The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: Baseline data and contemporary management of adult patients with cardiomyopathies

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Abstract

Aims

The Cardiomyopathy Registry of the EURObservational Research Programme is a prospective, observational, multinational registry of consecutive patients with four cardiomyopathy subtypes: hypertrophic (HCM), dilated (DCM), arrhythmogenic right ventricular (ARVC) and restrictive (RCM). We report the baseline characteristics and management of adults enrolled in the registry.

Methods and results

3208 patients were enrolled by 69 centers in 18 countries [HCM (n=1739); DCM (n=1260); ARVC (n=143) and RCM (n=66)]. Differences between cardiomyopathy subtypes ($p<0.001$) were observed for age at diagnosis, history of familial disease, history of sustained ventricular arrhythmia, use of magnetic resonance imaging or genetic testing, and implantation of defibrillators. As compared to probands, relatives had a lower age at diagnosis ($p<0.001$), but a similar rate of symptoms and defibrillators. As compared to the Long-Term phase, patients of the Pilot phase (enrolled in more expert centers) had a more frequent rate of familial disease ($p<0.001$), were more frequently diagnosed with a rare underlying disease ($p<0.001$), and more frequently implanted with a defibrillator ($p=0.023$). Comparing four geographical areas, patients from Southern Europe had a familial disease more frequently ($p<0.001$), were more frequently diagnosed in the context of a family screening ($p<0.001$), and more frequently diagnosed with a rare underlying disease ($p<0.001$).

Conclusions

By providing contemporary observational data on characteristics and management of patients with cardiomyopathies, the registry provides a platform for the evaluation of guideline implementation. Potential gaps with existing recommendations are discussed as well as some suggestions for improvement of health care provision in Europe.

Key-words: cardiomyopathy, registry, hypertrophic, dilated, restrictive, arrhythmogenic right ventricular

LIST OF ABBREVIATIONS

Main abbreviations	Definition of abbreviations
AEPC WG	Association for European Paediatric and Congenital Cardiology Working Group on Genetics, Basic Science and Inherited Muscle Diseases
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
CRF	Case Report Form
DCM	Dilated Cardiomyopathy
ECG	Electrocardiogram
EORP	EURObservational Research Programme
ESC	European Society of Cardiology
HCM	Hypertrophic Cardiomyopathy
MRI	Magnetic resonance imaging
RCM	Restrictive Cardiomyopathy

INTRODUCTION

Cardiomyopathies are a heterogeneous group of disorders characterized by structural and functional abnormalities of the myocardium that are not explained solely by coronary artery disease or abnormal loading conditions (1). These disorders represent a significant health burden since they can cause premature death from arrhythmia, progressive heart failure or stroke (2-9). To date, most information about the presentation and natural history of cardiomyopathies has derived from cohort studies in a small number of specialised centers and there is very little data describing the contemporary profile and the practical management of the patients outside highly expert units.

The EURObservational Research Programme (EORP) Cardiomyopathy registry was conceived by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Disease, to collect clinical data on patients with a confirmed diagnosis of a cardiomyopathy (Figure 1). The general aim of the registry is to provide a summary of contemporary features and management of patients with cardiomyopathy or myocarditis, across a large range of centres in Europe in order to improve clinical service provision and therapy.

In this paper, we present the data on the adult population with a cardiomyopathy, combining Pilot and Long-Term phases. Enrollment of patients with a myocarditis, or paediatric patients with a cardiomyopathy, is still ongoing.

METHODS

General design

This is a prospective observational multinational multicenter registry of consecutive patients presenting to cardiology centers in European countries. Participating centers were selected using pre-specified criteria (Supplementary File S1). Each center was asked to enter about 40 consecutively-assessed patients (up to 40 in Pilot phase, minimum 40 in LT phase) over a 12-month period. The study was approved by each local Ethical Committee according to the local rules. Written informed consent was obtained from all participants before data collection. All diagnostic or management procedures were left to the discretion of the attending physician, including the clinical investigations made at the time of enrollment, and diagnostic criteria were not centrally verified. Baseline data were collected (including demographic, clinical, cardiac, genetic and therapeutic parameters) using a web-based electronic case report form. The EORP department of the ESC was responsible for study management, data quality control and statistical analyses.

The registry was conducted by an Executive Committee and managed by the EORP department of the ESC. A pilot phase of the registry, restricted to adult patients with a cardiomyopathy, was conducted for validating the structure and quality of the data set (10). A Long-Term phase was subsequently agreed and extended in three directions: (i) further enrollment of adult patients with a cardiomyopathy, (ii) extended enrollment of paediatric patients with a cardiomyopathy, in collaboration with the Association for European Paediatric and Congenital Cardiology Working

Group on Genetics, Basic Science and Inherited Muscle Diseases (AEPC WG), (iii) extended enrollment of patients with clinically suspected or biopsy-proven myocarditis.

Patients and Cardiomyopathies sub-types

Patients with one of four major cardiomyopathy subtypes were eligible for the study: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and restrictive cardiomyopathy (RCM). Familial/genetic forms and non-familial/non-genetic forms were included. Patients met the following inclusion criteria for the adult cardiomyopathies registry: (i) age at enrollment greater than 18 years, (ii) willing and able to give informed consent, (iii) able to comply with all study requirements, (iv) documented cardiomyopathy fulfilling standard diagnostic criteria for probands or for relatives (see Supplementary File S2). Relevant definitions used for analyses of subgroups (including definition of regions) are included in the Supplementary File S3.

Statistical analyses

Univariable analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean ± SD and/or as median and Interquartile Range (IQR) when appropriate. Among-group comparisons were made using a non-parametric test (Kruskal-Wallis). Categorical variables were reported as percentages. Among-group comparisons were made using a Chi-square test or a Fisher's exact test if any expected cell count was less than five. A two-sided p-value

of <0.05 was considered as statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Enrollment

69 centers from 18 countries participated in the study (Figure 2, Supplementary Table 1, Supplementary Figure 1). A total of 3208 consecutive adult patients with a cardiomyopathy were enrolled (Table 1), including 42.9% incident patients vs 57.1% prevalent patients, 83.0% proband vs 17.0% relatives, 34.8% patients from the Pilot phase vs 65.2% from the Long-Term phase, 59.7% outpatients versus 40.3% inpatients. Median age at enrollment was 55.0 years (IQR 43-64) and there was a male predominance for all cardiomyopathy subtypes except RCM (p<0.001). The mean number of patients enrolled per center was 46.5 (median 40, IQR 22-50).

Diagnosis

The commonest diagnosis was HCM (n=1739, 54.2%), then DCM (n=1260, 39.3%), ARVC (n=143, 4.4%) and RCM (n=66, 2.1%) (Table 1). In addition, left ventricular non-compaction (LVNC) was reported in 4.1% of total patients. Median age at diagnosis was 49.0 years (IQR 38-59) (Figure 3), differed significantly between cardiomyopathies (p<0.001) and was lower in patients with ARVC (39.0 years IQR 30-51) than in patients with RCM (54.0 years IQR 37-65). A large distribution for age at diagnosis was observed for all subtypes, with a "lower extreme limit" of box-plot that was 0 years for HCM, 13 years for DCM, 15 years for RCM and 2 years for ARVC.

Familial disease and aetiology

A history of familial disease was observed in 38.9% of the total population (Table 1), with significant differences according to cardiomyopathy subtypes ($p<0.001$). The proportion was higher in HCM and ARVC (48.5% and 40.6% respectively) and lower in RCM and DCM (30.0% and 25.2% respectively). Details concerning rare causes of cardiomyopathy subtypes are reported in Supplementary Table 2.

History of arrhythmia, symptoms and diagnostic tests

Main symptoms, history of arrhythmia or stroke and use of cardiac investigations are reported in Table 1. History of sustained ventricular tachycardia was observed most often in patients with ARVC (39.2%) and the least in RCM (1.5%). History of atrial fibrillation was recorded most frequently in patients with RCM (48.5%) and the least in ARVC (14.0%). ECG and echocardiogram were performed in nearly all patients (≥95.1%). Magnetic resonance imaging (MRI) was performed most frequently in patients with ARVC (51.0%) and least frequently in DCM (20.6%) (global comparison: $p<0.001$). Genetic testing was performed in 35.7% of patients. Endomyocardial biospsy was performed in 119 patients (10.7% of the patients for whom this item was completed).

Drugs and therapeutic procedures prior to enrollment

Table 2 describes medications and procedures prior to enrollment. Beta-blockers were the most frequently recorded drugs (80.6% of all patients). Implantable cardioverter defibrillator (ICD) was reported in 25.9% of the whole population

(primary prophylaxis 81.4%), most frequently in patients with ARVC (56.6% of patients) followed by DCM (31.7%), HCM (19.9%) and RCM (9.1%). A pacemaker was implanted in 10.2% of the whole cohort, most frequently in patients with DCM (14.3%) and least frequently in ARVC (2.8%).

Subgroups

Subgroup analyses are presented in Table 3.

Relatives as compared to probands were characterized by a lower median age at diagnosis (39.0 years, IQR 24-50, vs 50.0 years, IQR 38-59, p<0.001), they underwent cardiac investigations (ECG, echocardiogram, holter-ECG, MRI) in a similar or greater proportion and a defibrillator was implanted as frequently (25.6% vs 25.0%).

Incident patients as compared to prevalent patients were characterized by a greater median age at diagnosis (51.0 years, IQR 40-60, vs 47.0 years, IQR 35-57, p<0.001), were more frequently probands (89.0% vs 77.5%, p<0.001), had a familial disease less frequently (28.7% vs 45.7%, p<0.001) and had a defibrillator implanted less frequently (16.7% vs 33.6%, p<0.001).

Patients of the Pilot phase, as compared to the Long-Term phase, were more frequently relatives (52.9% vs 9.7%, p<0.001), had a familial disease more frequently (46.4% vs 34.4%, p<0.001), were more frequently diagnosed in the context of a family screening (16.1% vs 9.1%, p<0.001), more frequently diagnosed with a rare underlying disease (6.2% vs 3.1%, p<0.001) and were more frequently implanted with a defibrillator (28.3% vs 24.7%, p=0.023).

Considering the four main regions, patients from South area were most frequently relatives (25.0%, global comparison, p<0.001), had a familial disease most frequently (49.4%, p<0.001), were most frequently diagnosed in the context of a family screening (17.1%, p<0.001) and more frequently diagnosed with a rare underlying disease (5.7%, p<0.001). Patients from East area were less likely to undergo MRI and genetic testing but more had Holter-ECG. Patients from West area were more frequently implanted with a defibrillator (32.7%, p<0.001).

DISCUSSION

This is the first multinational European registry on cardiomyopathies. The analysis shows that the mode of presentation varies substantially between cardiomyopathy subtypes, and that all patients, whether probands or relatives, undergo multiple cardiac investigations and require substantial medical and device therapy. By providing real-world contemporary data on clinical characteristics and management, the registry provides a platform for the evaluation of guideline implementation across a range of different health care providers and organizations in Europe and elsewhere.

Cardiomyopathy subtypes

As anticipated from previous studies (3-6,11), HCM was the most frequent cardiomyopathy in the registry, followed by DCM, and then ARVC and RCM. The design of the registry did not allow us to estimate population prevalence of specific phenotypes, but it is notable that the ratio for DCM/HCM patients in this consecutive series was unexpectedly high, suggesting that the true prevalence of DCM could be higher than previously estimated and closer to the estimated prevalence of HCM. The

study also shows the diversity and frequency of diagnostic tests that were performed, either for assessment of the cardiomyopathy, management of symptoms or stratification of risk. This is illustrated by MRI, performed in nearly one third of all patients, or by genetic testing, performed in more than one third of patients. All these results emphasize the multidisciplinary approach and expertise that is required for the management of patients with a cardiomyopathy (6,12-17).

Arrhythmia burden

All cardiomyopathies increase the odds for life-threatening arrhythmias, but the degree to which they do so continues to raise controversy (3-9). While recognizing that the patients enrolled in this series are necessarily selected, the frequency of malignant ventricular arrhythmia and atrial fibrillation was impressively high. This was paralleled by a high prevalence of prophylactic ICD implantation (3-8, 18,19), ablation procedures and pacemaker implantation. Importantly, the arrhythmic risk varied substantially between cardiomyopathy subtypes with ventricular arrhythmia or ICD implantation most frequently reported in ARVC and atrial fibrillation being the dominant rhythm issue in RCM. The fact that Holter-ECG and exercise test were performed in two-third or less of patients, even in incident patients where investigations are expected to be optimal, suggest a gap in cardiac investigations.

Familial forms and age at diagnosis

The registry emphasizes the high prevalence of inherited disease, with nearly 40% of the entire cohort reporting a familial disease, and the importance of referring relatives for evaluation since two-thirds of relatives were diagnosed through family

screening. In addition the burden of the disease in relatives was important since prevalence of symptoms and ICD implantation were as frequent as in probands. The fact that the number of relatives in the registry was relatively low (less than one fifth) suggests there is still a gap in family screening (7,8,15,16). In the total cohort of probands and relatives, the median age at diagnosis was relatively low, below or equal to 50 years of age for all cardiomyopathies except RCM (3-6). Age at diagnosis was variable, in agreement with the known age-related penetrance of these diseases. Distribution of age at diagnosis was, however, unexpectedly wide with the "extreme upper limit" beyond 70 years of age for all cardiomyopathy subtypes and the "extreme lower limit" well below 10 years of age for HCM and ARVC. These results may suggest a modification of the recommendations about family screening in relatives (7,8,15,16), starting family screening earlier than the current threshold of ~10 years of age and extending family screening or follow-up beyond the currently recommended age of 50 to 60 years.

From gaps to improvement of health care

The identification of potential gaps with existing recommendations is also supported by the heterogeneous management we observed between centers and between geographical areas. Important differences were especially observed between the Pilot phase, where centers were preselected because of a high level of expertise, and the Long-Term phase, were centers had a more variable level of expertise. This is illustrated by the high percentage of relatives in the Pilot phase, which probably reflects more developed family screening programs. The careful analysis of the Registry findings therefore suggests that some characteristics may be considered as

potential markers of excellence in the context of quality evaluation of health services, particularly in the perspective of dedicated multidisciplinary heart teams that might be useful as shown in other areas (20,21). These indicators of expertise for a given center may include the percentage of cardiac and extra-cardiac investigations performed in patients, the ratio of relatives versus probands, the rate of patients with a rare cause, the median age at diagnosis of patients.

Finally, differences we observed among the various geographic areas suggest that comparing the organization of health care systems for cardiomyopathies in the various countries may provide valuable insights that can be used for improvement of health care services in Europe. Since recommendations or expert consensus for the management of the patients and families are available, it can be hypothesized that variations in service provision are mostly related to economical or structural reasons.

Limitations

Similar to registries in other fields, the voluntary nature of the enrolling centers, associated with their predefined characteristics, inevitably implies an uncertain representativeness of the enrolling network with respect to Europe as a whole.

Conclusions

This is the first European registry focused on adult patients with the various cardiomyopathy subtypes. It provides a unique picture of contemporary features and management of these patients. The results emphasize the complexity of services and multidisciplinary expertise required for the management of patients with a cardiomyopathy. The analysis of the results also identified potential gaps with

existing recommendations. Work is warranted to understand the large variation in services provision as well as renewed efforts to provide evidence-based diagnostic processes and therapies.

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Conflict of interest

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Figure Legends

Figure 1

General plan of the Cardiomyopathy Registry

Figure 2

Pie chart showing the proportion of patients recruited in the global registry (n=3208) enrolled in each participating country.

Figure 3

Box-plot with distribution of age at diagnosis for each cardiomyopathy subtype.

ARVC=arrhythmogenic right ventricular cardiomyopathy; DCM=dilated cardiomyopathy; HCM=hypertrophic cardiomyopathy; RCM=restrictive cardiomyopathy.

Distribution is presented with mean, lower extreme, 1st quartile (25th percentile), median (50th percentile), 3rd quartile (75th percentile), upper extreme and outliers.

TABLES

TABLE 1. BASELINE CHARACTERISTICS IN RELATION TO CARDIOMYOPATHY SUBTYPES

TABLE 2.THERAPEUTICS AT BASELINE OR PRIOR TO ENROLLMENT IN RELATION TO CARDIOMYOPATHY SUBTYPES

TABLE 3. SUMMARY OF BASIC FEATURES IN ADULT PATIENTS WITH A CARDIOMYOPATHY ACCORDING TO PREFINED SUB-GROUPS

Supplementary material

- Supplementary File S1: Pre-specified criteria for selection of Participating centers.
- Supplementary File S2: Standard diagnostic criteria for proband, or for relatives, for each cardiomyopathy subtypes (HCM, DCM, ARVC, RCM)
- Supplementary File S3: Definitions of subgroups
- Supplementary Figure 1: Box-plot with distribution of items for all centers involved in adult cardiomyopathy registry
- Supplementary Table 1: Number of enrolled patients per country
- Supplementary Table 2: Rare aetiologies in relation to cardiomyopathy subtypes in proband patients
- Supplementary Appendix 1: Listing Registry Committees and Investigators

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