ORIGINAL ARTICLE

The Portuguese Registry of Hypertrophic Cardiomyopathy: Overall results

Nuno Cardim a,*, Dulce Brito b, Luis Rocha Lopes c, d, António Freitas e, Carla Araújo f, Adriana Belo g, Lino Gonçalves h, Jorge Mimoso i, Iacopo Olivotto j, m, Perry Elliott k, m, Hugo Madeira l, on behalf of the participating centres 1

a Hospital da Luz, Lisboa, Portugal; Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal
b Hospital de Santa Maria, Centro Hospitalar Lisboa Norte (CHLN), Centro Cardiovascular da Universidade de Lisboa (CCUL), Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
c Centros Heart Centre, Barts Health NHS Trust; Institute of Cardiovascular Science, University College London, United Kingdom
d Centro Cardiovascular da Universidade de Lisboa, Lisboa, Portugal
e Hospital Fernando da Fonseca, Amadora-Sintra, Portugal
f Centro Hospitalar de Trás-os-Montes e Alto Douro, EPE, Hospital de São Pedro, Vila Real, Portugal; Epidemiology Research Unit (EPIUnit), Instituto de Saúde Pública, Universidade de Porto (ISPUP), Porto, Portugal
g Sociedade Portuguesa de Cardiologia, Departamento de Bioestatística, Coimbra, Portugal
h Centro Hospitalar e Universitário de Coimbra-Hospital Geral; Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal
i Centro Hospitalar do Algarve, Faro, Portugal
j Careggi University Hospital, Florence, Italy
k Barts Heart Centre, Barts Health NHS Trust / Institute of Cardiovascular Science, University College London, United Kingdom
l Centro Cardiovascular da Universidade de Lisboa, Lisboa, Portugal
m Member of the Scientific Committee of PRo-HCM

Received 17 July 2017; accepted 8 August 2017

KEYWORDS
Hypertrophic cardiomyopathy; Registry; Left ventricular hypertrophy; Outcome

Abstract

Introduction: We report the results of the Portuguese Registry of Hypertrophic Cardiomyopathy, an initiative that reflects the current spectrum of cardiology centers throughout the territory of Portugal.

Methods: A direct invitation to participate was sent to cardiology departments. Baseline and outcome data were collected.

Results: A total of 29 centers participated and 1042 patients were recruited. Four centers recruited 49% of the patients, of whom 59% were male, and mean age at diagnosis was 53 ± 16 years. Hypertrophic cardiomyopathy (HCM) was identified as familial in 33%. The major reason for diagnosis was symptoms (53%). HCM was obstructive in 35% of cases and genetic testing

* Corresponding author.
E-mail address: cardimnuno@gmail.com (N. Cardim).
1 List of participating centers and principal investigators are provided in Appendix A.

2174-2049/© 2017 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. All rights reserved.
Registo Português de Miocardiopatia Hipertrófica: resultados globais

Resumo
Objetivo: Apresentação dos resultados do Registo Português de Miocardiopatia Hipertrófica.

Metodologia: Convite direto aos diferentes centros de cardiologia de Portugal, com análise de dados basais e de seguimento.

Resultados: Foram 29 os centros participantes e 1042 doentes incluídos. Quatro centros incluíram 49% dos doentes, 59% do sexo masculino, idade média de diagnóstico 53 ± 16 anos. A doença foi considerada familiar em 33% e a presença de sintomas foi a principal causa de diagnóstico (53%). A miocardiopatia hipertrófica foi obstrutiva em 35%. O estudo genético foi efetuado em 51%. Oito por cento dos doentes fizeram terapêutica invasiva de redução septal (23% dos doentes com obstrução). A maioria dos doentes (84%) apresentava um risco estimado de mortalidade súbita aos 5 anos < 6%. Em 13% foi colocado desfibrilhador cardioversor implantável. Após um seguimento de 3,3 anos, intervalo interquartil (P25-P75): 1,3–6,5 anos, 31% estavam assintomáticos. A mortalidade total foi de 1,19%/ano e a cardiovascular de 0,65%/ano. A incidência de morte por insuficiência cardíaca foi de 0,25%/ano, a de morte súbita de 0,22%/ano e a de morte por acidente vascular cerebral de 0,04%/ano. A mortalidade por insuficiência cardíaca e transplante cardíaco foi de 0,27%/ano e a de morte súbita e equivalentes de 0,53%/ano.

Conclusões: A miocardiopatia hipertrófica em Portugal apresenta idade de diagnóstico elevada e é frequente o tratamento invasivo de formas obstrutivas. A mortalidade é baixa, a insuficiência cardíaca é a principal causa de mortalidade, seguida pela morte súbita. A doença apresenta elevada morbidade, realçando a necessidade do desenvolvimento de tratamentos específicos com impacto na sua história natural.

© 2017 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. Todos os direitos reservados.

List of abbreviations
ICD implantable cardioverter-defibrillator
AF atrial fibrillation
IVS interventricular septum
ASA alcohol septal ablation
LVH left ventricular hypertrophy
CRF case report form
PPro-HCM Portuguese Registry of Hypertrophic Cardiomyopathy
HCM hypertrophic cardiomyopathy
SCD sudden cardiac death
HF heart failure
TIA transient ischemic attack
Introduction

Hypertrophic cardiomyopathy (HCM) represents an important health burden as a cause of sudden cardiac death (SCD), heart failure (HF), atrial fibrillation (AF) and stroke. HCM shares many disadvantages of rare diseases, including limited recognition, lack of prospective studies assessing treatment, and little or delayed access to advanced treatment options without enjoying their regulatory benefits.1-4 Randomized clinical trials are infrequent in HCM and recommendations are largely based on expert consensus.1-4 Additionally, the majority of studies still originate from tertiary referral centers, and little is known about the clinical profile and management of the disease at a nationwide level. The real impact of genetics and imaging techniques on earlier and wider recognition of HCM, as well as of advanced treatment options on outcomes, is also unknown. It is of paramount importance to capture these changes and to provide answers to these questions.1,2,5

Accordingly, the importance of clinical registries of HCM is increasing, since they provide the best source of real-world data in specific countries and geographical regions.

Assuming a prevalence of 1:5001 for HCM in general and of 1:3200 for ‘clinical HCM’6 (patients who come to medical attention), the number of patients with HCM in Portugal (population about 10 million) is respectively around 20,0001 and 3000.6 However, few studies have addressed this population.6-8 Besides its relevance to national cardiologists, the Portuguese HCM population represents an interesting sample because of the country’s relatively small size, homogeneous population and high penetration of health care.

The Portuguese Registry of Hypertrophic Cardiomyopathy (PRo-HCM) was instituted to collect information on the actual situation of HCM in Portugal. It specifically assessed epidemiological, sociodemographic and clinical data, current standards for diagnosis, treatment, follow-up, and outcomes. Another aim was to develop a reliable source of information for health professionals, patients and families, on appropriateness, effectiveness and quality of care.

Methods

Registry design and methodology

The PRo-HCM registry was conceived by the Working Group on Myocardial and Pericardial Diseases of the Portuguese Society of Cardiology, directed by an executive and a scientific committee, and managed in the Portuguese National Center for Data Collection in Cardiology (CNCD). This study was formulated and conducted in compliance with the principles of the declaration of Helsinki, and approved by the National Center for Data Protection. It was an observational, multicenter, voluntary, non-mandatory study, with a two-year enrollment period (April 2013-April 2015), retrospective but including a prospective update.

A direct invitation was made to cardiology departments nationwide, central and regional, public and private, academic and non-academic, covering rural and urban, coastal and inland areas. Additionally, the registry was advertised in the Portuguese Journal of Cardiology, meetings and newsletters. If the invitation was accepted, the principal investigator received detailed instructions, a center identification number and a unique username and password to gain access to the electronic case report form (CRF) (http://www.spc.pt/RegistosMiocardiopatia/Public/Login.aspx?ReturnUrl=%2fRegistosMiocardiopatia%2f). The CRF contained seven sections: (1) patient identification and demographic/epidemiological data; (2) past history and baseline clinical data; (3) mortality and risk stratification; (4) diagnostic tests; (5) genetic testing, family screening, and genetic counseling; (6) treatment; (7) last assessment (clinical course, follow-up, and outcomes). In the diagnostic tests section the investigators were asked to enter the exams performed at the time of first assessment, including electrocardiogram (ECG), echocardiogram, ambulatory ECG, exercise test, exercise echocardiogram, cardiac magnetic resonance (CMR), and cardiac computed tomography.

Centers were asked to include all patients with a diagnosis of HCM followed at the center currently or in the past (no retrospective time limit), including those already deceased at the time of enrollment. Written informed consent was obtained from living patients and from a proxy of deceased patients.

Inclusion criteria were age >18 years at the time of enrollment, and unexplained left ventricular hypertrophy (LVM): wall thickness ≥15 mm by imaging techniques (in first-degree relatives ≥14 mm in the inferior interventricular septum (IVS) or lateral wall or ≥13 mm in the anterior IVS or inferior wall).

Exclusion criteria were secondary LVM (grade ≥2 hypertension11), moderate or severe aortic stenosis,12 previously diagnosed cardiac or systemic disease, and metabolic or multi-organ syndrome associated with LVM.

After the inclusion period, extra time was provided to complete the CRFs and to clean the database. The final date of registry closure was December 31, 2015. CRFs were reviewed to confirm consistency of data. Whenever necessary, queries were sent to investigators. In the event of repeated patients (same initials, gender and birth date), the one with the longer follow-up time was included.

Definitions

Throughout the study, most data are relative to the time of first visit. When clinically relevant, data at the time of diagnosis of HCM are also shown.

Follow-up time was defined as time from initial assessment at the center to last assessment or death.

Sudden cardiac death (SCD) was defined as unexpected death occurring within one hour of symptom onset in patients who had previously experienced a relatively stable or uneventful clinical course. Resuscitation from cardiac arrest or appropriate implantable cardioverter-defibrillator (ICD) therapies for primary prevention were considered as equivalents of SCD.

HF-related death was defined as that occurring in the context of progressive cardiac decompensation, with decline in left ventricular function.13 Heart transplantation was considered as equivalent to HF-related death.

Stroke-related deaths in the setting of paroxysmal, persistent or permanent AF were classified as AF-stroke related
deaths. Stroke-related deaths in the absence of documented AF were not included in this group.

Thromboembolic events, defined as stroke, transient ischemic attack (TIA) or systemic peripheral embolism, were recorded.\textsuperscript{14}

The classification of identified genetic variants was assigned to the investigators, as pathogenic/probably pathogenic, of unknown significance or benign/probably benign, according to current knowledge of their pathogenicity,\textsuperscript{15,16} as provided by genetic laboratories (these data were not centrally reviewed or corrected by the coordinators of the registry). A genetic study was defined as negative if no pathogenic/probably pathogenic mutation was detected and as in progress if no result was provided at inclusion.

**Statistical analysis**

Continuous variables were expressed as mean and standard deviation or as median and interquartile range (IQR) (P25-P75). Categorical variables were given as total number and percentages. Chi-square or Fisher tests were used for comparisons of categorical variables and Student’s t tests for continuous variables. Survival was assessed by Cox proportional hazard regression. Survival curves were constructed according to the Kaplan-Meier method, and comparisons were performed using the log-rank test. All p-values were two-sided and considered significant when <0.05. All analyses were performed using SPSS 19.0\textsuperscript{18}.

**Results**

Of the 62 institutions contacted, 37 accepted, and the final number of participating centers was 29 (Figure 1). The total number of patients was 1042. Figures were compared with other national registries\textsuperscript{17,18} (Table 1).

**Baseline assessment**

Almost half of the patients (n=514, 49%) came from the four major centers with specific interest in HCM (the other 25 centers enrolled 528 patients, 51%) (Figure 1). The Lisbon region included the largest number, followed by the North region, the South and Islands, and the Central region. Of the 29 centers, only three included more than 100 patients and eight more than 50 patients. Twenty-one centers included fewer than 50 patients each, 13 centers fewer than 10 and six centers fewer than five.

The patient cohort showed a slight preponderance of males. Mean age at diagnosis was 53±16 years and more than one quarter were diagnosed over the age of 65 years. The disease was classified as familial in one third. At first consultation most patients were symptomatic\textsuperscript{19} (Table 2).

**Diagnostic tests**

The ECG was abnormal in 964 individuals (93%). AF was recorded in 117 (11%).
Table 1  Comparison between populations of national registries of hypertrophic cardiomyopathy.

<table>
<thead>
<tr>
<th></th>
<th>Portuguese registry (PRo-HCM)</th>
<th>Italian registry17</th>
<th>French registry18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country population</td>
<td>10 million</td>
<td>50 million</td>
<td>66 million</td>
</tr>
<tr>
<td>Patients in registry</td>
<td>1042</td>
<td>1677</td>
<td>1401</td>
</tr>
</tbody>
</table>

Estimated prevalence of HCM based on the CARDIA study: 1:5006

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM patients</td>
<td>20000</td>
</tr>
<tr>
<td>Male/female</td>
<td>613/429 59/41</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>53±16 (9-88)</td>
</tr>
<tr>
<td>Diagnosis &gt;50 years</td>
<td>605 58</td>
</tr>
<tr>
<td>Diagnosis &gt;65 years</td>
<td>281 27</td>
</tr>
<tr>
<td>Familial/sporadic</td>
<td>347/559 33/54</td>
</tr>
<tr>
<td>Non-obstructive HCM</td>
<td>613 59</td>
</tr>
<tr>
<td>Obstructive HCM</td>
<td>365 35</td>
</tr>
</tbody>
</table>

Risk stratification for sudden cardiac death at baseline (at the time of the first visit)

Based on the American Heart Association model for SCD20 (Supplementary Table 1), half of the patients had no risk factors, one third had one risk factor and 15% more than one risk factor. Our data also showed that according to the European Society of Cardiology SCD risk score, the majority of patients had a five-year risk lower than 4%.

Genetic testing

In total, 51% of the patients had undergone genetic testing and in 40% of these a pathogenic/probably pathogenic mutation was found (Table 3). In this group, when the causative gene mutation was reported, the two most frequent genes were MYBPC3 and MYH7.

Echocardiographic assessment at enrollment showed that HCM was non-obstructive (instantaneous peak Doppler intraventricular pressure gradient <30 mmHg) in 613 (59% of patients) and obstructive in 365 (35%) (Table 2). Of these, 323 (88%) had obstruction at rest and 42 (12%) had exercise-induced obstruction only, during exercise echocardiography. Obstruction was at the left ventricular outflow tract in 89%. An apical aneurysm was present in 23 patients (2%).

On ambulatory Holter ECG monitoring, AF was present in 118 patients (11%). An exercise test was carried out in less than half of the population and exercise echocardiography in approximately one fifth (Table 2).

CMR was performed in almost half of the cohort. Its incremental value over echocardiography was the assessment of fibrosis (59%), diagnosis in false-negative echocardiograms (6%) and detection of massive LVH (4%).

Table 2   Summary of baseline characteristics and diagnostic tests.

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM patients</td>
<td>1042 53</td>
</tr>
<tr>
<td>Male/female</td>
<td>613/429 59/41</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>53±16 (9-88)</td>
</tr>
<tr>
<td>Diagnosis &gt;50 years</td>
<td>605 58</td>
</tr>
<tr>
<td>Diagnosis &gt;65 years</td>
<td>281 27</td>
</tr>
<tr>
<td>Familial/sporadic</td>
<td>347/559 33/54</td>
</tr>
<tr>
<td>Non-obstructive HCM</td>
<td>613 59</td>
</tr>
<tr>
<td>Obstructive HCM</td>
<td>365 35</td>
</tr>
</tbody>
</table>

CA: cardiac angiography; CCT: cardiac computed tomography; CMR: cardiac magnetic resonance; EMB: endomyocardial biopsy; HCM: hypertrophic cardiomyopathy; NYHA: New York Heart Association functional class.

Risk stratification for sudden cardiac death at baseline (at the time of the first visit)

Based on the American Heart Association model for SCD20 (Supplementary Table 1), half of the patients had no risk factors, one third had one risk factor and 15% more than one risk factor. Our data also showed that according to the European Society of Cardiology SCD risk score, the majority of patients had a five-year risk lower than 4%.

Genetic testing

In total, 51% of the patients had undergone genetic testing and in 40% of these a pathogenic/probably pathogenic mutation was found (Table 3). In this group, when the causative gene mutation was reported, the two most frequent genes were MYBPC3 and MYH7.

Echocardiographic assessment at enrollment showed that HCM was non-obstructive (instantaneous peak Doppler intraventricular pressure gradient <30 mmHg) in 613 (59% of patients) and obstructive in 365 (35%) (Table 2). Of these, 323 (88%) had obstruction at rest and 42 (12%) had exercise-induced obstruction only, during exercise echocardiography. Obstruction was at the left ventricular outflow tract in 89%. An apical aneurysm was present in 23 patients (2%).

On ambulatory Holter ECG monitoring, AF was present in 118 patients (11%). An exercise test was carried out in less than half of the population and exercise echocardiography in approximately one fifth (Table 2).

CMR was performed in almost half of the cohort. Its incremental value over echocardiography was the assessment of fibrosis (59%), diagnosis in false-negative echocardiograms (6%) and detection of massive LVH (4%).
Table 3 Results of genetic testing.\textsuperscript{15,16}

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCM patients tested</strong></td>
<td>528</td>
<td>51</td>
</tr>
<tr>
<td>Positive</td>
<td>210</td>
<td>40</td>
</tr>
<tr>
<td>VUS</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td><strong>Pathogenic/probably pathogenic mutation</strong>^a</td>
<td>210</td>
<td>49</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>99</td>
<td>49</td>
</tr>
<tr>
<td>MYH7</td>
<td>56</td>
<td>28</td>
</tr>
<tr>
<td>TNNT2</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>TNNI3</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>TPM1</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>CRSP3</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>MYL3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>MYL2</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\^a Raw data derived from CRF data, inserted by the investigators as reported by the genetic laboratory and not confirmed by the coordinators of the registry, including the attributed classification of ‘pathogenic/probably pathogenic mutation’.

Table 4 Treatment in the PRo-HCM registry.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>768</td>
<td>74</td>
</tr>
<tr>
<td><strong>CCBs</strong></td>
<td>262</td>
<td>25</td>
</tr>
<tr>
<td><strong>Disopyramide</strong></td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>151</td>
<td>15</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td>276</td>
<td>27</td>
</tr>
<tr>
<td><strong>VKAs</strong></td>
<td>208</td>
<td>75</td>
</tr>
<tr>
<td><strong>NOACs</strong></td>
<td>60</td>
<td>22</td>
</tr>
<tr>
<td><strong>ACEIs</strong></td>
<td>226</td>
<td>22</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td>178</td>
<td>17</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>252</td>
<td>24</td>
</tr>
<tr>
<td><strong>Nitrates</strong></td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td><strong>ASA</strong></td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>61</td>
<td>6</td>
</tr>
<tr>
<td><strong>ICD</strong></td>
<td>140</td>
<td>13</td>
</tr>
<tr>
<td><strong>Primary prevention</strong></td>
<td>123</td>
<td>88</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td><strong>Pacemaker</strong></td>
<td>92</td>
<td>9</td>
</tr>
<tr>
<td><strong>Bradyarrhythmia</strong></td>
<td>64</td>
<td>70</td>
</tr>
<tr>
<td><strong>Gradient reduction</strong></td>
<td>19</td>
<td>21</td>
</tr>
</tbody>
</table>

\textsuperscript{15,16} ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; ASA: alcohol sepal ablation; CCBs: calcium channel blockers; ICD: implantable cardioverter defibrillator; NOACs: new oral anticoagulants; VKAs: vitamin K antagonists.

Follow-up, morbidity and mortality

Mean follow-up was 5.3±6.1 years, median 3.3 years (IQR [P25-P75] 1.3-6.5 years). At last assessment, most patients were symptomatic (Figure 2), usually with mild to moderate symptoms. A small number (n=42, 4%) developed systolic dysfunction.

All-cause mortality was 6.2% (Table 5). Cardiovascular mortality was 3.4%, most frequently due to HF, followed by SCD and by stroke-related death.

In univariate analysis, 16 of the predefined variables were significantly related to mortality. Multivariate analysis showed four major risk indicators of cardiovascular mortality: late diagnosis (>60 years), family history of SCD, progressive systolic dysfunction and obstructive HCM (Supplementary Table 2).

Of the 12 patients with SCD, seven were between 40 and 65 years old, three were older than 65, and only two were aged under 40 years. In a number of patients SCD was aborted by appropriate ICD shocks in the setting of primary prevention or documented successful in- and/or out-of-hospital resuscitation. Therefore, actual plus aborted SCD occurred in 29 patients.

The incidence of all-cause and cardiovascular mortality was 1.19%/year and 0.63%/year, respectively; the incidence of HF-related death was higher than that of SCD, and the latter was higher than that of stroke. However, the incidence of SCD death plus equivalents was higher than the incidence of HF death, with or without equivalents (Table 5 and Figure 3).

Thromboembolic events occurred in 65 patients (6%) (stroke n=52, TIA n=11, peripheral embolism n=2). Of these, half had documented AF.

Compared with low-volume centers (<15 patients included, n=16), high-volume (>100 patients, n=3) centers had younger patients and more familial HCM and performed more genetic testing, family screening and exclusion of phe- nocopies (Supplementary Table 3). Additionally, despite the higher number of diagnostic tests and of drug prescriptions of high-volume centers, no major differences in outcomes were found.

Discussion

The PRo-HCM registry provides a detailed contemporary assessment of the clinical profile, management strategies and outcomes of HCM in Portugal. While most data are consistent with the existing literature,\textsuperscript{17,18,22} the present findings show elements of novelty and some differences from the guidelines.\textsuperscript{1,2} Our results are important at both national and international level, as several countries, worldwide, may face similar conditions in the management of the disease.

Epidemiological and sociodemographic data

The total number of patients included represents about 5% of the estimated prevalence in Portugal,\textsuperscript{5,7} but up to one third of the Portuguese population with ‘clinical’ HCM.\textsuperscript{6} Accordingly, this is, to our knowledge, the most comprehensive national HCM registry published.\textsuperscript{17,18,22} This national effort provides credibility to our data as representative of the real Portuguese scenario. The distribution of patients between referral and community-based centers (four centers included half of the patients and 25 centers the other half) shows that a significant number of patients are followed in non-referral centers. Of note, however, was the
low proportion of reported familial HCM, probably reflecting a low rate of systematic family screening programs and/or a referral center bias in another registry.22

Baseline assessment

Over a decade since the publication of another national registry,17 the clinical spectrum of HCM appears very similar, suggesting that its clinical profile is not undergoing major changes in the Western world. The major difference is the older age at diagnosis, with more than one fourth of patients diagnosed over the age of 65 years. This finding may reflect delayed disease penetrance, lack of systematic family screening, and – potentially – an increased diagnostic yield in older patients.1,2 By contrast, the association found in our cohort of a low rate of familial HCM, later age of presentation, and low risk profile, may more closely mirror the real-world disease scenario, reflecting the inclusion of these unselected lower-risk HCM patients in the cohort. Recent reports have in fact identified a lower-risk cohort of HCM patients, with later onset and lower rate of familial disease,23,24 which may explain our findings.

The proportion of obstructive forms in our cohort, about one third, basically reflects patients with obstruction at rest, and is consistent with the existing literature for resting obstruction.1,2 Accordingly, due to the low rate of exercise echocardiography performed,25 many patients with labile obstruction were probably not detected and were classified as non-obstructive, which at first sight suggests a deviation from the guidelines. However, as the recommendations1,2 for the use of exercise echocardiography in non-obstructive HCM at rest are relatively recent, some of these patients, assessed earlier, have not undergone exercise echocardiography and were diagnosed as non-obstructive in this observational study.

Diagnostic tests and sudden cardiac death risk stratification at baseline

Our data show a relatively limited penetration of CMR, despite the evidence of its incremental value.1,3 These results reflect its high costs, limited availability, and relatively recent introduction in clinical practice.1,3,4 By contrast, despite the factors that limit the dissemination of genetic testing1,2 (price, lack of co-payment, low availability), half of the patients underwent genetic study, which in many cases is already part of routine practice.26 The proportion of tests in which a variant was found15,16,27,28 and the relative prevalence of the disease-causing genes is mostly similar to what has been described.1,2,15,16,27,28 However, according to the results provided by the investigators, an unexpectedly high prevalence of pathogenic/probably pathogenic mutations15,16,27,28 was found in the TPM1 and CSR53 genes.17 These results should be interpreted with caution, because they are derived from CRF raw data that were not centrally reviewed or corrected by the PRo-HCM coordinators.

Both of the contemporary models for SCD risk1,2,20,21 show that our cohort was, at baseline, a low-risk population for SCD, which partially explains the low rate of SCD and of ICD implantations.

Treatment

Invasive septal reduction was offered to almost one fourth of obstructive patients, including those who were mildly
symptomatic. Although it cannot be excluded that this rate is biased by the low number of patients detected with labile obstruction, it probably also results from knowledge of the adverse long-term effects of obstruction, as well as from the safety of invasive procedures, which may impact future HCM guidelines.

Of note, the number of surgical myectomies was much higher than the number of ASA procedures, which is partially explained by the late introduction of the latter in Portugal (2009). The fact that the two procedures were performed in different centers deserves reflection, taking into account the known effect of expertise on results.1,2

Finally, fewer than 15% of patients received an ICD during follow-up, reflecting the low risk profile of our non-selected population.

**Follow-up, morbidity and mortality**

Overall, our data suggest that in Portugal, in the era of better diagnostic and therapeutic techniques, HCM has low mortality but high morbidity.

Additionally, despite greater use of diagnostic tests and differences in medical treatment, outcomes of high-volume centers are similar to those of low-volume centers, calling into question the value of HCM centers and of the 'hub and spoke' model.7

Outcome data show that the SCD rate in HCM patients in Portugal is very low. Even though this finding may be partially explained by lives saved by successful resuscitation and ICD implantation, the incidence of SCD is still low after including these SCD equivalents in the SCD rate. As a consequence of the efficacy of these preventive measures, HF has become the leading cause of death in HCM patients in Portugal.

Our figures are in overall agreement with those from other groups,30 showing that overall mortality in treated HCM in Portugal is 1.19%, similar to that of the general Portuguese population (around 1.1% year).31 Importantly, at follow-up most patients were symptomatic, confirming that disease morbidity represents a significant burden to patients, health care services and providers. Accordingly, the “contemporary treatable disease” has become, at least in Portugal, a “contemporary chronic treatable disease” in which, side by side with ICDs, the role of chronic medical treatment is increasing.

**Limitations**

Despite their inherent limitations, registries provide realistic geographical data on disease course and management.

The inclusion of mostly symptomatic patients with advanced, established disease (mainly included by HCM referral centers) is a limitation of this registry, providing a biased view of the disease (selection bias, a common limitation of many HCM studies).

Additionally, disease-related mortality is underestimated, as patients who died before diagnosis were not included. This survival bias partially explains the low rate of events, especially the low rate of SCD.

Children were excluded because of important clinical differences.12
Future directions

The identification, at a national level, of discrepancies between our data and the guidelines is an important finding, warranting a national effort to correct them (for instance to include exercise echocardiography as a standard initial assessment of non-obstructive HCM at rest, to better detect labile obstruction).

Because of the large volume of data, we were unable to cover some important topics in depth. Accordingly, further work will be directed at comparisons between subgroups, addressing family screening, genetic testing (including founder effects, differences in phenotype between genes, and analysis of specific mutations considered as pathogenic/probably pathogenic by the investigators), awareness of phenocopies (for instance Fabry disease), and detailed assessment of clinical HCM profiles.

Conclusions

The PRO-HCM registry provides comprehensive data on the management of HCM in Portugal in the era of genetics, CMR, ICDs and ASA, and indicates the need for better access to resources and some deviations from guidelines.

Contemporary HCM in Portugal is characterized by relatively advanced age at diagnosis, and a high proportion of invasive treatment of obstructive forms at rest. Long-term mortality is low, and HF is the most common cause of death followed by SCD (excluding equivalents). However, morbidity remains considerable, emphasizing the need for disease-specific treatments that impact the natural history of the disease.

Funding (unrestricted grants to the Portuguese Society of Cardiology for all myocardial and pericardial disease registries)

Gold: Jaba Recordati, Merck Serono, Sanofi-Genzyme, Shire; Silver: Medinifar, Servier

IOI was supported by the Italian Ministry of Health ("LVH in aortic valve disease and HCM: genetic basis, biophysical correlates and viral therapy models" (RF-2013-02356787), and NET-2011-02347173 ("Mechanisms and treatment of coronary microvascular dysfunction in patients with genetic or secondary LVH"); and by Telethon Italy (GGP13162).

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

We are grateful to CNCDG staff, especially Dr. Sandra Corker, and to Infortucano staff.

Appendix A. Participating centers and principal investigators

Centro Hospitalar de Leiria: Joana Correia; Centro Hospitalar de Lisboa Norte - Hospital de Santa Maria: Dulce Brito; Centro Hospitalar de Lisboa Ocidental, Serviço de Cardiologia: João Abecasis; Centro Hospitalar de Lisboa Ocidental - Hospital São Francisco Xavier - Serviço de Medicina III: Cândida Fonseca; Centro Hospitalar de Trás os Montes e Alto Douro - Hospital São Pedro: Carla Alexandra R. Araújo; Centro Hospitalar de Vila Nova de Gaia/Espinho: Conceição Fonseca; Centro Hospitalar do Algarve - Hospital de Faro: Nuno Marques; Centro Hospitalar do Alto Ave - Hospital da Senhora da Oliveira: Olga Azevedo; Centro Hospitalar do Baixo Vouga - Hospital Infantil D. Pedro: José António Nobre dos Santos; Centro Hospitalar do Oeste Norte - Centro Hospitalar das Caldas da Rainha: Ana Filipa Pereira Rodrigues; Centro Hospitalar do Porto - Hospital de Santo António: Patricia Fernandes Rodrigues; Centro Hospitalar do Tâmega e Sousa - Unidade Padre Américo: Maria Conceição Queirós; Centro Hospitalar e Universitário de Coimbra - Cardiologia B - Hospital Geral: Joana Delgado Silva; Centro Hospitalar Tondela Viseu - Hospital de São Teotónio: Carlos Emanuel Correia; CUF Infante Santo Hospital: Pedro Matos; Hospital Beatriz Ângelo: Luís Sargento; Hospital da Luz Lisboa: Nuno Cardim; Hospital das Forças Armadas: Sara Ferreira; Hospital de Braga: Nuno Salomé; Hospital de Santa Maria Maior de Barcelos - Serviço Cardiologia: Alexandra Sousa; Hospital de Santo Espírito de Angra do Heroísmo: Rute Couto; Hospital de São João: Elisabete Martins; Hospital do Espírito Santo: Agostinho Caeiro; Hospital Garcia de Orta: Luís Rocha Lopes; Hospital Prof. Doutor Fernando Fonseca: Francisco Madeira; Hospital SAMS: Berta Carola; HPP Hospital de Cascais - Hospital Dr. José de Almeida: Gonçalo Proença; Unidade Local de Saúde da Guarda - Hospital Sousa Martins: Maria Cristina Gamboa.

Appendix B. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rep.2017.08.005.

References

15. Ackerman MJ, Priori SG, Willems S, et al. HRS/ EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8:1308–39.