ESC HEART FAILURE
ESC Heart Failure (2020)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12925

ORIGINAL RESEARCH ARTICLE

ESC EORP Cardiomyopathy Registry: real-life practice of genetic counselling and testing in adult cardiomyopathy patients

Tiina Heliö[1*‡†], Perry Elliott[2‡†], Juha W. Koskenvuo[3,4], Juan R. Gimeno[5‡†], Luigi Tavazzi[6‡†], Michal Tendera[7‡†], Juan Pablo Kaski[8‡†], Nicolas Mansencal[9], Zofia Bilińska[10], Gerry Carr-White[11], Thibaud Damy[12], Andrea Frustaci[13], Ingrid Kindermann[14], Tomas Ripoll-Vera[15], Jelena Čelutkienė[16], Anna Axelsson[17], Massimiliano Lorenzini[2], Aly Saad[18], Aldo P. Maggioni[6,19‡†], Cécile Laroche[19], Alida L.P. Caforio[20‡†], Philippe Charron[21‡†] and on behalf of the EORP Cardiomyopathy Registry Investigators Group[†‡]

[1]*Department of Cardiology, University of Helsinki, Helsinki, University Hospital, Helsinki, Finland;* [2]*University College London, St. Bartholomew's Hospital, London, UK;* [3]*Blueprint Genetics, Helsinki, Finland;* [4]*Clinical Physiology and Nuclear Medicine, Turku University Hospital, University of Turku, Turku, Finland;* [5]*Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain;* [6]*Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy;* [7]*Department of Cardiology and Structural Heart Disease, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland;* [8]*Cardiology Department, Great Ormond Street Hospital for Children, London, UK;* [9]*Hôpital Ambroise Paré, Centre de Référence des Cardiomyopathies, Assistance Publique-Hôpitaux de Paris, Inserm U1018, CESP, UVSQ, Boulogne-Billancourt, France;* [10]*Unit for Screening Studies in Inherited Cardiovascular Diseases, The Cardinal Stefan Wyszynski Institute of Cardiology, Warsaw, Poland;* [11]*St Thomas' Hospital, London, UK;* [12]*CHU Henri Mondor, Créteil, France;* [13]*Policlinico Umberto I, Rome, Italy;* [14]*Department of Internal Medicine III, Saarland University Hospital, Saarland University, Homburg, Germany;* [15]*Hospital Universitario Son Llatzer, IdISBa, Palma de Mallorca, Spain;* [16]*Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania;* [17]*Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [18]*Zagazig University, Zagazig, Egypt;* [19]*EURObservational Research Programme, European Society of Cardiology, Sophia-Antipolis, France;* [20]*Department of Cardiological, Thoracic and Vascular Sciences and Public Health, University of Padova, Padova, Italy;* [21]*Centre de Référence des Maladies Cardiaques Héréditaires, Assistance Publique-Hôpitaux de Paris, ICAN, Inserm UMR1166, Hôpital Pitié-Salpêtrière, Sorbonne Université, Paris, France*

Abstract

Aims Cardiomyopathies comprise a heterogeneous group of diseases, often of genetic origin. We assessed the current practice of genetic counselling and testing in the prospective European Society of Cardiology EURObservational Research Programme Cardiomyopathy Registry.

Methods and results A total of 3208 adult patients from 69 centres in 18 countries were enrolled. Genetic counselling was performed in 60.8% of all patients [75.4% in hypertrophic cardiomyopathy (HCM), 39.2% in dilated cardiomyopathy (DCM), 70.8% in arrhythmogenic right ventricular cardiomyopathy (ARVC), and 49.2% in restrictive cardiomyopathy (RCM), $P < 0.001$]. Comparing European geographical areas, genetic counselling was performed from 42.4% to 83.3% ($P < 0.001$). It was provided by a cardiologist (85.3%), geneticist (15.1%), genetic counsellor (11.3%), or a nurse (7.5%) ($P < 0.001$). Genetic testing was performed in 37.3% of all patients (48.8% in HCM, 18.6% in DCM, 55.6% in ARVC, and 43.6% in RCM, $P < 0.001$). Index patients with genetic testing were younger at diagnosis and had more familial disease, family history of sudden cardiac death, or implanted cardioverter defibrillators but less co-morbidities than those not tested ($P < 0.001$ for each comparison). At least one disease-causing variant was found in 41.7% of index patients with genetic testing (43.3% in HCM, 33.3% in DCM, 51.4% in ARVC, and 42.9% in RCM, $P = 0.13$).

Conclusions This is the first detailed report on the real-life practice of genetic counselling and testing in cardiomyopathies in Europe. Genetic counselling and testing were performed in a substantial proportion of patients but less often than recommended by European guidelines and much less in DCM than in HCM and ARVC, despite evidence for genetic background.

Keywords Cardiomyopathy; Registry; Genetic testing; Genetic counselling; Mutation; Disease-causing variant

Received: 14 April 2020; Revised: 24 June 2020; Accepted: 13 July 2020
**Correspondence to: Tiina Heliö, Department of Cardiology, University of Helsinki, Helsinki University Hospital, Haartmaninkatu 4, Helsinki 00290, Finland. Tel: +358 428 6589; Fax: +358 9 47175893.*
Email: tiina.helio@hus.fi
‡See Appendix 1 for the complete list of the EORP Cardiomyopathy Registry Investigators Group.
†European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-Heart)

Introduction

Cardiomyopathies are a heterogeneous group of diseases characterized by abnormal function and structure of the cardiac muscle not caused by hypertension, coronary artery disease, valvular defects, or congenital heart disease.[1,2] As a disease group, cardiomyopathies are an important cause of heart failure, arrhythmias, and sudden cardiac death (SCD). As genetic causes explain a substantial proportion of cardiomyopathies, patients need dedicated genetic counselling, information about the risk of inheritance, and organized cardiac family screening and diagnostic genetic testing in the context of family cascade screening strategy to improve the management of patients and the family. The expected clinical benefit has been translated into various guidelines or position statements since 2010, with a high level of recommendation, so that genetic counselling and testing of these patients have rapidly diffused into the cardiology community.[3–6] However, economical and organizational aspects may affect the implementation of these recommendations, and there are few data on the current practices of genetic counselling and testing of these patients, especially in the era of next-generation sequencing.

The EURObservational Research Programme Cardiomyopathy Registry, initiated by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases, was conducted to provide real-life data on the current practices and management of patients with cardiomyopathies and myocarditis from a large number of specialized centres.[7,8]

The main objectives of this ancillary study were (i) to evaluate how often genetic counselling and testing are performed in real life and (ii) to understand heterogeneous practices and search for predictors of these practices. To analyse the yield of genetic testing was only a secondary and exploratory objective because of heterogeneous molecular analyses performed by centres and the absence of centralized interpretation, reflecting daily practice.

Methods

Registry design

Sixty-nine centres from 18 countries participated in this prospective, observational European multinational and multicentre registry on adult patients with cardiomyopathies.[7,8] The registry consists of Pilot and Long-term phases. The centres invited to the Pilot phase were selected as highly expert centres in myocardial diseases. Enrollment of adult patients with cardiomyopathies took place between December 2012 and November 2013 for the Pilot Registry and between June 2014 and December 2016 for the Long-term Registry. Each centre provided about 40 consecutive adult cardiomyopathy patients over 1 year period. The approvals of local ethics committees were obtained by each participating centre. Written informed consent was required before including the patient into the registry. The study complies with the Declaration of Helsinki. Diagnostic and treatment decisions were solely performed by the attending physician. The registry has been conducted by the executive committee, whereas the management of the study, data quality control, and statistical analyses have been carried out by the EURObservational Research Programme department of the ESC.

Patients

The inclusion criteria for the adult cardiomyopathy registry were age at enrollment, >18 years, written informed consent from the patient, ability to comply with the study requirements, and a documented cardiomyopathy, which fulfilled the study criteria for probands or relatives.

Definitions of cardiomyopathies, subgroups, and geographical areas have been previously published.[7,8] The patient population reported here comprises 3208 consecutive adult patients, with hypertrophic cardiomyopathy (HCM, n = 1739), dilated cardiomyopathy (DCM, n = 1260), arrhythmogenic right ventricular cardiomyopathy (ARVC, n = 143), and restrictive cardiomyopathy (RCM, n = 66). Although the concept of arrhythmogenic cardiomyopathy has recently been introduced, the term 'ARVC' is still used here because of the planned strict inclusion criteria. The baseline clinical characteristics of the patients have been published earlier.[7,8]

Genetic testing and findings

The inclusion of patients in the registry had no impact on the management of the patient by the local investigators. The data we studied therefore reflect the local practice of centres at this era, which was the focus of the study. As a consequence, heterogeneous molecular analyses were performed by centres, with a range of genetic testing techniques from sequencing after Sanger to large-scale next-generation sequencing.[9] The data on genetic findings collected into the case report form comprised the genes tested, and recorded variants were described using either nucleotide or amino acid alterations. These variants had been classified independently by each centre/investigator as to wild type, variant of unknown significance (VUS), or probably disease-causing variant (DCV). It should be noted that systematic American College of Medical Genetics and Genomics classification scheme was not available at the beginning of patient enrollment, and thus, we use here the term DCV instead of the 'pathogenic'

or 'likely pathogenic' American College of Medical Genetics and Genomics terms to define variants.[9]

Statistical analyses

Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean ± standard deviation and/or as median and interquartile range when appropriate. Among-group comparisons were made using the non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Among-group comparisons were made using the χ^2 test or a Fisher's exact test if any expected cell count was <5. 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

Genetic counselling

Information on whether genetic counselling was performed or not was available for 91.6% of the population (2939/3208 patients), and data on whether the patient was an index patient or a relative were available for 2324/3208 (72.4%) of all the participants. Genetic counselling was performed in 1786/2939 (60.8%) of all patients, 1077/1760 (61.2%) of index patients, and 315/376 (83.8%) of relatives. When all patients were considered, the main clinical features associated with genetic counselling were younger age at diagnosis [median (Q1–Q3): 45 (32–57) vs. 52 (41–61) years, $P < 0.001$], gender ($P = 0.04$), family history of SCD (19.9% vs. 13.2%, $P < 0.001$), and familial disease (51.5% vs. 18.6%, $P < 0.001$). The patients receiving counselling had fewer co-morbidities and alcohol use than those who were not counselled (Supporting Information, *Table S1*). In index patients, clinical features associated with genetic counselling were younger age at diagnosis [median (Q1–Q3): 46 (34–57) vs. 52 (42–61) years], higher proportion of familial disease (47.7% vs. 16.6%), and less symptoms (66.4% vs. 83.1%) ($P < 0.001$ for each comparison). Supporting Information, *Table S2* shows the proportions of patients with genetic counselling and with or without genetic testing.

When geographical areas were considered, genetic counselling was performed in 42.4% of all patients in West Europe, 56.7% in North Europe, 58.7% in East Europe, 67.8% in South Europe, and 83.3% of patients from a single centre in North Africa (*Table 1*). When cardiomyopathy subtypes were considered, genetic counselling was provided to 1221/1619 (75.4%) of HCM, 442/1127 (39.2%) of DCM, 92/130 (70.8%) of ARVC, and for 31/63 (49.2%) of RCM patients ($P < 0.001$). Genetic counselling was provided by a cardiologist for 85.3%, by a geneticist for 15.1%, by a genetic counsellor for 11.3%, and by a nurse for 7.5% of counselled subjects (*Table 1*). Cardiologists were predominantly involved in all geographical regions except in West Europe where geneticists/genetic counsellors were predominant (*Table 1*).

Genetic testing

Information on whether genetic testing was performed or not was available for 92.4% (2963) of the patients, including index patients, relatives, and those with unknown family status. Genetic testing was carried out in 1105/2963 (37.3%) of all adult cardiomyopathy patients. It was performed less frequently in index patients (643/1772, 36.3%) as compared with relatives (234/376, 62.2%, $P < 0.001$). Genetic testing was carried out more frequently in the Pilot (selected as highly expert centres) as compared with the Long-term phases (centres with variable degree of expertise) (43.9% vs. 33.8%, $P < 0.001$). The clinical features of all index patients with or without genetic testing are shown in *Table 2*. The index patients with genetic testing were younger at diagnosis [median (Q1–Q3): 45 (33–57) vs. 50 (40–59) years, $P < 0.001$], more frequently male (63.6% of index patients were male; genetic testing performed in 39.5% of female patients and 34.7% of male patients, $P = 0.04$), more often had familial disease (60.0% vs. 22.0%, $P < 0.001$) or family history of SCD (21.7% vs 10.8%, $P < 0.001$), had implantable cardioverter defibrillators (30.5% vs. 20.6%, $P < 0.001$), and had less often hypertension (30.6% vs. 43.3%, $P < 0.001$), type 2 diabetes (8.9% vs. 14.3%, $P < 0.001$), or alcohol use (17.4% vs. 44.4%, $P < 0.001$) as compared with those without.

Table 1 shows the extremely wide range in the degree of genetic testing between predetermined geographical regions: 49.7% in South Europe, 40.4% in West Europe, 34.6% in North Europe, 15.2% in East Europe, and 0% in North Africa ($P < 0.001$). In index patients, genetic testing was performed differently according to cardiomyopathy subtypes ($P < 0.001$): in 462/967 (47.8%) of HCM, 132/697 (18.9%) of DCM, 35/71 (49.3%) of ARVC, and 14/37 (37.8%) of RCM index patients (*Table 3*). In contrast, genetic testing was frequently performed in relatives (>56%) without significant differences among cardiomyopathy subtypes (*Table 3*).

Genetic results

Results of genetic testing were reported for all 643 index patients with genetic testing performed. At least one DCV was reported in 41.7% of all tested index patients (*Table 4*). Two or more DCVs were found in <2% of the probands. At least one VUS was found in 17.3% of all index cases. Regarding the cardiomyopathy subtypes, one or more DCVs were found

Table 1 Regional differences in practices of genetic counselling and testing

	East Europe (n = 713)	North Europe (n = 543)	South Europe (n = 1,427)	West Europe (n = 481)	North Africa (n = 44)	All (n = 3208)	P-value
Genetic counselling performed, n (%)	393/670 (58.7)	294/519 (56.7)	907/1338 (67.8)	157/370 (42.4)	35/42 (83.3)	1786/2939 (60.8)	<0.001
Geneticist, n (%)	9/393 (2.3)	28/294 (9.5)	168/907 (18.5)	64/157 (40.8)	0/35 (0.0)	269/1786 (15.1)	<0.001
Genetic counsellor, n (%)	5/393 (1.3)	24/294 (8.2)	99/907 (10.9)	74/157 (47.1)	0/35 (0.0)	202/1786 (11.3)	<0.001
Cardiologist, n (%)	386/393 (98.2)	233/294 (79.3)	838/907 (92.4)	31/157 (19.8)	35/35 (100.0)	1523/1786 (85.3)	<0.001
Nurse, n (%)	0/393 (0.0)	47/294 (16.0)	87/907 (9.6)	0/157 (0.0)	0/35 (0.0)	134/1786 (7.5)	<0.001
Genetic testing performed, n (%)	102/672 (15.2)	181/523 (34.6)	659/1326 (49.7)	163/404 (40.4)	0/38 (0.0)	1105/2963 (37.3)	<0.001

One patient could receive genetic counselling from several professionals.
Geographical areas were defined according to United Nations geoscheme for Europe (https://unstats.un.org/unsd/methodology/m49/).
The table includes data on index patients, relatives, and those with unknown family position.

in 43.3% of HCM, 33.3% of DCM, 51.4% of ARVC, and 42.9% of RCM index patients (P = 0.13).

Supporting Information, *Table S3* shows the genes tested in HCM patients and the reported yields of DCVs and VUSs per individual gene tested. Mutations were most frequently identified in *MYBPC3*, *MYH7*, and *TNNT2* genes. HCM index patients with at least one DCV, as compared with those with none, were younger at diagnosis [median (Q1–Q3): 39 (27–31) vs. 50 (39–60) years, $P < 0.001$) and more often had familial disease (75.1% vs. 46.9%, $P < 0.001$), asymmetrical septal hypertrophy (83.7% vs. 71.1%, P = 0.002), ventricular arrhythmias (14.5% vs. 5.0%, $P < 0.001$), or an implanted cardioverter defibrillator (33.0% vs. 14.5%, $P < 0.001$) (not shown). They less often had hypertension (26.0% vs. 42.4%, $P < 0.001$), hyperlipidaemia (29.5% vs. 43.9%, P = 0.002), or significant left ventricular outflow tract gradient at rest (16.8% vs. 30.5%, P = 0.02) (not shown).

Supporting Information, *Table S4* shows the genes tested in DCM patients and their reported yields of DCVs and VUSs per individual gene tested. Mutations were most frequently identified in *MYH7*, *TCAP*, *LMNA*, and *MYBPC3*. In titin gene (*TTN*), a DCV was found only in 3 out of 56 (5.4%) tested patients. DCM index patients with at least one DCV had more often familial disease (72.2% vs. 47.6%, P = 0.018) and extracardiac signs (33.3% vs. 10.3%, P = 0.003) (not shown).

In ARVC index patients, Supporting Information, *Table S5* describes the number of DCVs and VUSs per gene related to the total number of patients genotyped for any of the genes. DCVs were most frequently identified in *PKP2*, *DSG2*, and *DSC2*.

In RCM, 14 probands underwent genetic testing. DCVs were reported in *DES*, *GLA*, *MYBPC3*, *TNNT2*, and *TTN*, one in each gene.

Discussion

We report the first detailed study of the practice of genetic counselling and testing in cardiomyopathies in Europe. The data were prospectively collected on consecutive patients from a large range of centres between December 2012 and December 2016. They reflect contemporary management of cardiomyopathy patients and local practices in the context of existing recommendations on these issues by various academic societies.

Genetic counselling

We observed that genetic counselling was provided in two-thirds of patients and to a lesser extent to index patients as compared with relatives. The total number of counselled patients was lower than expected given several

Table 2 Clinical characteristics of all adult cardiomyopathy index patients with or without genetic testing performed

	Genetic testing performed (n = 643)	Genetic testing not performed (n = 1129)	P-value
Age at enrollment (years), n Median (Q1–Q3)	55 (43–65)	55 (45–64)	0.27
Age at diagnosis (years), n Median (Q1–Q3)	45 (33–57)	50 (40–59)	<0.001
Female, n (%)	234/592 (39.5)	358/592 (60.5)	0.04
Male, n (%)	409/1180 (34.7)	771/1180 (65.3)	
Family history of SCD, n (%)	133/612 (21.7)	114/1052 (10.8)	<0.001
Familial disease, n (%)	296/493 (60.0)	194/882 (22.0)	<0.001
SCD/cardiac arrest, n (%)	15/587 (2.6)	13/1087 (1.2)	0.04
NYHA class, n (%)			
NYHA I	147/486 (30.3)	171/956 (17.9)	
NYHA II	239/486 (49.2)	481/956 (50.3)	
NYHA III	94/486 (19.3)	258/956 (27.0)	
NYHA IV	6/486 (1.2)	46/956 (4.8)	<0.001
Hypertension, n (%)	197/643 (30.6)	489/1129 (43.3)	<0.001
Diabetes Type 1, n (%)	3/643 (0.5)	5/1129 (0.4)	1.0
Diabetes Type 2, n (%)	57/643 (8.9)	161/1129 (14.3)	<0.001
Hyperlipidaemia/dyslipidaemia, n (%)	223/643 (34.7)	546/1129 (48.4)	<0.001
Renal impairment, n (%)	70/643 (10.9)	158/1129 (14.0)	0.06
Alcohol use (yes/no), n (%)	83/478 (17.4)	445/1002 (44.4)	<0.001
Skeletal muscle impairment, n (%)	21/643 (3.3)	49/1129 (4.3)	0.26
AV block,[a] n (%)	102/531 (19.2)	163/1057 (15.4)	0.06
Atrial fibrillation of flutter, n (%)	193/643 (30.0)	314/1129 (27.8)	0.32
Ventricular arrhythmias, n (%)	85/643 (13.2)	138/1129 (12.2)	0.54
Associated LV non-compaction, n (%)	29/636 (4.6)	44/1103 (4.0)	0.57
Pacemaker implanted, n (%)	73/637 (11.5)	116/1126 (10.3)	0.45
Cardioverter defibrillator implanted, n (%)	196/643 (30.5)	232/1129 (20.6)	<0.001
Cardiac medication, n (%)	487/534 (91.2)	857/928 (92.4)	0.44

AV, atrioventricular; LV, left ventricular; NYHA, New York Heart Association; SCD, sudden cardiac death.
All sample size includes index patients with or without genetic testing (those with data lacking on genetic testing were excluded).
[a]AV block includes history of AV block or first-degree, second-degree, or third-degree block.

Table 3 Genetic testing performed in separate cardiomyopathy groups

	HCM (n = 1739)	DCM (n = 1260)	ARVC (n = 143)	RCM (n = 66)	All (n = 3208)	P-value
Index patients, n (%)	462/967 (47.8)	132/697 (18.9)	35/71 (49.3)	14/37 (37.8)	643/1772 (36.3)	<0.001
Relatives, n (%)	166/263 (63.1)	50/88 (56.8)	16/23 (69.6)	2/2 (100.0)	234/376 (62.2)	0.48
All,[a] n (%)	789/1616 (48.8)	214/1150 (18.6)	75/135 (55.6)	27/62 (43.6)	1105/2963 (37.3)	<0.001

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.
[a]Including index patients and relatives and those unknown for the family status, whether they were index patients or probands.

Table 4 DCV and VUS in index patients according to cardiomyopathy subtypes

	HCM (n = 462)	DCM (n = 132)	ARVC (n = 35)	RCM (n = 14)	All index patients (n = 643)	P-value
At least one DCV, n (%)	200/462 (43.3)	44/132 (33.3)	18/35 (51.4)	6/14 (42.9)	268/643 (41.7)	0.13
At least two DCVs, n (%)	8/462 (1.7)	3/132 (2.3)	1/35 (2.9)	0/14 (0.0)	12/643 (1.9)	0.72
At least one VUS, n (%)	65/462 (14.1)	37/132 (28.0)	8/35 (22.9)	1/14 (7.1)	111/643 (17.3)	0.001
At least one VUS in patient with a DCV, n (%)	12/200 (6.0)	8/44 (18.2)	3/18 (16.7)	0/6 (0.0)	23/268 (8.6)	0.03

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; DCV, disease-causing variants; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; VUS, variant of unknown significance.

recommendations published from 2010 to promote genetic counselling in cardiomyopathies.[3–6,10]

In this registry, those individuals who received counselling were younger and more often had familial disease. However, older patients should also be counselled, especially in the context of increasingly recognized diseases, which occur at later age such as familial *TTR* amyloidosis or Fabry disease. Similarly, the familial context may be absent in the case of *de novo* mutation and or a mutation transmitted by a parent with a non-penetrant mutation. Genetic counselling was performed less frequently in DCM patients as compared with other subtypes, although DCM is now considered to be familial or genetic in at least 30–50% of cases. The proportion of counselled patients greatly varied in different geographical

areas, suggesting an area of potential improvement especially for some European regions. The registry also provided information on the person who gave genetic counselling. Cardiologists were most often involved except for West Europe where genetic counselling was mostly provided by genetic counsellors and geneticists. This may reflect heterogeneous availability of genetic counsellors and geneticists in different countries or individual practices of the participating centres. The scope of genetic counselling has been detailed in previous recommendations[3–6,10] and should include information about the genetic origin of cardiomyopathies, the mode of inheritance and the potential risk for relatives, who carry the mutation, the natural history with frequent delayed cardiac onset, the benefits and organization of a cardiac screening within the family, the risk of worsening of the disease during pregnancy, availability of genetic testing, medical sources of information, and existing patient associations. Unfortunately, we do not have more detailed data on the contents of the genetic counselling delivered by centres or on a possible specific board qualification when cardiologists were involved. To develop dedicated training for cardiologists may be an area for improvement.

Genetic testing

Genetic testing was performed in about one-third of index patients and over half of the relatives. This low proportion of genetic testing is not in line with the existing recommendations.[3–6,10] For example, in an ESC Working Group statement[3] where genetic testing is recommended in all index patients with definite clinical diagnosis of a cardiomyopathy, to enable predictive diagnosis in first-degree relatives according to a cascade screening strategy, and when a specific aetiology of cardiomyopathy is suspected in the index patient in order to confirm the specific cause and appropriately manage the patient and the family. It should be noticed that the relatives included in this registry fulfilled the diagnostic criteria of clinical cardiomyopathy, and thus, genetic testing has been diagnostic, not predictive.

About two-thirds of the index patients were male, which may reflect the natural course of cardiomyopathies with delayed expression in female patients. Index patients who were genetically tested were younger at diagnosis, more often had familial disease or family history of SCD, and fewer co-morbidities as compared with those who were not genetically tested. Genetic testing was also less frequently performed in DCM patients as compared with other subtypes. The fact that DCM was under-investigated might be related to the heterogeneous aetiology of the disease with many acquired causes[2,10–13]but may also be related to the low yield of mutation identification until recently when the prominent role of *TTN* was recognized along with the development of high-throughput sequencing.[14–16] Large regional differences were observed in genetic testing with the lowest rates in East Europe and North Africa. They possibly reflect geographical differences in economic status of the countries or variable insurance modalities for covering the costs of genetic testing.

Genetic findings

The yield of genetic testing was relatively high with ~42% of tested index patients having at least one DCV. However, the interpretation of these data should be cautious and considered only as exploratory because results were self-reported by investigators who used various sequencing methods (from focused Sanger sequencing to small or large high-throughput sequencing panels) with a local classification of variants' pathogenicity determined at the time of inclusion.

Nevertheless, in HCM index patients, a DCV was found in 43.3% of cases, in agreement with the usual figure of 30–60% according to populations studied and genes investigated.[17,18] HCM results also support the major role of sarcomeric genes.[18] In DCM, the proportion of index patients with a DCV was one-third, which is relatively low but consistent with the fact that *TTN* gene, now recognized as the major gene in DCM, was analysed in only few patients in our population, probably because high-throughput sequencing of this gene was not yet widely available at that moment.[14–16] In ARVC patients, a DCV was identified in half of the patients in line with the current literature.[19,20] There were few patients with RCM, and the results of genetic testing support earlier observations on the heterogeneous genetic background.[21]

Perspectives

Altogether, our results show that the translation of guidelines or position statements about genetic counselling/testing into clinical practice is substantial but still needs to be improved. This is especially important in the field of cardiomyopathies because genetics is a key tool for the improvement of patients and family management through personalized medicine as illustrated by family cascade screening strategy or refined prognosis stratification along with the development of recent innovative therapeutics based on new small molecules or gene-editing approaches. [22,23]

We consistently identified determinants of genetic counselling/testing practice *per se* as it was performed more often in patients who are younger, had more familial disease/family history of SCD, less co-morbidities, and less often in DCM as compared with other subtypes. These determinants are meaningful because they are usually also predictors of the yield of genetic sequencing in cardiomyopathies, and

interestingly, we also identified these predictors for mutation identification rate in HCM patients.[24] However, to restrict genetic counselling/testing to this subpopulation is misleading because there is an increasing evidence for important genetic component in patients who are older (role of *TTR* amyloidosis for example) or who have DCM[14–16] or peripartum cardiomyopathy.[25] Further efforts are needed to offer genetic counselling/testing to a larger proportion of patients with a cardiomyopathy, whatever age, familial status, or comorbidities.

We also observed large heterogeneity in European regions, and it can be hypothesized that variations in service provision are mostly related to economical or structural reasons. To promote a dedicated organization of healthcare systems for hereditary diseases, including cardiomyopathies, at a national or European level is suggested, and initiatives underway such as the European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-Heart for cardiac disease, https://guardheart.ern-net.eu/) should be supported.

Finally, a better organization of healthcare system at local level is probably another way to progress. To identify and build dedicated multidisciplinary heart teams might be useful as shown in other areas.[26] The fact that genetic counselling was performed by cardiologist in 85% of cases in our study supports the proposal of more interactions with other disciplines such as clinical geneticists. Another way to achieve the objective may be to construct and diffuse clinical integrated care pathways for cardiomyopathy patients as a tool used to manage the quality in healthcare and diffuse the standardization of care processes.[27]

Study limitations

This observational registry study provides innovative data but has several limitations. Some data were missing such as family status (index patients or relatives) for about one-fifth of patients who were therefore excluded from part of analyses about genetic testing. The content of genetic counselling that was delivered was not recorded in the case report form and thus not studied. The genetic results should be considered as exploratory because of the heterogeneous molecular methods used by the various centres and the variable listing of genes. In addition, the classification of the genetic variants was purely based on the data provided by the participating centres. As detailed original genetic molecular data about the variants have not been gathered in this registry, it was not possible to reclassify the variants according to current standards. We cannot exclude that some variants were misclassified, especially in the context of evolving knowledge and rules about interpretation of genetic variants.

Conclusions

This is the first detailed report on the real-life practice of genetic counselling and testing in cardiomyopathies in Europe. Genetic counselling and testing were performed in a substantial proportion of patients but less than expected by European guidelines. European regional differences in providing counselling and testing were considerable and differed between cardiomyopathy phenotypes.

Acknowledgements

EORP Oversight Committee, The Registry Executive Committee of the EURObservational Research Programme (EORP). Data collection was conducted by the EORP department from the ESC by Rachid Mir Hassaine as clinical project manager; Emanuela Fiorucci, Myriam Glemot, and Patti-Ann McNeill as project officers; and Marème Konté and Sebastien Authier as data managers. Statistical analyses were performed by Cécile Laroche. Overall activities were coordinated and supervised by Dr A.P.M. (EORP Scientific Coordinator). All investigators are listed in Appendix 1.

Conflict of interest

Dr T.H. reports cardiology consultant at the Blueprint Genetics, personal fees from Sanofi Genzyme, personal fees from Amgen, personal fees from Pfizer, non-financial support from Alnylam, and non-financial support from MSD outside the submitted work. Dr J.W.K. reports other from Blueprint Genetics outside the submitted work. Dr L.T. reports personal fees from Servier and CVie Therapeutics outside the submitted work. Dr M.T. reports personal fees from Bayer, Cadila Pharmaceuticals, Janssen-Cilag, Kowa, PERFUSE Group, Servier, UCB Pharmaceuticals, and OncoArendi outside the submitted work. Dr Z.B. reports grants from ERA-CVD DETECTIN-HF outside the submitted work. Dr T.D. reports grants, personal fees, and non-financial support from Pfizer and Alnylam; grants, personal fees, and non-financial support from Akcea Therapeutics; personal fees from GSK; and grants, personal fees, and non-financial support from Novartis outside the submitted work. Prof. I.K. reports personal fees from AstraZeneca GmbH, Servier Germany GmbH, Novartis Pharma GmbH, Pfizer Germany GmbH/Pfizer Pharma GmbH, Akcea Therapeutics, Fresenius Medical Care GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Vifor Pharma Germany GmbH, and Bayer Pharma AG outside the submitted work. Dr J.Č. reports personal fees from AstraZeneca, Berlin-Chemie, Novartis, and Pfizer outside the submitted work. Dr M.L. reports personal fees from Pfizer outside the submitted work. Dr A.S. has nothing to disclose. Dr A.P.M. reports

personal fees from Bayer, Fresenius, and Novartis outside the submitted work. Dr P.C. reports personal fees from Amicus and Pfizer and grants from Sanofi and Shire outside the submitted work. Other authors have nothing to disclose.

Funding

This work was supported by Abbott Vascular International (2011–2021), Amgen Cardiovascular (2009–2018), AstraZeneca (2014–2021), Bayer AG (2009–2018), Boehringer Ingelheim (2009–2019), Boston Scientific (2009–2012), The Bristol Myers Squibb and Pfizer Alliance (2011–2019), Daiichi Sankyo Europe GmbH (2011–2020), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014–2017), Edwards (2016–2019), Gedeon Richter Plc. (2014–2016), Menarini Int. Op. (2009–2012), MSD–Merck & Co. (2011–2014), Novartis Pharma AG (2014–2020), ResMed (2014–2016), Sanofi (2009–2011), Servier (2009–2021), and Vifor (2019–2022). Funders had no role in the study design, data analyses, and manuscript drafting.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1 Supporting Information

Table S1. *Clinical characteristics of all adult cardiomyopathy patients with or without genetic counselling performed*

Table S2. *Proportions of patients with genetic counselling and with or without genetic testing*

Table S3. *Genes tested and genetic findings in HCM index patients*

Table S4. *Genes tested and genetic findings in DCM index patients*

Table S5. *Genes examined and genetic findings in ARVC index patients*

References

1. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res* 2017; **121**: 722–730.
2. Braunwald E. Cardiomyopathies: an overview. *Circ Res* 2017; **121**: 711–721.
3. Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, Helio T, Keren A, McKenna WJ, Monserrat L, Pankuweit S, Perrot A, Rapezzi C, Ristic A, Seggewiss H, van Langen I, Tavazzi L, European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2010; **31**: 2715–2728.
4. Zamorano JL, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Haqeqe AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H, 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 (ESC). *Eur Heart J* 2014; **35**: 2733–2779.
5. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C. 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 Aug; **8**: 1308–1339. Available from. http://www.ncbi.nlm.nih.gov/pubmed/21787999
6. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic evaluation of cardiomyopathy—a Heart Failure Society of America Practice Guideline. *J Card Fail* 2018; **24**: 281–302. Available from. https://doi.org/10.1016/j.cardfail.2018.03.004
7. Elliott P, Charron P, Blanes JR, Tavazzi L, Tendera M, Konte M, Laroche C, Maggioni AP, EORP Cardiomyopathy Registry Pilot Investigators. European Cardiomyopathy Pilot Registry. EURObservational Research Programme of the European Society of Cardiology. *Eur Heart J* 2016; **37**: 164–173.
8. Charron P, Elliott PM, Gimeno JR, Caforio AL, Kaski JP, Tavazzi L, Tendera M, Maupain C, Laroche C, Rubis P, Jurcut R, Calò L, Heliö TM, Sinagra G, Zdravkovic M, Kavoliuniene A, Felix SB, Grzybowski J, Losi MA, Asselbergs FW, García-Pinilla JM, Salazar-Mendiguchia J, Mizia-Stec K, Maggioni AP, EORP Cardiomyopathy Registry Investigators. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. *Eur Heart J* 2018; **39**: 1784–1793.
9. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Heqde M, Lyon E, Spector E, Voelkerding K, Rehm HL, ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; **17**: 405–424.
10. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, Duboc D, Gimeno J, de Groote P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio AL, Charron P, Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice. A position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J* 2016; **37**: 1850–1858.
11. Ware JS, Amor-Salamanca A, Tayal U, Govind R, Serrano I, Salazar-Mendiguchía J, García-Pinilla JM, Pasqual-Fiqal DA, Nuñez J, Guzzo-Merello G, Gonzalez-Vioque E, Bardaji A, Manito N, López-Garrido MA, Padron-Barthe L, Edwards E, Whiffin N, Walsh R, Buchan RJ, Midwinter W, Wilk A, Prasad S, Pantazis A, Baski J, O'Regan

DP, Alonso-Pulpon L, Cook SA, Lara-Pezzi E, Barton PJ, Garcia-Pavia P. Genetic etiology for alcohol-induced cardiac toxicity. *J Am Coll Cardiol* 2018; **71**: 2293–2302.
12. Wasielewski M, van Spaendonck-Zwarts KY, Westerink ND, Jongbloed JD, Postma A, Gietema JA, van Tintelen JP, van den Berg MP. Potential genetic predisposition for anthracycline-associated cardiomyopathy in families with dilated cardiomyopathy. *Open Heart* 2014; **1**: e000116.
13. McNally EM, Mestroni L. Dilated cardiomyopathy: genetic determinants and mechanisms. *Circ Res* 2017; **121**: 731–748.
14. Herman DS, Lam L, Taylor MRG, Wang L, Teekakirikul P, Christodoulou D, Conner L, DePalma SR, McDonough B, Sparks E, Teodorescu DL, Cirino AL, Banner NR, Pennell DJ, Graw S, Merlo M, Di Lenadra A, Sinagra G, Bos JM, Ackerman MJ, Mitchell RN, Murry CE, Lakdawala NK, Ho CY, Barton PJR, Cook SA, Mestroni L, Seidman JG, Seidman CE. Truncations of titin causing dilated cardiomyopathy. *N Engl J Med* 2012; **366**: 619–628.
15. Pugh TJ, Kelly MA, Gowrisankar S, Hynes E, Seidman MA, Baxter SM, Bowser M, Harrison B, Aaron D, Mahanta LM, Lakdawala NK, McDermott G, White ET, Rehm HL, Lebo M, Funke BH. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. *Genet Med* 2014; **16**: 601–608.
16. Akinrinade O, Ollila L, Vattulainen S, Tallila J, Gentile M, Salmenperä P, Koillinen H, Kaartinen M, Nieminen MS, Myllykangas S, Alastalo TP, Koskenvuo JW, Heliö T. Genetics and genotype-phenotype correlations in Finnish patients with dilated cardiomyopathy. *Eur Heart J* 2015; **36**: 2327–2337.
17. Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, Shen J, McLaughlin HM, Clark EH, Babb LJ, Cox SW, DePalma SR, Ho CY, Seidman JG, Seidman CE, Rehm HL. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. *Genet Med* 2015; **17**: 880–888.
18. Cirino AL, Harris S, Lakdawala NK, Michels M, Olivotto I, Day SM, Abrams DJ, Charron P, Caleshu C, Semsarian C, Ingles J, Rakowski H, Judge DP, Ho CY. Role of genetic testing in inherited cardiovascular disease. *A Rev JAMA Card* 2017; **2**: 1153–1160.
19. Gandjbakhch E, Redheuil A, Pousset F, Charron P, Frank R. Clinical diagnosis, imaging, and genetics of arrhythmogenic right ventricular cardiomyopathy/dysplasia: JACC state-of-the-art review. *J Am Coll Cardiol* 2018; **72**: 784–804.
20. Corrado D, Basso C, Judge DP. Arrhythmogenic cardiomyopathy. *Circ Res* 2017; **121**: 784–802.
21. Muchtar E, Blauwet LA, Gertz MA. Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017; **121**: 819–837.
22. Wahbi K, Ben Yaou R, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, Stalens C, Sacher F, Babuty D, Trochu JN, Moubarak G, Savvatis K, Porcher R, Laforêt P, Fayssoil A, Marijon E, Stojkovic T, Béhin A, Leonard-Louis S, Sole G, Labombarda F, Richard P, Metay C, Quijano-Roy S, Dabaj I, Klug D, Vantyghem MC, Chevalier P, Ambrosi P, Salort E, Sadoul N, Waintraub X, Chikhaoui K, Mabo P, Combes N, Maury P, Sellal JM, Tedrow UB, Kalman JM, Vohra J, Androulakis AF, Zeppenfeld K, Thompson T, Barnerias C, Bécane HM, Bieth E, Boccara F, Bonnet D, Bouhour F, Boulé S, Brehin AC, Chapon F, Cintas P, Cuisset JM, Davy JM, De Sandre-Giovannoli A, Demurger F, Desguerre I, Dieterich K, Durigneux J, Echaniz-Laguna A, Eschalier R, Ferreiro A, Ferrer X, Francannet C, Fradin M, Gaborit B, Gay A, Hagège A, Isapof A, Jeru I, Juntas Morales R, Lagrue E, Lamblin N, Lascols O, Laugel V, Lazarus A, Leturcq F, Levy N, Magot A, Manel V, Martins R, Mayer M, Mercier S, Meune C, Michaud M, Minot-Myhié MC, Muchir A, Nadaj-Pakleza A, Péréon Y, Petiot P, Petit F, Praline J, Rollin A, Sabouraud P, Sarret C, Schaeffer S, Taithe F, Tard C, Tiffreau V, Toutain A, Vatier C, Walther-Louvier U, Eymard B, Charron P, Vigouroux C, Bonne G, Kumar S, Elliott P, Duboc D. Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation* 2019 Jul 23; **140**: 293–302.
23. Repetti GG, Toepfer CN, Seidman JG, Seidman CE. Novel therapies for prevention and early treatment of cardiomyopathies. *Circ Res* 2019; **124**: 1536–1550.
24. Bos JM, Will ML, Gersh BJ, Kruisselbrink TM, Ommen SR, Ackerman MJ. Characterization of a phenotype-based genetic test prediction score for unrelated patients with hypertrophic cardiomyopathy. *Mayo Clin Proc* 2014; **89**: 727–737.
25. Van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, Hilfiker-Kleiner D, Bollen IA, Sliwa K, Alders M, Almomani R, van Langen IM, van der Meer P, Sinke RJ, van der Velden J, van Veldhuisen DJ, van Tintelen JP, Jongbloed JD. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. *Eur Heart J* 2014; **35**: 2165–2173.
26. Masters J, Morton G, Anton I, Szymanski J, Greenwood E, Grogono J, Flett AS, Cleland JG, Cowburn PJ. Specialist intervention is associated with improved patient outcomes in patients with decompensated heart failure: evaluation of the impact of a multidisciplinary inpatient heart failure team. *Open Heart* 2017; **4**: e000547.
27. Kinsman L, Rotter T, James E, Snow P, Willis J. What is a clinical pathway?: development of a definition to inform the debate. *BMC Med* 2010; **8**: 31.