The Portuguese Registry of Hypertrophic Cardiomyopathy: global results

Registo Português de Miocardiopatia Hipertrófica: resultados globais

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ABSTRACT

Aim - We report the results of the Portuguese Registry of Hypertrophic Cardiomyopathy, a contemporary effort representing the spectrum of cardiology centres over the national territory. **Methods**- A direct invitation to participate was sent to cardiology departments. Baseline and outcome data were collected. **Results -** 29 centres participated, 1042 patients were recruited. Four centres recruited 49% of the patients, 59 % males, mean age at diagnosis 53±16 years. Hypertrophic Cardiomyopathy was identified as familial in 33%. The major reason for diagnosis was symptoms (53%). Hypertrophic Cardiomyopathy was obstructive in 35%; Genetic testing was performed in 51%. Invasive septal reduction therapy was offered to 8% (23% of obstructive patients). Most patients (84%) had an estimated 5-year risk of sudden death <6%. Thirteen per cent received an implantable cardioverter defibrillator. After a median follow-up of 3.3 years, interquartile range (P25-P75) 1.3 - 6.5 years, 31% were asymptomatic. All-cause mortality was 1.19 %/year and cardiovascular mortality 0.65 %/year. The incidence of heart failure-death was 0.25%/year, of sudden cardiac death 0.22%/year and of stroke-related death 0.04%/year. Heart failure-death plus heart transplant occurred 0.27%/year and sudden cardiac death plus equivalents occurred 0.53%/year. **Conclusions –** Contemporary Hypertrophic Cardiomyopathy in Portugal is characterized by relatively advanced age at diagnosis, and a high proportion of invasive treatment of obstructive forms. Long-term mortality is low, heart failure is the most common cause of death followed by sudden cardiac death. However, the burden of morbidity remains considerable, emphasizing the need for disease-specific treatments impacting the natural history of the disease.

Keywords: hypertrophic cardiomyopathy; registry; left ventricular hypertrophy; outcome

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RESUMO

Objectivo – 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** - 29 centros participantes, 1042 doentes incluídos. Quatro centros incluiram 49% dos doentes, 59 % do sexo masculino, idade média de diagnóstico 53±16 anos. A doença foi considerada familiar em 33% sendo a presença de sintomas a principal causa de diagnóstico (53%). A miocardiopatia hipertrófica foi obstrutiva em 35%. O estudo genético foi efectuado em 51%. Oito por cento dos doentes realizaram terapêutica invasiva de redução septal (23% dos doentes com obstrução). A maioria dos doentes (84%) apresentava um risco estimado de morte 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 asintomáticos. A mortalidade total foi 1.19 %/ano e a cardiovascular 0.65 %/ano . A incidência de morte por insuficiência cardiaca foi 0.25%/ ano, a de morte súbita 0.22%/ano e a de morte por acidente vascular cerebal 0.04%/ano. A mortalidade por insuficiência cardíaca e transplante cardíaco foi 0.27%/ano e a de morte súbita e equivalentes 0.53%/ano. **Conclusões –** A miocardiopatia hipertrófica em Portugal apresenta idade de diagnóstico elevada sendo frequente o tratamento invasivo de formas obstrutivas. A mortalidade é baixa, sendo a insuficiência cardiaca a principal causa de morte, seguida pela morte súbita. A doença apresenta elevada morbilidade, realçando a necessidade do desenvolvimento de tratamentos específicos com impacto na sua história natural.

Palavras chave: miocardiopatia hipertrófica; registo; hipertrofia ventricular esquerda; prognóstico

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QUADRO DE ABREVIATURAS - Inglês

HCM - Hypertrophic cardiomyopathy
SCD - sudden cardiac death
HF - heart failure
AF - atrial fibrillation
PRo-HCM - Portuguese Registry of Hypertrophic Cardiomyopathy
CRF - case report form
ECHO - echocardiogram
EE - exercise echo
CMR - cardiac magnetic resonance
IVS - left interventricular septum
LVH - left ventricular hypertrophy
ICD - implanted cardioverter defibrillators
LV – left ventricle
TE - Thrombo-embolic events
CVA - cerebrovascular accidents
TIA - transient ischaemic attacks
ASA - Alcohol Septal Ablation

Hypertrophic cardiomyopathy (HCM) represents an important health burden, as a cause of sudden cardiac death (SCD), heart failure (HF) and atrial fibrillation (AF) / stroke. HCM shares many disadvantages of rare diseases including limited recognition, lack of prospective studies assessing treatment, reduced/delayed access to advanced treatment options without enjoying their regulatory benefits [1,2,3,4]. Randomized clinical trials are infrequent in HCM and recommendations are largely based on expert consensus [1,2,3,4]. Additionally, the vast majority of studies still originate from tertiary referral centres, and little is known about the clinical profile and management of the disease at a nation-wide level. It is also unknown the real impact of genetics and imaging techniques in the earlier and wider recognition of HCM as well as of advanced treatment options in outcomes. It is of paramount importance to capture these changes, providing answers to these questions [1,2,5].

Accordingly, the importance of clinical registries of HCM is increasing, providing the best source of "real-world" data in specific countries/geographical regions.

Assuming a prevalence of 1:500 [5] for HCM in general and of 1:3200 for "clinical HCM" [6] (patients that come to medical attention), the number of Portuguese patients with HCM (population about 10 millions) is respectively around 20.000 [7] and 3.000 [6]. However, rare studies have addressed this population [8,9]. Besides its relevance to national cardiologists, Portugal represents an interesting paradigm because of its 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 reality of HCM in Portugal. It specifically assessed epidemiological, socio-demographic and clinical data, current standards for diagnosis, treatment, follow-up, and outcomes. Other aims were 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 was conceived by the Working Group on Myocardial & Pericardial Diseases of the Portuguese Society of Cardiology, conducted by an Executive and a Scientific Committee and managed in the Portuguese National Centre of Cardiologic Data Collection. This study was formulated and conducted in compliance with the principles of the declaration of Helsinki, and approved by the National Centre of Data Protection. It was an observational and multi-centric volunteer, non-mandatory study, with a 2-year enrolment 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 or not, covering rural and urban, coastal and interior areas. Additionally, the Registry was advertised in the Portuguese Journal of Cardiology, meetings and newsletters. In case of acceptance, the principal investigator received detailed instructions, a centre 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 included 7 sections: 1. Patient identification and demographic/ epidemiological data; 2. Past history-baseline clinical data; 3. Death and risk stratification; 4. Diagnostic tests; 5. Genetic test, family screening, genetic counseling; 6. Treatment; 7. Last evaluation- evolution, follow-up, outcomes. In the diagnostic tests section the investigators were asked to insert the exams performed at the time of first evaluation, including ECG, echocardiogram (echo), ambulatory ECG, exercise test, exercise echo (EE), cardiac magnetic resonance (CMR), cardiac computed tomography.

Inclusion and exclusion criteria

Centres were asked to include all patients with a diagnosis of HCM followed at the centre presently or in the past (no retrospective time limit), including those already deceased at

the time of enrolment. Written informed consent was obtained from living patients and from a proxy of deceased patients.

Inclusion criteria:

a) Adults >18 years old at the time of enrolment.

b) Unexplained left ventricular hypertrophy (LVH): wall thickness ≥ 15mm by imaging techniques (in first-degree relatives[10] ≥ 14 mm - inferior interventricular septum (IVS)/lateral wall- or ≥ 13 mm -anterior IVS/ inferior wall).

Exclusion criteria:

Secondary LVH (arterial hypertension ≥ grade 2 [11]), ≥ moderate aortic stenosis [12], previously diagnosed cardiac or systemic disease, metabolic or multi-organ syndrome associated with LVH.

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

Definitions

Throughout the document, 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 evaluation at the centre to last evaluation or death.

Sudden cardiac death (SCD) was defined as unexpected death occurring 1 hour from the onset of symptoms in patients who had previously experienced a relatively stable or uneventful clinical course. Resuscitation from cardiac arrest or appropriate implanted cardioverter defibrillators (ICD) interventions 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 LV function[13]. Heart transplants were considered as equivalents to HF deaths.

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.

Thrombo-embolic events (TE), defined as cerebrovascular accidents (CVA), transient ischaemic attacks (TIA), or systemic peripheral embolus were registered [14].

The classification of identified genetic variants was assigned to the investigators, as pathogenic/probably pathogenic, variant of unknown significance or benign/probably benign, according to the state of the art for their pathogenicity [15,16], as provided by genetic laboratories (these data were not centrally reviewed/corrected by the coordinators of the registry). A genetic study was defined as "negative" if no pathogenic/probably pathogenic was detected and "in progress" if no result was provided at inclusion.

Statistical methods

Continuous variables were expressed as mean and standard deviation or as median and interquartile ranges (IQR). Categorical variables were given as total number and percentages. Chi-square or Fisher tests were used for categorical variables comparisons and Student t-tests for continuous variables. Survival was assessed by Cox proportional hazard regression. The survival curve was constructed according to the Kaplan-Meier method, and comparisons were performed using the log-rank test. P-values are two-sided and considered significant when <0.05. All analyses were performed using SPSS 19.0®.

RESULTS

Of the 62 institutions contacted, 37 accepted and the final number of participating centres was 29 *(Figure 1).* The total number of patients was 1042. Figures were compared with other national Registries [17,18] (*Table 1).*

I- Baseline evaluation

Almost half of the patients (514, 49%) originated from the 4 major centres with specific interest in HCM (the remaining 25 centres enrolled 528 patients, 51%) *(Figure 1).* The Lisbon region included the highest number, followed by the North region, the South & Islands and by the Central region. Of the 29 centres, only 3 included more than 100 patients and 8 more than 50 patients. Twenty one centres included less than 50 patients each, 13 centres less than 10 and 6 less than 5.

The patient cohort showed a mild preponderance of males. Mean age at diagnosis was 53±16 years and more than one quarter were diagnosed at an age higher than 65 years. The disease was classified as "familial" in one third. At first consultation most patients were symptomatic [19] (*Table 2*).

II- Diagnostic Tests

The ECG was abnormal in 964 individuals (93%). AF was recorded in 117 (11%).
The echo assessment at enrolment showed that HCM was non obstructive (intraventricular instantaneous peak Doppler pressure gradient lower than 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%) only had exercise-induced obstruction, during EE. Obstruction was at the left ventricular outflow tract in 89%. An apical aneurysm was present in 23 patients (2%).

In the ambulatory ECG Holter monitoring, AF was present in 118 patients (11%). An exercise test was carried out in less than half of the population and an EE in approximately one fifth (*Table2*).

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

SCD risk stratification at baseline (at the time of the first visit)

Based on the American Heart Association model for SCD [2,20] (*Supplementary File 1*), half of the patients had no risk factors (RF), one third had one RF and 15% more than one RF. Our data also showed that according to the European Society of Cardiology SCD risk score [1, 21], the majority of patients had a 5-year risk lower than 4%.

III-Genetic Testing

In total, 51% of the patients had 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*.

IV-Treatment

Most patients (87%; n=909) received medical treatment (*Table 4*). Septal reduction therapy was performed in 8% of the cohort, 23% of the obstructive group. Cardiac surgery was performed 2.6 times more frequently than ASA. Surgery was performed in 11 centres (of these, only two with more than 10 surgeries). ASA was performed in 4 centres (only one reached 10 procedures).

An ICD was implanted in 13% of the population, mainly for primary prevention. A pacemaker was received by 9%, usually for conduction disorders.

V-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/moderate symptoms. A small number (42, 4%) developed systolic dysfunction.

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

In the univariate analysis, 16 of the predefined variables were significantly related to mortality. Multivariate analysis showed 4 major risk indicators of CV mortality: late diagnosis (> 60 years), family history of SCD, progressive systolic dysfunction and obstructive HCM

(*Supplementary File 2*).

Of the 12 patients with SCD, 7 were between 40 and 65 years old, 3 were older than 65, and only 2 were younger than 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.

Incidence of all-cause and CV mortality was 1.19%/year and 0.65%/year, respectively; incidence of HF death was higher than incidence of SCD and this incidence higher than the one of stroke. However, the incidence of SCD death plus equivalents was higher than the incidence of HF death, with or without equivalents (*Table 5*, *Figure 3*).

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

When compared with low enrolment centres (< 15 patients included, n=16), high enrolment ones (> 100 patients, n=3) had younger patients, more familial HCM and received more genetic testing, family screening and exclusion of phenocopies (*Supplementary File 3*). Additionally, despite the higher number of diagnostic tests and of drug prescriptions of high enrolment centres, no major differences in outcomes were found.

DISCUSSION

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

Epidemiological and socio-demographic data

The total number of patients included represents about 5 % of the estimated prevalence in Portugal [5,7] but up to one third of the “clinical HCM” Portuguese population [6]. Accordingly,

this is to our knowledge, the most comprehensive national HCM registry published [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 centres (4 centres included half of the patients and 25 centres the other half) show that an important number of patients are followed in non-referral centres. 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 centre bias in another registry [22].

Baseline evaluation

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 65 years old. This finding may reflect delayed disease penetrance, lack of systematic family screening, and – potentially – an increased diagnostic yield in older patients [1,2]. In opposition, the association, found in our cohort, of low rate of familial HCM, later age of presentation, and low risk profile, may more closely mirror the true real world disease scenario, reflecting the inclusion of these unselected lower risk HCM patients in the cohort. As a matter of fact, recent reports have identified a lower risk cohort of HCM patients, with later onset and lower rate of familial disease[23,24], potentially explaining our findings.

The proportion of obstructive forms of our cohort, about one third, basically reflect patients with obstruction at rest, consistent with existing literature for rest obstruction [1,2]. Accordingly, due to the low number of EE performed [25], many patients with labile obstruction were probably not detected and were classified as non-obstructive, suggesting, at first sight a deviation from guidelines. However, as the recommendations[1,2] for the use of EE in non obstructive HCM at rest are relatively recent, some of these patients, assessed before, have not performed EE and were diagnosed as non obstructive in this observational study.

Diagnostic tests and SCD risk stratification at baseline

Our data show the relatively limited penetration of CMR, despite the evidence of its incremental value [1-4]. These results reflect its high costs, limited availability, and relatively recent introduction in clinical practice. [1-4]

Conversely, considering the factors that limit the dissemination of genetic testing [1,2] (price, lack of co-payment, low availability), half of the patients performed genetic studies, in many cases already part of routine practice [26]. The prevalence of tests in which a variant was found[15,16,27,28] 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 mutations[15,16,27,28] in *TPM1* and *CSRP3* genes was found [17]. These results must be interpreted with caution, because they are derived from CRF raw-data, not centrally reviewed/corrected by the PRo-HCM coordinators.

Both the contemporary models for SCD risk [1,2,20,21] show that our cohort was, at baseline, a low risk population for SCD, partially explaining the low rate of SCD and of ICDs implantations.

Treatment

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

Of note, the number of surgical myectomies was much higher than the number of ASA, partially explained by its late introduction in Portugal (2009) [29]. The fact that both procedures were performed in different centres deserves a reflection, taking into account the known importance of expertise in the results [1,2].

Finally, less than 15% of the 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, outcomes of high enrolment centres (despite higher use of diagnostic tests and differences in medical treatment) are similar to those of low inclusion ones, bringing into discussion the relevance of HCM centres and of the hub and spoke model [7].

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

Our figures are overall in agreement with those from other group [30] showing that treated- HCM global mortality in Portugal is 1.19%, similar to the one of general Portuguese population- around 1,1% year [31]. Importantly, at follow-up most patients were symptomatic, confirming that disease morbidity carries an important burden to patients, health care services and providers. Accordingly, the “contemporary treatable disease” [30] has became, at least in Portugal, a "contemporary chronic treatable disease" where, side by side with ICDs, the role of chronic medical treatment is increasing.

Limitations

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

The inclusion of mostly symptomatic patients with advanced, established disease (primarily included by HCM referral centres) is a limitation of this Registry, providing a biased view of the disease (selection bias, a classical limitation of many HCM studies).

Aditionally, disease related mortality is underestimated as deceased patients before the diagnosis were not included. This survival bias partially explains the low rate of events, specifically the low rate of SCD.

Children were excluded because of important clinical differences [1,2].

Future directions

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

Because of the great amount 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 (founder effects, differences in phenotype between genes, analysis of specific mutations considered as pathogenic/probably pathogenic by the investigators), awareness of phenocopies (for instance Fabry disease) and detailed assessment of the 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, pointing out needs for a 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, HF is the most common cause of death followed by SCD (excluding equivalents). However, the morbidity remains considerable, emphasizing the need for disease-specific treatments impacting the natural history of the disease.

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References:

1-Elliott PM, Anastasakis A, Borger MA et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology. Eur Heart J 2014;35:2733–79.

2- Gersh BJ, Maron BJ, Bonow RO et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. *J Am Coll Cardiol* 2011;58:e212–60.

3- Nagueh SF, Bierig SM, Budoff MJ et al. American Society of Echocardiography Clinical Recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2011;24:473–98.

4- Cardim N, Galderisi M, Edvardsen T et al. Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16(3):280.

5- Maron BJ, Gardin JM, Flack JM et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation 1995;92(4):785-9.

6- Maron MS, Hellawell JL, Lucove JC et al. Occurrence of Clinically Diagnosed Hypertrophic Cardiomyopathy in the United States. Am J Cardiol 2016;15;117(10):1651-4.

7- Cardim N, Freitas A, Brito D. From HCM centres to inherited cardiovascular units: a small

or a major step? Rev Port Cardiol 2011;30(11):829-35.

8- Gonçalves LM, Vieira M, Faro C et al. Providência LA. Identification of an Arg403Gln beta myosin heavy chain gene mutation in a Portuguese family with hypertrophic cardiomyopathy. Rev Port Cardiol 2000;19(4):431-43.

9- Brito D, Richard P, Komajda M et al. Familial and sporadic hypertrophic cardiomyopathy: differences and similarities in a genotyped population. A long follow-up study. Rev Port Cardiol 2008;27(2):147-73.

10- McKenna WJ, Spirito P, Desnos M et al. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. Heart 1997;77:130–2.

11-Mancia G, Fagard R, Narkiewicz K at al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart Journal 2013;34:2159–2219.

12- Vahanian A, Alfieri O, Andreotti F at al. Guidelines on the management of valvular heart disease (version 2012) Eur Heart Journal 2012;33, 2451–2496.

13- Olivotto I, Cecchi F, Poggesi C et al.Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 2012;5:535–46.

14- Guttmann OP, Pavlou M, O'Mahony C et al. Prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy (HCM Risk-CVA). Eur J Heart Fail 2015;17, 837–845.

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.

16- Burke MA, Cook SA, Seidman JG et al. Clinical and mechanistic insights into the genetics of cardiomyopathy. J Am Coll Cardiol 2016;68:2871–86.

17- Cecchi F, Olivotto I, Betocchi S et al. The Italian registry for hypertrophic cardiomyopathy: a nationwide survey. Am Heart J 2005;150:947-54.

18- Mirabel M, Reant P, Donnal E at al. REMY: the hypertrophic cardiomyopathy registry of the French Society of Cardiology [abtract]. Eur Heart J 2016

19-Magalhães-Ribeiro C, Freitas J. Syncope in the young athlete: Assessment of prognosis in subjects with hypertrophic cardiomyopathy. Rev Port Cardiol 2016;35(7-8):433-40.

20- Maron BJ, Olivotto I, Spirito P at al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000;102:858–64.

21- O'Mahony C, Jichi F, Pavlou M at al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010–2020.

22- Elliott P, Charron P, Blanes JR at al. EORP Cardiomyopathy Registry Pilot Investigators. European Cardiomyopathy Pilot Registry: EURObservational Research Programme of the European Society of Cardiology on behalf of the EORP Cardiomyopathy Registry Pilot Investigators. Eur Heart J 2016;37;164–173.

23 - Ingles J, Burns C, Bagnall R et al. Nonfamilial Hypertrophic Cardiomyopathy: Prevalence, Natural History, and Clinical Implications. Circ Cardiovasc Genet 2017;10(2)

24 - Ko C, Arscott P, Concannon M et al. Genetic testing impacts the utility of prospective familial screening in hypertrophic cardiomyopathy through identification of a nonfamilial subgroup. Genet Med 2017

25- Shah JS, Esteban MT, Thaman R at al. Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. Heart 2007;94:1288–94.

26- Brito D, Miltenberger-Miltenyi G, Vale Pereira S et al. Sarcomeric hypertrophic cardiomyopathy: genetic profile in a Portuguese population. Rev Port Cardiol 2012;31(9):577-87.

27- Lopes LR, Rahman MS, Elliott PM. A systematic review and meta-analysis of genotype-phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations. Heart 2013;99(24):1800-1.

28- Lopes LR, Zekavati A, Syrris P et al. Genetic complexity in hypertrophic cardiomyopathy revealed by high-throughput sequencing. J Med Genet 2013;50(4):228-39.

29- Fiarresga A, Cacela D, Galrinho A et al. Alcohol septal ablation in obstructive hypertrophic cardiomyopathy: four years of experience at a reference centre. Rev Port Cardiol 2014;33(1):1-10.

30 -Braunwald E, Maron B. Evolution of Hypertrophic Cardiomyopathy to a Contemporary Treatable Disease. Circulation 2012;126:1640-1644.

31- www.pordata.pt. Pordata, the database of contemporary Portugal, Francisco Manuel dos Santos Foundation (Assessed November 2016).

Figure Legends

Figure 1. Participating centres, distribution by regions and by centre

Left- PRo-HCM participating centres (n=29); **right, top** - distribution of the 1042 patients by regions of Portugal: Lisbon region included the highest number of patients and the central region of Portugal the lowest; **right, bottom**- notice the heterogeneity in terms of enrolled patients per centre

Figure 2. Follow-up data: symptoms at last evaluation

At the last evaluation most patients were symptomatic (left), and the vast majority had mild to moderate symptoms (right)

Figure 3 -Kaplan-Meier estimate of the cumulative hazard function for mortality during follow-up

Left- cumulative hazard function for mortality; right- cumulative hazard function for mortality, including SCD and HF equivalents. See text for description

(**CV**-cardiovascular mortality; **HF** - heart failure mortality; **HF+Equiv** - heart failure mortality+ equivalents; **Stroke**- stroke related mortality**; Sudden** - sudden cardiac death mortality**; Sudden +Equiv** - sudden cardiac death mortality + equivalents)

Tables

***Participating centres 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 Infante 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: Patrícia 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

Table 1- PRo-HCM: Comparison between populations of national registries of HCM

	Portuguese Registry	Italian Registry[17]	French Registry[18]
Registry Period	2013-2015	2000-2002	2005-2015
Inhabitants	10 million	50 million	66 million
Patients – Registry	**1042**	**1677**	**1401**
	HCM *CARDIA based* Prevalence 1:500 [5]		
HCM patients	20 000	100 000	132 000
Patients included - Registry	**5%**	**2%**	**1%**
	***"Clinical"* HCM Prevalence 1: 3200** [6]		
"Clinical" HCM patients	3 125	16 000	18 750
Patients included - Registry	**33%**	**10%**	**7%**

HCM- Hypertrophic Cardiomyopathy

Table 2 - General Data: Summary of Baseline characteristics and Diagnostic Tests

Population General Data	n	%
HCM patients	1042	
Male/Female	613/429	59%/41%
Age at diagnosis	53±16 (9-88)	
Diagnosis >50 y	605	58%
Diagnosis >65 y	281	27%
Familial/Sporadic	347/559	33%/54%
Non-Obstructive HCM	613	59%
Obstructive HCM	365	35%
Reason for diagnosis		
Symptoms	551	53%
Incidental	319	31%
Family screening	129	12%
Symptoms at first consultation		
Asymptomatic	311	30%
Symptomatic	715	69%
Dyspnea	328	32%
Angina	241	23%
Palpitations	189	18%
Syncope	95	9%
NYHA I/II/III/IV	146/792/94/10	14%/76%/9%/1%
Imaging method of diagnosis		
Echocardiography	932	89%
CMR/CCT	110	11%
Diagnostic Tests		
HOLTER	867	83%
EXERCISE TEST	437	42%
EE	175	17%
CMR	475	46%
CA	122	12%
EMB	12	1%
GENETIC TEST	528	51%

CA – Cardiac Angiography; **CCT-** Cardiac Computed Tomography; **CMR -** Cardiac Magnetic Resonance; **EE –** Exercise Echocardiography; **EMB -** Endomyocardial Biopsy; **HCM-** Hypertrophic Cardiomyopathy; **HF –** Heart Failure

Table 3- Genetic Test results [15,16]

Genetic Test	n	%
HCM Patients tested	528	51%
Positive	210	40%
VUS	40	8%
Pathogenic/Probably Pathogenic Mutation*	210	
MYBPC3	99	49%
MYH7	56	28%
TNNT2	25	12%
TNNI3	10	5%
TPM1	8	4%
CRSP3	8	4%
MYL3	2	1%
MYL2	1	0.5%

CRSP3 – Muscle LIM Protein; **HCM –** Hypertrophic Cardiomyopathy; **MYBPC3 -** Cardiac Myosin-binding Protein C; **MYH7 -** β-Myosin Heavy Chain; **MYL2 -** Regulatory Myosin Light Chain; **MYL3 –** Essential Myosin Light Chain; **TNNI3** - Cardiac Troponin I; **TNNT2** – Cardiac Troponin T; **TPM1** - α-Tropomyosin; **VUS** – Variants of Unknown Significance

* 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-General data- Treatment

Treatment		
Betablockers	768	74%
Calcium Receptor Blockers	262	25%
Disopyramide	19	2%
Amiodarone	151	15%
Anticoagulants	276	27%
Vitamin K antagonists	208	75%
New oral anticoagulants	60	22%
ACEI	226	22%
ARB	178	17%
Diuretics	252	24%
Nitrates	24	2%
ASA	23	2%
Surgery	61	6%
ICD	140	13%
1ry Prevention	123	88%
2ry Prevention	15	11%
Pacemaker	92	9%
Bradyarrhythmia	64	70%
Gradient Reduction	19	21%

ACEI – Angiotensin Converting Enzyme Inhibitor; **ARB -** Angiotensin Receptor Blockers; **ASA** - Alcohol Septal Ablation; **CV –** Cardiovascular; **ICD -** Implantable Cardioverter Defibrillator; **SCD-** Sudden Cardiac Death

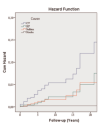
Table 5- PRo-HCM: Mortality

Mortality		
Parameter	**n**	**Mortality Rates**
Total mortality	65	1.19%/year
CV Mortality	36	0.65%/year
HF Death	14	0.25%/year
SCD	12	0.22%/year
Stroke related death	2	0.04%/year
Other	8	0.15%/year
SCD Equivalents	17	0.31%/year
SCD Death+ Equivalents	29	0.53%/year
HF Equivalents	1	0.02%/year
HF Death+ Equivalents	15	0.27%/year

CV- Cardiovascular; **HF –** Heart Failure; **SCD-** Sudden Cardiac Death


Population (Pre-HCM)
327
178
Asymptomatic
Symptomatic


(Pre-HCM) Symptomatic Patients
320
11
10
Mildly/Moderately
Severe
Endstage/Advanced


Hazard Function
Cases
Cox
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Cum Hazard
0.00
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20
Follow-up (Years)
Hazard Function
Cases
Cox
Gehan
Tarone
Kalbfleisch-Prentice
Cum Hazard
0.00
0.04
0.08
0.12
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Follow-up (Years)