Prospective follow-up

in various subtypes of cardiomyopathies:

Insights from the ESC EORP Cardiomyopathy Registry

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Abstract

Aims: The ESC EORP Cardiomyopathy Registry is a prospective multinational registry of consecutive patients with cardiomyopathies. The objective of this report is to describe the short term outcomes of adult patients ($\geq$18 years old).

Methods and Results: Out of 3,208 patients recruited, follow-up data at 1 year were obtained in 2,713 patients (84.6%) [1,420 with hypertrophic (HCM); 1,105 dilated (DCM); 128 arrhythmogenic right ventricular (ARVC) and 60 restrictive (RCM) cardiomyopathies]. Improvement of symptoms (dyspnoea, chest pain and palpitations) was globally observed over time ($p<0.05$ for each). Additional invasive procedures were performed: prophylactic implantation of ICD (5.2%), pacemaker (1.2%), heart transplant (1,1%), ablation for atrial or ventricular arrhythmia (0.5% & 0.1%). Patients with AF increased from 28.7% to 32.2% of the cohort. Ventricular arrhythmias (VF/VTs) in ICD carriers (primary prevention) at 1 year were more frequent in ARVC, then in DCM, HCM and RCM (10.3%, 8.2%, 7.5% and 0%, respectively). Major cardiovascular events (MACE) occurred in 29.3% of RCM, 10.5% of DCM, 5.3% of HCM and 3.9% of ARVC ($p<0.001$). MACE were more frequent in index patients compared to relatives (10.8% vs 4.4%, $p<0.001$), more frequent in East Europe centres (13.1%) and least common in South Europe (5.3%) ($p<0.001$). Subtype of cardiomyopathy, geographical region and proband were predictors of MACE on multivariable analysis.

Conclusions: Despite symptomatic improvement, patients with cardiomyopathies remain prone to major clinical events in the short term. Outcomes were different not only according to cardiomyopathy subtypes but also in relatives versus index patients, and according to European regions.

Keywords: cardiomyopathy, registry, prognosis, MACE

Introduction

Cardiomyopathies are a heterogeneous group of disorders characterised by structural and functional abnormalities of the myocardium that are unexplained solely by coronary artery disease or abnormal loading conditions [1]. Individually, the various subtypes of cardiomyopathy are relatively uncommon, but collectively they represent a major health burden for the European population [2,3,4,5,6,7,8]. All cardiomyopathies can cause premature death from arrhythmia and progressive heart failure [2,4,5,6,7,8,9].

To date, most information about the presentation and natural history of cardiomyopathies in adults has come from retrospective cohort studies in a few centres and without considering all cardiomyopathy subtypes together. The European Society of Cardiology (ESC) launched the European Observational Research Programme (EORP) in 2009 with the explicit aim of improving the understanding of medical practice through prospective collection of observational data in patients with heart muscle disease recruited in centres across Europe [9]. [http://www.escardio.org/The-ESC/Communities/Working-Groups/Working-Group-on-Myocardial-and-Pericardial-Diseases/About]. The baseline data on the adult population have been published [3]. This second report describes clinical work-up and outcomes at 1-year follow-up of patients enrolled in the registry.

The primary aims of the follow-up phase of the registry were (i) to record the current practices for diagnostic workup and clinical follow-up of patients; (ii) to describe the therapeutic approaches implemented during the follow-up; (iii) to report the major clinical events or complications during the follow-up.

Methods

Registry Design & patients

Participating centres in each country were selected using pre-specified inclusion and exclusion criteria [3,9]. Four major phenotypes of cardiomyopathy were eligible for inclusion:

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hypertrophic (HCM), dilated (DCM), arrhythmogenic right ventricular (ARVC) and restrictive (RCM). Age at enrolment had to be ≥18 years old. Each centre was asked to enter about 40 consecutively assessed patients over a 12-month period. The study was approved by each local Ethics Committee according to the local rules. Written informed consent was obtained from all participants before data collection. All diagnostic or therapeutic procedures were left to the discretion of the attending physician. The registry was conducted by an Executive Committee and managed by the EORP department of the ESC which also performed statistical analyses. Definitions used for analyses of subgroups (including definition of regions) were previously detailed [3,9].

A total of 3,208 adult patients with a cardiomyopathy were enrolled in the pilot and long-term phases of the registry by 69 centres in 18 countries. There were 2 periods of inclusion: from Dec-12 to Nov-13 and from Jun-14 to Dec-16 [9]. The cardiomyopathy subtypes were: HCM (n=1,739); DCM (n=1260); ARVC (n=143); and RCM (n=66). Median age at enrolment was 55 [IQR, 43–64] [3,9].

A follow-up at 1 year was planned by EORP, without additional FU period in this registry. Information was taken from clinical visits or clinical records.

Combined endpoints for outcomes were defined as:

1. Major arrhythmic event: Sudden death or resuscitated ventricular fibrillation/cardiac arrest or sustained ventricular tachycardia.

2. Major heart failure event: Heart failure death or heart transplant or ventricular assist device implantation.

3. Vascular death: Death due to acute myocardial infarction, ischaemic stroke, hemorrhagic stroke, pulmonary or peripheral embolism.

4. Cardiovascular death: Death due to arrhythmia, heart failure or any cardiovascular cause (resuscitated cardiac arrest, other life-threatening arrhythmia and transplants were excluded).

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5. Major cardiovascular events (MACE): any type of cardiovascular death or hospital urgent admission for cardiac reason (combined endpoint n°4 + urgent cardiac admissions).

Statistical Analysis

Univariable analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean±SD. Among-group comparisons were made using a non-parametric test (Kruskal-Wallis test). For the comparisons of repeated measures, the sign test was used. Categorical variables were reported as counts and percentages. Among-group comparisons 2x2 were made using a chi-square test or Fisher's Exact test if any expected cell count was less than five. For the comparisons of repeated measures, the Mc Nemar's test was used.

Univariate Cox regression analysis and plots of Kaplan-Meier curves for the combined events were performed. Cox proportional hazards model was used for survival estimates reporting hazard ratios (HR's) and 95% confidence intervals (95%CI's).

A stepwise multivariable logistic regression analysis was performed to establish the relationship between the patient characteristics and the major cardiovascular events including into the model all the candidate variables (p<0.10 in univariate). A significance level of 0.05 was required to allow a variable into the model (SLENTRY=0.05) and a significance level of 0.05 was required to stay in the model (SLSTAY=0.05). No interaction was tested. A Hosmer and Lemeshow Goodness-of-Fit test was used to verify that the model was optimal. Annual rates together with their 95%CI's were estimated.

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

Data collection

Follow-up data at 1-year (median 376 [363;438] days) were obtained in 2,713 patients

(84.6%), including 1,420 (52.3%) with HCM, 1,105 (40.7%) DCM, 128 (4.7%) ARVC and

60 (2.2%) RCM. A total of 1050 (38.7%) patients were enrolled in the pilot and 1663 (61.3%)

in the long-term phase. 1,543 (82.0% of those reported) were probands and 339 (18.0%) were

relatives. 1056 (39.6%) were incident (new cases) and 1607 (60.4%) prevalent cases.

Regarding geographical areas, there were 533 (19.6%) from East, 512 (18.9%) North, 1193

(44.0%) South and 452 (16.7%) West Europe. There were also 23 patients included from

North Africa (0.85%).

Symptoms during follow-up

Overall the proportion of patients in NYHA functional class III-IV decreased from 25.7% to

16.7% (p<0.001) during follow up compared to baseline. NYHA status improved in HCM,

DCM and ARVC but not in patients with RCM (table 1). The proportion of patients with

chest pain decreased from 26.7% to 12.5% during follow up (p<0.001). Suspected

cardiogenic syncope was reported in 2.4% of patients during follow-up which was higher in

ARVC (4.9%) and lower in RCM (1.9%).

Use of diagnostic tests

The utilisation of cardiac investigations is summarised in table 1. The majority of patients had

an ECG or echocardiogram performed at 1-year follow-up (69.2% and 60.4% respectively).

Ambulatory ECG monitoring was performed in a smaller proportion of patients (25.8%) and

was reported more frequently in ARVC and HCM groups (39.8 and 34.0% respectively) and

less in DCM and RCM (14.3% and 14.3% respectively) (p<0.001). Use of cardiac magnetic

resonance imaging was significantly lower during FU compared to baseline evaluation (4.9%

vs 30.1%, p< 0.001). Invasive procedures like biopsy were performed only in 20 patients (0.7%) during follow-up.

Medication

Distribution and proportion of medication at one year were generally similar to baseline profile (Sup table 1). There was a significant increase in the global use of anticoagulants in HCM patients whereas a decrease in the proportion of DCM patients on ACE inhibitors, beta-blockers and diuretics was seen.

Non-pharmacological therapeutic procedures

One hundred and nine (5.2%) patients underwent ICD implantation for primary and 23 (1.0%) for secondary prevention during follow-up (Table 2). The proportion of new prophylactic ICD implantations was highest in ARVC (8.0%) then DCM (5.8%), HCM (4.9%) and RCM (0.0%).

The number of patients with a pacemaker implanted during follow-up was 18 (0.7%); 11 (0.4%) patients (9 DCM and 2 HCM) underwent cardiac resynchronization therapy (CRT) device implantation.

Thirteen (0.49%) patients underwent AF ablation and 3 (0.11%) ventricular tachycardia ablation procedures during follow-up (1.8% and 1.0% at baseline respectively).

Sixteen patients (0.6%) underwent a ventricular assist device implantation for advance heart failure (15 DCM and 1 HCM patients).

Thirty-three (2.5%) patients with HCM underwent septal reduction procedures, including 23 surgical myectomies and 10 alcohol septal ablation procedures during follow-up.

Death and complications

There were 93 (3.4%) deaths, including 38 (40.9%) heart failure related deaths, 24 (25.8%) sudden cardiac deaths, 3 (3.2%) stroke related deaths, 1 (1.1%) arrhythmic (non-sudden), 1 acute myocardial infarction and 3 (3.2%) other cardiovascular deaths. Six (6.4%) deaths were

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procedure related. There were 7 (7.5%) unrelated with the disease and 10 (10.8%) unknown causes of death.

Thirty patients (1.1%) underwent heart transplantation, 39 (1.5%) were resuscitated from cardiac arrest and 40 (1.5%) had non-fatal stroke. There were 68 (10.6%) patients with ICD devices who developed ventricular arrhythmias (sustained VT/VF) (47/539 primary and 21/105 secondary prophylaxis).

The proportion of patients with new onset atrial fibrillation (AF) during follow up was 5.1% (28.7% at baseline). New AF proportion tended to be higher in RCM 10.3% followed by 5.5% in DCM, 4.8% in HCM, and 2.8% in ARVC .

Ventricular arrhythmias (ventricular fibrillation or sustained VT) at 1 year in patients with ICD for primary prevention were more frequent in ARVC than in DCM, HCM and RCM (10.3%, 8.2%, 7.5%, 0% respectively, ns). Similarly, rates of ventricular arrhythmias in ICD carriers for secondary prevention were higher in ARVC and DCM followed by HCM (32.3%, 15.1%, 5.1% respectively, p=0.015). There were only 3 patients with RCM who had history of cardiac arrest with an ICD implanted.

The various pre-defined combined end points for each cardiomyopathy subtype are detailed in Supplementary table 2 and Figure 1. MACE occurred in 29.3% of RCM, 10.5% of DCM, 5.3% of HCM and 3.9% of ARVC (p<0.001). RCM showed the highest annual rates for most of the combined events. ARVC showed a high proportion of major arrhythmic events, similar to RCM.

Using Cox survival analysis, RCM (OR: 20.17; CI:9.63;42.27, p<0.001) and DCM (OR: 4.27; CI:2.48;7.37, p<0.001) showed an increased risk of reaching the heart failure combined event compared to HCM. DCM patients were at increased risk of combined arrhythmic event compared to HCM (OR: 2.37; CI:1.05;5.36, p=0.039). Regarding total cardiovascular death, RCM (OR: 12.37; CI:5.88;26.01, p<0.001) and DCM (OR: 1.95; CI:1.15;3.30, p=0.014) were

at highest risk as compared to HCM. Consistently, the OR for combined major cardiovascular events (MACE) was higher in RCM (5.68; CI:3.20;10.06, p<0.001) and then in DCM (OR: 2.03; CI:1.51;2.73, p<0.001) as compared to HCM. MACE in ARVC was not significantly different from HCM.

Comparison of probands and relatives.

Outcomes in 1,543 probands were compared to those of 339 relatives. Probands were significantly older at inclusion (median 55.0 (44.0;64.0) years old) than relatives (47.0 (34.0;58.0) years old, p<0.001), and there were more males (67.0%) compared to relatives (54.6%), p<0.001). During follow-up probands had a higher proportion of dyspnea III-IV (19.7%) compared to relatives (7.9%), (p<0.001) but a similar proportion of cardiogenic syncope (2.7% vs 2.7%). All types of diagnostic tests during follow-up were more frequently performed in relatives compared to probands (ECG: 76.6% vs 69.0%; echocardiogram: 68.3% vs 60.3%, exercise test: 20.7% vs 15.0% and Holter: 36.3% vs 25.9%, all p≤0.01). MRI was the only test with similar proportion of use during follow-up in probands and relatives (5.5% vs 6.5%, p=0.443).

Use of medication (beta-blockers, ACE inhibitors, ARB-II blockers, spironolactone and anticoagulation) was significantly higher in probands compared to relatives (all p≤0.05). Major arrhythmic events (5.7% vs 3.6%, p=0.119) were similar in probands and relatives. Major heart failure events (3.7% vs 0,9%, p=0.008), cardiovascular death (3.2% vs 0.9%, p=0.018) and combined major cardiovascular events (MACE) (10.8% vs 4.4%, p<0.001), were more common in probands.

Geographical differences across Europe.

Clinical characteristics and follow-up of patients regarding geographical areas are described in Supplementary table 3. There was a difference in age and in the proportion of probands

between the 5 regions (p=0.011, p<0.0001 respectively). Patients were younger and there were more probands in the East.

Proportion of patients with dyspnoea (NYHA III/IV) and syncope during follow-up were different between areas (p<0.001, p=0.017). The rate of new implantation of devices was globally low in all geographical areas with no significant differences.

When considering combined MACE there were significant differences between areas with the highest rate in East Europe (13.1%) and lowest in South Europe (5.4%) (p<0.001 for univariate analysis) (Figure 3).

The rate of sudden death and major arrhythmic events during follow-up was similar across Europe. Major heart failure events, as well as heart transplants, were higher in West and lowest in South area (p<0.001, p<0.001). Cardiovascular death was globally low during follow-up, being higher in the West and East compared to the North and South (p<0.010). (Figure 3).

Multivariable analysis of variable associated with MACE

Variables with p<0.10 in univariate were included in the multivariable analysis for predictors of MACE at 1 year, including cardiomyopathy subtype, proband or relative, and geographical region. (Suppl table 4).

Compared to the RCM group, ARVC, DCM and HCM had better survival (OR: 0.126 [0.037-0.435], p<0.001, OR: 0.313 [0.148-0.660], p=0.002 and OR: 0.179 [0.084-0.381], p<0.001, respectively). Compared to South, East and North European centres had a higher rate of MACE (OR: 2.057 [1.385-3.054], p<0.001 and OR: 1.629 [1.022-2.597], p=0.040). Probands compared to relatives had an increased rate of MACE (OR: 1.828 [1.044-3.203], p=0.035).

Discussion

The present work reports unique data regarding the management, follow-up and outcomes of adult patients with cardiomyopathy across a broad range of centres in Europe.

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There is no similar study with observational data collected prospectively on consecutive adult patients on the various cardiomyopathy subtypes across Europe. In contrast, some information on the burden of cardiomyopathies has been reported previously in the paediatric population [10,11,12].

Our study provides real-world contemporary data on adult patients and we show a significant global burden of major clinical events at short term. The under-recognized burden of cardiomyopathies is consistent with recent epidemiological data[13]. We also show differences in outcome not only according to cardiomyopathy subtypes but also in relatives versus index patients, and according to European regions.

Diagnostic/prognostic workup

Interestingly, clinical improvement was observed during follow-up in patients with HCM, DCM and ARVC, but not in RCM. This finding suggests effective therapeutic management of symptoms in the short term in most cardiomyopathy subtypes but also confirms the particularly adverse outcome in RCM patients.

First-line tests like echocardiogram and ECG were performed in two-thirds of patients during follow-up, which is consistent with recommendations from guidelines [8]. The use of Holter ECG monitoring was however unexpectedly low (one-third) and far from recommendations [8][14]. The low percentage of some cardiac examination during FU might be hypothesized as playing a role in the adverse event but can not be affirmed.

The results from this registry highlight the need for implemented guidelines on the recommended tests for the evaluation and FU of patients with cardiomyopathies. Apart from HCM in which the periodicity of the cardiac tests is specifically recorded in the 2014 ESC guidelines, for other Cardiomyopathies the recommendations are scarce and available only from expert consensus documents[14,15]. A summary of the recommendations for periodical tests is included in suppl. table 5.

Medical Therapy

The proportion and distribution of medication was generally similar during 1-year follow-up compared to baseline. There was however a significant increase of anticoagulation in HCM, probably related to occurrence of new onset AF and new stroke, whereas a decrease of diuretics, beta-blockers and ACE inhibitors was surprisingly observed in DCM patients, possibly related to the introduction of new agents (sacubitril/valsartan).

Non-pharmacological therapies

A small but significant proportion of patients required ICD implantation during follow-up (mostly for primary prevention), in keeping with the arrhythmic nature of these cardiac conditions [16-18]. The proportion was particularly high for ARVC, with 2 out of 3 patients carrying an ICD.

A relatively low proportion of HCM patients required invasive septal reduction procedures, with an observed unexpected predominance of myectomy over ablation, likely reflecting preferences of referral centres [9].

Clinical outcomes

The direct comparison between subtypes of cardiomyopathies regarding prognosis is one of the original contributions of the registry (Figure 1). MACE were relatively low in HCM and DCM but very important in ARVC and RCM.

The risk of reaching combined arrhythmic, heart failure or cardiovascular major events was consistently higher (OR ~2) for DCM as compared with HCM patients, which is consistent with the literature[10,12,14,19]. Indeed, annual rates of events (sudden death and heart failure) in DCM series varies from 2 to 6% per year respectively [14]. For HCM, sudden death is the major cause of death and the annual rate in the larger cohorts published is around 1% [19]. In contrast, outcome was most severe in RCM patients (OR for MACE ~5 and OR

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for cardiovascular death ˜12 as compared to HCM) and medication/devices do not seem to prevent the progression of the disease.

Despite the development of new risk stratification scores for HCM, ARVC[20,21] and the results from large registries in DCM[22], patients with cardiomyopathy continue to die suddenly (annual rate 1.0%), and about two-third of those with sudden or arrhythmic death had a diagnosis of DCM. These results highlight the limitations of current SCD risk stratification strategies in cardiomyopathies, particularly in DCM in which indications for ICD are still somewhat controversial[22]. Emerging new data show that the role of genetic background might be broader than previously estimated and that some genes (such as *LMNA, FLNC, RBM20*) that are underdiagnosed in routine practice are associated with a high risk of SCD[14]. To progress towards a better prognosis of patients with cardiomyopathies may therefore require more detailed etiology work-up, refined risk stratification including recent data on MRI and genetics, and may suggest more pro-active use of available therapeutics. Another way is probably to promote the development of "Cardiomyopathies multidisciplinary teams" and not only "Heart failure teams" in order to manage the various aspects of these diseases including etiology-oriented management.

Probands and relatives

The higher proportion of diagnostic tests performed during follow-up in relatives compared to probands was not expected but might be related to the date of diagnosis and a higher proportion of incident vs prevalent cases within relatives as compared to probands. Despite the fact that probands were older, more symptomatic and required more medication than relatives, rates of combined arrhythmic and heart failure major events were not different in both groups of patients. However, probands reached a significantly higher rate of MACE, including urgent admissions, which was double that in relatives.

Geographical differences across Europe

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One of the main goals of the Cardiomyopathy registry was to report on standards of diagnosis and management across Europe, to show adherence to guidelines and to provide important information on provision of care. Geographical differences in the type of patients seen, incident or prevalent, probands and relatives, sporadic or familial, and the use of specific diagnostic tests or therapies have been demonstrated in earlier publications from this cohort [3,9].

In this follow-up analysis, differences in outcomes have arisen. While these differences may represent real variation in accessibility to expert teams and to some advanced therapies like heart transplantation, they might be also related to differences in the cohorts. In particular, East Europe had a higher proportion of probands, which are known to have a higher risk of events. In contrast, the South had the higher percentage of patients with early diagnosis through family screening. However, multivariable analyses still confirmed the regional differences in MACE across Europe. Therefore, improvement in access to optimal care and global equity across Europe should be promoted.

Limitations

Follow-up information was not available in 495/3208 (15.4%) of the initial cohort but patients with missing data were similar to patients with available FU for most variables (suppl. table 6) (including age at enrolment, age of diagnosis, gender distribution, NYHA status) but had fewer ICD, were most frequently probands and incident cases. There were also differences across Europe, with more patients with missing FU information from East Europe, followed by South and then North and West regions. Finally the FU period was limited to one year, without planned extension, and our results may not apply to a longer FU period.

Conclusions

The present work reports unique data regarding the management, follow-up and outcomes of adult patients with various cardiomyopathy subtypes across a range of centres in Europe. We

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observed that a significant number of diagnostic and prognostic tests are required during follow-up, for management of these patients. Despite a significant symptomatic improvement after the first year of medication and invasive therapies, arrhythmic and heart failure complications occurred frequently, demonstrating a significant global burden of major clinical events at short term. Outcomes were different not only according to cardiomyopathy subtypes but also in relatives versus index patients and according to European regions.

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Conflict of interest statement

JR. Gimeno, PM. Elliott, C. Laroche, E. Biagini, E. Arbustini, L. Rocha-Lopes, A.Linhart, J. Mogensen, MA. Espinosa, A. Saad, A. LP Caforio: Conflict of Interest: none declared.

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Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

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Figures legends

Figure 1. Rate of the combined events at 1 year follow-up for each subtype of

cardiomyopathy. (Combined endpoints as defined in methods).

Figure 2. Rate of the combined events at 1 year follow-up regarding probands vs relatives.

Combined endpoints as defined in figure 1.

Figure 3. Rate of the combined events at 1 year follow-up regarding geographical areas.

Combined endpoints as defined in figure 1.

 Supplementary figure 1. Proportion of advanced heart failure therapies at 1 year follow-up.

Ventricular assist devices and heart transplant per geographical areas.

Table 1. Symptoms and examinations at baseline and at 1-year follow-up for each subtype of cardiomyopathy.

Table 2. Non-pharmacological therapies at baseline and at 1-year follow-up for each subtype of cardiomyopathy.

Supplementary table 1. Medications at baseline and at 1-year follow-up for each subtype of cardiomyopathy.

Supplementary Table 2. Combined events at 1-year follow-up for each subtype of cardiomyopathy

Supplementary table 3. Clinical characteristics of patients regarding geographical areas. Symptoms, examinations and events at 1-year follow-up.

Supplementary table 4. Results from multivariable analysis of variables associated with MACE at 1 year.

Legend: Seven variables were selected for analysis: gender, age, cardiomyopathy subtype, proband or relative, familial disease, incident or prevalent and geographical region. Only three remained significant: cardiomyopathy subtype, geographical region and proband vs relative.

Supplementary table 5. Recommended tests during follow-up in patients with different cardiomyopathies.

Supplementary table 6. Clinical characteristics of patients with missing follow-up information compared to those with available data.

Table 1

Table 1. Symptoms and examinations at 1 year follow-up for each type of cardiomyopathy.

Symptoms	HCM			DCM			RCM			ARVC		
	Baseline (N=1420)	FU (N=1420)	P-value	Baseline (N=1105)	FU (N=1105)	P-value	Baseline (N=60)	FU (N=60)	P-value	Baseline (N=128)	FU (N=128)	P-value
Dyspnoea												
NYHA I	401/1127 (35.58%)	435/1127 (38.60%)		172/845 (20.36%)	255/845 (30.18%)		10/50 (20.00%)	8/50 (16.00%)		49/83 (59.04%)	52/83 (62.65%)	
NYHA II	543/1127 (48.18%)	529/1127 (46.94%)		363/845 (42.96%)	390/845 (46.15%)		20/50 (40.00%)	15/50 (30.00%)		32/83 (38.55%)	28/83 (33.73%)	
NYHA III	175/1127 (15.53%)	150/1127 (13.31%)	0.041	245/845 (28.99%)	168/845 (19.88%)	<0.001	19/50 (38.00%)	18/50 (36.00%)	0.017	2/83 (2.41%)	3/83 (3.61%)	0.815
NYHA IV	8/1127 (0.71%)	13/1127 (1.15%)		65/845 (7.69%)	32/845 (3.79%)		1/50 (2.00%)	9/50 (18.00%)		0/83 (0.00%)	0/83 (0.00%)	
Chest pain	414/1217 (34.02%)	185/1217 (15.20%)	<0.001	200/992 (20.16%)	108/992 (10.89%)	<0.001	6/54 (11.11%)	10/54 (18.52%)	0.157	15/107 (14.02%)	10/107 (9.35%)	0.275
Palpitations	440/1217 (36.15%)	298/1217 (24.49%)	<0.001	371/992 (37.40%)	217/992 (21.88%)	<0.001	10/54 (18.52%)	9/54 (16.67%)	0.739	65/107 (60.75%)	41/107 (38.32%)	<0.001
Syncope (suspected arrhythmic/cardiogenic)	146/1172 (12.46%)	27/1172 (2.30%)	<0.001	79/913 (8.65%)	24/913 (2.63%)	<0.001	6/52 (11.54%)	1/52 (1.92%)	0.059	34/103 (33.01%)	5/103 (4.85%)	<0.001
Atrial fibrillation	377/1372 (27.48%)	48/995 (4.82%)	-	323/1075 (30.05%)	41/752 (5.45%)	-	24/53 (45.28%)	3/29 (10.34%)	-	18/124 (14.52%)	3/106 (2.83%)	-

Examinations

ECG	1357/1403 (96.72%)	980/1403 (69.85%)	<0.001	1079/1092 (98.81%)	743/1092 (68.04%)	<0.001	56/56 (100.00%)	34/56 (60.71%)	-	127/128 (99.22%)	98/128 (76.56%)	<0.001
Echocardiography	1339/1403 (95.44%)	855/1403 (60.94%)	<0.001	1060/1091 (97.16%)	666/1091 (61.04%)	<0.001	53/56 (94.64%)	22/56 (39.29%)	<0.001	122/128 (95.31%)	74/128 (57.81%)	<0.001
Holter ECG	950/1404 (67.66%)	477/1404 (33.97%)	<0.001	397/1092 (36.36%)	156/1092 (14.29%)	<0.001	19/56 (33.93%)	8/56 (14.29%)	0.008	90/128 (70.31%)	51/128 (39.84%)	<0.001
Exercise test	612/1404 (43.59%)	235/1404 (16.74%)	<0.001	324/1092 (29.67%)	125/1092 (11.45%)	<0.001	5/56 (8.93%)	5/56 (8.93%)	1.000	66/128 (51.56%)	20/128 (15.63%)	<0.001
MRI scan	495/1404 (35.26%)	89/1404 (6.34%)	<0.001	211/1092 (19.32%)	31/1092 (2.84%)	<0.001	19/56 (33.93%)	3/56 (5.36%)	<0.001	69/128 (53.91%)	7/128 (5.47%)	<0.001

Legend:

ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy

DCM: Dilated Cardiomyopathy

HCM: Hypertrophic Cardiomyopathy

RCM: Restrictive Cardiomyopathy

FU: Follow-up.

Table 2

Table 2. Non-pharmacological therapies at baseline and at 1-year follow-up for each type of cardiomyopathy.

Variable	HCM			DCM			RCM			ARVC		
	Baseline (N=1420)	FU (N=1420)	P-value	Baseline (N=1105)	FU (N=1105)	P-value	Baseline (N=60)	FU (N=60)	P-value	Baseline (N=128)	FU (N=128)	P-value
Pacemaker implanted	97/1383 (7.01%)	14/1286 (1.09%)	-	46/1079 (4.26%)	4/1033 (0.39%)	-	8/54 (14.81%)	0/46 (0.00%)	-	3/125 (2.40%)	0/122 (0.00%)	-
CRT	8/1368 (0.58%)	2/1360 (0.15%)	-	113/1073 (10.53%)	9/960 (0.94%)	-	0/53 (0.00%)	0/53 (0.00%)	-	0/125 (0.00%)	0/125 (0.00%)	-
ICD primary prophylaxis	260/1401 (18.56%)	56/1141 (4.91%)	-	294/1091 (26.95%)	46/797 (5.77%)	-	1/56 (1.79%)	0/55 (0.00%)	-	39/127 (30.71%)	7/88 (7.95%)	-
ICD secondary prophylaxis	38/1328 (2.86%)	0/1290 (0.00%)	-	52/1028 (5.06%)	0/976 (0.00%)	-	3/56 (5.36%)	0/53 (0.00%)	-	31/119 (26.05%)	0/88 (0.00%)	-
Ablation for atrial fibrillation	33/1403 (2.35%)	6/1370 (0.44%)	-	14/1091 (1.28%)	6/1077 (0.56%)	-	1/56 (1.79%)	1/55 (1.82%)	-	1/127 (0.79%)	0/126 (0.00%)	-
Ablation for ventricular tachycardia	0/1403 (0.00%)	1/1403 (0.07%)	-	15/1091 (1.37%)	1/1076 (0.09%)	-	0/56 (0.00%)	0/56 (0.00%)	-	11/127 (8.66%)	1/116 (0.86%)	-
Ventricular assist device	0/777 (0.00%)	1/777 (0.13%)	-	18/778 (2.31%)	15/760 (1.97%)	-	0/32 (0.00%)	0/32 (0.00%)	-	0/73 (0.00%)	0/73 (0.00%)	-

Heart Transplant	0/1403 (0.00%)	3/1403 (0.21%)	-	6/1090 (0.55%)	25/1084 (2.31%)	-	0/56 (0.00%)	2/56 (3.57%)	-	0/127 (0.00%)	0/127 (0.00%)	-

CRT : cardiac resynchronization therapy. ICD: Implantable cardioverter defibrillator.

Legend: similar to table 1

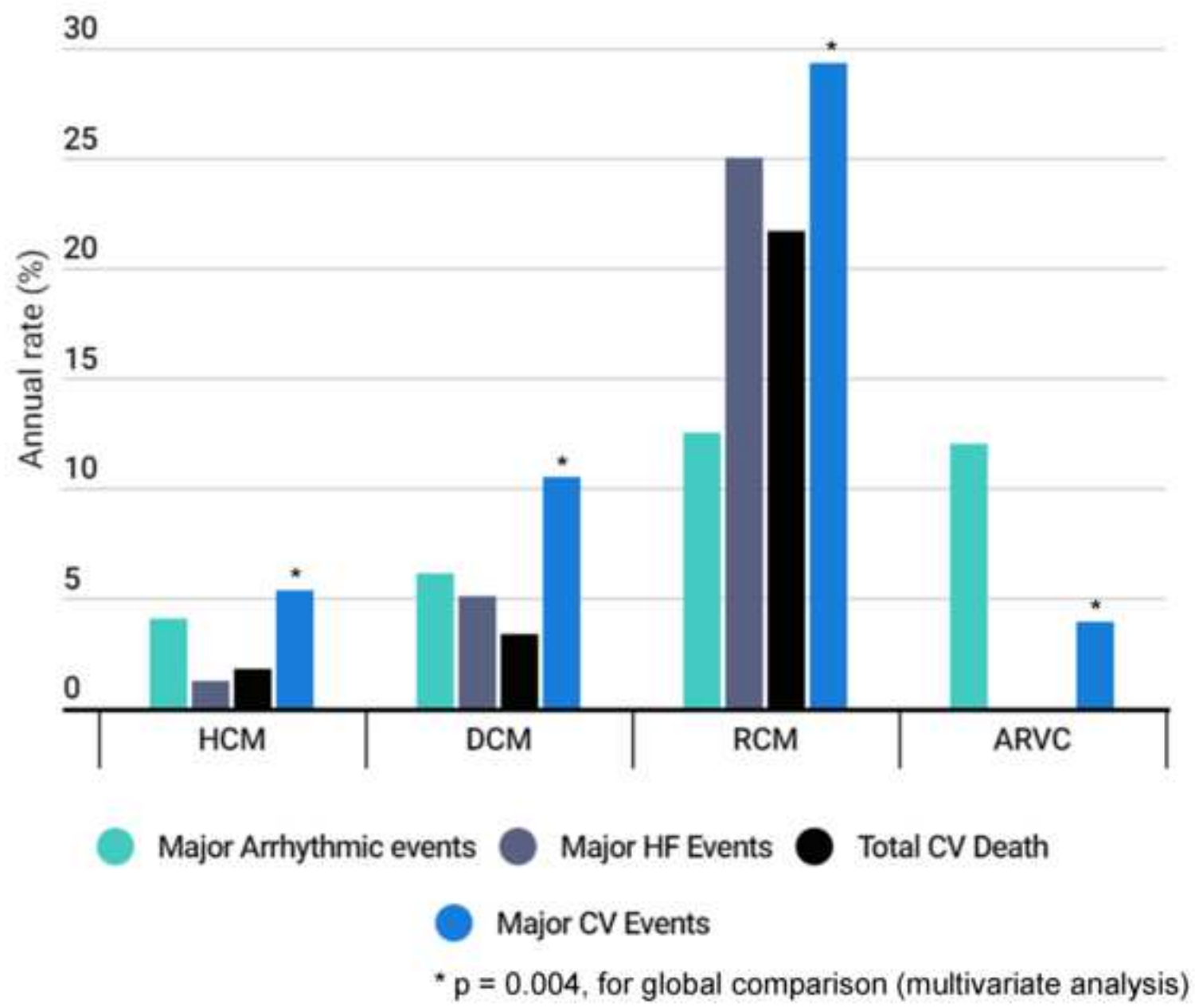**Significance not applicable as differences in denominators from baseline to follow-up**
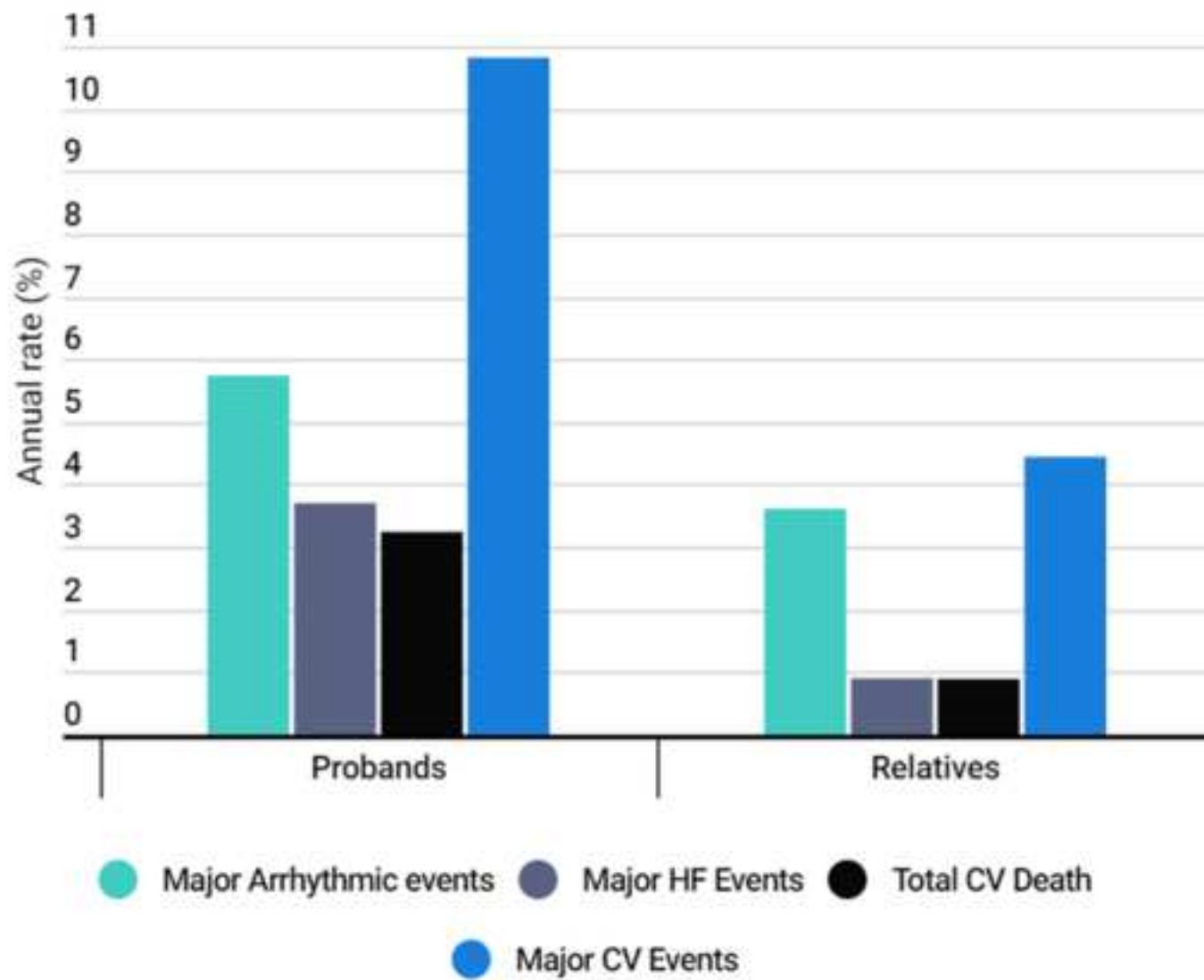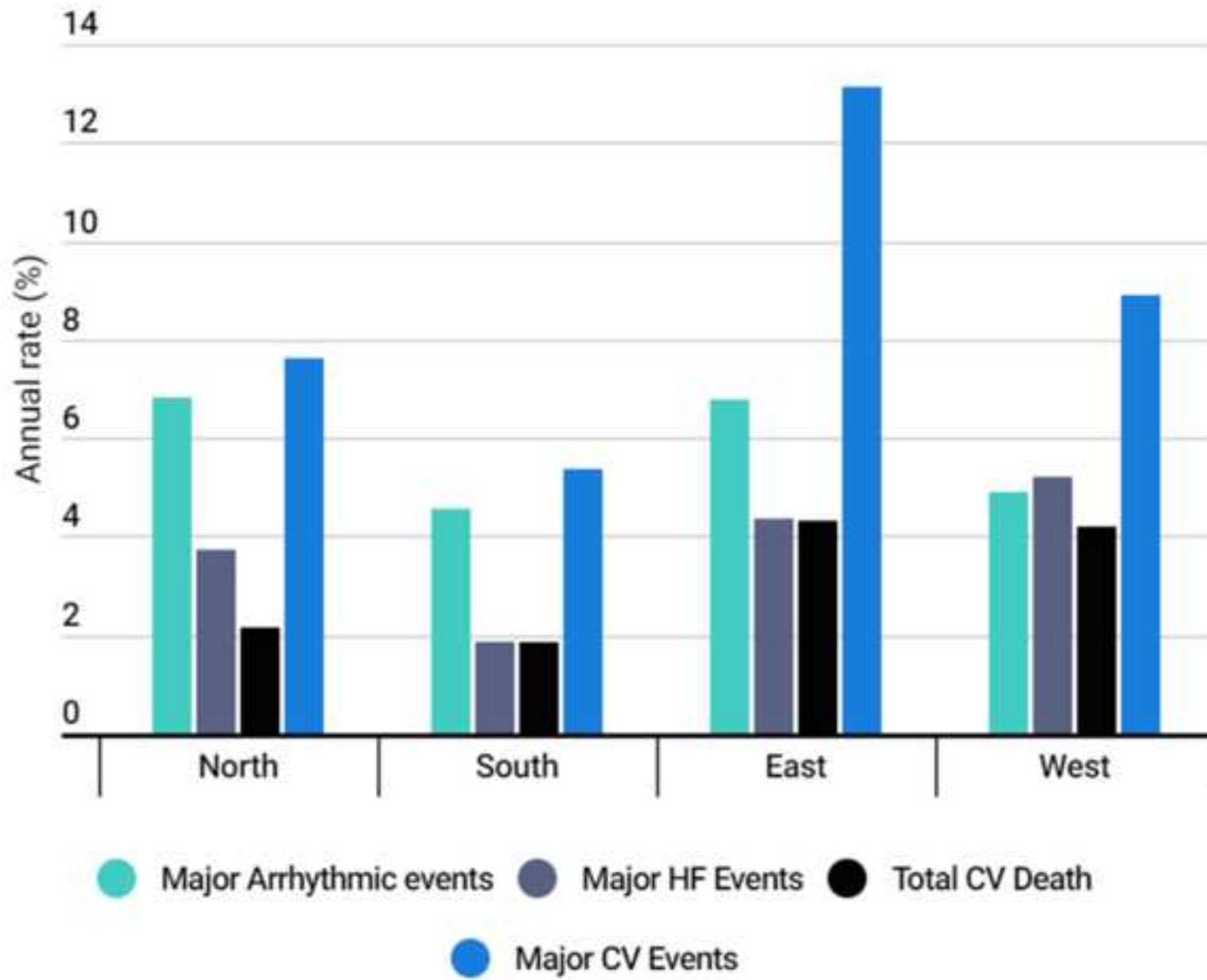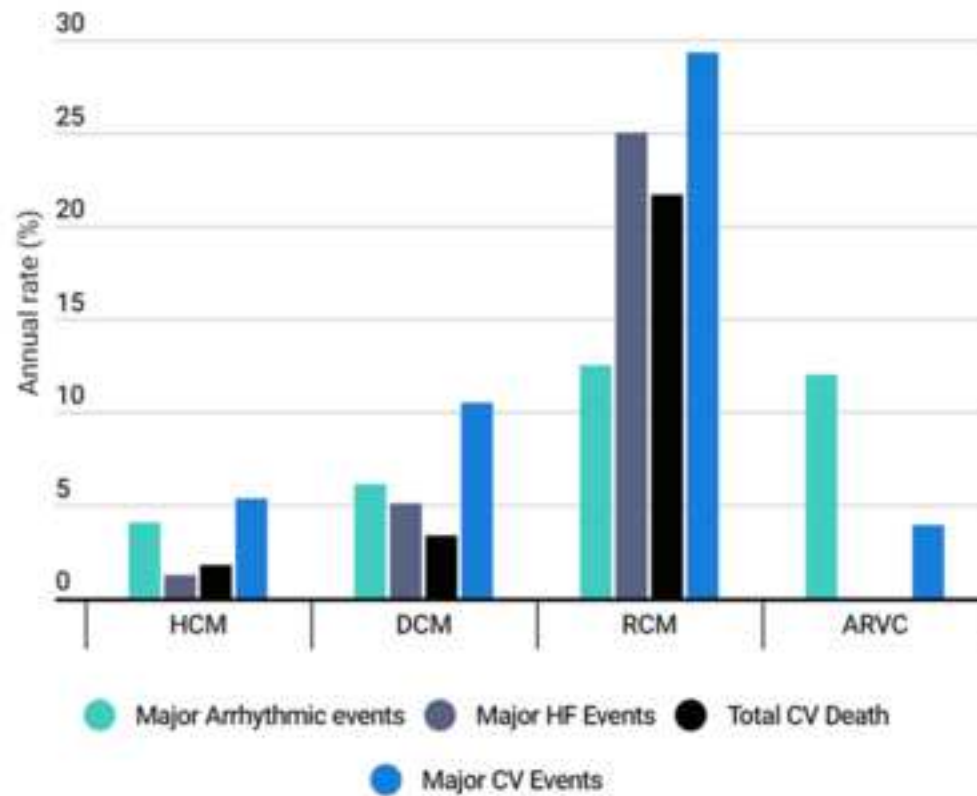
Figure 1

Figure 2

Figure 3

Graphical Abstract

Patients with cardiomyopathies experience a significant burden of short term major clinical events but with large heterogeneity, not only according to cardiomyopathy subtypes but also according to familial status and according to European regions.