations per patient were not possible due to limitations on the patient identification variable, hence hospital readmissions were not possible to ascertain. Length of stay and the above-mentioned measures are affected by discharge policies and the availability and use of intermediate care between countries.(Bottle et al., 2013) Therefore, interpretation of results should take that into consideration.

3.3.2 Rate standardization for comparisons between groups

Differences observed in outcome rates between groups or within a group over different periods of time may be masked (either exacerbated or attenuated) by differences or changes in the distribution of underlying characteristics in those groups that are related with the outcome. For example, the difference between crude death rates from two different countries may be distorted by the composition of the age structure of the two populations. That is, one of the countries may have a higher crude death rate simply because its population tends to be older and hence a higher proportion of the population is naturally at higher risk of dying. Therefore, comparisons across groups, whether these are different countries or different hospitals, should use methods for controlling for confounding effects so that comparisons are valid.

One of the simplest ways to adjust for confounders is to standardize outcome rates based on a standard population. The standardized rate corresponds to the rate that would occur if the observed distribution of the risk of outcome across confounder variables (e.g. age-specific rates) were present in a population with the distribution equal to that of a standard population.(Anderson and Rosenberg, 1998, Bains, 2009) Standardization may be implemented according to two methods: direct standardization and indirect standardization. The main difference between these methods is that the former uses knowledge about the risk observed in the study population to estimate the expected outcome events in a standard population whereas the latter uses the knowledge about the risk in a standard population to estimate the expected outcome events in the study population. (See formulas in Supplementary data section 7.3).

Direct standardization is preferable to indirect standardization because it uses information on the actual frequencies of outcome events in the study population rather than inferring the risk of the outcome from another population (the standard population). However, standardized rates become unstable when the outcome is rare or when we want to control for many confounder variables, which easily generates small numbers or zero events per stratum. In those cases indirect standardization works better because it makes use of information based on more stable rates from a larger population.(Ash et al., 2012, Bains, 2009, Normand et al., 2016, Normand and Shahian, 2007)

For many disease outcomes, risk factors include demographic characteristics (age and sex), disease-specific risk factors (e.g. clinical indicators of risk), and indicators of health status (e.g., presence of comorbid

conditions).(Steinwachs and Hughes, 2008) While age and sex already account for important epidemiologic confounding effects, whenever possible the inclusion of other potential confounders in risk-adjustment models is of crucial importance so that comparisons between groups are as even as possible. For reasons explained above, this is usually implemented through indirect standardization using regression models fitted on a standard population to compute expected outcome events of groups under study.(Ash et al., 2012, Normand et al., 2016, Normand and Shahian, 2007)

3.3.3 Generalized linear mixed models for clustered data

Hierarchical data refer to a data structure in which lower-level units are nested within higher-level units, such as clustered data or repeated-measures data. This type of data arises when observations are made on different subjects within the same cluster or multiple observations are made per subject. Inherent to the multilevel nature of the data lays the fact that measures within a higher-level unit are not independent from one another. For example, shared medical practice among patients treated within the same hospital tends to yield more homogenous health outcomes within hospitals than between hospitals. Failing to address this intrinsic correlation can lead to spurious estimates.(Ash et al., 2012, Austin and Merlo, 2017, Daniels and Gatsonis, 1999, Gelman and Hill, 2006, Houchens et al., 2007, Normand et al., 2016, West et al., 2007) Moreover, substantive information may be gained by explicitly acknowledging the data hierarchy when analyzing processes that are thought to operate at more than one level. If the research interest is focused on describing the variability and heterogeneity in the population, rather than on the average values, estimating level-specific effects (e.g. hospital effects), and assessing the pathways through which these effects operate, that is effects associated with level-specific covariates (e.g. hospital-level covariates).(European eGovernment Services, 2017, Austin and Merlo, 2017, Austin et al., 2017, Daniels and Gatsonis, 1999, Houchens et al., 2007, Larsen and Merlo, 2005, Merlo et al., 2006, Merlo et al., 2016, Normand et al., 2016)

The scope of this thesis falls within the field of health services research, addressing aspects regarding variations in the provision and outcome of health care. The latter are thought to result from processes dependent both on characteristics of hospitals providing health care (also known as contextual effects) as well as on characteristics of patients receiving the health care in those hospitals (also known as composition effects), hence the data sets have a clustered data structure. In this section we introduce generalized linear mixed models (GLMM) also known as hierarchical generalized linear models (HGLM). These consist of statistical models increasingly used to address research questions focusing on variations by explicitly recognizing the nested structure of data, which are adequate for binary outcomes and that appropriately adjust estimates for within-cluster correlations.(Austin and Merlo, 2017) The GLMM represents an analytic strategy that accounts for correlations induced by clustering via modeling the outcome conditional on random effects (also known as the unobserved cluster effect).(Daniels and Gatsonis, 1999, Houchens et al., 2007, West et al., 2007) In its simplest formulation (random intercept models), the random effect represents random deviations from the relationships described by fixed effects. In contrast to

fixed effects, random effects are represented as random variables in a GLMM.(Houchens et al., 2007, West et al., 2007)

The use of random effects permits explicit modeling of sources of variability added at each level of the hierarchy. Assuming that the data subject of study consist for example of observations regarding patients clustered within hospitals, within-hospital variability refers to the variability of outcomes across patients within hospitals; and between-hospital variability refers to the variability across hospitals. Within-cluster variation is less intuitive for models with binary outcomes, where, by definition, the outcome variable takes only two possible values. In such cases, it is common practice to reason about within-cluster variance with help of a latent variable model. Where the binary outcome results from a dichotomization of the latent variable – the unobservable propensity of the event.(Austin and Merlo, 2017, Merlo et al., 2006, Teixeira-Pinto and Normand, 2009)

For the purpose of model specification within the context of GLMM consider a sample of observations regarding in-hospital mortality of patients clustered within the hospital where patients received treatment. Let Y_{ij} be 1 if the ith patient admitted to the jth hospital died during the hospitalization and 0 if the patient survived. The GLMM of a basic random intercept model can be specified as follows (Austin and Merlo, 2017, Goldstein, 2003):

$$Y_{ij}\big|u_{0j} \sim ind\ Bernoulli(p_{ij})$$
$$E(Y_{ij}) = p_{ij}$$
$$\eta_{ij} = g(p_{ij}) = \log\left(\frac{1-p_{ij}}{p_{ij}}\right) = logit(p_{ij})$$
$$\eta_{ij} = \underbrace{\beta_0 + \beta_1 X_{1ij}^{p} + \beta_2 X_{2ij}^{p} + \cdots + \beta_{k-1} X_{(k-1)ij}^{h} + \beta_k X_{kij}^{h}}_{\text{Fixed effects}} + \underbrace{u_{0j} Z_{ij}}_{\text{Random effects}}$$
$$u_{0j} \sim iid\ N(0, {\sigma_{u0}}^2)$$

where,

- $E(Y_{ij})=p_{ij}$ is the expected value of the Bernoulli variable which corresponds the probability of death of the ith patient admitted to the jth hospital;
- g is the logit transformation of the expected probability, $logit(p_{ij})$, which corresponds to the log odds of death ($Y_{ij}=1$). The log odds has a linear relationship with the covariates;
- X_{kij} is the observation for the ith patient admitted to the jth hospital regarding k^{th} covariate, superscript indicates whether the covariate represents a patient-level covariate (p) or a hospital-level covariate (h);
- β_k is the fixed effect associated with a one-unit change in the corresponding k^{th} covariate on the mean log odds of death (β_0 corresponded to the overall intercept, the mean log odds of death when all covariates are zero);
- $\exp(\beta_k)$ is adjusted death odds ratio due to an one-unit change in the kth covariate, given that all other covariates and random effects remain fixed;
- Z_{ij} is equal to 1 in the random intercept model;

- u_{0j} is the hospital random intercept, which is a normally-distributed random variable with zero mean and standard deviance σ_{u0}. Represents the distribution of hospital-specific intercepts.

In this specification it is implicitly assumed that, conditional on covariates and on the hospital random effect, outcomes among patients treated in the same hospital are independent, and the random intercept is independent of the model covariates (X).(Gelman and Hill, 2006, Normand et al., 2016) Furthermore, several metrics have been proposed (Austin and Merlo, 2017, Krumholz et al., 2011, Krumholz et al., 2006, Larsen and Merlo, 2005, Merlo et al., 2006, Merlo et al., 2016) to extract from this type of models insights regarding the extent to which hospital represents a contextual effect and which patient and hospital characteristics influence hospital heterogeneity. Table 3.2 lists these metrics along with their definition and purpose/interpretation.
Finally, while not explored in this thesis, the basic intercept random model can easily be extended to include a random coefficient (also known as random slope). This model allows the magnitude of patient-level associations (e.g. the association between a patient's age and mortality) to vary across hospitals.(Gelman and Hill, 2006, Goldstein, 2003)

Table 3.2. Common metrics used to assess contextual effects within the context of clustered data.(Austin and Merlo, 2017, Krumholz et al., 2011, Krumholz et al., 2006, Larsen and Merlo, 2005, Merlo et al., 2006, Merlo et al., 2016)

Name of the metric	Formula	Description	Purpose/Interpretation
Intraclass correlation coefficient (ICC)	$\frac{{\sigma_{u0}}^2}{{\sigma_{u0}}^2 + \frac{\pi^2}{3}}$	Describes the extent of correlation among observations within the hospitals.	The larger the ICC the more relevant is the hospital contextual effect.
Proportional change in variance (PCV)	$\frac{{\sigma_{u0}}^2 - {\sigma'_{u0}}^2}{{\sigma_{u0}}^2}$, where ${\sigma_{u0}}^2$ and ${\sigma'_{u0}}^2$ are the estimated variances of nested models	PCV is defined by the proportion of the between-hospital variance that is explained by the additional covariates between two nested models.	The larger the PCV the more influential are covariates in the extended model relative to the nested model.
OR between a hospital ±1 SD relative to the average hospital	$exp\left(2 \times \sqrt{{\sigma_{u0}}^2}\right)$	OR between a patient in hospital one SD above the average hospital relative to a hospital one SD below the average hospital.	The larger the OR the more heterogeneous is the risk of patients across hospitals. In other words, the more relevant is the choice of hospital where the patient is treated.
Median odds ratio (MOR)	$\exp\left(0.6745 \times \sqrt{2 \times {\sigma_{u0}}^2}\right)$	MOR is defined as the median value of the distribution of OR obtained when randomly picking two similar patients from two hospitals, and comparing the one from higher risk hospital to the one from the lower risk hospital. The MOR is comparable with patient-level ORs.	The larger the MOR the more heterogeneous is the risk of patients across hospitals. In other words, the more relevant is the choice of hospital where the patient is treated.
Proportion of opposed odds ratios (POOR)	$\phi\left(-\beta/\sqrt{2 \times {\sigma_{u0}}^2}\right)$, where ϕ represents the cumulative distribution function for the normal distribution; and beta represents the fixed effect associated with a hospital-level covariate	Let pairwise OR be computed from comparing two subjects whose values of the given cluster-level covariate differ by one unit, but who have identical values for the other hospital-level and patient-level covariates. The POOR is then defined by the proportion of pairwise ORs with opposite direction to the cluster-level covariate OR.	POOR may vary between 0% (all ORs have the same sign) and 50% (half of the ORs are of the opposite sign). A POOR of 50% suggests that the association between the cluster-level covariate and outcome is very heterogeneous.
Interval odds ratio (IOR)	$IOR_L = exp\left(\beta + \sqrt{2 \times {\sigma_{u0}}^2} \times \phi(0.1)\right)$ $IOR_L = exp\left(\beta + \sqrt{2 \times {\sigma_{u0}}^2} \times \phi(0.9)\right)$	The IOR is an interval covering the middle 80% of the distribution of odds ratio that result from comparing two subjects whose values of the given cluster-level covariate differ by one unit, but who have identical values for the other hospital-level and patient-level covariates.	The wider the IOR the more heterogeneous is the association between the cluster-level covariate and outcome.

4 Results

4.1 Paper 1

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ORIGINAL ARTICLE

The Atlantic divide in coronary heart disease: Epidemiology and patient care in the US and Portugal

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Abstract
Introduction and Objectives: We aimed to compare access to new health technologies to treat coronary heart disease (CHD) in the health systems of Portugal and the US, characterizing the needs of the populations and the resources available.
Methods: We reviewed data for 2000 and 2010 on epidemiologic profiles of CHD and on health care available to patients. Thirty health technologies (16 medical devices and 14 drugs) introduced during the period 1980-2015 were identified by interventional cardiologists. Approval and marketing dates were compared between countries.
Results: Relative to the US, Portugal has lower risk profiles and less than half the hospitalizations per capita, but fewer centers per capita provide catheterization and cardiothoracic surgery services. More than 70% of drugs were available sooner in the US, whereas 12 out of 16 medical

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devices were approved earlier in Portugal. Nevertheless, at least five of these devices were adopted first or diffused faster in the US. Mortality due to CHD and myocardial infarction (MI) was lower in Portugal (CHD: 72.8 vs. 168 and MI: 48.7 vs. 54.1 in Portugal and the US, respectively; age- and gender-adjusted deaths per 100 000 population, 2010); but only CHD deaths exhibited a statistically significant difference between the countries.
Conclusions: Differences in regulatory mechanisms and price regulations have a significant impact on the types of health technologies available in the two countries. However, other factors may influence their adoption and diffusion, and this appears to have a greater impact on mortality, due to acute conditions.
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PALAVRAS-CHAVE
Tecnologias em saúde;
Acesso;
Difusão;
Comparação internacional;
Doença coronária;
Cardiologia de intervenção;
Sistemas de saúde

A divisão atlântica na doença coronária: epidemiologia e cuidados de saúde nos Estados Unidos e Portugal

Resumo
Introdução e objetivos: O objetivo deste estudo é comparar o acesso a novas tecnologias em saúde no tratamento da doença coronária (CHD), entre os sistemas de saúde de Portugal e dos Estados Unidos (US), caracterizando as necessidades das populações e disponibilidade de recursos.
Métodos: Foram comparados dados (2000 e 2010) de Portugal e US para descrever perfis epidemiológicos e recursos disponíveis na prestação cuidados de saúde na CHD. Trinta tecnologias de saúde (16 dispositivos médicos e 14 medicamentos), introduzidas durante 1980-2015, foram identificadas por cardiologistas de intervenção e calcularam-se as diferenças entre as datas de autorização de introdução no mercado/comercialização nos dois países.
Resultados: Relativamente aos US, Portugal apresenta perfis de risco mais baixos, menos hospitalizações *per capita*, menor número de centros *per capita* com valência para cateterismo coronário e cirurgia cardiotorácica. Mais de 70% dos medicamentos foram comercializados mais cedo nos US, enquanto 12 dos 16 dispositivos médicos obtiveram autorização para comercialização mais cedo em Portugal. Contudo, pelo menos cinco destes dispositivos foram adotados primeiro ou sofreram uma difusão mais rápida nos US. A mortalidade por CHD e enfarte agudo do miocárdio (EAM) foi inferior em Portugal (CHD: 72,8 [Portugal] *versus* 168 [US]; AMI: 48,7 [Portugal] *versus* 54,1 [US]; mortes por 100 000 habitantes, padronizada por idade e sexo, 2010), tendo-se apenas verificado uma diferença significativa entre os países na mortalidade por CHD.
Conclusões: Diferenças nos mecanismos de regulação e controlo de preços têm um impacto significativo no tipo de tecnologias disponíveis nos dois países. Contudo, outros fatores influenciam a sua adoção e difusão, tendo um maior impacto na mortalidade em condições mais agudas.
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Introduction

The use of health technologies has grown dramatically in recent decades in developed countries, and now accounts for a considerable share of national health expenditure.[1–7] Sustainability of access to health technologies has become a major priority in Portugal and worldwide, one that is grounded on ethical principles aiming at maximizing health gains given limited available resources.[8] A national system for health technology assessment (SiNATS) is currently being implemented in Portugal. It is expected to extend the existing health technology assessment system to medical devices and to include new ways to support decision-making based on risk-sharing tools and real-world data monitoring.[9] This context makes it an opportune time to assess contemporary access to medical devices and drugs in Portugal.

Different healthcare systems adopt new health technologies at different speeds and usage rates, leading to disparities in quality of care between patients in different countries.[10–12] This results from a combination of various factors related to different barriers and needs, including the efficiency of the regulatory process, limitations of the reimbursement system, economic capacity, availability of resources, and the epidemiology of the target

AHA	American Heart Association
CE	Conformité Européenne
CHD	coronary heart disease
CVD	cardiovascular disease
DES	drug-eluting stent
EU	European Union
FDA	Food and Drug Administration
ICB	intracoronary brachytherapy
INFARMED	Portuguese National Authority for Medicines and Health Products
ISR	in-stent restenosis
LVS	left ventricular support
MI	myocardial infarction
NHANES	National Health and Nutrition Examination Survey
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
TAVR	transcatheter aortic valve replacement

populations.[11–14] Understanding these factors and how they relate to access to and initial use of health technologies is of crucial importance to improve quality of care, particularly when new health technologies have been proven to be cost-effective compared to previously available alternatives. International comparisons can provide insight into these issues by analyzing alternative settings, needs, and outcomes, and providing useful information on factors that are likely to affect access to health technologies. This exchange of experiences is crucial to generating enhanced information that can support decision-making for improved quality of care.

Treatment of coronary heart disease (CHD) has benefited significantly from technological innovations, both medical devices and drugs, which have improved clinical outcomes and quality of care.[2,15–19] However, CHD remains one of the leading causes of death in most countries, with significant economic costs.[2,20–23] With this in mind, our aim was to provide a contemporary historical overview of the situation in Portugal regarding access to innovations in health technology that are adjuvant or alternative CHD therapies against the backdrop of the risk profile of the population, available resources and mortality rates, using information from the US as a benchmark. The intention is to bridge the gap from previous international comparison studies assessing health technology access that typically focus on market-related aspects, few of which characterize populations' needs and the resources available that may also impact access to and diffusion of new health technologies.[11–13,24,25] We chose the US because of its contrasting healthcare system, which is driven by the private sector and is characterized by strikingly high per capita health expenditures, and because its regulatory agency, the Food and Drug Administration (FDA), is a world reference for drug and medical device assessment. Moreover, as reported by Danzon et al.,[13] the US launched more drugs with shorter launch delays from approval compared to Portugal and other major markets during the 1990s. On the other hand, the efficiency of the European Union (EU)'s system for marketing approval of medical devices is often considered a key feature of the better access to medical devices in EU countries compared to the US.[26–28] This makes the US an interesting contrast to Portugal that may improve our understanding of factors impacting access to and adoption of health technologies in the two health systems.

Methods

We conducted a comprehensive literature review using publications from national governmental agencies, international organizations, professional associations, and scientific journals. Information was abstracted on prevalence of risk factors and diseases, hospitalization and mortality rates, infrastructure and human resources associated with CHD observed between 2000 and 2010, in Portugal and in the US. Approval dates of selected medical devices and drugs were abstracted for chronological characterization of access to healthcare technology using databases available at the FDA and the Portuguese National Authority for Medicines and Health Products (INFARMED) (personal contact with INFARMED).[29–32]

Epidemiologic profiles of coronary heart disease

Self-reported prevalence rates of risk factors for CHD in Portugal, including overweight and obesity, hypercholesterolemia, hypertension, diabetes and current smoking, were abstracted from the AMALIA study on the prevalence and distribution of cardiovascular risk factors in Portugal.[33] The continuous datasets of the National Health and Nutrition Examination Survey (NHANES) were used to calculate comparable rates for the US, applying the same age inclusion criteria, time period and definitions of risk factors as in AMALIA whenever possible.[33,34] Rates for the US were calculated for adults aged 40 years or older surveyed in the 2005-2006 and 2007-2008 NHANES cycles. Calculations of rates were based on data of self-perceived hypertension, hypercholesterolemia, and diabetes, defined as the participant's awareness of or current medication use for that condition, and smoking status was defined as one of the following: current smoker, ex-smoker or non-smoker. However, overweight/obesity prevalence rates for the US were based on actual measurements of weight and height, whereas AMALIA used self-reported measures. Age-adjusted prevalence rates were computed for comparison between the countries, standardized to the 2010 US population (Table A1 in Appendix A. Supplementary Material). US rates were computed using SAS 9.4 with code available on the NHANES tutorial website.[35]

CHD prevalence rates are not available for Portugal. Instead estimates of myocardial infarction (MI) prevalence were retrieved from the 2005-06 National Health Survey cycle and standardized to the 2010 US population controlling for gender and age.[36] Both CHD and MI estimates for the US were abstracted from statistical reports available from the American Heart Association (AHA) for 2010.[2] Crude per capita hospitalizations rates were produced based on the numbers reported by the AHA for the US, and by the Directorate-General of Health for Portugal divided by estimates of the total population.[37–39]

Crude rates of all-cause mortality and mortality from cardiovascular disease (CVD), CHD and MI were calculated from vital statistics data and estimates of the total populations.[37,38,40,41] Age- and gender-adjusted mortality rates were obtained by direct standardization to the 2010 US population (Table A1 in Appendix A. Supplementary Material). Rate ratios were computed for analysis of within- and between-country variations in death rates.

Medical devices and drugs

A list of procedures and medical device categories and another of active substances and therapeutic uses were drawn up by interventional cardiologists who gave their subjective assessment as to which were technological breakthroughs in the field of interventional cardiology between January 1980 and February 2015. Several cardiovascular devices reviewed were outside the scope of CHD treatment, but were included for a better understanding of the dynamics of the two healthcare systems. After this list was drawn up, the first device model approved for each procedure and device category in each of the two countries was then determined. Similarly, the first drug brand approved for marketing for each active substance and therapeutic use was identified.

In the US, approval dates of most medical devices and drugs are available from FDA databases.[30–32] The only approval date that had to be retrieved from a medical journal was of the first percutaneous transluminal coronary angioplasty (PTCA) balloon. In Portugal, approval and marketing dates of drugs are well documented but medical device data are not. We therefore relied on a combination of different sources of information to obtain dates that devices obtained the CE (Conformité Européenne) mark. The CE mark is the certification attributed to certain products, including medical devices, when approved for marketing in the EU. These sources included medical device industry representatives, online press releases and news agencies, medical device industry associations in the EU and Portugal (Eucomed and the Portuguese Association of Medical Device Companies [APORMED]), and scientific journals. However, approval dates of some devices were not available for Portugal and the dates of first use were considered as a time reference of their approval. These dates refer to the first use in the interventional cardiology ward of Santa Cruz Hospital, which is a reference hospital and pioneer in many interventional cardiology procedures in Portugal.[42] Both approval and marketing dates of drugs were abstracted from INFARMED, but only marketing dates were used for comparison with the US in the results.

First device models and drug brands were determined according to the earliest approval date among their device or active substance class in each country. For comparison between countries, the lag in access to healthcare technology between the US and Portugal was defined as the difference between approval/first use/marketing dates, calculated as the US date minus the date for Portugal. February 13, 2015, the most recent date for which data are available, was used to compute the difference if the technology was still unavailable in one of the countries. In the event of missing information on the specific day or month of dates, the last day of the month or the month of June, respectively, were used to calculate the difference.

Table 1 Self-reported prevalence rates (%) of risk factors in the US and Portugal in adults aged ≥40 years.

Risk factor	US		Portugal	
	Crude	Age-adjusted	Crude	Age-adjusted
Overweight/obesity				
Both sexes	71.6	71.6	51.6	51.3
Males	77.8		-	
Females	66.1		-	
Hypertension				
Both sexes	32.8	33.7	23.5	22.8
Males	30.3		21.8	
Females	35.1		24.9	
Hypercholesterolemia				
Both sexes	48.1	48.1	19.7	19.4
Males	50.0		18.6	
Females	46.4		20.7	
Diabetes				
Both sexes	12.3	12.6	8.9	8.5
Males	12.1		8.5	
Females	12.4		9.3	
Smoking				
Both sexes	20.3	19.8	16.3	17.1
Males	22.6		25.3	
Females	18.3		8.8	

Human and infrastructure resources

In order to characterize the available human and infrastructure resources, information was collected on the number of cardiothoracic surgeons, cardiologists, hospitals with cardiac catheterization laboratories and hospitals with cardiac surgery facilities in 2000 and in 2010 for the US and Portugal (personal contact with the hospitals).[43–45] Per capita rates were then computed based on estimates of the total populations of the two countries.[37,38]

Results

In 2010, the Portuguese population was 10.6 million, 19% of whom were aged 65 years or more, and healthcare coverage was universal; the 2010 US population was 309.3 million, 13% of whom were aged 65 years or older, and 16.3% had no health insurance (Table A2 in Appendix A. Supplementary Material). Table 1 presents crude and age-adjusted prevalence rates of CHD risk factors, indicating lower numbers for Portugal compared to the US.

In 2010, 64 out of 1000 US adults had CHD, of whom approximately half had suffered an MI. We were unable to obtain CHD prevalence rates for Portugal, but MI was less frequent in Portugal than in the US in 2010 (US: 2900 vs. Portugal: 1687, age- and gender-adjusted rates per 100 000 population) (Table 2). Furthermore, the number of hospitalizations per capita in the US was almost three times

Table 2 Coronary heart disease prevalence rates (per 100 000 population) in the US and Portugal, 2010.

	US		Portugal	
	n	Rate	n	Rate
Prevalence (≥20 years)				
CHD	15 400 000	6400	-	-
Males	8 800 000	7900	-	-
Females	6 600 000	5100	-	-
MI	7 600 000	2900	134 481[a]	1771[a]
Males	5 000 000	4200	93 286[a]	2596[a]
Females	2 600 000	1700	41 195[a]	1030[a]
Hospitalizations (all ages)				
CHD	1 346 000	435.2	18 075	1710
Males	828 000	544.1	-	-
Females	518 000	329.7	-	-
MI	-	-	9268	87.7
STEMI	-	-	4308	40.7
NSTEMI	-	-	5320	50.3

CHD: coronary heart disease; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

[a] Self-reported prevalence of myocardial infarction in adults (≥25 years) abstracted from the National Health Survey, 2005/2006 cycle.[36]

higher than in Portugal (US: 435.2 vs. Portugal: 171.0, crude rates per 100 000 population) (Table 2), which is consistent with the populations risk profiles in Table 1. However, it should be noted that the figures for Portugal refer to hospitalizations in coronary care units, whereas US hospitalizations refer to any hospitalization for CHD at an acute care hospital.

Age- and gender-adjusted death rate ratios between 2000 and 2010 show a significant decrease in mortality due to CVD and CHD in both countries, but only Portugal exhibited a statistically significant decrease in MI mortality in this decade. Relative to the US, CHD mortality rates were significantly lower in Portugal in 2010, but there was no statistically significant difference in CVD or MI mortality rate ratios between the two countries (Table 3).

Access to health technologies and patient care

Figures 1 and 2 depict the lag in access to selected devices and drugs between the US and Portugal. Brand names and their approval/first use/marketing dates have been omitted from this article but are available as supplementary material (Tables A4 and A5 of Appendix A. Supplementary Material).

Access to medical devices in the US is slower than in Portugal, with only four of the 16 devices reviewed being available first in the US. Moreover, on average, it took 22 months longer to approve the first device model in the US than in Portugal (median time difference 27 months). The drug-eluting balloon for percutaneous coronary intervention (PCI) was the most recent device approved in Portugal, in 2009, and this is still unavailable in the US.

New drugs are more readily available in the US than in Portugal. Only four out of the 14 drugs included in this

Table 3 Coronary heart disease mortality rates (per 100 000 population) in the US and Portugal, 2010, age ≥20 years.

	US					Portugal					Ratio between countries (US/PT), 2010	
	n	Rate		Change (2000/2010)		n	Rate		Change (2000/2010)		Rate ratio	95% CI
		Crude	Age- and gender-adjusted	Rate ratio	95% CI		Crude	Age- and gender-adjusted	Rate ratio	95% CI		
CHD	379 486	168.3	168.3	1.6	1.08-1.65	7501	89.2	72.8	1.5	1.47-1.56	2.3	1.29-3.33
Males	207 533	190.1				3969	100.5					
Females	171 953	147.9				3532	79.1					
MI[a]	122 038	54.1	54.1	1.9	0.93-1.93	4974	59.1	48.7	1.6	1.55-1.67	1.1	0.08-2.14
Males	67 417	61.7				2739	69.4					
Females	54 621	47.0				2235	50.1					
CVD	782 945	347.2	347.2	1.4	1.07-1.45	33 756	401.4	322.6	1.6	1.55-1.60	1.1	0.07-2.09
Males	384 700	352.3				14 951	378.8					
Females	398 245	342.5				18 805	421.4					

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; MI: myocardial infarction; PT: Portugal.

[a] Includes subsequent MI. Rates standardized to the 2010 US population (Table A1 in Appendix A. Supplementary Material).

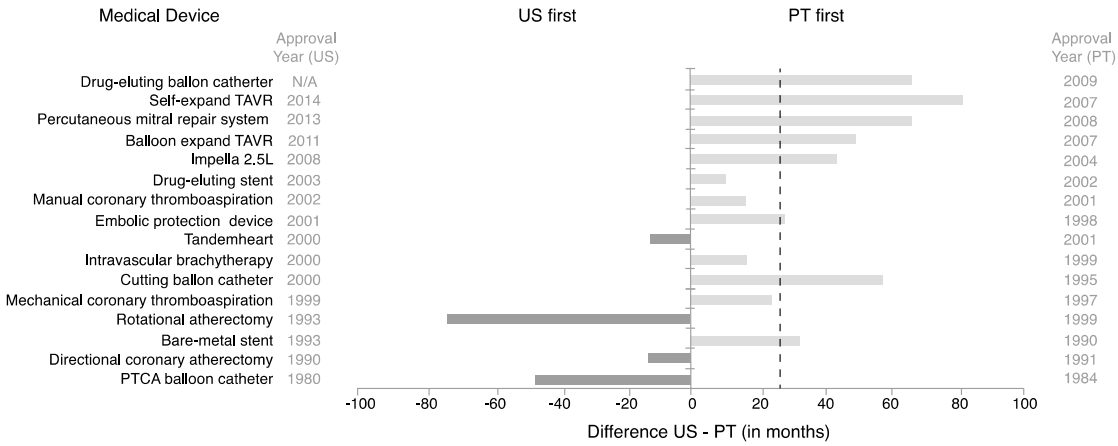

Figure 1 Lag in access to selected interventional cardiology devices between the US and Portugal. Dashed line represents median time lag (US-Portugal). N/A: not available; PT: Portugal; PTCA: percutaneous transluminal coronary angioplasty; TAVR: transcatheter aortic valve repair. The lag in access to devices was determined based on approval dates for the US available from the Food and Drug Administration (in one case from a medical journal), and, for Portugal, dates of CE marking retrieved from personal communication with medical device industry representatives, online press releases, EUCOMED, and scientific journals, and first use dates in Santa Cruz Hospital (raw data available in Table A4 in Appendix A. Supplementary Material).

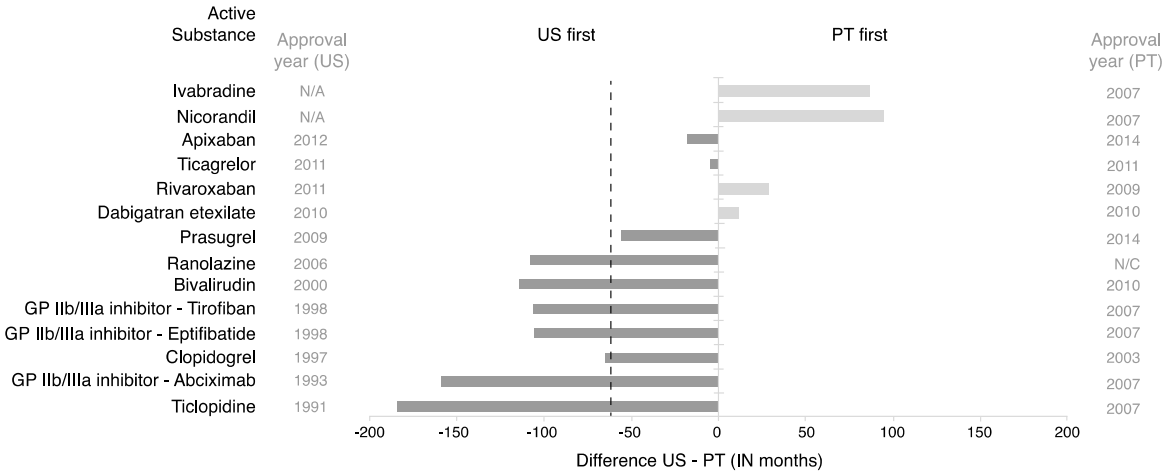

Figure 2 Lag in access to selected interventional cardiology drugs between the US and Portugal. Dashed line represents median time lag (US-Portugal). GP: glycoprotein; N/A: not available; N/C: not marketed; PT: Portugal. Lag in access to active substances was determined based on approval dates available for the US from the Food and Drug Administration and marketing dates for Portugal from INFARMED (raw data available in Table A5 in Appendix A. Supplementary Material).

study were available first in Portugal. On average, drugs were available 51 months sooner in the US (median time difference 61 months). However, up to February 13, 2015, nicorandil and ivabradine had not been approved in the US but have been marketed in Portugal since 2007, and ranolazine had not been marketed in Portugal, despite approval in Portugal in 2008 and in 2006 in the US.

Table 4 provides information regarding diagnostic and treatment facilities as well as medical specialties available in each country. Relative to Portugal, in 2010 the US had nearly double the number of hospitals per capita with cardiac catheterization facilities and four times the number of hospitals per capita with cardiothoracic surgery services. However, while the number of cardiothoracic surgeons per capita was higher in the US, there were more cardiologists per capita in Portugal.

Discussion

There are dramatic differences between Portugal and the US regarding the availability of healthcare technologies and resources for the treatment of coronary heart disease, as well as different epidemiologic risk profiles.

Medical devices

Of the medical devices studied, the majority were approved earlier in the EU/Portugal than in the US, showing that the EU approval system is more time efficient than that of the US (the FDA), as reported by other researchers.[10,26,28] This study adds to the current evidence that this time

Table 4 Availability of specialized health facilities and personnel for treatment of coronary heart disease in the US and Portugal, 2000 and 2010.

Variable (no. per 100 000 population)	US		Portugal	
	2000	2010	2000	2010
Hospitals/centers				
Cardiac catheterization laboratory	-	0.5	0.2	0.3
Cardiothoracic surgery facilities	-	0.4	0.1	0.1
Medical specialties				
Cardiologists	7.2	7.2	6.8	7.8
Cardiothoracic surgeons	1.7	1.4	0.9	1.1

The number of centers providing cardiothoracic surgery in the US in 2000 was not available at the Area Health Resource Files (AHRF).[43] The number of centers providing cardiac catheterization in 2000 was omitted given that the AHRF used different measures over the years, but numbers for 2010 were consistent with those reported by the American Hospital Association Annual Survey Database for the fiscal year 2010.

advantage remains when considering the first model of a new technological family.

Earlier approval does not always translate into earlier use of devices. The first medical device approved for intracoronary brachytherapy (ICB) received the CE mark in 1999 but only diffused into Portugal in January 2001. This was motivated by the FDA's approval of the Novoste Beta-Cath system (Novoste Corp.) in that year, establishing ICB as an adjuvant therapy of PCI for in-stent restenosis (ISR).[46] Nevertheless, it ceased to be used within six months of its adoption. In the US, ICB saw moderate and decreasing use due to a combination of factors, including the approval of drug-eluting stents (DES) two years later, which significantly reduced the occurrence of ISR, the logistic complexity associated with ICB, and the increasing evidence favoring DES over ICB to treat ISR.[19,47–49] Dangas et al. reported that most hospitals no longer possess the necessary facilities to provide ICB in the US.[50]

DES were rapidly adopted in both countries after their approval. Routine implantation of DES began immediately after approval, in 2002 in Portugal and in 2003 in the US.[51,52] By 2003, Portugal had the highest rate of DES implantation in Europe, in 55% of PCI procedures, and by the third quarter of 2005 the use of DES per PCI peaked at nearly 90% in the US.[51,53] However, it should be noted that Portugal has the lowest primary PCI rates per capita in Western Europe and, until 2007, thrombolysis was more commonly used than angioplasty in the treatment of ST-elevation myocardial infarction.[54,55] The number of PCIs per in-patient case in Portugal is less than half of that in the US.[5] This is also consistent with the established capacity to treat patients assessed by the number of specialized physicians and existing infrastructure in each country (Table 4). Considerable differences were observed between the two countries regarding the per capita number of cardiothoracic surgeons and specialized facilities. Only the number of cardiologists per capita was comparable. Moreover, the balance between the number of cardiac catheterization laboratories, cardiac surgery centers, interventional cardiologists and cardiothoracic surgeons, and the potential number of patients to treat is an important but complex topic of discussion with impact on access and quality of care.[51,56,57] Although outside the scope of this paper, this is an important issue, given the public vs. private nature of the two healthcare systems, their economic capacity, and observed differences in CHD incidence (Tables 2 and A2).

To our knowledge there are few publications reporting on the real-world implantation of left ventricular support (LVS) devices, specifically the Impella 2.5 (Abiomed Inc.) and TandemHeart (CardiacAssist Inc.). Results from the Europella, EUROSHOCK and USpella registries indicate that the US was faster in adopting the Impella, perhaps in response to early European experience with these devices. Three years after the approval of the Impella (data collected between July 2004 and December 2007), 144 elective high-risk PCI patients with prophylactic LVS using the Impella were registered in the Europella registry over 10 European centers, including one from Portugal.[58] Hence, on average, five patients per center per year were implanted with this device. Maini et al. reported the first results in the USpella registry of 276 high-risk PCI patients across 34 US centers.[59] The authors do not clearly specify the reporting period of the data but given the initial collection date (March 2010) and the submission date of the article (June 2011), it can be assumed that these numbers represent a one-year span. Thus, on average, eight patients per center per year were implanted with the Impella 2.5. It is worth noting that the intra-aortic balloon remains the most frequently used device for LVS.[60–62]

Transcatheter aortic valve replacement (TAVR) devices also saw early adoption and rapid increase in use following market approval in both countries.[63,64] According to the TAVR registry in Portugal, TAVR use plateaued in 2010 with more than 20 implants per center (6.1 implants per million population).[64] In the US, Brennan et al. observed a significant increase in the volume of TAVR use based on TAVR records collected between 2008 and 2013.[63] In 2012, one year after the first TAVR device was approved by the FDA, approximately 20 TAVR procedures per center were performed (15.8 implants per million population).

There was a five-year gap between approval of the MitraClip device (Abbott Vascular) in Portugal and the US. However, according to numbers presented at a scientific conference in April 2014, the first case treated using the MitraClip in Portugal was in late 2012, four years after its market approval.[65] Since then, a total of nine cases have been treated with this device.[65] In the US, adoption appears to have been much faster, given that more than five hundred cases had been treated in the US by the end of August 2014, around a year after its approval, according to figures from the TVT registry presented by Sorajja et al. at the American College of Cardiology 2015 Scientific Sessions.[66] Furthermore, by August 2014, there were 76 centers in the US providing MitraClip therapy (around 0.25 centers per million

population) as opposed to two in Portugal (0.19 centers per million population).[67,68]

Drugs

In contrast to devices, information on approval dates of drugs in Portugal is readily available. In addition to approval dates, INFARMED provides information on effective marketing dates of drugs. On average, marketing of drugs in Portugal was delayed by 81 months from approval (median 65 months lag). Although almost 60% of the selected drugs were approved earlier in Portugal, 61% were marketed earlier in the US (Figure 2 and Table A5 in Appendix A. Supplementary Material). In particular, outpatient prescription of clopidogrel in Portugal started in 2003, the same year this drug became eligible for reimbursement and the same year that effective marketing is reported by INFARMED.[12] By contrast, in the US, sales of clopidogrel, marketed as Plavix, have increased since its approval in 1997.[69] Longer launch times in Portugal may be driven by both implementation of maximum prices and reimbursement regulations that aim to control the governmental budget, but also depend on the launch strategies of pharmaceutical companies, which ultimately decide when to launch new drugs onto the market. Given the pricing rules of each country, there will be a specific order to be followed by each proposed drug, so as to optimize pricing. External (cross-country) price referencing means that low prices tend to spill over across countries, often delaying launches of new drugs by companies in countries with low expected prices and small volume sales such as Portugal.[13]

Implications of results on mortality

Our results show that CHD deaths were significantly lower in Portugal compared to the US, but no statistical difference was observed for MI deaths between countries. These observations, combined with the fact that MI is the most acute manifestation of CHD, for which the use of health technologies by trained professionals and adequately equipped health facilities may prolong both duration and quality of life, suggest that differences between Portugal and the US in available resources and access to health technologies (faster access to drugs, earlier adoption and/or faster diffusion of devices, and more specialized health facilities and professionals in the US compared to Portugal) may play an important role in quality of care, mitigating differences in epidemiologic risk profiles. Nevertheless, only Portugal exhibited a statistically significant decrease in MI mortality in the decade under study, suggesting that healthcare for these patients has significantly improved in Portugal. Therefore, it is possible that the trends of approval lags observed in Figures 1 and 2, increasingly favorable to Portugal in more recent years, may have contributed to this improvement.

Limitations

Our study has some limitations. First, rates based on self-perceived measurements likely underestimate the prevalence of risk factors. However, additional evidence confirms that most risk factors are less prevalent in Portugal than the US. Only hypertension appears to be more prevalent in Portugal (further details available as supplementary material). Furthermore, risk profiles were determined considering the overall populations of the two countries. The actual profiles of the CHD populations were not studied, which could explain the differences in usage patterns and mortality rates. Second, routine in-hospital use of clopidogrel, ticlopidine, and abciximab in Portugal began prior to the marketing date provided by INFARMED.[53,70–72] Particularly in the case of the drugs indicated for exclusive hospital use (e.g. glycoprotein IIb/IIIa inhibitors), these reports substantially contradict INFARMED's marketing dates. Therefore, information on marketing should be regarded with caution with regard to drugs that are to be used in-hospital only. Third, the brief discussion on adoption and diffusion of healthcare technology is based on key scientific papers for a few technologies. A deeper understanding of the adoption mechanisms is thus required. Furthermore, death certificates may inaccurately state the cause of death and fail to describe the effectiveness of technologies. There is thus a need for better knowledge of the diffusion patterns and effectiveness of health technologies, ideally through the development and analysis of equivalent datasets from the two healthcare systems.

Conclusions

Our results show that differences in regulatory mechanisms and price regulations have a significant impact on market access strategies and on the types of treatment available for CHD, benefiting the US in the case of drug availability while favoring Portugal in the case of medical devices. Differences in risk profiles and available resources may partially explain the differences in adoption of devices after approval on the two sides of the Atlantic, as at least five devices considered were adopted first or diffused faster in the US despite the initial advantage of earlier approval in Portugal. Other factors may also play an important role. On the other hand, the ability of the US to adopt and diffuse health technologies faster and over more centers may have contributed to better quality of acute care compared to Portugal, mitigating differences between the two countries in epidemiologic risk profiles.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflicts of interest

The work was conducted under a grant from the Harvard Medical School – Portugal Program. ATP was partially supported by an NHMRC Program Grant. SLN is under contract with the Massachusetts Department of Public Health to monitor the quality of cardiovascular procedures and surgeries in all non-federal acute care Massachusetts hospitals, and provides statistical consultation to the Yale New Haven Hospital for their contract with the US Centers for Medicare and Medicaid Services to develop and apply hospital-specific public reports involving cardiovascular disease as well as care provided in accountable care organizations, for which she receives fees.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2016.09.021.

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4.2 Paper 2

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Article

A comparison of in-hospital acute myocardial infarction management between Portugal and the United States: 2000–2010

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Abstract

Objective: To compare healthcare in acute myocardial infarction (AMI) treatment between contrasting health systems using comparable representative data from Europe and USA.
Design: Repeated cross-sectional retrospective cohort study.
Setting: Acute care hospitals in Portugal and USA during 2000–2010.
Participants: Adults discharged with AMI.
Interventions: Coronary revascularizations procedures (percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery).
Main Outcome Measures: In-hospital mortality and length of stay.
Results: We identified 1 566 601 AMI hospitalizations. Relative to the USA, more hospitalizations in Portugal presented with elevated ST-segment, and fewer had documented comorbidities. Age-sex-adjusted AMI hospitalization rates decreased in USA but increased in Portugal. Crude procedure rates were generally lower in Portugal (PCI: 44% vs. 47%; CABG: 2% vs. 9%, 2010) but only CABG rates differed significantly after standardization. PCI use increased annually in both

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countries but CABG decreased only in the USA (USA: 0.95 [0.94, 0.95], Portugal: 1.04 [1.02, 1.07], odds ratios). Both countries observed annual decreases in risk-adjusted mortality (USA: 0.97 [0.965, 0.969]; Portugal: 0.99 [0.979, 0.991], hazard ratios). While between-hospital variability in procedure use was larger in USA, the risk of dying in a high relative to a low mortality hospital (hospitals in percentiles 95 and 5) was 2.65 in Portugal when in USA was only 1.03.

Conclusions: Although in-hospital mortality due to an AMI improved in both countries, patient management in USA seems more effective and alarming disparities in quality of care across hospitals are more likely to exist in Portugal.

Key words: acute myocardial infarction, patient management, international comparison

Introduction

Different health systems have varying abilities to adopt new health technologies with potential impact on their healthcare performance. Particularly when these have been proven to be cost-effective compared to other therapeutic alternatives. Reasons for the differences are likely related to variations in regulatory processes that approve new technologies, in healthcare practice patterns, and in the organization and economic capacity of health systems to provide new treatments [1–5]. As such, differences may be even more apparent between the USA and countries in Europe, which significantly contrast in their gross domestic products, regulatory framework of new medical device approval, capacity to adopt and diffuse new health technology, and population epidemiological profiles [6–8]. Moreover, although controversial, the WHO ranked the health system of the US behind many of its counterparts in Europe, reflecting its incapacity to transform higher per capita expenditure in healthcare in proportional higher accessible quality of care when compared to most European countries [9].

Acute myocardial infarction (AMI) is a common, fatal and costly disease. Despite significant declines in mortality during the last decade notably as a result from the advent of new health technologies it remains a considerable societal burden [10–13]. Therefore, regular monitoring is of crucial importance. Several observational studies compared AMI management between the USA and European countries [1, 2, 4, 7, 11, 14, 15], however, little is known about how different countries compare regarding within-country disparities in healthcare quality in AMI treatment across hospitals. According to previous findings AMI patients in the USA are more frequently subject to invasive coronary procedures, face fewer in-hospital deaths, shorter hospital stays and more readmissions when compared to European countries. However, two studies observed no significant differences between USA versus Sweden in survival after an AMI in adults [1, 3], and vital statistics data indicate that AMI mortality *per capita* in the USA is comparable to European average.

In this study, we sought to characterize AMI incidence, hospital management, and outcomes in the two sides of the Atlantic using comparable inpatient hospitalizations data covering the period between 2000 and 2010 from Portugal and the USA exploring for potential differences in inter-hospital disparities within countries. We chose this period because it encompassed important advances in AMI treatment [2]. We chose Portugal because performance of its health system has been ranked ahead of the health system of the USA (12th vs. 37th); [9] Portugal saw one of the most enthusiastic adoption rates of the drug-eluting stent (DES) per percutaneous coronary intervention (PCI) in Europe [16] followed by an increase in PCI use that eventually became the preferred therapy in elevated ST-segment AMI management when compared to thrombolysis; and AMI death rates in Portugal are comparable to the average rate of European countries [10, 17, 18] thus making it a interesting candidate for transatlantic comparisons of AMI management and outcomes.

Material and Methods

Data sources

Portugal data

We used billing information for all public sector hospitalizations in Portugal occurring between 1 January 2000 and 31 December 2010. These data were obtained from the *Administração Central do Sistema de Saúde, IP* (ACSS) in Portugal and represent ~85% of all Portuguese hospital inpatient discharges [19].

US data

The Nationwide Inpatient Sample (NIS) with hospitalizations occurring over the same period in the USA was obtained from the Health Care Utilization Project (HCUP), made available by the Agency for Healthcare Research and Quality (detailed information is available at https://www.hcup-us.ahrq.gov/nisoverview.jsp). This is the largest publicly available all-payer inpatient healthcare database in the USA, containing a nationwide representative 20% stratified random sample of discharges from short-term non-federal American hospitals.

Comparability of data sets

Billing data from the two countries consist of similar diagnosis and procedure codes (based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)), including primary and secondary diagnoses, type of admission and discharge status, patient demographic characteristics, length of stay (LOS), severity metrics and comorbidity measures. The majority of the variables included in the data have equivalent definitions and coding levels between the two countries with some minor differences. The number of potential diagnosis or procedure codes is 15 in the USA and 20 in Portugal, no race/ethnicity information is available for Portugal, 'urgent' and 'emergency' are different types of admission in the USA but used interchangeably in Portugal, and inpatient hospitalization is defined as an over-night or longer stay in the USA while in Portugal is defined as a 24-h or longer stay.

Patient population

We identified adults aged 20 years or older at admission, discharged alive or dead with a primary diagnosis of a new AMI. Discharges for ST-segment elevation myocardial infarction (STEMI) and non-STEMI were further identified based on the primary diagnosis (ICD-9-CM codes available in Supplementary data Table S1) [20]. We excluded hospitalizations of patients discharged alive in the same day of admission or who left against medical advice because they are unlikely to have had an AMI [21, 22]. Admissions associated with zero charges (USA) or invalid discharges identified by duplicate data in all variables of the database (Portugal) were also excluded. Moreover, patients discharged to hospice were also excluded using a Discharge Disposition variable available in both data sources given that this disposition status may miss to classify episodes with adverse outcome [22]. Finally, hospitalizations with missing values in variables for gender, patient disposition status at discharge and LOS were further excluded given that they are used as predictor or outcome variables.

Patient characteristics

To characterize the cohorts, we identified demographic, risk factors and comorbidities utilizing US' Centers for Medicare and Medicaid Services (CMS) AMI hospital mortality assessments codes, selecting 27 risk factor and comorbid conditions variables proposed by Krumholz *et al.* [21]. to profile hospitals based on 30-day mortality rates in patients with AMI (see Supplementary data Table S5) [21]. The variables utilized by the CMS have shown superior predictive capacity of outcomes when compared with several severity scores [23]. Moreover, while these are based on cohorts aged 65 or older at the time of their AMI, they have been also utilized in younger populations [24]. All discharges were included, regardless of admission path. In particular, patients transferred in or out of hospital were included in all analyses as separate hospitalizations given that patient id was not traceable.

In-hospital procedures and outcomes

Annual hospitalization rates were computed over all, and separately for STEMI and Non-STEMI discharges. In-hospital cardiac catheterization, PCI, coronary artery bypass graft (CABG) surgery, valve procedures and pacemaker/heart assist/defibrillation-related procedures were identified based on ICD-9-CM codes documented in the procedures variables (see Supplementary data Table S1). During our observational period, several new technologies were introduced. Coronary brachytherapy was introduced in early 2001 simultaneously in the USA and in Portugal; and trials indicating no differences between CABG performed on- and off-pump appeared in the early 2000s for low risk patients and in 2010 for high-risk patients [25, 26]. While drug-eluting coronary stents were approved in the US in 2003 and a year earlier in Europe, coding inaccuracies in the Portugal database prevented a comparative assessment. To minimize this pitfall, we identified implantation of coronary stents, either bare-metal stents or DES.

Two in-hospital outcomes were assessed: in-hospital mortality, regardless of cause and hospital LOS operationalized as the date of discharge minus the date of admission plus one.

Statistical analyses

The data use policy prohibited sharing of discharge-level data between Portugal and the USA. We thus adopted a distributed computing and modeling approach. Statistical summaries (frequencies, percentages, means, standard errors (SE) and sample sizes) were distributed between the two research teams.

We were unable to analyze the data at the patient level because we were working with a 20% random sample of inpatient discharges for the US and patient identification in Portugal is only available within the same hospital and year of discharge. Therefore, the unit of analysis considered throughout the analysis is hospital discharge.

Unadjusted procedure, diagnoses and mortality rates, and mean LOS (MLOS) were calculated for each country. For between-country comparison, age-sex-adjusted rates, rate ratios and mean difference (Portugal relative to the US) were estimated using the 2010 US population as the reference population (Supplementary data Table S2) [27] considering 10-year age intervals or wider-range age intervals in the case of low-frequency events. All estimates for the US data were computed using discharge weights to account for the complex design sampling of the NIS.

Within-country risk-adjusted procedure rates were estimated using hierarchical logistic regression separately for each country where random intercepts were included to account for correlation among patients treated at the same hospitals. The random intercepts were assumed to arise from a normal distribution [28]. We included patient demographic information (including an age and sex interaction effect) whether the admission status was classified as emergent/urgent, risk factor, comorbidity and year of discharge in the model. Because in-hospital mortality was observed, rather than 30-day mortality, risk-adjusted in-hospital hazard ratios were estimated. We used semi-parametric shared frailty models considering the same independent variables as before [Model 1], in which the frailty parameter was assumed to arise from a one-parameter Gamma distribution and was included to account for within-hospital data correlation [28]. We extended this model with predictor variables for revascularization procedures (PCI or CABG) to obtain risk-adjusted in-hospital mortality rates per procedure and assess between-hospital variability in in-hospital mortality after adjusting for therapeutic management [Model 2]. Between-hospital variability modeled through hierarchical logistic regression was summarized as 2 times the square root of the between-hospital variance component and then exponentiated. This corresponds to a change in the odds of the event for an increase of ± 1 standard deviation of the mean hospital rate. Between-hospital variability modeled through shared frailty models was summarized as the ratio between the hazard of dying in the hospital denoted by the 95 percentile of the one-parameter gamma distribution and the hazard of dying in the hospital denoted by percentile 5. This corresponds to the risk of a patient dying in hospital when treated in a high-mortality hospital relative to being treated in a low mortality hospital.

Results

Study populations

In 2010, the US population was 309.3 million, 13% was aged 65 years or older, and 16.3% had no health insurance; the 2010 Portuguese population was 10.6 million, 19% aged at least 65 years, and universal healthcare coverage (see Supplementary data Table S3). We identified a total of 1 566 601 AMI hospitalizations: 123 442 in Portugal from 83 hospitals and 1 443 159 in the USA from 3853 hospitals representing 7 084 136 AMI patients nationwide (Fig. 1, Table 1). Compared with the USA, AMI hospitalizations in Portugal of female patients and of elderly patients were less

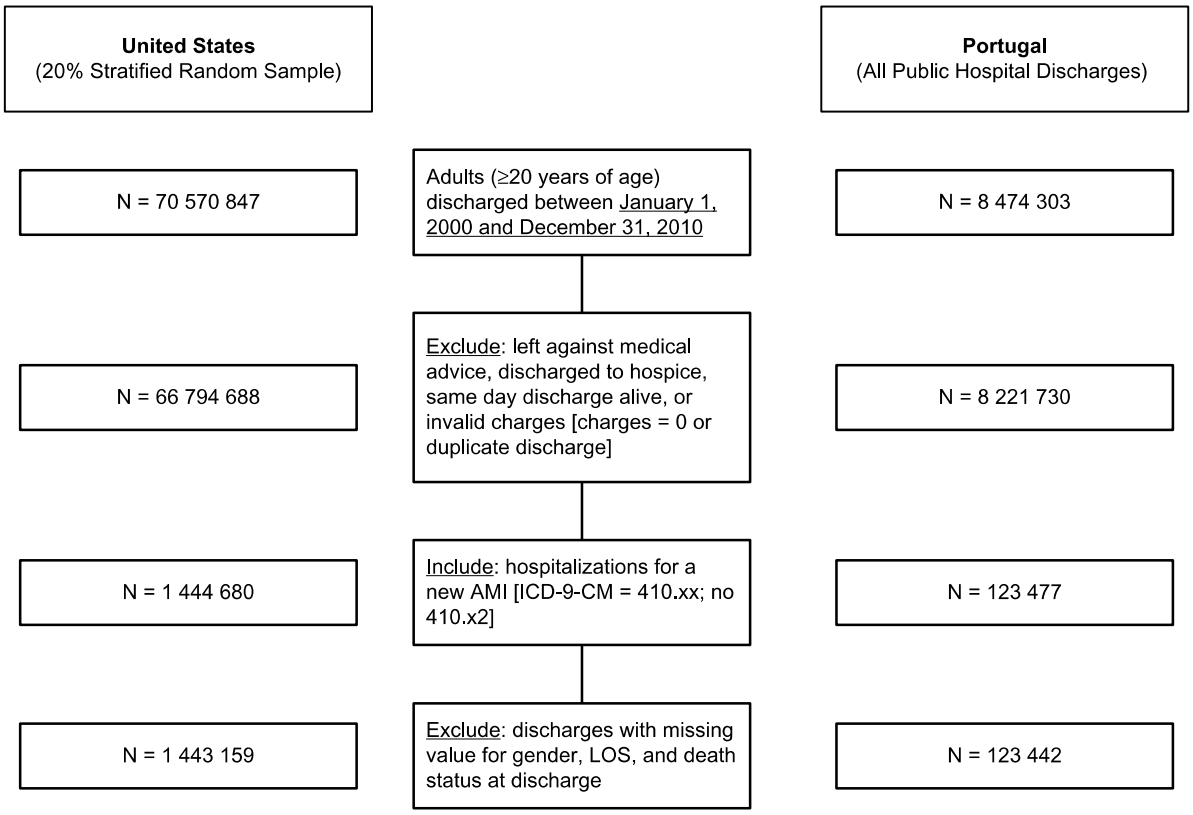

Figure 1 Number of hospitalizations by inclusion and exclusion criteria. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

common, there were more emergent/urgent admissions, and more were likely to be STEMI admissions (Table 1). Comorbid conditions were higher in the US—the single exception was cerebrovascular disease (3.5% in Portugal versus 3.0% in the USA).

Principal findings

Crude hospitalization rates declined in the USA but increased in Portugal (Table 2). The age-sex adjusted AMI hospitalization rates decreased from 27 per 1000 person-years in 2000 to 19 in 2010 in the USA (RR = 0.695; 95% CI = [0.693, 0.696]) but increased in Portugal (11 to 13, RR = 1.16 [1.12, 1.19]). These patterns were driven by a decrease of STEMI hospitalizations in the USA and an increase of Non-STEMI hospitalizations in Portugal (Fig. 2). Moreover, age-sex adjusted Non-STEMI hospitalization rates were more prevalent than STEMI hospitalizations in the USA but less prevalent in Portugal (Fig. 2).

Crude procedure rates (Table 2) were generally lower in Portugal but only CABG rates differed significantly between the countries in 2010 after age-sex standardization (2010: RR = 0.19 [0.14, 0.27]). CABG surgery decreased in the US (105 per 1000 person-years to 81, RR = 0.77 [0.75, 0.78]) but doubled in Portugal (11 to 16, RR = 1.47 [0.68, 3.16]). Of those undergoing CABG surgery, off-pump use increased between 2000 and 2010 in Portugal, and was higher in Portugal compared with the USA. PCI use increased annually in both countries. Use of coronary stents was high in the USA and remained high throughout our study period. The crude rate of stenting more than doubled in Portugal. Adjusted rates (Table 3) indicated females had lower odds of undergoing revascularization compared with males regardless of country. Between-hospital variability in procedure use was lower in Portugal compared with the USA. For instance, the odds of undergoing PCI in a moderately high PCI hospital (+1 Standard Deviation) was nearly 19 times that when admitted to a moderately low PCI hospital in Portugal; in the US, these odds were more than 250.

Mean hospital LOS (MLOS) decreased in both countries. However, longer MLOS were observed in Portugal (mean difference 2.77 [2.73, 2.82] in 2010), being longer among survivors when compared to non-survivors in Portugal and shorter in the USA. Females had a higher risk of in-hospital mortality following AMI compared with males in both countries but this disparity was negligible in the USA (Table 4). Annual declines in mortality were observed in both countries and in-hospital revascularization strategies increased survival to discharge. However, the effectiveness of these strategies was much larger in Portugal (Table 4). Between-hospital variation in mortality was smaller in the USA relative to Portugal—the hazard of dying in a high-mortality US hospital was essentially no different than that in a modestly low mortality hospital, the hazard ratio was equal to 1.03; in Portugal, this hazard ratio was 2.65.

Discussion

International comparisons may yield insights on healthcare expectations of patients exposed to different medical care practice patterns. With this in mind, we produced a comprehensive analysis about AMI patient management across contrasting healthcare systems in the two sides of the Atlantic. Our results show substantial differences between the two countries regarding incidence of AMI hospitalizations, risk

Table 1 Characteristics of patients hospitalized for AMI in Portugal and the USA, 2000–2010

Characteristic	Portugal	USA
Number of hospitals	83	3853
Number of discharges	123 442	1 443 159
Number of weighted discharges		7 084 136
Mean age, mean ± SE	68 ± 0.04	68 ± 0.09
Aged ≥ 80 years, *N* [%]	26 841 [21.7]	1 602 160 [22.6]
Female, *N* [%]	42 975 [34.8]	2 878 972 [40.6]
Race/ethnicity, *N* [%]		
White	Not collected	4 217 227 [79.3]
Black		461 448 [8.7]
Hispanic		358 802 [6.7]
Asian/Pacific Islander		97 603 [1.8]
Native American		25 240 [0.5]
Other		31 825 [2.2]
Missing/Invalid/not available		358 553 [25.0]
Year of discharge, *N* [%]		
2000	8749 [7.1]	692 349 [9.8]
2001	9775 [7.9]	736 307 [10.4]
2002	10 809 [8.8]	716 965 [10.1]
2003	11 829 [9.6]	696 603 [9.8]
2004	11 799 [9.6]	644 628 [9.1]
2005	11 396 [9.2]	617 246 [8.7]
2006	11 528 [9.3]	636 678 [9.0]
2007	11 816 [9.6]	580 179 [8.2]
2008	12 273 [9.9]	600 063 [8.5]
2009	11 762 [9.5]	596 287 [8.4]
2010	11 706 [9.5]	566 830 [7.9]
ST-segment elevated MI, *N* [%]	75 202 [60.9]	2 481 562 [35.0]
Location of MI, *N* [%]		
Anterior	30 426 [24.6]	955 728 [13.5]
Inferior	28 784 [23.3]	1 279 239 [18.1]
All other locations	64 232 [52.0]	4 849 170 [68.5]
Emergent/urgent admission	118 909 [96.3]	5 975 639 [84.4]
Cardiovascular morbidity, *N* [%]		
History of PTCA (V45.82)	3564 [2.9]	567 240 [8.0]
History of CABG Surgery (V45.81)	2616 [2.1]	499 647 [7.1]
History of congestive heart failure (MCC80, 429)	22 534 [18.3]	2 478 716 [35.0]
History of AMI (412, 410.x1)	7448 [6.0]	642 150 [9.1]
Unstable angina (411, 410.x2)	1934 [1.6]	137 117 [1.9]
Atherosclerosis (413, 414, 746.85)	47 938 [38.8]	5 182 245 [73.1]
Cardiorespiratory Failure or Shock (MCC79)	10 364 [8.4]	973 405 [13.7]
Valvular or rheumatic heart disease (MCC86)	12 195 [9.9]	864 488 [12.2]
Other Comorbidity, *N* [%]		
Hypertension (MCC89)	56 966 [46.2]	3 798 914 [53.6]
Stroke (MCC95)	1498 [1.2]	118 006 [1.7]
Cerebrovascular disease (MCC97)	4263 [3.5]	216 754 [3.1]
Renal failure (MCC131)	6310 [5.1]	1 098 118 [15.5]
Chronic obstructive pulmonary disease (MCC108)	5284 [4.3]	1 222 102 [17.3]
Pneumonia (MCC111)	4772 [3.9]	604 371 [8.5]
Diabetes without or with complications (MCC15)	33 136 [26.8]	2 170 938 [30.6]
Hypercholesterolemia (272.0)	5571 [4.5]	859 192 [12.1]
Protein-calorie malnutrition (MCC21)	119 [0.1]	102 106 [1.4]
Dementia or senility (MCC49)	2212 [1.8]	373 042 [5.3]
Hemiplegia, paralysis, or functional disability (MCC67)	3441 [2.8]	196 216 [2.8]
Peripheral vascular disease (MCC104)	4383 [3.6]	701 249 [10.0]
Metastatic cancer or acute Leukemia (MCC7)	619 [0.5]	86 565 [1.2]
Trauma (MCC154)	870 [0.7]	141 191 [2.0]
Major psychiatric disorders (MCC54)	452 [0.4]	104 965 [1.5]
Liver or biliary disease (MCC25)	499 [0.4]	47 561 [0.7]

profiles of patients, and in-hospital revascularization strategies use, particularly in earlier years of the study's reporting period. Higher procedures use rates in the USA were accompanied by significantly lower mortality and shorter stays when compared to Portugal. However, substantial differences were also found in the risk profiles of the two populations in the two countries.

Table 2 Procedures and outcomes of patients hospitalized for AMI in Portugal and the USA, 2000 and 2010

Country	Portugal		USA		2010 standardized rate ratio[a]
Discharge year	2000	2010	2000	2010	
Number of AMI discharges	8749	11 706	141 583	113 339	
Number of AMI discharges (weighted)			692 349	566 830	
Number of hospitals	76	51	932	916	
Number of hospitals (weighted)			4523	4446	
AMI hospitalizations[b], %	1.2	1.6	2.6	1.9	0.85 [0.83, 0.86]
In-hospital procedures, %					
Cardiac catheterization	18.2	51.7	49.7	64.8	0.88 [0.75, 1.03]
CABG surgery	0.9	1.8	10.9	8.8	0.19 [0.14, 0.27]
Off-pump, % of CABG surgeries	33.3	53.1	22.2	27.7	0.39 [0.27, 0.56]
Off-pump, % of AMI	0.3	1.0	2.4	2.5	
PCI	15.6	44.1	28.5	46.5	1.09 [0.99, 1.19]
Stented, % of PCI	40.4	86.7	87.9	92.4	0.95 [0.86, 1.04]
Stented, % of AMI	38.3	63.0	25.2	42.8	
Brachytherapy	0	0	<0.00001	0	
Revascularization[c]	16.2	45.8	38.7	54.3	0.98 [0.84, 1.15]
Defibrillator, heart assist, or pacemaker procedures	2.4	2.9	2.8	2.6	1.19 [0.82, 1.71]
In-hospital outcomes					
In-hospital mortality, %	14.4	9.8	8.7	5.6	2.15 [1.59, 2.91]
Mean ± SE LOS, days	10.8 ± 0.09	9.0 ± 0.08	5.6 ± 0.06	4.8 ± 0.05	2.77 [2.73, 2.82]
Survivors	11.6 ± 0.09	9.2 ± 0.08	5.6 ± 0.06	4.8 ± 0.05	
Non-survivors	6.4 ± 0.3	7.5 ± 0.35	5.7 ± 0.13	4.9 ± 0.12	

[a]2010 age-sex standardized rates ratios (Portugal relative to USA), using the 2010 US population as reference population.
[b]Per adult discharge.
[c]Revascularization denotes PCI or CABG within the same hospitalization.

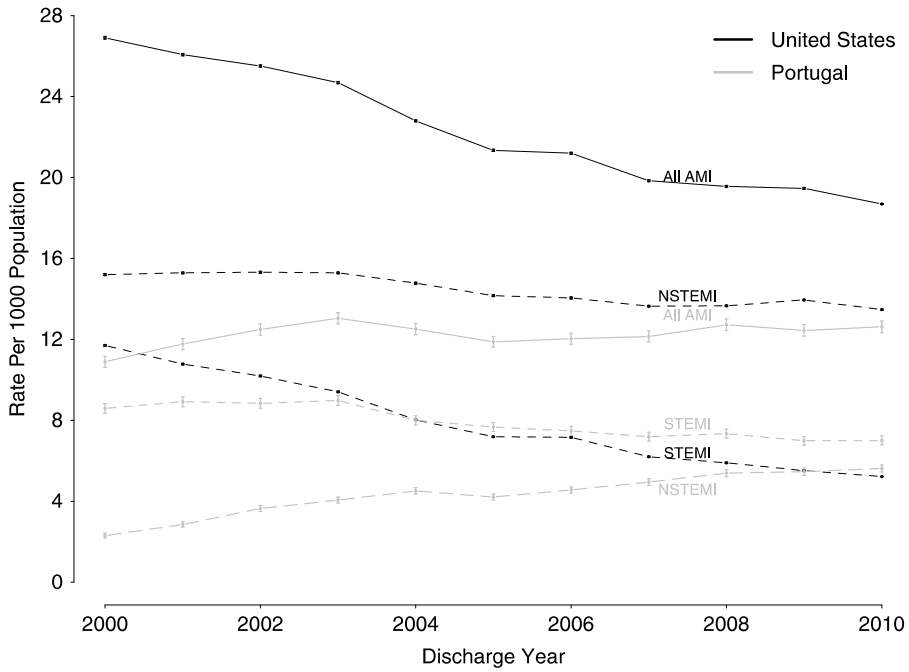

Figure 2 Trends in AMI hospital admission rates in Portugal and the United States, 2000–2010. Point estimates and confidence intervals age-sex standardized to the US population.

Although AMI events were more likely to occur in the USA than in Portugal, age-sex-adjusted STEMI rates in Portugal remained stable throughout the study period while they declined in the USA (Fig. 2). Therefore, and since STEMI events are associated with worse prognosis when compared to Non-STEMI, this risk pattern may aid to explain why Portugal exhibited higher in-hospital mortality than the US.

Table 3 Adjusted odds ratios for Coronary Artery Bypass Grafting Surgery (CABG), PCI and revascularization (PCI or CABG) procedures, in Portugal and the USA, 2000–2010

Country	Portugal		USA	
Parameters	Adjusted odds ratio	95% confidence interval	Adjusted odds ratio	95% confidence interval
Outcome = CABG				
Female vs. Male[a]	0.67	(0.593, 0.760)	0.62	(0.608, 0.624)
5-year age increase[b]				
Females	0.89	(0.851, 0.927)	0.92	(0.920, 0.927)
Males	0.97	(0.947, 0.997)	0.99	(0.987, 0.993)
Annual change[c]	1.04	(1.024, 1.066)	0.95	(0.944, 0.949)
Between-hospital variance (SE[d])	5.0331 (1.2464)		5.2887 (0.1728)	
Outcome = PCI				
Female vs. Male[a]	0.73	(0.703, 0.752)	0.88	(0.875, 0.892)
5-year age increase[b]				
Females	0.83	(0.821, 0.840)	0.91	(0.905, 0.909)
Males	0.85	(0.845, 0.857)	0.90	(0.902, 0.906)
Annual change[c]	1.21	(1.208, 1.221)	1.13	(1.126, 1.130)
Between-hospital variance (SE[d])	2.1598 (0.4208)		7.9518 (0.2298)	
Outcome = Revascularization				
Female vs. Male[a]	0.70	(0.680, 0.728)	0.68	(0.670, 0.683)
5-year age increase[b]				
Females	0.83	(0.816, 0.835)	0.88	(0.874, 0.879)
Males	0.85	(0.841, 0.853)	0.88	(0.877 0.881)
Annual change[c]	1.22	(1.214, 1.227)	1.10	(1.103 1.107)
Between-hospital variance (SE[d])	2.2149 (0.4304)		9.4608 (0.2681)	

[a]Calculated at mean age = 68.
[b]Average expected change in the odds of observing revascularization procedure in a hospitalization per a 5-year increase in the patient's age.
[c]Average annual change expected in the odds of observing revascularization procedure in a hospitalization.
[d]SE, standard error.
Estimates adjusted for variables in Table 1 with the exception of Race/Ethnicity.

Table 4 Adjusted in-hospital mortality hazard ratios in Portugal and the USA, 2000–2010

Country	Portugal		USA	
Parameters	Adjusted hazard ratio	95% confidence interval	Adjusted hazard ratio	95% confidence interval
Model 1				
Female vs. Male[a]	1.21	(1.16, 1.268)	1.03	(1.009, 1.041)
5-Year age increase[b]				
Females	1.22	(1.205, 1.236)	1.23	(1.223, 1.234)
Males	1.28	(1.266, 1.292)	1.25	(1.243, 1.252)
Annual change[c]	0.97	(0.963, 0.974)	0.97	(0.965, 0.969)
Between-hospital Variance	0.0845		0.0001	
Model 2 = Model 1 + CABG + PCI				
Female vs. Male[a]	1.18	(1.126, 1.232)	1.177	(1126, 1.231)
5-year age increase[b]				
Females	1.19	(1.177, 1.207)	1.21	(1.203, 1.213)
Males	1.24	(1.232, 1.256)	1.23	(1.226, 1.235)
Annual change[c]	0.99	(0.979, 0.991)	0.97	(0.969, 0.973)
CABG	0.47	(0.397, 0.555)	0.78	(0.76, 0.79)
PCI	0.39	(0.369, 0.416)	0.80	(0.789, 0.816)
Between-hospital variance	0.0853		0.0001	

[a]Calculated at mean age = 68.
[b]Expected increase in risk of dying at hospital by a 5-year age increase.
[c]Expected annual increase in risk of dying at hospital.
Model 1: Estimates adjusted for Table 1 variables with the exception of Race/Ethnicity (see Supplementary data Table S4 for complete list of hazard ratios of Model 1); Model 2: Estimates adjusted for variables in Model plus Coronary Artery Bypass Graft (CABG) and PCI use.

Given that primary PCI is the recommended reperfusion therapy in STEMI [29], a large incidence of STEMI hospitalizations would anticipate a high PCI use rate. However, differences in STEMI rates were not mirrored by statistically significant different PCI use rates in 2010 between the two countries. Being PCI a complex and expensive procedure, countries with lower economic

capacity, such as Portugal, are likely to experience more constraints in its use. On the other hand, the general belief that PCI use is helpful even in less acute manifestations of AMI associated with higher economic capacity, such as the US, is also likely to further aggravate the difference (or lack of difference) between practice patterns in these countries [30]. In fact, in 2010 the USA had nearly double the number of hospitals per capita with cardiac catheterization facilities and four times the number of hospitals per capita with cardiothoracic surgery services, which is in line with the revascularization procedures utilization rates ratios observed in this study [2].

Furthermore, while unadjusted and risk-adjusted analysis show that both countries saw a decline in in-hospital mortality throughout the period, these results also indicate that there was a larger increase in the use of PCI and CABG procedures in Portugal. Since the hazard ratio for annual change in the extended frailty model [Model 2], which included additional predictor variables to control for PCI and CABG use, increased for Portugal when compared to the same hazard ratio in the base frailty model [Model 1], which only included patient characteristics as predictors variables, the larger uptake on revascularization procedures seems to have contributed for the in-hospital mortality reduction in Portugal.

Our findings regarding STEMI trends are consistent with those reported by others for Portugal and USA using independent data sources as well as other studies covering transatlantic comparisons which also observed lower relative weight of STEMI cases in AMI hospitalizations in the USA when compared to the EU [4, 20, 31–33]. Moreover, similar gaps in PCI and CABG use in AMI treatment have been observed by others comparing data from Sweden, UK and the USA [1, 3, 4, 34, 35]. However, contrary to our results, lower procedure use in Sweden was not associated with increased risk of short-term death when compared to the USA.

We observed significant between-hospital variability in procedure use and in survival across hospitals in Portugal. Such variability indicates a closer positive relationship among discharges of the same hospital and greater heterogeneity between hospitals. Between-hospital variability in survival was less pronounced but substantially higher in Portugal than in the USA. We also observed this behavior with the extended frailty model [Model 2]. Thus suggesting that hospitals with similar practice patterns have similar survival profiles in the USA, whereas there is considerable variation in AMI survival across hospitals with similar practice patterns in Portugal.

Since the Portuguese healthcare system provides universal coverage through a comprehensive network of hospitals, primary care centers and healthcare providers mainly financed through general taxation, we would expect Portugal to require and to achieve control of disparities across hospitals more easily than the USA, which can be thought of as multiple systems bound to a wider diversity of actors. On the other hand, it supports that governmental programs to monitor hospital quality of care in the USA (e.g. the national hospital public reporting program, https://www.medicare.gov/hospitalcompare/search.html) and the lack of validated standard definitions of quality indicators in AMI in Europe may have paved the way for such consistent quality of care across hospitals in the USA with unparalleled behavior in Europe [36]. Some of the heterogeneity in survival across hospitals in Portugal might be explained by hospital characteristics such as type of services available and training level of providers [37–39]. Therefore, understanding these factors and how they relate to AMI management and outcomes is an important next step.

Limitations

This study has several limitations to consider. First, the accuracy and consistency of diagnostic and procedures coding for AMI has been assessed in the USA but has not been assessed in Portugal [20, 40–42]. However, previously published information compiled from independent data sources (e.g. national registry data and survey data) regarding the incidence of STEMI vs. Non-STEMI and revascularization practice patterns agree with proportions and trends observed in our data [32, 33, 43, 44]. Second, due to coding inaccuracies and limitations of the ICD-9-CM in discriminating hospital procedures limited our comparisons to broader classes of health technologies use, such as coronary stenting (DES or BMS) and PCI (stenting, PTCA or coronary atherectomy) and prevented inclusion of fibrinolysis use in our analysis. Another limitation with claims data is the lack of detailed information about the patient's clinical characteristics, such as coronary anatomy, extent of disease, ejection fraction, surgical risk, pain/door-to-balloon times, which may further help to characterize the two cohorts. Third, although the US sample was obtained through a stratification design that provides nationwide representativeness of hospitals, it is possible that AMI hospitalizations are either over- or under-represented. Forth, age-sex-adjusted death rates based on vital statistics data indicate lower AMI mortality in Portugal when compared to the USA [31]. This exposes the possibility that a higher proportion of AMI patients in the USA may not have access to treatments or they might die outside the hospital where treatment was provided. Finally we were unable to analyze the data at the patient level, therefore we could not evaluate readmission rates nor patient transfers across hospitals, both of which would aid in understanding treatment practice patterns. We did observe that patients discharge alive in the USA were more likely to get transferred to another care facility when compared with Portugal (USA: 20% vs. Portugal: 13%, of discharges in 2010), however, excluding these discharges would not significantly affect differences in crude in-hospital mortality between countries.

Conclusions

Our findings support that differences observed in patterns of utilization of revascularization procedures and STEMI burden likely contribute to the unfavorable mortality rates in Portugal. However, in-hospital mortality systematically declined in both countries with Portugal facing alarming between-hospital asymmetries—a better understanding of processes of care for these patients is urgently required.

Supplementary material

Supplementary material is available at *International Journal for Quality in Health Care* online.

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4.3 Paper 3

Understanding hospital heterogeneity in quality of care for acute myocardial infarction

ABSTRACT

Background Between 2000-2010, acute myocardial infarction (AMI) hospitalizations increased 33% in Portugal. While in-hospital mortality rates among AMI patients declined by 32%, marked disparities across geographical regions and hospitals were observed.

Objective To study the variation of risk of mortality and readmission in AMI patients across hospitals using contemporary datasets, assessing the impact of patient and hospital characteristics in between-hospital variability.

Methods Retrospective observational study of AMI cohorts using administrative hospital data of adults discharged between 2012 and 2015 from all acute care public hospitals in Portugal. All-cause in-hospital mortality in AMI patients and 30-day all-cause unplanned readmission in patients surviving the AMI were studied in separate cohorts. Crude rates were computed overall, across years and across hospital characteristics. Hierarchical generalized linear models were implemented using a step-up strategy that quantifies between-hospital variance.

Results The mortality cohort included 38059 patients while the readmission cohort included 34256. 10% died and 8% of patients were readmitted. Between-hospital variability was larger in the mortality cohort. Patient characteristics accounted for a larger share of the explained between-hospital variance regardless of cohort, with hospital characteristics explaining an additional 2% and 12% of hospital heterogeneity in the mortality and the readmission cohorts respectively. Admissions to hospitals with low AMI caseload or located in Alentejo/Algarve and Lisbon had higher risk of mortality. Discharges from larger-sized hospitals were associated with increased risk of readmissions.

Conclusions Hospital represents a contextual effect as relevant as a patient characteristic. However, while hospital characteristics substantially explain this effect in readmissions, practically no between-hospital variability was explained by hospital characteristics in the mortality cohort. Further investigation addressing geographical disparities, hospital caseload and practices is needed.

Keywords: acute myocardial infarction, administrative data, hierarchical regression models, hospital healthcare quality, in-hospital mortality, 30-day unplanned readmissions.

INTRODUCTION

Acute myocardial infarction (AMI) remains one of the leading causes of death in most developed countries.[1] Moreover, expensive health care management,[2,3] and high risk of re-hospitalization make AMI a significant economic burden to health care systems.[4-6] Therefore, regular monitoring is essential for an understanding of factors that can alleviate this burden and improve health care quality. With increasing numbers of AMI discharges,[1] patients hospitalized for AMI in Portugal have higher in-hospital mortality risk compared to other countries with marked differences across geographical regions and hospitals.[1,7-9] Prior research indicated that the risk of dying in a high mortality hospital relative to a low mortality hospital in Portugal was more than double, after adjusting for patient case-mix.[9] Whether similar heterogeneity across hospitals in other quality metrics exists is unknown. For example, unplanned readmissions within 30-days of discharge may reflect suboptimal care during the index hospitalization or poor transition from inpatient to outpatient care. Consequently, 30-day all-cause unplanned readmissions have been endorsed by various professional societies and health systems as a meaningful quality metric. Only a few studies have examined readmissions after a AMI in Portugal, with most based on single-center experiences that lack national representativeness or focus on 6-month readmission rates which is less likely to be associated with the quality of care provided during the index hospitalization.[10-16] Moreover, no study has characterized variability across different hospitals in readmission rates.

An increasing body of evidence shows that several key hospital characteristics are associated with quality of care for patients hospitalized for AMI.[4,17-19] For example, centers providing percutaneous coronary interventions (PCI) and coronary artery bypass graft (CABG) surgery have lower mortality when compared to centers without these services.[17,19] Hospital size, AMI volume, and teaching status are also positively

associated with hospital's quality of care.[4,17,18] Whether hospital characteristics are associated with quality of care for AMI patients treated in Portugal and how much of between-hospital variation is associated with these characteristics is unknown.

We thus sought to assess heterogeneity in quality of care in AMI management across hospitals in Portugal using a contemporary cohort of adults treated for AMI. Specifically, after adjusting for patient characteristics, we quantify between-hospital variability in in-hospital mortality odds and in 30-day unplanned readmission odds for those surviving the index admission. We also determine if hospital characteristics account for some of this heterogeneity.

METHODS

Data Sources

We identified hospitalizations occurring between January 1st 2011 and January 30th 2016 from all mainland public hospitals in Portugal kept at the Central Administration of the Health System (ACSS).[20] Public hospitals account for 79% of all inpatient discharges and represent 52% of all hospitals in Portugal.[21-23] The data maintained by ACSS includes information about patient demographic characteristics, principal and secondary diagnoses, discharge status, type of admission, admission and discharge dates, length of stay, unique hospital identifiers, and in-hospital procedures. Diagnoses and procedures utilized the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) system. Information collected reflects both inpatient and outpatient hospital care. Patient traceability is available through a unique and anonymous patient identification variable provided by ACSS.

We obtained hospital characteristics using multiple data sources. These included hospital account reports describing the number of hospital beds available at ACSS and or at hospital websites; information regarding geographical classification was retrieved from *Eurostat*; annual reports published by the *National Program on Cerebral and Cardiovascular Diseases* [24] as well as personal communication with hospitals confirmed hospital history of provision of coronary revascularization procedures; and official documents of laws enacted in Portugal (dre.pt) were used to track hospital merges over time.

Episode of care

Hospitalizations in which the patient was transferred in or out within the same episode of care were identified. These consisted of hospitalizations sharing the same patient identification and one of the following was verified: 1) dates of admission and discharge of one hospitalization were enclosed in the dates of admission and discharge of another hospitalization; 2) discharge date of the initial hospitalization and admission date of the subsequent hospitalization differed by ≤1 day and there was indication of the hospital id where the patient was transferred from or to; b) the date of admission of the subsequent hospitalization occurred on the same day of discharge from the initial hospitalization; c) the initial and subsequent hospitalizations had overlapping admission and discharge dates. In the case 1), the hospital with longer stay was considered responsible for admitting and discharging the patient. The disposition status of an episode of care was defined by the disposition status of the final hospitalization; the length of stay was computed as the difference between the discharge date of the final hospitalization and the admission date of the initial hospitalization.

Study Cohorts/Participants

We created two cohorts, the mortality cohort and the readmission cohort (Figure 1). All inpatient discharges of adults (≥20 years at admission) with a principal diagnosis of AMI (ICD-9-CM code of 410.xx, except if a 2 in the fifth digit) discharged between January 1st 2012 and December 31st 2015 were identified. In the event of episodes with multiple hospitalizations, an AMI episode of care was defined if both principal diagnoses of the initial and final hospitalizations of that episode were an AMI. Only the initial hospitalization was included in the mortality cohort (referred as index hospitalization in this cohort), while only the final hospitalization was included in the readmission cohort (referred as index hospitalization in the readmission cohort). Therefore, the responsibility for the episode was attributed to the admitting hospital in the mortality cohort and to the discharging hospital in the readmission cohort.

We excluded hospitalizations of patients discharged alive on the same day of admission or who left against medical advice or discharged from a specialized hospital (oncological, psychiatric, maternity) and without a transfer to another hospital status because these are unlikely to represent an AMI. Even after combining hospitalizations into a single episode of care, a few discharges remained with a disposition status of transfer to another acute care facility (n=981, 2%). Although we cannot rule out issues related with patient identification, this can happen if for example the admitting hospital transfers temporarily the patient to another hospital to receive a revascularization procedure returning to the initial hospital and both hospitalizations are documented with a transfer out status. These were excluded since it is not possible to ascertain the final disposition of the patient. Hospitals with fewer than 25 index events over the entire time frame were also excluded given the insufficient data for evaluating hospital performance.[4,19,25]

In the mortality cohort we randomly selected an AMI hospitalization per patient with a discharge date occurring between January 1st 2012 and December 31st 2015. Patients

discharged to hospice were excluded from the mortality cohort because these patient are more likely to die in the immediate time after discharge.[26] The readmission cohort included all first AMI hospitalization of patients discharged alive between January 1st 2012 and December 31st 2015. This approach allows for a clear clustered data structure (one episode per patient) in this cohort as well, hence minimizing issues related with correlation among outcomes observed for the same patient.

Patient characteristics

We considered demographic information (age and sex), risk factors and comorbidities to characterize patients in the cohorts. For risk-adjustment we identified 29 risk factors and comorbid conditions variables derived from the (principal and secondary) diagnoses codes and procedure codes of (inpatient and outpatient) hospitalizations of the patient occurring during 1 year before the index hospitalization; and secondary diagnoses of the index hospitalization.[5,27] These represent pre-existing conditions that are clinically relevant and have a relationship with the outcome. In the event of episodes of care with multiple hospitalizations in the readmission cohort, complications arising in prior hospitalizations within the same episode will also be considered as pre-existing conditions so that the final hospital is not accountable for those complications. Inpatient data within 30 days after discharge of patients surviving the index hospitalization were used to identify readmissions.

Hospital characteristics

Hospitals were characterized by their teaching status, capability to provide PCI and CABG procedures, volume of AMI cases, number of beds, and geographical location. Teaching status was determined according to the Medical National Federation.[28] We defined a hospital with capacity to provide PCI and with capacity to provide CABG procedures if, in

2010, that hospital had a catheterization lab and cardiothoracic surgery service respectively; hospital AMI volume was estimated from the inpatient data during 2011; the number of inpatient beds were determined in 2010/2011 (or nearest year); geographical location was assigned based on the second level of the Nomenclature of Territorial Units for Statistics (NUTS II) that divides mainland Portugal into 5 regions (North, Center, Lisbon, Alentejo and Algarve).[29] The region of Algarve was combined with Alentejo because there was only one hospital in that region and Algarve only borders with Alentejo in the south of Portugal (Figure S1). Hospital identification expresses the merges of hospitals into hospital centers, which occurred mostly in the previous decade. Two hospital merges occurred during the study period. In these cases we considered the hospital center throughout the entire period, hence their characteristics result from the combination of the individual hospital characteristics (e.g. size corresponds to the sum of beds of all hospitals included in the hospital center). Characterization of each hospital is provided as supplementary data (Table S1).

Outcome measures

We examined two outcome measures. All-cause in-hospital mortality was accessed through the mortality cohort and 30-day all-cause readmission through the readmission cohort. The latter was defined by an unplanned re-hospitalization in any public hospital (excluding hospitals in insular territory) due to any cause within 30 days after discharge of an index AMI hospitalization. Unplanned hospitalizations were identified if *urgent* status was assigned in the variable Admission Type, otherwise the hospitalization was considered elective. Readmissions that occur in private hospitals are not captured in this database.

Statistical Analysis

Data checks and integrity tests were carried to assure quality of the data. Hospitalizations with an admission date after the discharge date, or hospitalizations belonging to the same patient with a disposition status of death in the earlier hospitalization, or hospitalizations of patients with unknown gender were excluded. We characterized the cohorts of patients overall and across years computing the appropriate metrics for the type of data (count, percentage, mean, standard deviation (SD) or median and interquartile range (IQR)). Crude readmission and mortality rates were also computed overall and by hospital characteristics levels. Funnel plots of hospital-specific risk-standardized rates, defined as the observed-expected ratio of deaths/readmission in a hospital times the crude death/readmission national rate, were produced by hospital characteristics to assess performance of hospitals against a measure of its precision.[30]

We estimated hierarchical models that incorporate the multilevel structure of the data (patient discharges within hospitals) and provide measures of source of variability across the different data levels.[31] Particularly, we implemented generalized linear mixed models to account for data clustering at the hospital level and to explicitly estimate between-hospital variability, assuming a normally distributed random intercept for hospital. We estimated a series of models that differed in terms of the characteristics included. We first specified an empty model (Model 0) that provided unadjusted rates that accounted for clustering. Next, we included patient-level variables (Model 1), and then added hospital-level variables to Model 1 (Model 2) (model specification is available as supplementary data).

We estimated the Intraclass Correlation Coefficient (ICC) to describe the extent of correlation among observations within the hospitals.[32,33] Caterpillar plots were used to summarize hospital random effects across the different models. To further characterize between-hospital variation we estimated the odds of the outcome for a patient treated at a moderately high (+1 SD) relative to a moderately low (-1 SD) mortality/readmitting

hospitaland the median odds ratio (MOR), which is defined as the median value of the distribution of odds ratio (OR) obtained when randomly picking two similar patients from two different hospitals, and comparing the one from higher risk hospital to the one from the lower risk hospital.[5,33] To quantify the association of patient and hospital characteristics with hospital heterogeneity, we computed proportional change in variance (PCV) defined by the proportion of the between-hospital variance that is explained by the additional covariates between two nested models.[34,35] We additionally computed the proportion of opposed odds ratios (POOR) for hospital-level covariates to assess the degree of heterogeneity of the association of this variables within hospital characteristics.[34,35] The c-statistic was also computed to assess quality of classification of the different models.

RESULTS

In-Hospital Mortality

We identified 38 059 AMI index hospitalizations in 37 hospitals. Most hospitalizations belonged to male patients and mean age of patients was 69 (±14) years. Coronary atherosclerosis (67%), diabetes mellitus (35%), valvular rheumatic heart disease (18%), angina pectoris (13%), iron deficiencies (13%), and history of percutaneous transluminal coronary angioplasty (PTCA) (11%) were the most common comorbidities. The median length of stay was 5 days (IQR = [4,9]) and 10% of patients died during the hospitalization (Table 1). The mean number of index hospitalizations per hospital ranged from 250 (SD=176) in 2012 to 264 (SD=184) in 2015. Forty-six percent of hospitals exhibited risk-adjusted in-hospital mortality rates outside the expected range of normal sampling variation, half of which were above the upper 95% limit (Figures S2 (A)).

Table 2 summarizes results obtained from the stepwise multivariable analysis carried. The estimated between-hospital variance ignoring the effect of patient and hospital characteristics (Model 0) was 0.277 (SE=0.0697) in the mortality cohort, indicating that 8% of the total

variation is due to between-hospital variation (ICC=0.078). Inclusion of patient characteristics (Model 1) reduced between-hospital variation to 0.135 (SE=0. 03586), a 51% decline. The risk of mortality of patients in a hospital 1 SD above average is 2.08 times that of patients in a hospital 1 SD below average. The MOR was 1.42, which represents the median increased odds of mortality if a patient would be admitted at another hospital with higher risk. Only nine of patient-level characteristics exhibited an OR larger than MOR. Adding hospital characteristics (Model 2) further reduced between-hospital variability to 0.129 (SE=03867), representing a 4% relative decrease (Table 2, Figure S3). AMI volume (OR=0.86, 95% CI: [0.74,0.98] for a 100-AMI case increase) and geographical location of hospital (Alentejo or Algarve: OR=1.58, 95% CI: [1.05,2.36]; Lisbon: OR=1.43, 95% CI: [1.01,2.01] relative to the North region) had, on average, significant associations with mortality. However, these associations, in particular AMI volume, were heterogeneous (POOR= 50%, 19% and 24% respectively).

Table 1. Characteristics of patients in the mortality cohort.

Year	**2012**	**2013**	**2014**	**2015**	**All**
#Discharges	9239	9608	9442	9770	38059
#Hospitals	37	37	37	37	37
LOS, median (IQR) days	6 [4,9]	5 [4,8]	5 [4,9]	5 [4,9]	5 [4,9]
Female, % of discharges	34.7	35.3	35.2	35.0	35.0
Age, mean (SD)	69 (14)	69 (14)	69 (14)	69 (14)	69 (14)
≥ 80 years, % of discharges	26.0	26.1	26.5	26.6	26.3
Cardiovascular comorbidities, %					
MI Location, %					
Anterior (410.0x, 410.1x)	19.6	19.5	18.5	18.8	19.1
Other location (410.2x - 410.6x)	20.7	21.1	20.4	19.5	20.4
History of CABG (V45.81, 36.10-36.16)	4.0	4.2	4.4	3.9	4.1
History of PTCA (V45.82, 00.66, 36.01, 36.02, 36.05, 36.06, 36.07)	10.5	10.3	10.0	11.4	10.6
Angina Pectoris/Old Myocardial Infarction (CC 83)	12.8	12.6	13.3	13.4	13.0
Congestive Heart Failure (CC 80)	6.2	6.0	6.2	6.0	6.1
Coronary Atherosclerosis (CC 84)	63.1	66.5	69.8	69.1	67.2
Acute Coronary Syndrome (CC 81-82)	4.9	4.5	4.1	4.4	4.5
Specified Arrhythmias (CC 92-93)	4.9	4.9	5.7	5.7	5.3
Valvular or Rheumatic Heart Disease (CC 86)	17.3	18.3	17.9	16.9	17.6
Cerebrovascular Disease (CC 97-99, 103)	4.1	4.3	4.6	5.1	4.5
Stroke (CC 95-96)	1.2	1.0	1.2	1.2	1.1
Vascular or Circulatory Disease (CC 104-106)	2.9	3.0	3.3	3.4	3.2
Comorbidities, %					
Hemiplegia, Paraplegia, Paralysis, Functional Disability (CC 67-69, 100-102, 177-178)	1.6	1.9	1.8	1.9	1.8
Diabetes Mellitus (DM) or DM Complications (CC 15-19, 119-120)	33.4	34.7	34.9	35.2	34.6
Renal Failure (CC 131)	4.2	4.2	4.4	4.5	4.3
End-Stage Renal Disease or Dialysis (CC 130)	0.8	0.9	0.7	0.8	0.8
Other Urinary Tract Disorders (CC 136)	5.3	5.3	6.4	7.3	6.1
Chronic obstructive pulmonary disease (COPD) (CC 108)	5.9	6.4	6.4	6.8	6.4
Pneumonia (CC 111-113)	5.6	5.4	5.7	5.9	5.7
Asthma (CC 110)	1.2	1.2	1.4	1.7	1.4
Disorders of Fluid/Electrolyte/Acid-Base (CC 22-23)	2.8	3.7	3.9	4.2	3.7
History of infection (CC 1, 3-6)	2.6	2.9	2.7	3.1	2.8
Metastatic Cancer or Acute Leukemia (CC 7)	0.8	0.9	0.7	0.8	0.8
Cancer (CC 8-12)	3.1	3.4	3.3	3.4	3.3
Iron Deficiency or Other Unspecified Anemias and Blood Disease (CC 47)	13.1	13.2	13.5	13.8	13.4
Decubitus Ulcer or Chronic Skin Ulcer (CC 148-149)	0.7	0.7	0.8	0.8	0.7
Dementia or Other Specified Brain Disorders (CC 49-50)	4.2	4.0	4.8	5.5	4.6
Protein-Calorie Malnutrition (CC 21)	0.2	0.3	0.2	0.3	0.3
Outcome measures, %					
In-hospital deaths	11.1	10.1	10.4	9.5	10.3

LOS – Length of stay; IQR – Inter quartile range; SD – Standard deviation; MI – Myocardial infarction; CABG - Coronary Artery Bypass Graft; PTCA – Percutaneous Transluminal Coronary Angioplasty; CC – Condition category; DM – Diabetes Mellitus.

Table 2. Risk-adjusted odds ratios for 30-day all-cause in-hospital mortality after AMI. Age centered at 68 years, northern region used as reference class in geographical location. Bold font indicates statically significance odds ratios.

Model	**Model 0 (Empty model)**		**Model 1**			**Model 2**		
Covariate	OR	95% CI	OR	95% CI		OR	95% CI	
Intercept, Estimate (SE)	**-2.0845**	**(0.08886)**	**-2.2925**	**(0.07517)**		**-2.6619**	**(0.1825)**	
Patient characteristics								
5-year change increase			**1.32**	**1.28**	**1.34**	**1.32**	**1.29**	**1.34**
Female vs, Male			0.93	0.86	1.01	0.93	0.86	1.01
History of CABG			**1.27**	**1.06**	**1.53**	**1,27**	**1,06**	**1,53**
History of PTCA			**0.73**	**0.62**	**0.85**	**0,73**	**0,62**	**0,85**
Angina Pectoris/Old Myocardial Infarction			1.08	0.96	1.22	1,08	0,96	1,23
Congestive Heart Failure			1.12	0.96	1.31	1,12	0,96	1,31
Coronary Atherosclerosis			**0.36**	**0.33**	**0.39**	**0,36**	**0,33**	**0,39**
Acute Coronary Syndrome			1.09	0.91	1.32	1,09	0,91	1,31
Specified Arrhythmias			1.03	0.88	1.20	1,03	0,88	1,20
Valvular or Rheumatic Heart Disease			**0.90**	**0.81**	**0.99**	**0,90**	**0,82**	**0,99**
Cerebrovascular Disease			1.14	0.99	1.32	1,14	0,99	1,32
Stroke			1.04	0.78	1.39	1,04	0,78	1,39
Vascular or Circulatory Disease			1.10	0.91	1.33	1,10	0,91	1,33
Hemiplegia, Paraplegia, Paralysis, Functional Disability			**1.27**	**1.00**	**1.61**	**1,27**	**1,00**	**1,61**
Diabetes Mellitus (DM) or DM Complications			**1.13**	**1.04**	**1.21**	**1,13**	**1,04**	**1,21**
Renal Failure			**1.20**	**1.00**	**1.44**	**1,20**	**1,00**	**1,44**
End-Stage Renal Disease or Dialysi			**1.72**	**1.22**	**2.41**	**1,71**	**1,22**	**2,41**
Other Urinary Tract Disorders			**1.56**	**1.38**	**1.76**	**1,57**	**1,39**	**1,76**
Chronic obstructive pulmonary disease			**1.16**	**1.02**	**1.32**	**1,16**	**1,02**	**1,32**
Pneumonia			**2.09**	**1.86**	**2.34**	**2,08**	**1,86**	**2,34**
Asthma			**0.66**	**0.47**	**0.92**	**0,66**	**0,47**	**0,92**
Disorders of Fluid/Electrolyte/Acid-Base			1.01	0.85	1.20	1,01	0,84	1,20
History of infection			1.14	0.94	1.37	1,14	0,94	1,37
Metastatic Cancer or Acute Leukemia			**2.27**	**1.69**	**3.07**	**2,28**	**1,69**	**3,07**
Cancer			1.19	1.00	1.41	1,19	1,00	1,41
Iron Deficiency or Other Unspecified Anemias and Blood Disease			0.95	0.86	1.05	0,95	0,86	1,05
Decubitus Ulcer or Chronic Skin Ulcer			1.16	0.83	1.63	1,16	0,83	1,63

Dementia or Other Specified Brain Disorders				1.10	0.97	1.26	1,10	0,97	1,26
Protein-Calorie Malnutrition				**4.15**	**2.63**	**6.55**	**4,16**	**2,63**	**6,57**
Anterior location of MI				**2.29**	**2.09**	**2.52**	**2,30**	**2,09**	**2,52**
Other location of MI				**1.69**	**1.53**	**1.86**	**1,69**	**1,53**	**1,87**
Hospital characteristics									
100-case increase in AMI volume (centered at the mean)							**0.86**	**0.74**	**0.98**
POOR							49%		
100-bed increase (centered at the mean)							1.02	0.96	1.08
POOR							50%		
Teaching vs, non-teaching							1.09	0.73	1.62
POOR							44%		
Catheterization lab availability (yes vs, no)							1.13	0.78	1.65
POOR							40%		
Cardio-thoracic surgery capacity (yes vs, no)							1.56	0.97	2.53
POOR							19%		
Geographic location									
North		ref	ref	ref	ref	ref	ref	ref	ref
Alentejo or Algarve							**1.58**	**1.05**	**2.36**
POOR							19%		
Center							1.24	0.86	1.81
POOR							33%		
Lisbon							**1.43**	**1.01**	**2.01**
POOR							24%		
Variability components	Estimate	Standard error		Estimate	Standard error		Estimate	Standard error	
Between-hospital variance	0.277	(0.0697)		0.135	(0.03586)		0.129	(0.03867)	
ICC	0.078			0.039			0.038		
OR between a hospital ±1 SD relative to the average hospital[1]	2.86			2.08			2.05		
MOR	1.65			1.42			1.41		
PCV				51%			4%		
C-statistic	0.61	(0.0048)		0.80	(0.00359)		0.80	(0.00359)	

SE – Standard error; OR – odds ratio; CI – Confidence interval; POOR – proportion of opposed odds ratios ($\phi(-\beta/(\sqrt{2}\times\text{variance}))$, where ϕ represents the cumulative distribution function for the normal distribution) ; ICC – Intraclass correlation coefficient (variance/(variance+$\pi^2/3$)); MOR – Median odds ratio (exp[0.6745×√(2*varianace)]); PCV – proportional change in variance (($\text{variance}_{\text{model(n-1)}}$-$\text{variance}_{\text{model(n)}}$)/$\text{variance}_{\text{model(n-1)}}$).[33-35]

[1] =exp[(2*sqrt(variance))][5]

30-day Unplanned Readmissions

We identified 34 256 AMI hospitalizations occurring in 37 hospitals in the readmission cohort. Most hospitalizations were associated with male patients and mean age of patients was 68 (±14) years. The most prevalent comorbid conditions among the readmission cohort were coronary atherosclerosis (71%), diabetes mellitus (34%), valvular rheumatic heart disease (18%), angina pectoris (12%), iron deficiencies (12%), and history of PTCA (12%). 8% of patients discharged between 2012 and 2015 were readmitted within 30-days for an unplanned hospitalization. The median time between discharge and readmission was 10 days (IQR = [5,19]) (Table 3). Moreover, while crude readmission rates were stable throughout this period, the proportion of readmissions for a recurrent AMI decreased from 17% to 14%. The mean number of index hospitalizations per hospital was 230 (SD=171) in 2012 and 233 (SD=168) in 2015. Risk-adjusted readmission rates of 30% of hospitals fell outside the expected range of normal sampling variation, but were equally distributed below and above the 95% limits (Figures S2 (B)).

The estimated between-hospital variance in Model 0 was 0.080 (SE=0.026), hence 2% of the total variation is due to between-hospital variation (Table 4). Similarly to the mortality cohort, in the readmission cohort the inclusion of patient characteristics (Model 1) produced a 56% decline in the between-hospital variance to 0.035 (SE=0.013). The latter indicating that the odds of readmission of patients in a hospital 1 SD above average is 1.46 times that of patients in a hospital 1 SD below average. The MOR was 1.20, which represents a stronger association than 15 of patient-level variables. Adding hospital characteristics (Model 2) further reduced between-hospital variability to 0.027 (SE=0.014), a 23% relative decrease (Table 4, Figure S4). Finally, hospital size had a small but statistically significant effect on the risk of readmissions (OR=1.03, 95% CI: [1.002,1.06] for a 100-bed increase). However, this association was very heterogeneous (POOR= 49%).

Table 3. Characteristics of patients in the readmission cohort.

		Readmission cohort			
Year	**2012**	**2013**	**2014**	**2015**	**All**
#Discharges	8508	8731	8406	8611	34256
#Hospitals	37	37	37	37	37
LOS, median (IQR)	6 [4,9]	6 [4,9]	6 [4,9]	5 [4,9]	6 [4,9]
Female, % of discharges	33.6	34.0	34.1	33.9	33.9
Age, mean (SD)	68 (14)	67 (14)	68 (14)	68 (14)	68 (14)
≥ 80 years, % of discharges	22.9	23.0	22.9	23.6	23.1
Cardiovascular comorbidities, %					
MI Location, % of STEMI					
Anterior location of MI (410.0x, 410.1x)	18.7	19.2	18.3	18.8	18.7
Other location of MI (410.2x - 410.6x)	20.9	21.2	21.1	19.8	20.8
History of CABG (V45.81, 36.10-36.16)	4.2	4.1	4.3	3.7	4.1
History of PTCA (V45.82, 00.66, 36.01, 36.02, 36.05, 36.06, 36.07)	12.3	10.9	11.1	12.2	11.6
Angina Pectoris/Old Myocardial Infarction (CC 83)	13.1	12.1	12.2	12.0	12.4
Congestive Heart Failure (CC 80)	5.8	5.1	5.3	5.3	5.4
Coronary Atherosclerosis (CC 84)	67.8	70.1	73.6	73.3	71.2
Acute Coronary Syndrome (CC 81-82)	6.8	5.1	5.5	6.5	6.0
Specified Arrhythmias (CC 92-93)	5.1	4.4	5.3	5.6	5.1
Valvular or Rheumatic Heart Disease (CC 86)	17.9	18.0	17.4	16.9	17.6
Cerebrovascular Disease (CC 97-99, 103)	3.7	3.7	4.0	4.5	4.0
Stroke (CC 95-96)	1.1	0.9	1.1	1.1	1.0
Vascular or Circulatory Disease (CC 104-106)	3.0	2.6	3.1	3.1	2.9
Comorbidities, %					
Hemiplegia, Paraplegia, Paralysis, Functional Disability (CC 67-69, 100-102, 177-178)	1.5	1.6	1.7	1.6	1.6
Diabetes Mellitus (DM) or DM Complications (CC 15-19, 119-120)	34.1	34.0	34.7	34.6	34.4
Renal Failure (CC 131)	3.9	3.6	3.5	3.8	3.7
End-Stage Renal Disease or Dialysis (CC 130)	0.7	1.0	0.6	0.7	0.7
Other Urinary Tract Disorders (CC 136)	4.7	4.4	5.4	6.7	5.3
Chronic obstructive pulmonary disease (COPD) (CC 108)	5.7	5.9	6.2	6.5	6.1
Pneumonia (CC 111-113)	4.7	4.3	4.4	4.7	4.5
Asthma (CC 110)	1.3	1.2	1.5	1.8	1.4
Disorders of Fluid/Electrolyte/Acid-Base (CC 22-23)	2.6	3.2	3.5	3.8	3.3
History of infection (CC 1, 3-6)	2.3	2.5	2.4	2.7	2.5
Metastatic Cancer or Acute Leukemia (CC 7)	0.6	0.8	0.6	0.6	0.7
Cancer (CC 8-12)	2.8	3.0	3.0	3.1	3.0
Iron Deficiency or Other Unspecified Anemias and Blood Disease (CC 47)	12.6	12.3	12.2	12.6	12.4
Decubitus Ulcer or Chronic Skin Ulcer (CC 148-149)	0.5	0.6	0.7	0.7	0.6
Dementia or Other Specified Brain Disorders (CC 49-50)	3.4	3.3	4.1	4.7	3.9
Protein-Calorie Malnutrition (CC 21)	0.1	0.2	0.1	0.2	0.1
Outcome measures, %					
All-cause unplanned 30-day readmissions	7.8	7.9	7.9	7.8	7.8
Time to readmission, Median [IRQ]	11 [5,19]	10 [5,19]	9 [4,17]	12 [6,19]	10 [5,19]
AMI unplanned 30-day Readmissions (% of all-cause 30-day readmissions)	17.4	14.9	13.6	13.6	14.9

LOS – Length of stay; IQR – Inter quartile range; SD – Standard deviation; MI – Myocardial infarction; CABG - Coronary Artery Bypass Graft; PTCA – Percutaneous Transluminal Coronary Angioplasty; CC – Condition category; DM – Diabetes Mellitus.

Table 4. Risk-adjusted odds ratios for 30-day all-cause readmission following hospital discharge with AMI. Age centered at 68 years, northern region used as reference class in geographical location. Bold font indicates statically significance odds ratios.

Model	**Model 0 (Empty model)**		**Model 1**			**Model 2**		
Covariate	OR	95% CI	OR	95% CI		OR	95% CI	
Intercept, Estimate (SE)	**-2.4474**	**(0.05281)**	**-2.9388**	**(0.06284)**		**-3.0865**	**(0.1159)**	
Patient characteristics								
5-year change increase			**1.20**	**1.18**	**1.22**	**1.20**	**1.18**	**1.22**
Female vs, Male			0.95	0.87	1.04	0.95	0.87	1.04
History of CABG			1.01	0.84	1.23	1.01	0.84	1.23
History of PTCA			1.07	0.93	1.23	1.08	0.94	1.24
Angina Pectoris/Old Myocardial Infarction			1.09	0.96	1.23	1.09	0.96	1.24
Congestive Heart Failure			**1.33**	**1.13**	**1.57**	**1.32**	**1.12**	**1.56**
Coronary Atherosclerosis			**0.83**	**0.75**	**0.91**	**0.83**	**0.76**	**0.92**
Acute Coronary Syndrome			1.03	0.87	1.22	1.03	0.87	1.22
Specified Arrhythmias			1.06	0.90	1.25	1.07	0.91	1.26
Valvular or Rheumatic Heart Disease			**1.24**	**1.12**	**1.37**	**1.26**	**1.14**	**1.40**
Cerebrovascular Disease			**1.21**	**1.03**	**1.43**	**1.21**	**1.03**	**1.43**
Stroke			0.99	0.71	1.37	0.98	0.71	1.36
Vascular or Circulatory Disease			**1.29**	**1.06**	**1.57**	**1.29**	**1.06**	**1.56**
Hemiplegia, Paraplegia, Paralysis, Functional Disability			**1.35**	**1.05**	**1.74**	**1.36**	**1.05**	**1.75**
Diabetes Mellitus (DM) or DM Complications			**1.35**	**1.24**	**1.46**	**1.35**	**1.24**	**1.47**
Renal Failure			**1.26**	**1.04**	**1.53**	**1.26**	**1.04**	**1.52**
End-Stage Renal Disease or Dialysi			1.06	0.73	1.54	1.05	0.73	1.53
Other Urinary Tract Disorders			**1.31**	**1.14**	**1.52**	**1.33**	**1.15**	**1.53**
Chronic obstructive pulmonary disease			**1.35**	**1.18**	**1.56**	**1.36**	**1.18**	**1.57**
Pneumonia			**1.17**	**1.00**	**1.36**	1.16	1.00	1.36
Asthma			0.71	0.49	1.01	0.71	0.49	1.01
Disorders of Fluid/Electrolyte/Acid-Base			1.18	0.98	1.42	1.18	0.98	1.42
History of infection			1.16	0.95	1.44	1.16	0.94	1.43
Metastatic Cancer or Acute Leukemia			**1.77**	**1.20**	**2.60**	**1.77**	**1.20**	**2.61**
Cancer			1.04	0.85	1.28	1.04	0.85	1.28
Iron Deficiency or Other Unspecified Anemias and Blood Disease			**1.45**	**1.30**	**1.62**	**1.45**	**1.31**	**1.62**

Decubitus Ulcer or Chronic Skin Ulcer			1.06	0.73	1.54	1.06	0.73	1.55
Dementia or Other Specified Brain Disorders			**1.32**	**1.12**	**1.55**	**1.32**	**1.12**	**1.55**
Protein-Calorie Malnutrition			1.72	0.86	3.44	1.73	0.86	3.46
Anterior location of MI			**1.32**	**1.18**	**1.47**	**1.32**	**1.18**	**1.48**
Other location of MI			0.95	0.84	1.07	0.95	0.84	1.07
Hospital characteristics								
100-case increase in AMI volume (centered at the mean)						0.96	0.89	1.03
POOR						49%		
100-bed increase (centered at the mean)						**1.03**	**1.00**	**1.06**
POOR						49%		
Teaching vs, non-teaching						1.11	0.89	1.39
POOR						32%		
Catheterization lab availability (yes vs, no)						0.99	0.80	1.22
POOR						48%		
Cardio-thoracic surgery capacity (yes vs, no)						1.04	0.80	1.36
POOR						43%		
Geographic location								
North						1.00		
Alentejo or Algarve						1.24	0.96	1.59
POOR						18%		
Center						1.11	0.89	1.39
POOR						32%		
Lisbon						1.21	1.00	1.48
POOR						20%		
Variability components	Estimate	Standard error	Estimate	Standard error		Estimate	Standard error	
Between-hospital variance	0.080	(0.026)	0.035	(0.013)		0.027	(0.014)	
ICC	0.024		0.011			0.008		
OR between a hospital ±1 SD relative to the average hospital[1]	1.76		1.46			1.39		
MOR	1.31		1.20			1.17		
PCV			56%			23%		
C-statistic	0.58	(0.01)	0.72	(0.01)		0.72	(0.01)	

SE – Standard error; OR – odds ratio; CI – Confidence interval; POOR – proportion of opposed odds ratios ($\phi(-\beta/(\sqrt{2}\times\text{variance}))$, where ϕ represents the cumulative distribution function for the normal distribution) ; ICC – Intraclass correlation coefficient (variance/(variance+$\pi^2/3$)); MOR – Median odds ratio (exp[0.6745×√(2*varianace)]); PCV – proportional change in variance ((variance$_{model(n-1)}$-variance$_{model(n)}$)/variance$_{model(n-1)}$).[33-35]

[1] =exp[(2*sqrt(variance))][5]

DISCUSSION

In this study, we used a large contemporary dataset of administrative hospital data, covering all mainland Portuguese public hospitals, to assess the impact of patient and hospital characteristics on between-hospital variability associated with the risk of in-hospital mortality and 30-day unplanned readmissions in AMI patients. Health systems should provide low global adverse event rates with health care provided on equal terms regardless of the hospital in which patients are treated.[36]

One in every ten patients treated for AMI in public Portugal hospitals do not survive. Which indicates no improvements from the previous decade as suggested by the comparison of our results with those in previous studies.[7,9] Variance across hospitals regarding the risk of in-hospital mortality declined over 50% after controlling for patient characteristics - the odds of mortality of a patient admitted to a moderately high risk hospital is 2.08 times of that of patient admitted to a moderately low risk hospital. These odds remained substantial even after adjusting for hospital characteristics. Therefore, supporting that the risk of mortality is heterogeneous across hospitals and heterogeneity remains even among hospital with similar characteristics. Patients admitted to hospitals with lower AMI case volume or to hospitals located in Alentejo or Algarve and Lisbon seem to be more likely to die than patients in higher caseload or northern hospitals respectively. Even though hospital AMI volume and geographical location may explain only a small share of hospital-level variance (4%) and to have heterogeneous associations with mortality (i.e. large POOR), an in-depth understanding of regional variations and the impact of caseload practices on in-hospital mortality are needed to ensure consistent quality across the country.

Only 8% of AMI inpatient survivors were re-hospitalized within 30 days after discharge with an unplanned admission during 2012-2015. This figure represents about half of readmissions rate reported for US,[5,37,38] however between-hospital variance adjusted to patient case-

mix observed by Krumholz *et al*. was approximately two thirds of that observed in this study (0.023 (SE=0.005) vs. 0.035 (SE=0.013)).[5] This suggests that overall Portugal hospitals have lower readmission rates than US hospitals, yet in the US the performance across hospitals is more consistent. Furthermore, while variability across hospitals seems to be substantially explained by the patient case-mix of hospitals, hospital characteristics also explained an additional 12% of the initial variability across hospitals (PCV=23%). Patients discharged from larger hospitals are, on average, more likely to be readmitted than those discharged from smaller hospital – all else equal, a 100-bed increase in hospital size is associated a 3% increase in the odds of an urgent readmission. However, this association is extremely heterogeneous (POOR=50%) therefore it is very likely to find a patient discharged from a smaller hospital with higher odds of readmission when compared to a similar patient discharged form larger hospital.

Even though the proportions of variability explained by hospital were only 8% and 2% in the mortality and readmissions cohorts respectively, the MORs observed were as high as a majority of patient-level variables ORs. Therefore, our findings suggest that hospital represents a contextual effect in both mortality and readmissions as relevant as a patient characteristic. Hospitals are not performing homogeneously and the risk of patients tends to be consistently good in some hospitals and consistently poor in other hospitals. However, while hospital characteristics substantially explain this effect in readmissions, the same was not observed for the mortality cohort – practically no between-hospital variability was explained by hospital characteristics. Therefore, a large portion of variability between hospitals remains not modeled by our choice of hospital characteristics and further investigation is necessary.

Awareness of such behaviors should be incorporated in health policies aiming at improving quality of care of AMI patients.[36] For example, it would not be sensible to direct measures

to improve mortality to all hospitals since the risk seems to vary dramatically across hospitals, with some hospitals excelling. Measures should rather be addressed to specific hospitals depending on their risk level, while particular attention should be given to hospital policies as they relate to caseload and practices.

Limitations

This study has several limitations to consider. First, because linkage between hospital claims data and the vital statistics database in Portugal was not available, it is not possible to distinguish between patients discharged alive who died within 30 days of discharge from those who survived and have not been readmitted within the 30-day time window. Moreover, even though the vast majority of inpatient hospitalizations occur in public hospitals any unplanned readmissions taking place in private hospital is cannot be identified. While we believe this will be unlikely if a patient is readmitted with a recurrent AMI other emergencies (e.g. COPD) may be lost. Second, for efficiency purposes of the Portuguese National Health Service most hospitals were merged into hospital centers and the individual hospitals became untraceable. While we believe that hospitals within the same hospital center still represent a contextual effect, it is possible that in some cases there is variability among hospitals within the same hospital center. Third, hospital claims data lack detailed information about the patient's clinical characteristics, on the other hand, we used a validated model based on claims data [5] and correspond to the most comprehensive hospital database in Portugal, including the vast majority of inpatient hospitalizations in Portugal. Finally, we fixed hospital-level characteristics to a single year after observing that, in general, the characteristics did not change of our study period with the exception of AMI volume. However, for simplicity, characterized hospitals according to their AMI volume in the year 2011.

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CONTRIBUTORS

ATP oversaw the overall study implementation and ATP, SL and ACP designed the study and supervised the choice of data analysis. ML, FL and AF contributed for the identification of hospital episodes. ML, VA and AF implemented the data analysis. ML and VA wrote the initial draft of the present paper. All authors critically reviewed and approved the final manuscript**.**

COMPETING INTERESTS

Nothing to declare

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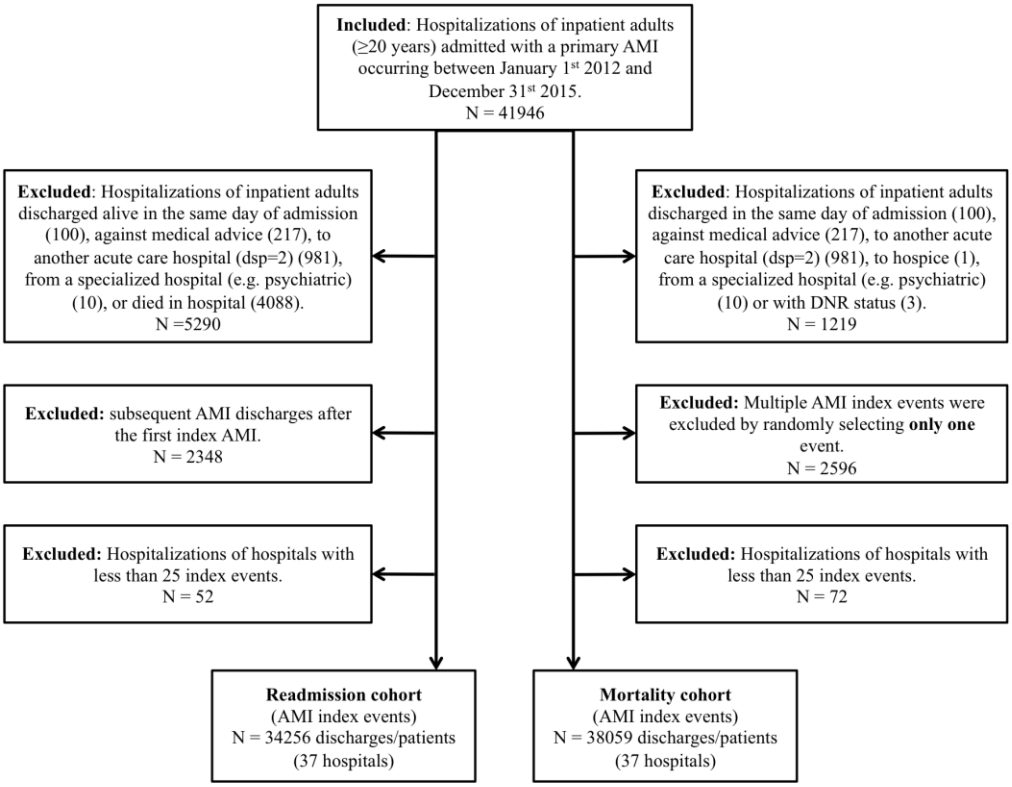
FUGURE

Figure 1. Diagram flow of samples selection.



AMI – Acute myocardial infarction; dsp – disposition status of patient.

5 Discussion and recommendations

This chapter provides a general discussion of results obtained in the three papers that compose this thesis. Furthermore, building on the experience and insights gained throughout this work, we propose a series of recommendations and future research addressing the impact of our research in health policies in CHD health care; and addressing limitations and strengths in the utilization of administrative data sources for health services research within the context of CHD.

5.1 Implication of main findings

Transatlantic comparisons, conducted in the two first papers of this thesis, revealed differences between Portugal and the US in the epidemiologic risk profiles of the populations, in the health technologies and services available, and in the quality of care provided for coronary heart disease treatment. Variations across hospitals within each country were dramatically different between the two countries, with Portugal exhibiting an alarming 2-fold risk hospital heterogeneity.

Our findings indicate that the US general population exhibits a higher risk profile when compared to that of Portugal (Lobo et al., 2017b), based on the prevalence of hypertension, diabetes, smoking, hypercholesterolemia, and overweight/obesity, which is concurrent with the larger AMI morbidity observed for the US (Lobo et al., 2017a, Lobo et al., 2017b). After narrowing down the scope of our analysis to AMI patients (Lobo et al., 2017a), the Portuguese AMI population reveals a higher share of STEMI cases when compared to the US, yet comorbidity conditions are more frequently documented in the US AMI population. These results are concurrent with previous findings reporting a higher prevalence of STEMI in European countries relative to the US.(Organisation for Economic Co-operation and Development, 2018, Puymirat et al., 2013, Santos et al., 2009, Smith et al., 2013, Yeh et al., 2010)

With respect to our analysis focusing on access to new health technologies, we observed that medical devices in the US receive market approval later than in Portugal (assessed based on dates of market approval of the first medical model within therapeutic classes). Only four of the sixteen devices reviewed were available first in the US and, on average, it took 22 months longer in the US than in Portugal to approve the first device model. However, the initial advantage may not be materialized into an effective advantage, since adoption of new medical devices into routine use is likely to exhibit a different lag pattern, one that seems to dilute this initial advantage. For instance, there was no lag between countries regarding the adoption of intravascular brachytherapy despite market approval occurred one year earlier in Portugal. Faster diffusion of devices such as the DES, *Mitraclip* and TAVR, were more likely in the US than Portugal.(Lobo et al., 2015, Lobo et al., 2017b) Diffusion of newly approved medical devices into routine practice requires significant investment, both time- and money wise, in health professionals training and adapting structural organizations particularly when medical devices represent a truly innovative alternative to previous healthcare approaches. Moreover, early recommendations of use based on sound scientific evidence and continuous monitoring of clinical practice patterns may encourage a more swift and inclusive adoption in response to clear indications of use and identification of unmet needs.

Unlike medical devices, based on the list of selected drugs in Paper 1, commercialization of drugs begins earlier in the US than in Portugal. This was somewhat expected because the US represents a much larger market share and in which drugs reach higher prices than in Portugal and therefore is more attractive to

the pharmaceutical industry.(Danzon et al., 2005, Kanavos et al., 2011) The vast majority of EU countries use external price referencing to establish prices of new drugs. The fear that low price might jeopardize pricing prospects elsewhere may further detract distributors from launching new drugs into countries with lower prices.(Kanavos et al., 2011) Moreover, mechanisms to determine which pharmaceuticals are reimbursed under the NHS may further delay routine outpatient use of drugs in Portugal. That has been the case of *clopidogrel*, which effective commercialization was delayed by 6 years from market approval.(Stolk et al., 2008)

AMI in-hospital patient management assessed through administrative hospital data revealed that coronary revascularization procedures are more frequent in the US than in Portugal. Surgical procedure use in particularly varied by a staggering 5-fold among the two countries in 2010 even after controlling for the effect of age and sex.(Lobo et al., 2017a) Results from our first study (Lobo et al., 2017b) regarding the number of centers per capita providing advanced cardiovascular medical procedures in the two countries support these differences. Other international comparisons also report a more frequently use of these procedures in the US when compared to what is practiced in several European countries (Herlitz et al., 2003, McGovern et al., 1997, McNamara et al., 2014, Vargas et al., 2001), fueling concerns over suboptimal care either due to an over or under use of such in-hospital procedures in the two sides of the Atlantic respectively.(Cutler, 2014) Importantly these concerns may be within the context of effectiveness of health services provided, this study only scratches the surface of this discussion by contributing with few but important findings. Namely, in-hospital mortality declined in both countries during the period between 2000 and 2010, yet, by 2010, the age-sex-adjusted in-hospital mortality rate in Portugal was twice of that of the US. Revascularization procedures use remained high in the US throughout this period while it significantly increased in Portugal. Moreover, revascularization use was associated with improved survival at discharge in both countries but was larger in Portugal. The latter seemed to explain part of the annual decline observed in Portugal but not in the US. Therefore supporting that the increasing use of revascularization procedures in Portugal may have been decisive for improved outcomes among AMI patients in this country during the period between 2000-2010.

The differences we observed need to be interpreted in light of the characteristics of health systems compared. Many factors contribute to health services effectiveness. Successful in-hospital care is dependent both on pre- and in-hospital care provided as well as the risk of patients. For example, a poor emergency system with deficient services for patient referencing may jeopardize the chance the patient receives a primary PCI. In fact, age-sex-adjusted death rates based on vital statistics data indicate comparable AMI mortality between Portugal and the US (Lobo et al., 2017b), hence supporting comparable quality of overall health care between these countries. Reconciling in-hospital mortality with mortality based on vital statistics is not straightforward and different factors could explain the conflicting results. First, hospital administrative databases capture patients who were admitted and thereby tell us nothing of those who were not.(Bottle et al., 2013) Therefore, while inaccurate cause of death in death certificates may result in spurious vital statistics and could alone explain inconsistencies, poor pre- and post-hospital care, or unaffordability to obtain proper care in the US could explain that some deaths may occur outside the hospital where treatment was provided and result in apparent favorable in-hospital mortality. Second, according to Papanicolas and Jha (2017), the US health care system is optimized for short lengths of stay, tolerating a somewhat higher

readmission rate (but fewer total days in the hospital per population) when compared to European countries. This is concurrent with our findings indicating that the length of hospital stay in Portugal is, on average, approximately 3 days longer than hospitalizations in the US. In our opinion, this could further lead to deaths outside the hospital or during hospice or long term care, which would not be included in this cohort. Also on this note, the follow up time of patients is inherently constrained to the hospital length of stay when in-hospital mortality is adopted as the outcome measure. The latter may have biased comparisons, given the reliance of the US health system efficiency on hospital short stays. Whenever possible, linkage between claims data and vital statistics is advised, and outcome measures such as 30-day or 1-year mortality or survival should be preferred for international comparisons purposes. Notwithstanding this caveat, in-hospital mortality captures the patient's expectation of health care while in the hospital. Moreover, we analyzed in-hospital survival to minimize potential differences in follow up time.

Another major insight relates to differences observed in variations in in-hospital survival across hospital within the two countries. Between-hospital variation was smaller in the US relative to Portugal – the hazard of dying in a high-mortality US hospital was essentially no different than that in a modestly low mortality hospital, the hazard ratio was equal to 1.03; in Portugal, this hazard ratio was 2.65. One would expect that the public-based health system of Portugal, structured based on a NHS, out of obligation to provide universal coverage and pressured to control costs and disparities, would be able to optimize resources available to achieve a more homogeneous quality of health care services across hospitals when compared to the US, which can be seen as multiple systems providing health care services to a population that is 30 times larger than Portugal. The lack of validated AMI health care quality measures in Europe (Schiele et al., 2017), the strong tradition of monitoring quality of care indicators in the US with demonstrated association in health care quality improvements (Gupta et al., 2016, Jha et al., 2005, Joynt et al., 2012, Krumholz et al., 2011, Krumholz et al., 2006, Lindenauer et al., 2007) could explain these differences. However, other factors, such as hospital characteristics, not included in the model, or other relevant clinical information not observable in administrative data (e.g. pain/door-to-balloon times) could aid explaining the variation across hospitals in Portugal. Additionally, differences in organization of health systems mentioned earlier of the US prioritizing for short time hospital stays could again explain some of the minimal hospital heterogeneity observed for the US, since one would expect this to be more likely if standardized acute care services are optimized during the patient's first hospital encounter.

Despite potential caveats, our findings are suggestive of disconcerting variations in health care quality across hospitals in Portugal motivating an investigation on the pathways through which hospital effects operate. With this in mind, the last study of this thesis intended to assess whether hospital characteristics could partly explain variations across hospitals in Portugal. This opportunity was leveraged by using data reporting over a more recent period of time and by analyzing an additional quality of care outcome – readmissions.

Results based on data of hospitalizations occurring between 2012 and 2015 indicate that 10% of AMI patients die in hospital while 8% of AMI inpatient survivors are re-hospitalized within 30 days after discharge with an unplanned admission. Despite slight declines of crude in-hospital mortality throughout the period (2012:11% to 2015:10%), these findings (10% in-hospital mortality) suggest no improvement relative to 2010.(Lobo et al., 2017a) However, it is possible that previous estimates

were underestimated since patient identification was not available prior 2011 and we were not able to identify episodes of care, which might have increased the denominator and underestimated rates.

To our knowledge, all-cause 30-day unplanned readmission occurring after an AMI discharge has never been studied in Portugal, hence expanding existing knowledge on AMI health care quality in Portugal.

Eight percent of the variability in the mortality cohort was attributed to a hospital contextual effect. Hospital case-mix explained 51% of this variation. Yet, forty-six percent of hospitals exhibited risk-standardized in-hospital mortality rates (RSMR) outside the expected range of normal sampling variation, half of which were above the upper 95% limit. Among these hospitals, those with considerable volume of cases, and hence RSMR estimates are assumed more reliable, raise more concerns (Figure S2 of supplementary data 7.6). The odds of in-hospital mortality of patients in a hospital 1 SD above average is 2.08 times that of patients in a hospital 1 SD below average. Hospital characteristics explained a modest additional 2% of hospital heterogeneity in the mortality cohort. Importantly, hospitals in some geographical location and those with fewer AMI caseloads were significantly associated with increased risk of mortality. While these associations may be very heterogeneous (large proportion of opposed odds ratios (POOR)), further investigation addressing geographical disparities is urgently needed.

Between-hospital variability was smaller in the readmission cohort, when compared to the mortality cohort. Only 2.4% of the variability was attributed to a hospital contextual effect. Hospital case-mix explained 56% of this variation.

Risk-standardized readmission rates (RSRR) of 30% of hospitals fell outside the expected range of normal sampling variation, but were equally distributed below and above the 95% limits. A patient's odds of readmission in a hospital 1 SD above average relative to a hospital 1 SD below average is 1.46. Hospital characteristics explained an additional 12% of hospital heterogeneity in the readmission cohort and patients discharged from larger hospitals were significantly associated with increased risk of readmission.

Health systems should provide effective health services that are equally accessible regardless of the hospital treating the patients.(Austin et al., 2017, Bradley et al., 2010, Campbell et al., 2000, Ghaferi et al., 2009, Peiró and Maynard, 2015) This does not mean that all hospital should provide the same type of health services, but it assumes that patients should be promptly referred to the hospital with services that best suit their needs and that both referencing and health services are effective. The last study of this thesis provides insights into these questions by characterizing heterogeneity in quality of care in AMI patients across hospitals in Portugal. To our knowledge, this is the first study ever quantifying hospital heterogeneity in AMI quality of care in Portugal using two cohorts for this purposes – a mortality cohort to study in-hospital mortality and a readmission cohort to study all-cause 30-day unplanned readmissions.

Our findings suggest that hospital represents a contextual effect as relevant as a patient characteristic. This means that the risk of patients tends to be consistently larger in some hospitals and consistently smaller in other hospitals. Forthcoming health policies aiming at improving quality of care of AMI patients should incorporate such information. In our opinion these would seem to be more efficient if addressed to specific hospitals depending on their risk level, while particular attention should be given to hospital policies as they relate to caseload and practices.

While it seemed an “almost impossible mission” (Seabra, 2017), in our opinion this tale of two contrasting healthcare systems proved to be a valuable source of insight into questions related with quality of health care in AMI patient management, finding support among our peers (Chen et al., 2017). We believe that its merits lie mainly in the utilization of nationwide representative datasets, endorsed-based risk-adjustment model, hierarchical models, and an understanding of the main features of the two health systems as well as these could affect interpretations of results. However, important limitations regarding data quality issues and information captured by these datasets have also been acknowledged and prevented us at times to look into further details.

5.2 Recommendations and future investigation

5.2.1 Considerations about data quality - issues and strengths

Like in other research fields, quality of data is of paramount importance in HSR. In the course of this study we encountered several issues with the data sources analyzed. We believe that raising awareness for such issues is crucial to improve data quality and produce more reliable information, which ultimately will better serve decision-makers to address and improve health care quality. With this purpose, we make some recommendations related to data quality based on our experience.

1 *Infarmed* holds deficient historical data regarding marketing dates on drugs for in-hospital use and medical devices:
   - Dates of beginning of effective commercialization of drugs for in-hospital use only (e.g. GP IIb/IIIa inhibitors) may not translate the beginning of use of these drugs in Portugal. Several observational studies report the use of those drugs prior the dates provided by *Infarmed*; Since there was no explicit legal framework regarding pricing of medicines used in hospitals up until 2006 in Portugal (Ministério da Saúde, 2006), these medicines could have been purchased by hospitals directly to manufacturers even if these were not marketed in Portugal.
   - Whenever a new generation of a medical device model is approved, dates of market approval are updated onto the previous generation model and historical information is lost. With regards to coronary DES, this means that dates of approval of the first generation Cypher (Cordis Corp.) and Taxus (Boston Scientific) were replaced by recent models. This problem should be solved when the European Database on Medical Devices (EUDAMED) becomes fully operational collecting “Data related to certificates issued, modified, supplemented, suspended, withdrawn or refused according to established procedures”.(European eGovernment Services, 2017)

2 Limitations and strengths of administrative hospital data:

   <u>Limitations</u>:
   - Regardless of country, administrative hospital data lack on detailed information regarding patient’s clinical characteristics. In the context of this thesis, this limitation encompass the omission of information regarding

coronary anatomy, extent of disease, ejection fraction, surgical risk, pain/door-to-balloon times, which are relevant predictors of mortality in these patients.

- Coding consistency and accuracy lacks assessment for Portugal. Problems have been identified regarding documentation of type of coronary stents implanted. Coding inconsistencies across hospitals could undermine adjusted comparisons.
- The sampling procedure carried to obtain the Nationwide Inpatient Sample (NIS) breaks patient traceability and may result in samples in which, due to chance, AMI hospitalizations are either over- or under-represented.
- Patient traceability in Portugal data reporting to the period before 2011 is limited to hospitalizations occurring within the same hospital and the same year.
- Outcomes are restricted to events occurring during the hospital stay. The utilization of in-hospital mortality as a healthcare quality metric has been criticized previously.(Kristoffersen et al., 2012, Reineck et al., 2014) Particularly in international comparisons and/or hospital comparisons, variation in discharge patterns may result in a biased quality of care assessment.

Strengths:

- Systematically collected in both countries for over two decades mainly for hospital budgeting/financing purposes (Administração Central do Sistema de Saúde, 2017) and regularly audited.
- Holds a nationwide representativeness in both countries. In Portugal these data includes all inpatient hospitalizations occurring in all mainland public hospitals, representing the vast majority of inpatient cases in Portugal. In the US, the NIS is the largest publicly available all-payer inpatient healthcare database, consisting of a nationwide representative 20% stratified random sample of discharges from short-term non-federal American hospitals.
- By capturing actual clinical practice patterns, hospital administrative data may afford insights relevant to broader populations of patients, providers and health care systems.
- When compared with prospective registry and clinical trial data, administrative data is considerable less expensive.
- Discharge- and patient-level analyses with administrative health data are currently possible for Portugal. Since 2011, ACSS provides a patient identification variable, allowing for patients traceability across hospitals and across years. Patient traceability holds several advantages: it allows using information from prior hospitalizations to ascertain comorbidities of patients; identifying all hospitalizations corresponding to inter-hospital transfers within the same episode of care and therefore conduct patient-level analysis and or refine definition of denominators; and identifying patient's readmissions hence adding value to the process of health care quality assessment by introducing an additional outcome measure.

5.2.2 Recommendations and future investigation

Based on our results and data quality considerations, we make some practical recommendations regarding how to incorporate insights in health policies, future

work addressing research questions that have emerged from this study, and strategies to overcome data issues and maximize data strengths.

- In light of our findings supporting that hospital acts as a contextual effect, future health policies directed at improving hospital health care quality in AMI in Portugal should account for the fact that measures assuming “one size fits all” will likely be inappropriate given that it ignores that hospitals are not performing homogeneously and the risk of patients tends to be consistently greater in some hospitals and consistently lower in other hospitals. Accordingly, worst and best practices should be disseminated across all hospitals and this should then be used to elucidate on policies that might be established to direct certain kinds of patients toward appropriate types of hospitals for inpatient care.
- Metrics of variability regarding healthcare quality in AMI patient management across hospitals in Portugal could add valuable information into current programs monitoring health care quality in CHD such as the National Program for Cerebro- and Cardiovascular Diseases. Their inclusion could help raise awareness for issues related with hospital heterogeneity and engage healthcare providers and hospital directors in actions to improve disparities.
- Monitoring activities regarding hospital health care quality in Portugal should pay particular attention to geographical disparities, health care practices, and hospital size since these factors were found to be associated with increased risk of in-hospital mortality and urgent readmissions in AMI patients.
- Further investigation is urgently needed to better pinpoint and reason about patient and hospital factors associated with poorer health outcomes and responsible for the hospital heterogeneity observed, which will ultimately provide further scientific information for tailoring health policies. A large portion of variability between hospitals in Portugal remained not modeled by our choice of patient and hospital characteristics. With this in mind, we believe that future work should encompass the following aspects:
    - Because the time to receive treatment is crucial in the prognosis of AMI patients, assessing the impact of the organization of the patient referencing network and of the residence of patients in geographical disparities is an important next step.
    - Similarly, the transition of patients from acute care to cardiac rehabilitation represents a critical pathway for AMI patients with potential implications on urgent readmissions. This should also be investigated particularly in the context of large size hospitals.
    - Insights could be gained from looking into measures of process and compliance to guidelines since this might be helpful to understand the impact and maximize hospital caseload in healthcare quality, as this relate with certain high-risk group of patients.
- From our experience careful selection of inclusion and exclusion criteria increase the internal validity of studies based on hospital administrative data. Particularly when comparing different health systems, these are important tools to achieve meaningful/adequate comparability. Within the context of CHD analysis, opting for an analysis restricted on AMI cases holds better comparability across countries. Further sensitivity analysis based on type of AMI (STEMI and NSTEMI) are particular helpful to address differences in definitions of AMI across countries.

- In order to minimize bias due different practice patterns, follow up times considered for analysis should be independent from the patient's length of hospital stay and take in consideration the fact that patients may be transferred to another hospital to receive treatment. With this in mind, future research regarding comparative health care quality could benefit from:
    - Exploring distributed research networks. This refers to the incorporation of information from several data sources (e.g. hospital health care data and vital statistics). The integration of information regarding the date of death in the Portuguese hospital administrative database would capitalize greatly this database, as it would enable longer follow up times of patients (e.g. 30-day mortality, time to death), which would provide additional information regarding quality of health care, and would be less prone to bias due to variations in practice patterns across units of analysis (e.g. hospitals, countries). We strongly believe this to be possible to implement in Portugal since proof of concept has been established under the CUTEheart project. (Bacelar-Nicolau 2018) In the event that fixing a follow up time (independent from hospital stay) is unfeasible, analysis of in-hospital survival time rather than in-hospital mortality may improve comparability across countries or hospitals, if differential follow up times is suspected.
    - Developing a methodological framework to identify episodes of care taking advantage of patient traceability across hospitals such as that implemented in our third study. This improves identification of denominators reducing the risk of underestimating in-hospital mortality rates. Alternatively, excluding all discharges with a transfer to another acute care hospital status could be used with the same purpose, however, this would lead to other limitations: the discharging hospital would be always assumed responsible for the hospitalization, which could lead to less relevant interpretations if the purpose of the analysis is assessing hospital heterogeneity regarding patient mortality; procedures carried during initial/intermediary hospitalizations in episodes of care with a chain of hospital transfers with two or more hospitalizations could be lost.
- Following the approach used by CMS for Medicare data, patient identification should also be used to improve characterization of the patient's clinical information using historical data of hospitalizations available from a predefined period of time prior the index hospitalization. This provides better control of confounding effects without resorting to other sources of data.
- Prospective registry data maintained by the SPC (Sociedade Portuguesa de Cardiologia, 2018) hold detailed clinical information on the patient. Under the agreement celebrated in 2015 between SPMS and SPC (sociedade Portuguesa de Cardiologia, 2015), we believe that future work should take advantage from such agreement to incorporate data from the SPC's registries and hospital administrative data. This could further help to explain hospital heterogeneity by providing more information on patient characteristics (e.g. patient risk, door-to-needle times, etc.). Importantly, this should be used to validate models derived based on administrative data similarly to work conducted in the US (Krumholz et al., 2011, Krumholz et al., 2006), which could then be used to monitor AMI health care quality in hospitals.

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7 Supplementary material

7.1 Compatibility of variables in administrative data across countries

Table 7.1. Selection of variables in the inpatient hospital administrative data in Portugal and US.

	Portugal		US		
Variable label	**Variable available (variable name)**	**Description/Observations**	**Variable available (variable name)**	**Description/Observations**	**Need for reconciliation**
Patient demographic					
Patient identification	Yes, partially (patnum, n_ficticio_utente)	Pseudo patient identification is available. Between 2000-2010 patient id was valid only within hospital and year.	Yes, partially (UHIN)	Pseudo patient identification is available, but sampling process brakes traceability of patients.	
Gender	Yes (sexo)	1 - male; 2 - female	Yes (Gender)	1 - male; 2 - female	
Age at admission	Yes (idade)		Yes (AgeAdmit)		
Race	No		Yes (Race)		
Residence code	Yes (reside)	Patient residence based on DICOFRE classification system that maps residence up to the *freguesia* level (the smallest administrative level before street)	Yes (PL_UR_CAT4)	Is a four category urban-rural designation for the patient's county of residence	
Hospital information					
Hospital identification	Yes (hosp_id)		Yes (MDPHHospNumber)		
Hospital where patient was transferred form/to	Yes (hosp_to, hosp_from)	Information is collected but incomplete[1]	Yes (indexhosp, midlehosp, lasthosp)		
Total charges	No		Yes (zerocharge)		
Clinical information					
Admission date	Yes (data_entrada)		Yes (AdmitDt)		
Discharge date	Yes (data_saida)		Yes (DischDt)		
Length of stay (LOS)	Yes (dias_int)		Yes (LOS)	Calculated by subtracting the admission date (ADATE) from the discharge date (DDATE). Same-day stays are therefore coded as 0. Leave days are not subtracted.	LOS was operationalized as discharge data minus admission date plus one
Admission source	No		Yes (ASOURCE)	1 - Emergency department;2 - Another hospital; 3 - Other health facility including long-term care; 4 - Court/Law enforcement; 5 - Routine including births and other sources; . - missing	
Admission type	Yes (adm_tip)	1 - Elective; 2 - Urgent; 3 - *Programa de promoção de acesso*; 4 - PECLEC; 5 - Private practice; 6 - SIGIC; 7 - PACO. Categories 3, 4, 6 and 7 refer to	Yes (ATYPE)	1 - Emergency; 2 - Urgent; 3 - Elective; 4 - Newborn; 5 – Delivery/Trauma center 6 – Other; . – missing; A. – invalid; B. - Unavailable	New variables: UrgEm : 1 - Urgent/Emergency (adm_tip=2, AdmissionType=1 or 2) 2 – Elective (adm_tip=1,

		governmental programs introduced to reduce waiting lists			AdmissionType=3) 3 - Not available/missing
Cause for transfer	Yes (mot_transf)		No		
Patient disposition status	Yes (dsp)	1 - Home or self-care; 2 - Another short-term (general) hospital; 4 - Intermediate care facility or custodial/supportive care; 6 - Discharged/transferred to home under care of organized home health service organization; 7 - Left against medical advice or discontinued care; 13 – Discharged to rehabilitation hospital; 20 - Expired; 51 - Hospice- medical facility; 63 - Long-term care hospital	Yes (DISPUB92)	1 - Discharged home or self-care (routine discharge); 2 - Discharged to other short-term general hospital; 3 - Discharged Skilled Nursing Facility (SNF) ; 4 – Discharged to intermediate care facility (ICF) ; 5 – Discharged to other institution/referred outpatient services; 6 - Discharged home under home health service organization; 7 - Left against medical advice (AMA); 8 - Discharged home under home IV drug therapy provider; 9 - Not Used; 10 – Discharged to chronic hospital; 11 – Discharged to mental health hospital; 12 – Discharged to other; 13 – Discharged to rehabilitation hospital; 14 – Discharged to rest home; 15 – Discharged to shelter; 20 - Expired (or did not recover/Christian Science Patient) ; 43 - Discharged to federal healthcare facility; 50 - Discharged to hospice-Home; 51 – Discharged to hospice-Medical Facility; 62 - Discharged to inpatient rehabilitation facility; 63 - Discharged to Medicare certified long term care hospital; 65 – Discharged to psychiatric hospital or distinct unit of a hospital; 66 -Discharged critical access hospital (CAH)	New variables: Died: 1 – in-hospital death (dsp=20, DISPUB92=20); 0 – otherwise; AMA: 1 – Left against medical advice (dsp=7, DISPUB92=7); 0 otherwise Hospice: 1 – transferred to hospice (dsp=51, DISPUB92= 50 or 51); 0 – otherwise
Diagnoses	Yes (DXX1-DXX20)	Up to 20 diagnosis codes (ICD-9-CM) if reporting to 2000-2010, up to 70 if reporting to 2011 or afterwards. The first listed diagnosis (DXX1) is the principal diagnosis.	Yes (DX1-DX15)	Up to 15 procedure codes (ICD-9-CM) if reporting to 2000-2010. The first listed diagnosis (DX1) is the principal diagnosis.	New variables: DNR: 1 – do not resuscitate status (V49.86 in secondary diagnoses); 0 – otherwise AMIprimary: 1 – principal diagnosis of AMI (410.xx excl. 410.x2); 0 – otherwise
Diagnosis present on admission (POA)	Yes, partially	Collection of information regarding diagnosis present on admission was mandated in 2013 (Circular Normativa nº.8 de 04/03/2013) "Identifica se o diagnóstico estava	Yes, patially	Effective October 1, 2007, the Uniform Bill (UB) includes a POA indicator for each diagnosis field on Medicare claims. January 2011, the UB usage requirement for POA reporting was	

		presente aquando da admissão do doente, sendo: S-Yes; N – No; D – Unknown; I - Clinically undetermined; NA - Exempt from POA reporting		expanded to include hospital stays as mutually agreed for contracts with insurance programs.[3] Y – Yes; N – No; U – Unknown; W - Clinically undetermined; 1 – Exempt from POA reporting[4]	
Procedure	Yes (SRG1-SRG20)	Up to 20 procedure codes (ICD-9-CM) if reporting to 2000-2010, up to 70 if reporting to 2011 or afterwards.	Yes (PR1-PR15)	Up to 15 procedure codes (ICD-9-CM) if reporting to 2000-2010. The first listed procedure (PR1) is usually the principal procedure (i.e. the procedures performed for definitive treatment).	

Sources:

1 FREITAS, J., SILVA-COSTA, T., MARQUES, B. & COSTA-PEREIRA, A. Implications of data quality problems within hospital administrative databases. XII Mediterranean Conference on Medical and Biological Engineering and Computing 2010, 2010. Springer, 823-826.

2 https://www.hcup-us.ahrq.gov/db/nation/nis/DataElements_NIS_2004_Core_Volume1_A-M.pdf; https://www.hcup-us.ahrq.gov/db/nation/nis/DataElements_NIS_2004_Core_Volume2_A-M.pdf; https://www.hcup-us.ahrq.gov/db/nation/nis/nisfilespecs.jsp#2012NIS.

3 https://hcup-us.ahrq.gov/reports/methods/2011_05.pdf

4 https://hcup-us.ahrq.gov/datainnovations/clinicaldata/POAAddonfile042208AHRQMod.pdf

7.2 Summary description of data sources with potential use for comparative health care quality assessment

Table 7.2. List, description and availability status of datasets in Portugal and the United States.

Data name	US/ PT	Organization	Description	Available	website
Inpatient hospital database (IDD)	PT	ACSS	Portuguese inpatient discharge database that includes inpatient and outpatient data. Includes variables on demographic, diagnostic, procedure, DGR that can be linked to the DRG prices (proxy for charges).	Yes/used for Paper 2	http://www.acss.min-saude.pt http://portalcodgdh.min-saude.pt/index.php/Página_principal
SPMS data	PT	SPMS	Combines data from hospital (as in data from ACSS) with primary care settings, prescription and vital statistics data at the patient-level. Includes adult patients admitted to hospital with a primary AMI (410.xx) and discharged during the second semester of 2012. These patients are then followed through the calendar year of 2013 in the hospital, primary care and vital statistics databases. Depending on the dataset, includes information on demographics, hospital readmission, patient disposition, comorbidities, consultations, medical test/exams, diagnostics, prescribed/filled medication, prices of medication and date of death certificates.	Yes	http://spms.min-saude.pt/english-version/
National Registry for Interventional Cardiology (NRIC)	PT	SPC, CNCDC	Registry for PCI data that uses the CARDS instrument to collect information on patients demographics and disposition and procedures carried out in Portugal. Started in 2002. The number of hospital participations grew from 19 in 2002 and to all hospitals with a cath lab in 2011. (that's what they say!) Includes both public and private hospitals.	Yes but only in the form of aggregated data, we may request specific statistical analyses	http://www.spc.pt/CNCDC/ http://www.spc.pt/RegistosNacionaisSPC/Public/Login.aspx?ReturnUrl=%2fRegistosNacionaisSPC%2f
National Registry for Acute Coronary Syndromes	PT	SPC, CNCDC	Includes data on adults admitted with an acute coronary syndrome. Contains information about demographic, diagnostic elements, risk factors and history cardiovascular and non-cardiovascular	Yes/Same as above, access to aggregated data.	http://www.spc.pt/CNCDC http://www.spc.pt/DL/Home/listdestaques/Definicoes_das_Variaveis_RNSCA_

(NRACS)			events, characteristics of the acute event, medication, revascularization approach among others. Data is collected using the instrument described in links (in Portuguese).		2aFase_Final.pdf anamariagomes@med.up.pt
INFOMED – Drugs database	PT	INFARMED	Open access database that contains information regarding the identification of brands/generics and time periods for introduction (approval, commercialization) of medicines in Portugal. This is Portuguese equivalent to Drugs@FDA.	Yes/used for paper 1	http://www.infarmed.pt/91nformed/inicio.php
Registry of approved high-risk medical devices	PT	INFARMED	Open access database contains information regarding high-risk medical devices (Class III, active implantable, for in vitro diagnosis) that are currently approved in the Portuguese market. Contains information regarding manufacturer, distributor, brand, model, and device designation.	Open access	http://www.infarmed.pt/portal/page/portal/INFARMED/DISPOSITIVOS_MEDICOS/REGISTO_DE_DM_E_DIV/DISTRIBUIDORES
Prices of hospital episodes and medical exams	PT	Health Ministry	DRG prices tables are official tables published by the government and link each DRG with a price, relative weight, and normal length of stay for each DRG. These tables are commonly used as proxies of hospital charges/cost.	Open access through the dre.pt	
Hospital Benchmarking indicators	PT	Health Ministry	Presents benchmarking indicators (access, quality, performance, efficiency) for public hospitals and primary care centers. Years reporting: 2013, 2014.	Open Access	http://benchmarking.acss.min-saude.pt/monitormensal/enquadramento/objetivos.aspx
Characteristics of PT hospitals – annual economic reports	PT	ACSS	Annual accounting reports of Portuguese public hospitals. Provide a characterization of hospitals including information on the number of beds per ward, productivity, spending, length of stay, human resources, among others. Reports vary across ears and hospitals in respect to structure/information available.	Open Access	http://www.acss.min-saude.pt/Publicações/HospitaisEPEeSPA/HospitaisEPEeSPA/RelatórioseContas/tabid/230/language/pt-PT/Default.aspx
Portugal data about outpatient prescriptions	PT	SPMS, CCF	The CCF is the organization responsible for clearance of reimbursement of community pharmacies; medical care providers with agreement with the government for prescription and patient care under the SNS. CFF holds information on data at the patient-level of outpatient	No	https://www.ccf.min-saude.pt/portal/page/portal/publico

			drugs (prescribed under the SNS). The data from SPMS contains two tables where the source is the CFF. One from prescribed drugs and another from filled prescriptions. In these tables there's no information on the date of prescription but there is information on the price.		
HCUP (Healthcare Cost and Utilization Project)	US	AHRQ	National (Nationwide) Inpatient Sample (NIS) The National (Nationwide) Inpatient Sample (NIS) is the largest publicly available all-payer hospital inpatient care database in the United States. Researchers and policymakers use NIS data to identify, track, and analyze trends in health care utilization, access, charges, quality, and outcomes.	Yes/used for Paper 2	http://www.hcup-us.ahrq.gov/nisoverview.jsp
MA Hospital Inpatient Discharge Database (HIDD)	US	CHIA	Comprehensive patient-level information including socio-demographics, clinical data, and charge data.	Yes	http://chiamass.gov/acute-hospital-case-mix-data-how-to-apply/
MA Outpatient Emergency Department Database (ED)	US	CHIA	Patient demographics, clinical characteristics, services provided, charges, and hospitals and practitioner information, as well as mode of transport/data elements that are similar to those contained in the inpatient and observation stay databases, with some additions relevant to the ED setting.	Yes	http://chiamass.gov/acute-hospital-case-mix-data-how-to-apply/
Outpatient Hospital Observation Discharge Database (OOA)	US	CHIA	Comprehensive patient-level information, including socio-demographics, clinical data, and charge data	Yes	http://chiamass.gov/acute-hospital-case-mix-data-how-to-apply/
Massachusetts Data Analysis Center clinical registry (MassDAC);	US	CHIA	High-quality data that contains detailed information on cardiac surgery and PCI on adults performed under inpatient setting only	Yes	http://www.massdac.org/
Massachusetts all-payer Claims Database (APCD).	US	CHIA	Database comprised of medical, pharmacy, and dental claims, and information about member eligibility, providers, and products from public and private payers	Not available	http://chiamass.gov/ma-apcd/

7.3 Standardization and Risk-adjustment formulas

Rate standardization

For the purposes of illustration consider that we are interested in estimating death rates in a study population controlling for the confounder effect of age. In other words we are interested in computing the age-standardized mortality rate of a study population using a standard population for reference.

Let

Study population

D_i – the number of deaths in age interval i,
P_i – population of age interval i in the study population
The age-specific death rate (R_i) is then given by
$R_i = D_i / P_i$

$D=\sum_i D_i$ – the number of deaths in the study population
$P=\sum_i P_i$ – the total study population
R=D/P – crude death rate in the study population

Standard population

P_{si} - the standard population in age interval i.
$P_s=\sum_i P_{si}$ – the total standard population
The standard weights (w_{si}) are then given by
$w_{si} = P_{si} / P_s$ and $\sum_i w_{si} = 1$

R_{si} - the age-specific death rate in age interval i in the standard population
R_s – crude death rate in the standard population

Then

Direct standardized mortality rate (DSMR)

$$DSMR = \sum_i w_{si} \times \frac{D_i}{P_i} = \sum_i w_{si} \times R_i$$

Indirect standardized mortality rate (ISMR)

$$ISMR = \sum_i \frac{D}{R_{si} \times P_i} \times R_s = SMR \times R_s$$

where SMR is the standardized mortality ratio.

Under the assumptions of homogeneity of risk across individuals among strata and that the number of deaths in a population follows a Poisson distribution then,

$$Var(DSMR) = \sum_i (w_{si})^2 \times Var(R_i) = \sum_i (w_{si})^2 \times \frac{{R_i}^2}{D_i}$$

which can then be used to compute the 95% confidence interval:

$$95CI_{DSMR}: DSMR \pm 1.96 \times \sqrt{Var(DSMR)}$$

For comparisons between two standardized rates ($DSMR_1$ and $DSMR_2$) the logarithm of the ratio between rates is assumed to follow a normal distribution with mean zero and variance as

$$Var\left(log\left(\frac{DSMR_1}{DSMR_2}\right)\right) = Var(\log(DSMR_1)) + Var(\log(DSMR_2)) =$$
$$= \frac{1}{{DSMR_1}^2}Var(DSMR_1) + \frac{1}{{DSMR_2}^2}Var(DSMR_2)$$

which can again be used to compute the 95% confidence intervals.(http://support.sas.com/documentation/cdl/en/statug/68162/HTML/default/viewer.htm#statug_stdrate_details14.htm.)

Generalization of indirect standardization using regression models

For illustration purposes consider that we are interested in comparing death rates in AMI patients across different hospital. Differences in hospital-specific mortality rates may be distorted by differences in the underlying risk of patients treated at the hospitals. Therefore, distorting our perception of differences in hospital performances. One way to compare hospitals correcting for patient case-mix is through risk-adjusted hospital rates.

Let Y_j=1 if the jth AMI patient dies and 0 otherwise, j=1,…, N. Then

$Y_j \sim Bernoulli(p_j)$, where $E(Y_j) = p_j$

$logit(p_j) = \beta_0 + \beta_1 X_1 + \cdots + \beta_p X_p$
where
p_j is the probability of death of patient j
X represents the potential confounder variables
β is the predicted log odds mean change of a patient's death associated risk with the presence of the corresponding comorbid condition/risk factor X.

Hospital-specific standardized mortality rate corresponds to the number of observed deaths divided by the number of expected deaths for a specific hospital multiplied by the crude death rate for the whole sample of hospitals. Where the number of expected death is obtained by summing predicted probabilities based on the coefficients of the logistic regression model fitted using the sample of patients from all hospitals as follows:

$$\frac{\sum_j Y_{jh}}{\sum_j E(Y_{jh})} \times \bar{Y} = SMR \times \bar{Y}, \quad \bar{Y} = \frac{\sum_j Y_j}{N}$$

where SMR is the hospital-specific risk-adjusted mortality ratio. This approach implicitly uses the whole sample as the standard population representing the average hospital performance.

7.4 Paper 1 supplementary data

The Atlantic divide in Coronary Heart Disease: Epidemiology and Patient Care in the US and Portugal

Lobo MF, Azzone V, Resnic FS, Melica B, Teixeira-Pinto A, Azevedo LF, Freitas A, Nisa C, Nicolau-Bacelar L, Rocha-Gonçalves F, Pereira-Miguel J, Costa-Pereira A, Normand SL

Supplementary Data

Regulatory mechanisms of health technologies

The Food and Drug Administration (FDA), in the US, and the *Autoridade Nacional do Medicamento e Produtos de Saúde I.P.* (INFARMED), in PT, represent the official local regulatory agencies of drugs and medical device marketing and post-market surveillance. However, other agencies within the European Union (EU) may articulate with INFARMED for marketing authorization of medicines and devices. Approval of medical devices and drugs follow different pathways and different levels of control in both countries.

Drugs

United States – The FDA approves drugs for marketing based on experimental data supporting safety and effectiveness of the medical product (drug or device) as well as information attesting adequate manufacturing and labelling. Drugs are approved if there is clear evidence that benefits outweigh the risks.[1] In order to improve the speed of approval reviews, as of 1992, review fees were introduced with the Prescription Drug User Fee Act and many special approval programs have been created ever since.[2-4] Production and marketing of pharmaceuticals is completely privatized but regulated by the FDA, which does not regulate the price of pharmaceuticals.[5] Prices result from market forces such as competition, and purchasers and customer negotiation power.[5,6] Unlike Portugal and most countries, direct-to-consumer advertising of prescription drugs is allowed in the US provided that the advertisements are accurate and not misleading.[5,7]

Drug coverage and type of cost-sharing vary among different health plans and insurers.[8] However, most employer-based health plans cover outpatient drugs in which employees typically prefer flat rate co-payment cost-sharing.[5,9,10] In addition, most outpatient drug coverage plan formularies follow a three-tier reimbursement scheme with lower co-payment for generics and higher co-payments for brand-name drugs with generic equivalent.[8,10]

Portugal – The European Union regulatory system for drug marketing approval, which comprises four possible procedures: centralized, decentralized, mutual recognition or national. Briefly, the centralized procedure is offered by the European Medicines Agency (EMA) and provides authorization for marketing a drug in all EU countries. The centralized procedure is compulsory for some drugs and optional to others. Drugs that fall outside the scope of EMA are approved for marketing using one of the other procedures depending on the countries for which marketing is sought.[11,12] In 2012, the EMA accounted for approximately 13% (66/521) of drug marketing approvals in Portugal.[13] Regardless of the type of procedure, drugs receive approval for marketing in Portugal, much like in the US, based on experimental data regarding quality, safety and efficacy. INFARMED further regulates standards regarding their manufacturing, distribution and labelling.[12]

Contrary to the FDA, INFARMED is responsible for price control and reimbursement eligibility of drugs within the NHS. With this purpose, pharmaco-economic and pharmaco-therapeutic reports need to be submitted so that a hospital price or a maximum retail price can be agreed with the pharmaceutical company, before asking the government for a reimbursement rate and then begin marketing.[14] Maximum prices are currently determined by INFARMED based on prices practiced in other European countries of similar GDP per capita to PT.[15] Outpatient drugs eligible for reimbursement by the NHS are assigned to one of four reimbursement rate categories based on a therapeutic classification.[14,16]

The use of the national drug formulary is mandatory for doctors prescribing in institutions within the NHS and is also an important guiding instrument for hospitals' pharmacy departments and their drug formularies.[17,18]

Medical devices

United States – Approval of medical devices is centralized at federal government under the FDA. Regulations aim to assure the safety and effectiveness of the devices according to a risk-tiered classification (Class I, II and III), where regulatory control increases from Class I to Class III depending on the risk the device poses to the patient but also on its intended use and indications for use.[19] Depending on the class assigned to the device, an additional pathway to general controls may be required. This may be either a premarket notification (510(k)), or a premarket approval application (PMA), where the PMA is the strictest and more formal regulatory control. At its inception, review of medical device applications was free of charge but as of 2003, the FDA may charge fees to medical device manufacturers. Additionally, a Third Party Program has been implemented which provides the option to seek

private parties to review applications. Such amendments have been implemented to improve the review process, which has been often criticized as a slow and lengthy process.[4,20]
Portugal – The medical device approval system falls under the decentralized regulatory system implemented at the EU [21,22] The procedure involves a Notified Body, which is private for-profit organization accredited by European authorities, that evaluates whether manufacturers are conforming to the EU's Medical Device Directives [21] Similar to the FDA system, control requirements depend on the associated-risk group (I, IIa, IIb and III) of the device. This review process has been criticized as having lack of transparency and vague requirements, which allows for different levels of standards between Notified Bodies.[20] For example, there is no publicly available list of all approved devices in EU nor of their review application information.[23,24] Furthermore, as emphasised by Fraser et al.[24] regulations provide detail on how clinical studies of devices should be performed, but they do not specify when they are required.
The Notified Bodies provide a CE (Conformité Européen) mark certification to the medical device if proven that it is safe and functions according to the manufacturer's intended use, enabling it to enter the EU market.[20] High-risk medical devices must be further registered with the INFARMED for commercialization.[22]

Table S1: Reference population used for direct standardization of rates – 2010 US population.

Age	Male	Female
20-24	11,014,176	10,571,823
25-29	10,635,591	10,466,258
30-34	9,996,500	9,965,599
35-39	10,042,022	10,137,620
40-44	10,393,977	10,496,987
45-49	11,209,085	11,499,506
50-54	10,933,274	11,364,351
55-59	9,523,648	10,141,157
60-64	8,077,500	8,740,424
65-69	5,852,547	6,582,716
70-74	4,243,972	5,034,194
75-79	3,182,388	4,135,407
80-84	2,294,374	3,448,953
85+	1,789,679	3,703,754

Source: Centers for Disease Control and Prevention, National Center for Health Statistics.[25]

Table S2. Comparison of health care systems between the US and Portugal, 2000 and 2010.

	US		Portugal	
Variable (Unit)	**2000**	**2010**	**2000**	**2010**
Population				
Total (million)	281•2	309•3	10•3	10•6
65 years or older (%)	12•4	13•1	16•3	18•7
Females (%)	50•9	50•8	51•7	52•2
White (%)	81•0	78•3	.	.
Health Coverage				
Uninsured (%)	13•1	16•3	0*	0*
Hospital capacity (per 1,000 population)				
Total hospital beds	3•5	3•1	3•7	3•4
Beds in public hospitals	0•9	0•8	2•9	2•5
Health costs				
Total health expenditure (% of GDP)	13•1	17•0	9•3	10•8
Total health expenditure per capita (US $ PPP)	4,790•5	8,243•5	1,645•9	2,793•1
Government share (% of total expenditure)	43•0	47•4	66•6	65•9
Private Insurance (% of total expenditure)	35•3	33•7	4•4	4•3
Out-of-Pocket (% of total expenditure)	14•9	12•0	23•4	25•8
Health status				
All-cause deaths (per 100,000 population, ≥20 years, crude rates)	1,169•0	1,074•7	1,309•4	1,255•3
Males	1,182•4	1,103•8	1,441•5	1,368•8
Females	1,156•5	1,047•4	1,190•4	1,154•9
All-cause deaths (per 100,000 population, ≥20 years, age-sex adjusted rates)	1,247•5	1,074•7	1291•4	1,040•7
Life expectancy at birth (years)	76•7	78•6	76•9	80•0
Males	74•1	76•2	73•3	76•8
Females	79•3	81•0	80•4	83•2

US $ PPP – Purchasing Power Parity in US dollars

* Implicit from universal coverage

Sources: OECD, US Census Bureau, CDC Wonder, Portugal Statistics, Eurostat.[26-30] Sex-age-adjusted death rates were computed using the 2010 US population as reference.

Table S3a: Sample characteristics of studies used for discussion of prevalence of risk factors.

Study	AMALIA [31]	PHYSA [32]	VALSIM [33]	Sardinha *et al.* [34]	Carreira *et al.* [35]
Time period	October 2006 to February 2007	November 2011 to December 2012	April 2006 to November 2007	2008 and 2009	-
Type of study	Cross-sectional study, using a structured questionnaire in a direct interview.	Cross-sectional survey with protocol-based interviews and examinations.	Cross-sectional study based on questionnaire on sociodemographic, clinical and laboratory data.	Cross-sectional study based on measurements of body mass, stature, and waist circumference.	Systematic review of nationally representative samples, published and available in Pubmed until 211
Sampling Method	The sample was stratified by gender, age-group and region and includes individuals of both genders, aged 40 years or more and resident in Portugal.	A multistage-stratified (by age and sex) cluster random sampling method was used to select a nationally (Portugal continental) representative sample of the general population aged 18-90 years based in 2001 recent National census data. Community local health service centers were the basis for recruitment	Stratified distribution and proportional to the population density of each region of mainland Portugal and the islands of Madeira and the Azores treated at primary health care centers.	Sample selection followed a multi-stage proportionate stratified cluster sampling procedure, considering population gender, age and geographical distribution. Controlled quota sampling was calculated taking into account the demographic data reported by National Census.	-
N	38893	3720	16,856	2539	
Age range	≥40 years	18-90 years	18-96 years	≥18 yeas	-

Sources: Methods of studies describing the CHD risk factors for PT [31-35].

Table S3b: Definitions used of risk factors in studies for discussion of prevalence of risk factors.

Study	AMALIA [31]	PHYSA [32]	VALSIM [33]	Sardinha *et al.* [34]	Carreira *et al.* [35]
Overweight	Declared weight, height as indicated on identity card	25≤BMI<30, BMI =weight/height^2 based on actual measurements of height and weight	25≤BMI<30, BMI =weight/height^2 based on actual measurements of height and weight	25≤BMI<30, BMI =weight/height^2 based on actual measurements of height and weight	-
Obesity	Declared weight, height as indicated on identity card	BMI ≥30M; BMI =weight/height^2 based on actual measurements of height and weight	BMI ≥30M; BMI =weight/height^2 based on actual measurements of height and weight	BMI ≥30M; BMI =weight/height^2 based on actual measurements of height and weight	-
Hypertension	Self-reported hypertension ("high blood pressure"); treatment and monitoring of each of the above conditions when present	Hypertension was defined as a systolic blood pressure (BP) of at least 140mmHg or diastolic BP of at least 90mmHg, or if the participant reported a history of hypertension, or if the participant reported taking antihypertensive medication in any moment of their life. Awareness of hypertension was defined as participant's self-reported of any previous diagnosis of hypertension by a healthcare professional (except if only during pregnancy). The treatment of hypertension was defined as self-reported use of a prescription medication for the treatment of hypertension in the past 2 weeks. Blood pressure was estimated as the average of three readings or the average of the two last readings if there was a difference of at least 10mmHg of BP from the first reading to the second;	Hypertension (HTA) was defined by a previous diagnosis of HTA or the presence of systolic BP >140 mmHg or diastolic BP >90 mmHg. BP was based on actual measurements.	-	-
Hypercholester o-lemia	Self-reported hypercholesterolemia ("Blood cholesterol") was defined treatment and monitoring of each of the above conditions when present	Self-perceived hypercholesterolemia was defined by "participant's awareness of these conditions or current use of antidyslipidemic drug"	HDL cholesterol<40mg/dL	-	-
Diabetes	Self-reported diabetes; treatment and monitoring of each of the above conditions when present	Self-perceived diabetes was defined by "participant's awareness of these conditions or current use of antidiabetic drug"	Diabetes was defined as a previous diagnosis or fasting glucose of >126 mg/dl, and impaired fasting glucose as fasting glucose 110-125 mg/dl.	-	-
Smoking	Smoking status was classified as: never smoked, ex-smoker (how long quit smoking? Smoked for how long? Cigarettes per day?), current smoker (how long smoker? Cigarettes per day?)	Smoking status was classified as: current, ex-smoker (not for at least 1 year), and non-smoker.	Self perceived; Smoker, Ex-smoker, Non-smokers	-	MISSING

Sources: Definitions in studies analyzing CHD risk factos for PT [31-35].

Table S3c: Prevalence of main CHD risk factors (%) - additional studies to characterize the risk of the PT population.

Country	**US**		**PT**									
Study	**NHANES**		**AMALIA [31]**		**PHYSA [32]**		**VALSIM [33]**		**Sardinha *et al.* [34]**		**Carreira *et al.* [35],**	
Risk factor	Crude rate	Age-adjusted rate	Crude rate	Age-adjusted rate	Crude rate	Sex-adjusted rate	Crude rate	Age-sex-adjusted rate	Crude rate	Age-sex-adjusted rate	Crude rate	Age-sex-adjusted rate
Overweight/Obesity												
Both sexes	71•6		51•6				-		64•99		-	
Males	77•8	71•6	-	51•3	53•1	51•6	-		67•35	62•07	-	
Females	66•1		-		50•1		-		63•22		-	
Hypertension												
Both sexes	32•8		23•5				65•46		-		-	
Males	30•3	33•7	21•8	22•8	44•4	40•9*	62•48	43•52	-		-	
Females	35•1		24•9		40•2		58•63		-		-	
Hypercholesterolemia												
Both sexes	48•1		19•7				27•46		-		-	
Males	50•0	48•1	18•6	19•4	29•1	33•2	47•74	39•46	-		-	
Females	46•4		20•7		37•0		34•29		-		-	
Diabetes												
Both sexes	12•3		8•9				-		-		-	
Males	12•1	12•6	8•5	8•5	11•4	10•3	-		-		-	
Females	12•4		9•3		9•2		-		-		-	
Smoking												
Both sexes	20•3		16•3				-		-		-	
Males	22•6	19•8	25•3	17•1	16•1	15•1	-		-		-	17•28
Females	18•3		8•8		14•1		-		-		-	

* age-sex-adjusted rate,

NHANES – National Health and Nutrition Examination Survey

Sources: Crude rates retrieved from [31-36]. Age-sex-adjusted rates were computed using the US 2010 population in Table S1 a reference population.

Table S4. Health technologies access lag between the US and Portugal per medical device class in selected interventional cardiology procedures.

Technology				Date (mm/dd/yy)	
Procedure name	**Device class**	**Country**	**First approved device (Model, Manufacturer)**	**Approval**	**Difference: US-PT (months)**
Percutaneous Coronary Intervention (PCI)	PTCA Balloon Catheter	PT	Unknown	May 1984[6]	-47
		US	Unknown	1980[4]	
	Bare-Metal Stent (BMS)	PT	Palmaz Schatz stent, Johnson & Johnson	6/21/90[6]	33
		US	Gianturco-Roubin coronary flex-stent, Cook, inc.	06/03/93[1]	
	Drug-Eluting Stent (DES)	PT	Cypher sirolimus drug eluting stent, Cordis	05/31/02[4, 6]	11
		US	Cypher sirolimus drug eluting stent, Cordis	04/24/03[1]	
	Cutting Balloon Catheter (CBC)	PT	Cutting Balloon, Interventional Technologies Inc.	1995[3]	58
		US	Flexatome Cutting Balloon, Boston Scientific	04/18/00[1]	
	Drug-Eluting Balloon Catheter (DEB)	PT	SeQuent Please, B Braun Melsungen AG	06/30/09[3]	67
		US	N/A	Not approved	
Percutaneous Ventricular support	Impella - catheter-based VAD	PT	Impella® 2.5, Abiomed	09/30/04[3, 6]	44
		US	Impella Recover LP 2.5 Percutaneous Cardiac Support System, Abiomed Inc.	05/30/08[2]	
	Percutaneous Ventricular Assist Device (PVAD)	PT	TandemHeart System, CardiacAssist Inc.	02/26/01[3]	-12
		US	AB-180 XC System, Cardiac Assist Inc.	02/25/00[3,1]	
Embolic Protection	N/A	PT	PercuSurge Guard Wire, PercuSurge Inc.	08/11/98[3]	29
		US	PercuSurge GuardWire Temporary Occlusion and Aspiration System, PercuSurge Inc.	06/01/01[2]	
Atherectomy	Rotational Atherectomy	PT	Rotablator, Boston Scientific Corp.	1999[3]	-73
			Rotablator®, Boston Scientific Corp.	05/28/93[1]	
	Directional Coronary Atherectomy (DCA)	PT	Unknown	10/23/91[6]	-13
		US	Simpson Coronary Atherocath, Devices for Vascular Intervention, Inc.	09/14/90[1]	
Coronary Thromboaspiration	Manual	PT	Diver CE, Invatec S. p. A.	07/06/01[3]	17
		US	Export Aspiration Catheter, Medtronic Vascular	10/29/02[2]	
	Mechanical	PT	Angiojet Series 3000 Rheolytic Thrombectomy Syste, Possis Meical Inc.	October 1997[3]	25
		US	AngioJet Rheolytic Thrombectomy System, Bayer Medical Care Inc.	03/12/99[1]	
Coronary Brachytherapy	Intravascular Radiation Delivery System/Device	PT	Novoste Beta-Cath System, Novoste Corp.	1999[4]	17
		US	Novoste Beta-Cath System, Novoste Corp.	12/13/00[1]	
Transcatheter Aortic Valve Replacement (TAVR)	Balloon expand	PT	Sapien TransCatheter Aortic Valve Edwards LifeSciences	September 2007[3]	50
		US	Sapien TransCatheter Aortic Valve Edwards LifeSciences	11/22/11[1]	
	Self-expand	PT	The CoreValve System, Medtronic	May 2007[3, 5]	82
		US	The CoreValve System, Medtronic	02/04/14[1]	
Percutaneous Reduction of Mitral Regurgitation	Percutaneous Mitral Repair System	PT	MitraClip, Abbott Vascular	March 2008[3]	67
		US	MitraClip, Abbott Vascular	10/24/13[1]	
				Mean difference:	**22**
				Median difference:	**27**

N/A: Not available.
Sources:

1 FDA Premarket Approval (PMA) [37]
2 FDA Premarket notification 510(k) [38]
3 Personal communication with MD industry representatives/press release/EUCOMED [39-43]
4 Scientific journal [44-46]
5 Personal communication with an interventional cardiology from Centro Hospitalar de Vila Nova de Gaia (Portugal)
6 First use in Santa Cruz Hospital [47]

Table S5. Health technologies access lag per active in selected therapeutic uses between the US and Portugal.

Therapeutic use	Active substance	Country	Approved drug (Brand name)	Date (mm/dd/yy) Approval	Marketing[1]	Difference between marketing dates: US-PT (months)
Platelet inhibitor	Ticlopidine	PT	Tiklyd	05/15/81	03/21/07	
		US	Ticlid	10/31/91		-185
	Clopidogrel	PT	Plavix	07/15/98	04/29/03	
		US	Plavix	11/17/97		-65
	Prasugrel	PT	Efient	02/25/09	04/01/14	
		US	Effient	07/10/09		-57
	Ticagrelor	PT	Brilique	12/03/10	12/19/11	
		US	Brilinta	07/20/11		-5
	GP IIb/IIIa inhibitor - Abciximab	PT	Reopro	02/12/96	03/21/07	
		US	Reopro	12/16/93		-159
	GP IIb/IIIa inhibitor - Eptifibatide	PT	Integrilin	07/01/99	03/21/07	
		US	Integrilin	05/18/98		-106
	GP IIb/IIIa inhibitor - Tirofiban	PT	Aggrastat	06/30/99	03/21/07	
		US	Aggrastat	05/14/98		-106
Anticoagulant	Bivalirudin	PT	Angiox	09/20/04	06/23/10	
		US	Angiomax	12/15/00		-114
	Rivaroxaban	PT	Xarelto	09/30/08	01/28/09	
		US	Xarelto	07/01/11		29
	Apixaban	PT	Eliquis	05/18/11	08/01/14	
		US	Eliquis	12/28/12		-19
	Dabigatran etexilate	PT	Pradaxa	03/18/08	05/01/10	
		US	Pradaxa	10/19/10		6
Antianginal	Nicorandil	PT	Dancor	08/03/96	03/21/07	
		US	N/A	N/A		95
	Ivabradin	PT	Procoralan	10/25/05	11/01/07	
		US	N/A	N/A		87
	Ranolazine	PT	Ranexa	07/09/08	N/C	
		US	Ranexa	01/27/06		-109
					Mean difference:	**-51**
					Median difference:	**-61**

N/A – Not available until February 13, 2015
N/C – Not commercialized until February 13, 2015
[1] Personal communication with INFARMED
Sources: US – FDA [48]; PT – INFARMED [49]

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7.5 Paper 2 supplementary data

A COMPARISON OF IN-HOSPITAL ACUTE MYOCARDIAL INFARCTION MANAGEMENT BETWEEN PORTUGAL AND THE UNITED STATES: 2000 – 2010

Supplementary Data

Expanded Methods and Results

Table S1. List of ICD-9-CM diagnosis and procedure codes.

Diagnosis/Procedure	ICD-9-CM code
Acute Myocardial Infarction	410.xx and no 410.x2
Elevated ST segment AMI (STEMI)	410.0-410.6, 410.8 and no 410.x2
Non-elevated ST-segment AMI (Non-STEMI)	410.7, 410.9 and no 410.x2
Cardiac catheterization	37.21 - 37.23
Percutaneous Coronary Intervention	36.01-36.07, 00.66, 92.27
Bare metal stent	36.06
Drug-eluting stent	36.07
Coronary Artery Bypass Graft (CABG)	36.10-36.17, 37.19
On-pump CABG	36.10-36.17, 37.19 <u>and</u> 39.61
Off-pump CABG	36.10-36.17, 37.19 and <u>no</u> 39.61
Valve procedures	35.00 – 35.99
Pacemaker/heart assist/defibrillated related procedures	00.50, 37.62, 37.65, 37.66, 37.94 – 37.99, 00.51 – 00.54
Coronary brachytherapy	92.27

Table S2. 2010 Age-Sex Distribution: United States population.

Sex	Age Group	Population Size
Male	20-29	21,649,767
	30-39	20,038,522
	40-49	21,603,062
	50-59	20,456,922
	60-69	13,930,047
	70-79	7,426,360

	≥ 80	4,084,053
Female	20-29	21,038,081
	30-39	20,103,219
	40-49	21,996,493
	50-59	21,505,508
	60-69	15,323,140
	70-79	9,169,601
	≥ 80	7,152,707

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Estimates of the April 1, 2010 U.S. Resident Population by Age and Sex, Prepared under a collaborative arrangement with the US Census (National Vital Statistics Report, Vol 61, No 4, May 8, 2013.

Table S3. Comparison of health care systems between the United States and Portugal, 2000 and 2010.

	United States		Portugal	
Variable (Unit)	**2000**	**2010**	**2000**	**2010**
Population				
Total (million)	281.2	309.3	10.3	10.6
65 years or older (%)	12.4	13.1	16.3	18.7
Females (%)	50.9	50.8	51.7	52.2
White (%)	81.0	78.3	.	.
Health Coverage				
Uninsured (%)	13.1	16.3	0	0
Hospital capacity (per 1,000 population)				
Total hospital beds	3.5	3.1	3.7	3.4
Beds in public hospitals	0.9	0.8	2.9	2.5
Health costs				
Total health expenditure (% of GDP)	13.1	17.0	9.3	10.8
Total health expenditure per capita (US $ PPP)	4,790.5	8,243.5	1,645.9	2,793.1
Government share (% of total expenditure)	43.0	47.4	66.6	65.9
Private Insurance (% of total expenditure)	35.3	33.7	4.4	4.3
Out-of-Pocket (% of total expenditure)	14.9	12.0	23.4	25.8
Health status				
All-cause deaths (per 100,000 population, ≥20 years, crude rates)	1,169.0	1,074.7	1,309.4	1,255.3
Males	1,182.4	1,103.8	1,441.5	1,368.8
Females	1,156.5	1,047.4	1,190.4	1,154.9
All-cause deaths (per 100,000 population, ≥20 years, age-sex adjusted rates)	1,247.5	1,074.7	1291.4	1,040.7
Life expectancy at birth (years)	76.7	78.6	76.9	80.0
Males	74.1	76.2	73.3	76.8
Females	79.3	81.0	80.4	83.2

Sources: Instituto Nacional de Estatística (INE). Resident population (Long series, start 1970 - No.) by Sex and Age; Annual. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_base_dados&contexto=bd&selTab=tab2 [Accessed April 15, 2014]; United States Sensus Bureau. National Intercensal Estimates (2000-2010). Available from: http://www.census.gov/popest/data/intercensal/national/nat2010.html [Accessed July 15, 20114]; Centers for Disease Control and Prevention (CDC). CDC WONDER – Wide-ranging Online data for Epidemiologic Research, Underlying Cause of Death, 1999-2010. Available from: http://wonder.cdc.gov/ucd-icd10.html [Accessed April 15, 2014]; Eurostat. Causes of death - absolute number - annual data [hlth_cd_anr]. Available from: http://ec.europa.eu/eurostat/web/health/causes-death/data/database [Accessed April 15, 2014]; Organisation for Economic Co-operation and Development. OECD.stat. Available from: http://stats.oecd.org [Accessed January 11, 2014].

Abbreviations:
GDP – Gross Domestic Product
PPP – Prices and purchasing Power Parity

Table S4. Characteristics of Hospitalized Patients with AMI, by Country and Year of Discharge (unweighted US estimates).

Variable	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	All years
# of AMI discharges[1]												
Portugal	8,749	9,775	10,809	11,829	11,799	11,396	11,528	11,816	12,273	11,762	11,706	123,442
U.S.	141,583	147,222	148,328	145,825	132,775	126,077	130,351	116,875	122,346	118,438	113,339	1,443,159
STEMI, %												
Portugal	77	74	68	66	61	62	59	55	54	52	50	61
U.S.	43	40	39	38	35	34	34	32	30	29	28	35
Anterior MI, %												
Portugal	31	30	28	26	25	24	23	23	22	21	21	25
U.S.	17	16	15	14	13	13	13	12	12	11	11	14
Infero MI, %												
Portugal	32	30	27	25	23	22	21	20	20	20	20	23
U.S.	22	21	20	19	18	17	17	16	16	15	15	18
Other MI locations, %												
Portugal	37	40	45	49	52	54	56	57	58	59	59	52
U.S.	61	64	64	67	69	70	70	71	72	74	74	68
Age 80+, %												
Portugal	16	17	20	20	22	22	22	24	24	24	25	22
U.S.	22	23	22	23	23	24	22	23	23	22	22	23
Mean Age [std]												
Portugal	67 [13]	67 [13]	67 [13]	68 [13]	68 [13]	68 [13]	69 [13]	69 [13]	69 [14]	69 [14]	69 [14]	68 [13]
U.S.	68 [14]	69 [14]	68 [14]	68 [14]	68 [14]	68 [15]	67 [15]	68 [15]	68 [15]	67 [14]	67 [14]	68 [14]

[1] For over 20 years old patients, after eliminating discharges indicating left against medical advice, patient discharged to hospice, or invalid charges.

Female, %												
Portugal	32	33	34	36	36	35	35	36	35	35	35	35
U.S.	41	41	41	41	41	41	40	40	40	39	39	41
Race , %[2]												
White	63	61	55	57	57	58	58	56	62	64	66	60
Black	5.2	5.6	5.8	6.4	6.5	5.3	6.2	7.3	7.2	7.6	9.6	6.5
Hispanic	3.8	4.6	4.6	5.8	4.8	5.3	5.6	5.4	5.1	6.0	6.1	5.1
Asian/Pacific Islander	1.1	1.1	1.2	1.3	1.3	1.1	1.4	1.6	1.7	1.7	2.0	1.4
Native American	0.2	0.3	0.1	0.1	0.2	0.2	0.4	0.5	0.8	0.5	0.7	0.4
Other	1.6	1.8	2.1	1.9	2.0	2.2	2.1	2.3	2.8	3.4	2.3	2.2
Missing	25	25	31	28	28	28	27	27	20	17	13	25
Emergent/Urgent Admission, %												
Portugal	97	97	96	97	97	98	97	97	96	94	93	96
U.S.	82	82	83	83	85	84	84	83	86	86	85	84

[2] Reported in U.S. only.

Variable	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	All years
Cardiovascular Morbidity, %												
History of PTCA/V45.82												
Portugal	0.5	1.1	1.2	1.6	2.1	2.5	2.9	3.8	4.1	4.9	6.2	2.9
U.S.	5.9	6.3	6.2	6.3	6.3	7.2	8.5	9.2	10.1	10.5	10.8	7.8
History of CABG/V45.81												
Portugal	1.0	1.3	1.4	1.9	2.0	2.3	2.3	2.8	2.5	2.3	3.0	2.1
U.S.	8.0	7.5	6.9	6.8	6.7	6.5	6.6	6.5	6.8	6.6	6.7	6.9
History of Congestive Heart Failure/MCC80, 429												
Portugal	14.3	15.2	15.8	18.0	18.2	18.0	18.2	19.8	20.4	20.2	20.9	18.3
U.S.	35.1	34.4	34.2	35.1	36.0	35.4	34.1	34.9	34.7	35.4	35.4	34.9
History of AMI/412, 410.x1												
Portugal	4.8	4.7	4.5	6.0	5.8	5.7	5.4	9.9	5.0	6.3	7.6	6.0
U.S.	8.2	8.1	8.3	8.0	8.3	8.4	9.1	9.6	10.0	11.2	11.4	8.9
Unstable Angina/ 411, 410.x2												
Portugal	3.5	3.0	2.1	1.7	1.3	1.1	2.0	1.2	0.7	0.7	0.8	1.6
U.S.	3.6	2.8	2.3	2.1	1.9	1.6	1.5	1.3	1.2	1.2	1.1	1.9
Chronic atherosclerosis/413, 414, 746.85												
Portugal	29.6	31.4	32.0	32.9	35.6	36.8	40.7	43.6	43.1	45.7	51.5	38.8
U.S.	66.9	68.1	70.0	70.9	71.4	72.8	75.1	75.4	77.6	80.2	80.0	73.1
Cardiorespiratory Failure and Shock/MCC79												
Portugal	8.1	8.4	7.7	8.5	8.6	9.0	8.4	8.0	8.0	8.5	9.2	8.4
U.S.	12.4	12.4	12.9	12.8	12.9	12.7	13.8	14.8	15.8	16.0	16.0	13.8
Valvular or Rheumatic Disease/MCC86												
Portugal	6.5	8.2	9.1	10.3	9.5	9.6	10.1	10.2	10.5	11.1	12.4	9.9
U.S.	11.5	11.4	12.3	12.1	12.1	13.0	13.6	12.9	11.4	12.0	12.0	12.2

Variable	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	All years
Comorbidities, %												
Hypertension/MCC89												
Portugal	32.4	39.1	42.0	44.5	45.6	47.3	47.7	48.8	49.1	52.2	53.9	46.2
U.S.	44.6	46.0	48.2	49.5	51.0	51.9	52.6	59.3	61.9	64.8	65.7	53.5
Stroke/MCC95												
Portugal	1.4	1.4	1.3	1.3	1.1	1.3	1.2	1.3	1.1	1.1	1.1	1.2
U.S.	1.8	1.8	1.7	1.7	1.7	1.7	1.7	1.6	1.7	1.5	1.4	1.7
Cerebrovascular Disease/MCC97												
Portugal	2.3	2.7	3.3	3.5	3.6	3.2	3.8	3.7	3.3	3.8	4.5	3.5
U.S.	2.9	2.8	2.9	2.8	2.9	2.9	2.9	3.0	3.3	3.7	3.6	3.1
Renal Failure/MCC131												
Portugal	2.3	3.1	2.9	2.9	3.3	3.9	4.3	5.4	7.2	8.9	10.9	5.1
U.S.	8.0	9.0	9.8	10.8	11.9	14.2	18.4	21.3	22.5	24.5	25.5	15.4
Chronic Obstructive Pulmonary Disease/MCC108												
Portugal	3.9	4.5	4.4	4.5	4.3	4.2	4.2	3.9	4.1	4.4	4.7	4.3
U.S.	16.6	16.3	17.5	17.3	17.5	18.4	17.9	18.0	16.6	17.1	16.9	17.3
Pneumonia/MCC111												
Portugal	3.3	3.1	3.4	3.6	3.7	3.9	3.8	4.2	4.2	4.3	4.8	3.9
U.S.	7.2	7.3	7.8	8.5	8.7	9.2	8.4	9.0	9.8	9.3	9.1	8.5
DM and DM complications//MCC15												
Portugal	22.1	23.1	24.1	25.7	26.4	27.3	27.4	29.1	28.6	29.1	30.4	26.8
U.S.	28.2	28.4	29.0	29.5	29.8	30.0	30.6	31.9	32.4	34.1	34.8	30.6
Pure Hypercholesterolemia/272.0												
Portugal	3.6	3.9	4.0	5.5	4.7	4.2	4.9	5.3	4.7	4.6	3.9	4.5
U.S.	13.2	13.4	13.7	12.7	13.4	12.0	11.3	11.5	10.3	9.8	9.5	12.0

Protein-Calorie malnutrition/MCC21												
Portugal	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
U.S.	1.0	1.0	1.0	1.1	1.3	1.3	1.4	1.6	2.1	2.3	2.3	1.4

Variable	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	All years
Comorbidity, %												
Dementia and Senility/MCC49												
Portugal	0.8	1.0	1.2	1.4	1.6	1.7	2.0	2.1	2.2	2.4	2.8	1.8
U.S.	4.1	4.5	4.8	4.9	5.1	5.4	5.3	5.7	6.1	6.2	6.3	5.2
Hemiplegia, Paralysis and Functional Disability/MCC67												
Portugal	2.3	2.4	2.7	2.7	2.8	3.0	2.6	2.9	3.0	3.1	3.0	2.8
U.S.	2.7	2.6	2.6	2.6	2.6	2.4	2.5	2.7	3.2	3.3	3.4	2.8
Peripheral Vascular Disease/MCC104												
Portugal	2.2	2.4	3.2	3.3	3.2	3.5	3.6	4.2	3.9	4.5	4.5	3.6
U.S.	7.8	8.2	8.7	8.9	9.4	9.6	10.2	11.0	11.4	12.7	12.0	9.9
Metastatic Cancer and Acute Leukemia/MCC7												
Portugal	0.4	0.4	0.6	0.5	0.5	0.4	0.4	0.5	0.6	0.6	0.7	0.5
U.S.	1.1	1.1	1.1	1.1	1.2	1.2	1.1	1.3	1.3	1.4	1.3	1.2
Trauma/MCC154												
Portugal	0.6	0.6	0.6	0.7	0.7	0.8	0.7	0.8	0.8	0.6	0.7	0.7
U.S.	2.0	2.3	2.7	1.6	1.7	1.7	1.7	1.9	2.1	2.2	2.1	2.0
Major Psychiatric Disorders/MCC54												
Portugal	0.3	0.4	0.3	0.4	0.3	0.3	0.3	0.3	0.5	0.5	0.4	0.4
U.S.	1.1	1.1	1.2	1.3	1.4	1.3	1.4	1.5	1.9	2.0	2.2	1.5
Liver and Biliary Disease/MCC25												
Portugal	0.4	0.4	0.4	0.3	0.4	0.4	0.3	0.4	0.3	0.6	0.6	0.4
U.S.	0.4	0.5	0.6	0.6	0.7	0.7	0.7	0.8	0.7	0.8	0.9	0.7

U.S. – United States
STEMI – ST-elevated segment myocardial infarction
MI – Myocardial Infarction

PTCA – Percutaneous transluminal coronary angioplasty
CABG – Coronary artery bypass graft
AMI – Acute myocardial infarction
DM – Diabetes Mellitus
MCC – Modified hierarchical condition categories

Table S5: Hazard ratios for comorbidities in survival models [Model 1].

Country	Portugal			United States		
Comorbidities	**Pr > ChiSq**	**Hazard Ratio**	**CI**	**Pr > ChiSq**	**Hazard Ratio**	**CI**
STEMI	<.0001	1.371	[1.302,1.444]	<.0001	1.209	[1.171,1.248]
Anterior MI	0.4581	0.981	[0.934,1.031]	0.8364	1.105	[1.067,1.143]
Inferior MI	<.0001	0.751	[0.710,0.793]	0.074	1.049	[1.014,1.086]
History of CABG/V45.81	0.5203	1.043	[0.918,1.185]	<.0001	1.014	[0.986,1.043]
History of PTCA/V45.82	0.0079	0.824	[0.715,0.951]	0.2058	0.962	[0.933,0.992]
History of Congestive Heart Failure/MCC80, 429	0.1354	1.029	[0.991,1.068]	<.0001	1.02	[1.006,1.033]
History of AMI/412, 410.x1	0.0811	0.935	[0.866,1.008]	0.0383	1	[1.006,1.033]
Unstable Angina/ 411, 410.x2	<.0001	0.704	[0.602,0.825]	0.0095	0.985	[0.942,1.031]
Chronic atherosclerosis/413, 414, 746.85	<.0001	0.524	[0.502,0547]	<.0001	0.717	[0.707,0.726]
Hypertension/MCC89	<.0001	0.610	[0.588,0.632]	<.0001	0.832	[0.821,0.843]
Cerebrovascular Disease/MCC97	0.058	1.073	[0.998,1.154]	0.7963	0.977	[0.707,0.726]
Chronic Obstructive Pulmonary Disease/MCC108	<.0001	0.819	[0.761,0.881]	<.0001	0.978	[0.964,0.993]
Dementia and Senility/MCC49	0.0078	1.122	[1.031,1.221]	<.0001	1.064	[1.04,1.088]
DM/DM with complications/MCC15	<.0001	1.092	[1.053,1.133]	0.0017	0.988	[0.974,1.002]
Pure hypercholesterolemia/272.0	<.0001	0.520	[0.456,0.592]	<.0001	0.907	[0.885,0.929]
Hemiplegia, paralysis and functional disability/MCC67	<.0001	1.242	[1.153,1.338]	<.0001	1.033	[0.999,1.069]
Liver and biliary disease/MCC25	0.0016	1.350	[1.120,1.626]	0.2802	1.019	[0.95,1.092]
Metastatic Cancer and acute leukemia/MCC7	<.0001	1.724	[1.495,1.988]	<.0001	1.049	[1.001,1.1]
Protein-Calories Malnutrition/MCC21	0.0127	1.403	[1.075,1.830]	0.0081	0.994	[0.965,1.024]

Pneumonia/MCC111	<.0001	0.809	[0.765,0.855]	<.0001	1.05	[1.033,1.066]
Major Psychiatric Disorders/MCC54	0.4704	0.913	[0.713,1.169]	0.7671	0.992	[0.943,1.043]
Peripheral Vascular Disease/MCC104	0.1439	1.056	[0.982,1.136]	<.0001	1.008	[0.99,1.028]
Renal Failure/MCC131	0.0003	1.098	[1.043,1.155]	<.0001	1.277	[1.258,1.295]
Cardiorespiratory failure and shock/MCC79	<.0001	5.695	[5.492,5.905]	<.0001	2.372	[2.339,2.406]
Stroke/MCC95	<.0001	1.437	[1.317,1.567]	<.0001	1.074	[1.041,1.108]
Trauma/MCC154	0.0003	0.739	[0.627,0.870]	0.0561	0.991	[0.957,1.026]
Valvular or rheumatic heart disease/MCC86	<.0001	0.601	[0.566,0.639]	<.0001	0.928	[0.913,0.944]

STEMI – ST-elevated segment myocardial infarction
CABG – Coronary artery bypass graft
PTCA – Percutaneous transluminal coronary angioplasty
MI – Myocardial infarction
AMI – Acute myocardial infarction
DM – Diabetes Mellitus
MCC – Modified hierarchical condition categories

7.6 Paper 3 supplementary data

Understanding hospital heterogeneity in quality of care for acute myocardial infarction

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Supplementary material

Extended Methods

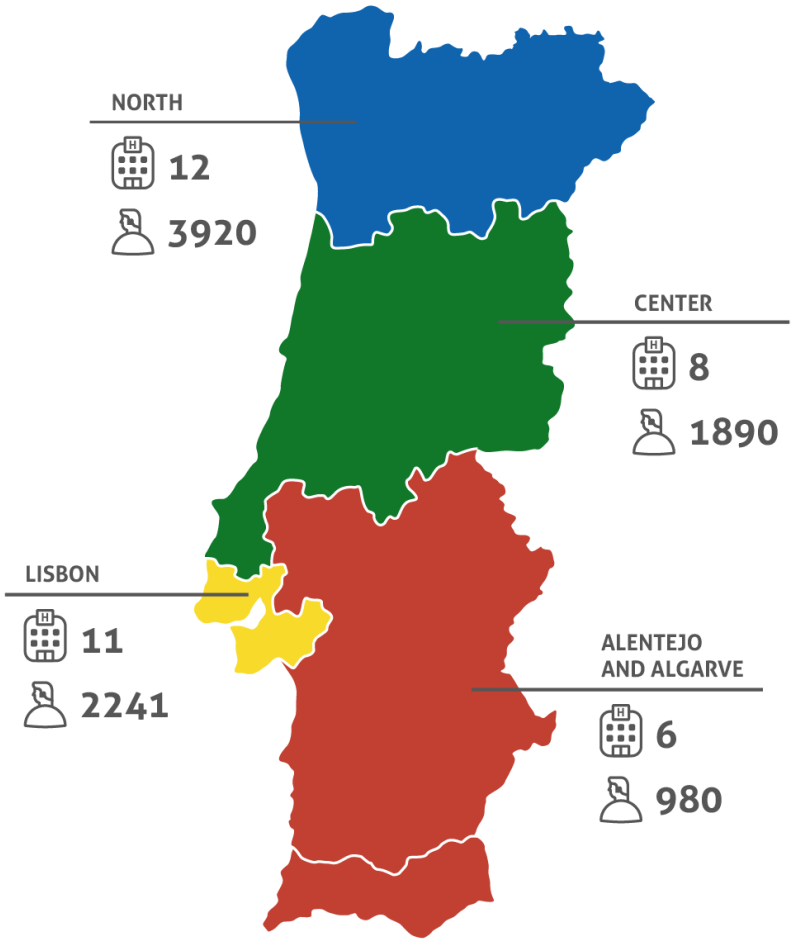
Table S1. Characteristics of hospitals in the study.

Hospital #	Geographic region	Teaching status	Catheterization laboratory on-site	Cardiac surgery on-site	AMI volume (2011)	# of index events (Readmission cohort)	Crude readmission rate (%)	# of index events (Mortality cohort)	Crude death rate (%)	Adult population (Census 2011)
1	Alentejo/Algarve	0	0	0	56	110	16.4	196	38.3	980 442
2	Alentejo/Algarve	0	0	0	66	191	15.2	282	26.2	
3	Alentejo/Algarve	0	0	0	118	271	11.1	320	15.0	
4	Alentejo/Algarve	0	0	0	224	579	4.7	621	7.2	
5	Alentejo/Algarve	0	1	0	279	995	6.6	1097	8.9	
6	Alentejo/Algarve	0	1	0	645	2126	6.6	2330	8.8	
7	Center	0	0	0	94	240	7.1	347	22.2	1 890 381
8	Center	1	0	0	116	326	10.4	384	13.3	
9	Center	0	0	0	128	282	6.0	340	16.8	
10	Center	0	0	0	211	876	9.0	1026	12.7	
11	Center	0	0	0	214	630	7.3	676	5.5	
12	Center	0	0	0	215	604	6.8	652	10.1	
13	Center	0	1	0	256	874	9.7	1005	12.8	
14	Center	1	1	1	789	2372	11.0	2591	9.4	
15	Lisbon	0	0	0	125	399	10.0	460	11.5	2 240 649
16	Lisbon	0	0	0	131	275	12.0	566	10.1	
17	Lisbon	0	0	0	145	558	7.9	525	22.5	
18	Lisbon	0	0	0	170	848	8.1	917	7.7	

19	Lisbon	0	1	0	236	954	8.5	1073	9.2	
20	Lisbon	0	1	0	322	1002	6.0	1327	11.4	
21	Lisbon	0	1	0	432	1717	6.8	2023	13.8	
22	Lisbon	0	1	0	451	1331	8.3	1476	10.3	
23	Lisbon	0	1	1	535	1599	8.0	1676	9.1	
24	Lisbon	1	1	1	663	1900	10.8	2151	13.7	
25	Lisbon	0	1	1	895	2273	6.9	2179	10.0	
26	Norte	0	0	0	69	180	11.1	223	22.4	3 920 372
27	Norte	0	0	0	79	177	6.8	198	11.1	
28	Norte	0	0	0	127	284	12.3	382	17.8	
29	Norte	0	0	0	180	741	4.9	746	6.6	
30	Norte	0	0	0	194	732	11.1	771	8.2	
31	Norte	0	0	0	195	649	7.4	676	5.6	
32	Norte	0	1	1	221	898	4.6	1014	7.6	
33	Norte	0	1	0	261	1114	7.4	1226	8.9	
34	Norte	0	1	0	266	1146	6.4	1180	5.3	
35	Norte	1	1	0	309	965	4.7	1073	9.7	
36	Norte	1	1	0	412	1996	5.9	2078	4.6	
37	Norte	1	1	1	566	2042	7.8	2252	8.3	

Hospital size has been omitted to protect hospital identification.

Figure S1. Geographical distribution of hospitals and adult population (Census 2011).



Implemented Models

Let Y_{ij} be 1 if the ith patient at the jth hospital was readmitted/died in hospital and zero otherwise then, the log odds of the ith patient admitted in the jth hospital being readmitted/dying during the hospitalization were modeled on a stepwise fashion through models 0 to 3 as follows:

Y_{ij} ~Bernoulli($P(Y_{ij}=1)$)

Model 0 (empty model): $\text{logit}[P(Y_{ij}=1|\ \beta_0)] = \beta_0 + u_{(hospital)j}$

Where,
β_0 – is the intercept, represents the log odds of a patient admitted being readmitted/dying in an average hospital;
$u_{(hospital)j}$ – is the random intercept for hospital, describes the variation of the jth hospital intercept relative to the average hospital, $u_{(hospital)j} \sim N(0,\sigma_{u(hospital)})$;

Model 1: $\text{logit}[P(Y_{ij}=1|\ \beta_0, \beta_p, h=j)] = \beta_0 + \beta_p * \text{Patient_characteristics}_{ij} + u_{(hospital)j}$

Where β_0 and $u_{(hospital)j}$ have the same interpretation as before and,
β_p – are the fixed effects of patient characteristics, represent log odds of being readmitted/dying when presenting that characteristic relative to not presenting it (patient-level predictor).

Model 2: $\text{logit}[P(Y_{ij}=1|\ \beta_0, \beta_p, \beta_h, h=j)] = \beta_0 + \beta_p * \text{Patient_characteristics}_{ij} + \beta_h * \text{Hospital_characteristics}_{ij} + u_{(hospital)j}$

Where β_0, β_p and $u_{(hospital)j}$ have the same interpretation as before and,
β_h – are the fixed effects of hospital characteristics, represent log odds of being readmitted/dying when the hospital presents that characteristic relative to not presenting it. Patients admitted to the same hospital share the same hospital characteristics (hospital-level predictor).

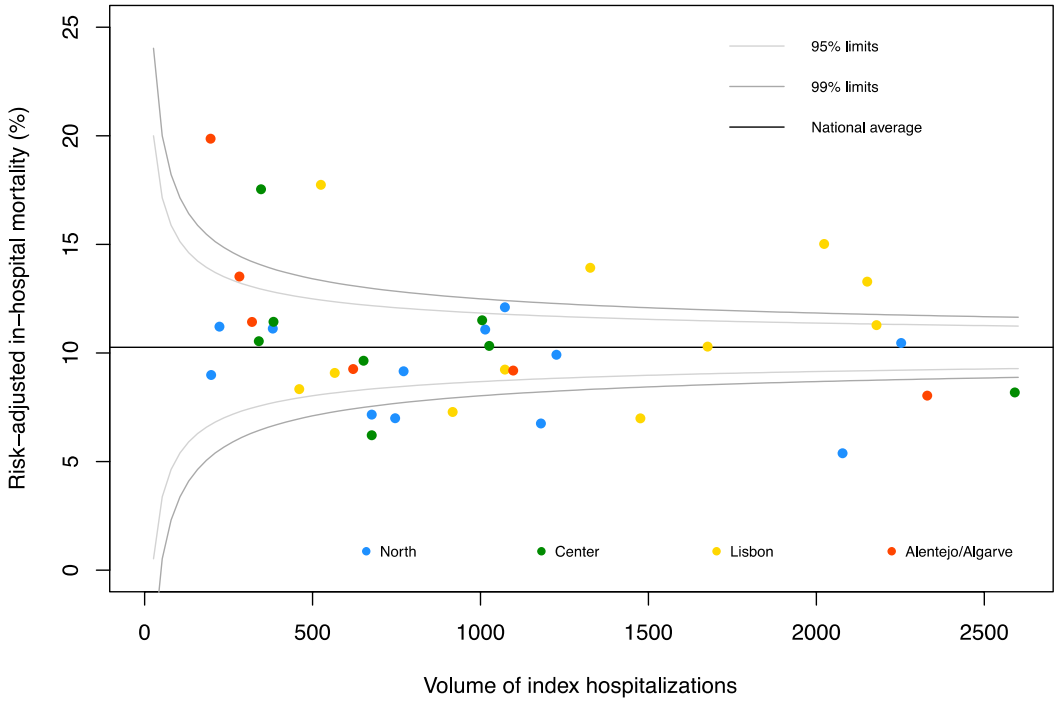
Extended Results

Table S2. Distribution of hospital characteristics, by cohort

Characteristic	# Hospitals	Mortality cohort		Readmissions cohort	
		#Discharges Median [IQR]	% In-hospital crude mortality Median [IQR]	# Discharges per hospital Median [IQR]	% Crude 30-day unplanned readmission Median [IQR]
All hospitals	37	917 [460,1327]	10.07 [8.26, 13.67]	848 [326, 1146]	7.84 [6.63, 10.43]
Teaching status					
Teaching hospital	6	2115 [1073,2252]	9.54 [8.26, 13.28]	1948 [965,2042]	9.13 [5.86,10.79]
Non-teaching hospital	31	746 [382,1180]	10.12 [8.17, 15.00]	732 [282,1002]	7.40 [6.63,10.03]
Size (number of beds)					
Above the median (>425 beds)	18	1203 [1014,2078]	9.54 [8.80, 12.67]	1130 [876,1900]	7.38 [6.63, 9.02]
Below the median (≤425 beds)	19	525 [340,771]	11.38 [8.17, 17.80]	399 [271,741]	7.89 [6.63, 11.07]
AMI volume					
Above the median (>215)	18	1402 [1073,2151]	9.15 [8.26, 10.30]	1239 [965,1996]	6.83 [5.99, 8.34]
Below the median (≤215)	19	460 [320,676]	12.67 [8.17, 22.19]	326 [240,649]	9.02 [7.08, 11.11]
Services provided, %					
Both catheterization lab and cardio-thoracic surgery	6	2165 [1676,2252]	9.22 [8.26, 10.00]	1971 [1599,2273]	7.92 [6.91, 10.79]
Only catheterization lab	11	1226[1073,2023]	9.23 [8.80, 11.38]	1114 [965,1717]	6.63 [5.99, 8.34]
No revascularization service	20	493 [330,676]	12.10 [7.96, 20.00]	363 [256,640]	8.58 [6.94, 11.09]
Geographic region					
North	12	893 [529,1203]	8.22 [6.09, 10.40]	820 [467,1130]	7.07 [5.36, 9.45]
Center	8	664 [366,1016]	12.75 [9.75, 15.02]	617 [304,875]	8.16 [6.94, 10.08]
Lisbon	11	1327 [566,2023]	10.30 [9.23, 13.67]	1002 [558,1717]	8.14 [6.91, 10.03]
Alentejo or Algarve	6	471 [282,1097]	11.97 [8.80, 26.24]	425 [191,995]	8.85 [6.63, 15.18]

Figure S2. Funnel plot of risk-adjusted (A) in-hospital mortality and (B) 30-day all-cause readmissions by hospital location.

(A) In-Hospital mortality



(B) 30-day all-cause readmissions

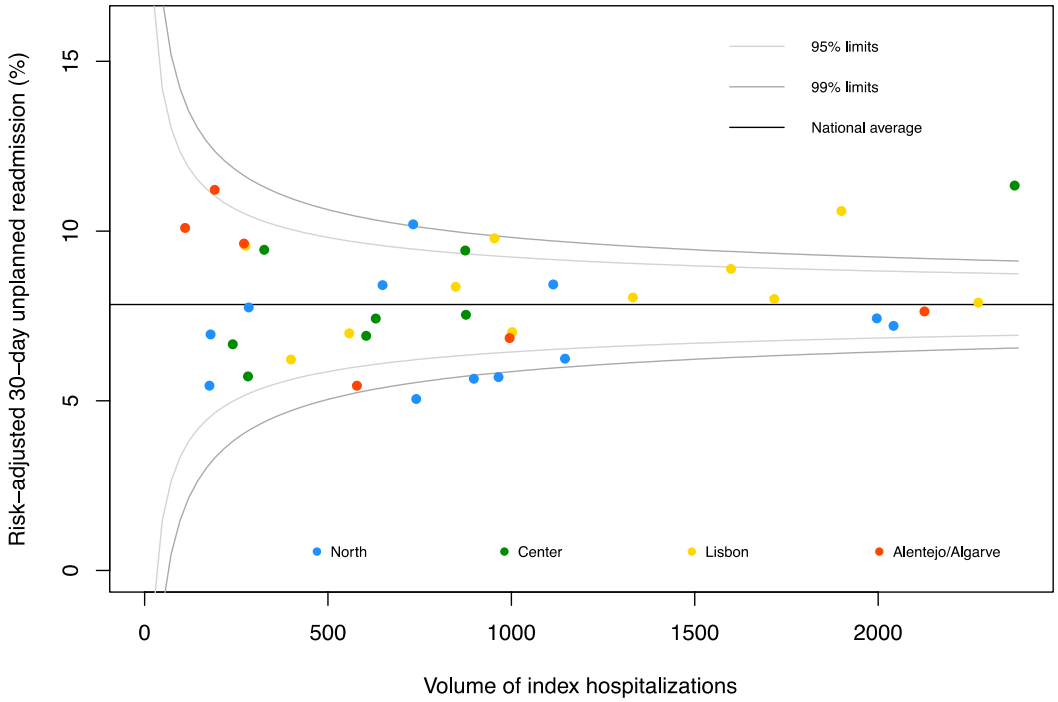


Figure S3. Caterpillar plots of hospital-specific mean predicted log odds of in-hospital mortality, by model. Predictions are for the reference patient. Colors characterize hospital regarding their geographical location: Blue – north; green – center; yellow – Lisbon; red – Alentejo or Algarve.

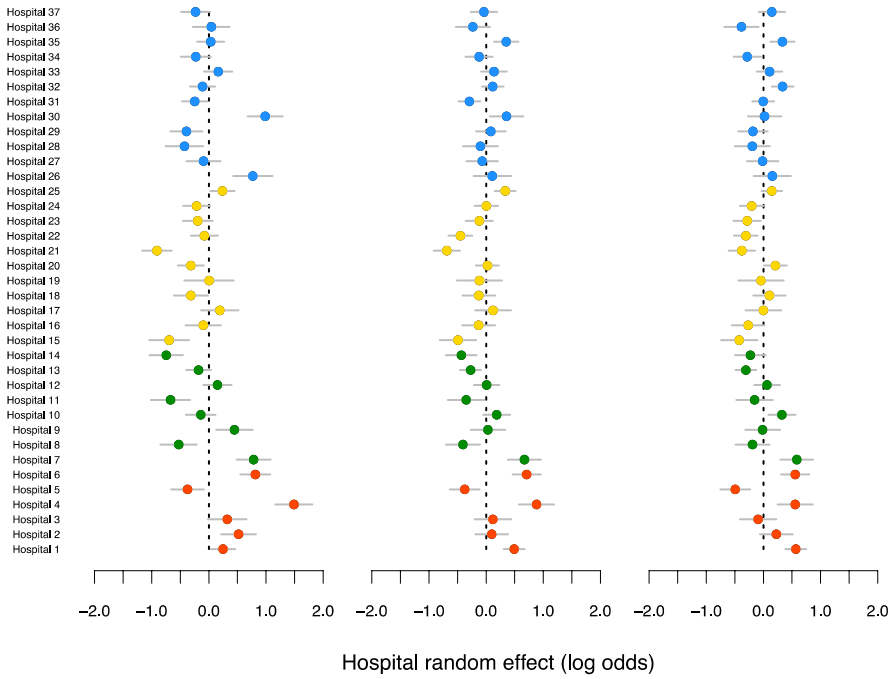
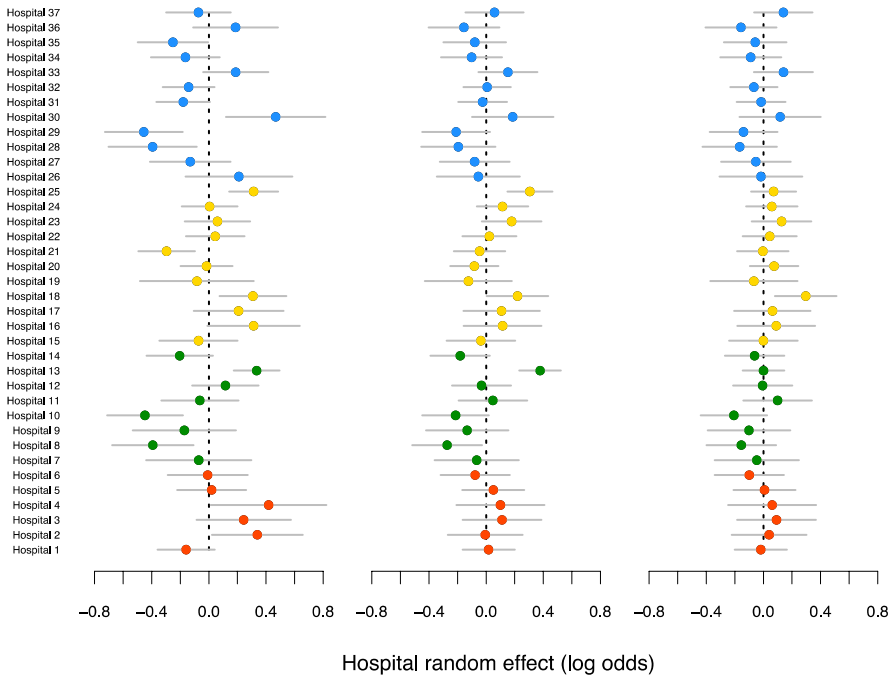



Figure S4. Caterpillar plots of hospital-specific mean predicted log odds of 30-day all-cause readmission, by model. Predictions are for the reference patient. Colors characterize hospital regarding their geographical location: Blue – north; green – center; yellow – Lisbon; red – Alentejo or Algarve.