Underwriting Inherited or Acquired Cardiomyopathies

Andrea Di Lenarda§°, Patrizia Marocco°, Giulia Barbati§*, Marco Merlo*, Marco Anzini*, Andrea Perkan*, Francesca Cettolo*, Bruno Pinamonti*, Gianfranco Sinagra*

° Assicurazioni Generali, Global Life, Risk Selection and Actuarial Services, Trieste, Italy

§ Cardiovascular Center, Ospedale Maggiore, and University of Trieste

* Cardiovascular Department, «Ospedali Riuniti», and University of Trieste

Introduction

Cardiomyopathies are a heterogeneous group of diseases in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular and congenital heart disease sufficient to cause the observed myocardial abnormality (1,2). The molecular genetics of myocardial disease has not been completely developed, yet, and more complex genotype–phenotype relationships continue to emerge for these diseases.

The present paper will focus on major primary, inherited or acquired, cardiomyopathies, notably on hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), dilated cardiomyopathy (DCM), and acute myocarditis (AM).

The Trieste Heart Muscle Disease Registry was established 40 years ago in the Cardiovascular Department of Trieste, one of the main referral centers for the diagnosis and treatment of myocardial diseases and heart failure (HF) in Italy. More than a thousand patients with different types of primary cardiomyopathies were enrolled.

Over the past decades, the outcome of cardiomyopathies has been substantially improving thanks to interventions such as periodic revision and implementation of screening processes, diagnostic methods and follow-up procedures as well as constant update (3) of pharmacological (mostly ACE-inhibitors, angiotensin II antagonists, beta-blockers and aldosterone antagonists), and non-pharmacological therapeutic strategies (implanted cardioverter defibrillator-ICD and cardiac resynchronization therapy). Moreover, the average follow-up of our population is around 10 years. Thus, the results of our analyses for underwriting of patients with cardiomyopathies should be applied only to

those on tailored and optimal treatment for a similar long-term view.

The Registry strongly underlines the limitation of a single assessment at the time of diagnosis since additive prognostic information derives from time-tabled reevaluation of patients during follow-up or at least (for the aim of underwriting) from a single multiparametric assessment after an adequate period of optimal tailored medical therapy (from a minimum of 6 months to 2 years or more). Nevertheless, since the complexity and heterogeneity of cardiomyopathies, it has to be underlined the need of an accurate evaluation of the single case beyond general prognostic indicators. Family history, myocardial phenotype, functional capacity, arrhythmic burden, adherence, tolerability and response to tailored medical therapy, associated comorbidities and evolution over time may significantly influence the long-term outcome of the single case.

Primary endpoints of our Registry were all-cause death, cardiovascular (CV) death or urgent (status I) heart transplant (HTx). The cause of CV death was based on a clinical history of sudden death (SD), or refractory HF. Since the young age of affected population, non CV death was relatively rare and unexpected within this limited period of observation. In order to compare mortality of patients with cardiomyopathies with mortality of the background Italian population, taking into account demographic characteristics (sex and age) and the year of diagnosis, relative survival techniques have been applied. In brief, a survival curve for the matched Italian population is being computed and compared to the survival curve of patients with cardiomyopathies, globally or stratified by a significant prognostic factor. Estimates of mortality ratios (MR) with their corresponding confidence intervals are subsequently derived (4,5). As an example, a MR of 200 % was considered corresponding to a twice as high mortality in comparison with matched Italian population, indicating a +100 % extramortality.

Hypertrophic Cardiomyopathy (HCM)

HCM is a disease of the heart muscle characterized by LV hypertrophy in the absence of known causes (6). The prevalence is around 1:500 individuals. HCM is an autosomal dominant genetic dis-

ease (> 1400 mutation in > 20 sarcomeric genes) with age-related penetrance.

Severity of hypertrophy is highly variable as the presence of an obstruction in the LV outflow tract (documented in about 25 % of cases). Diastolic dysfunction is the main hemodynamic abnormality of HCM and is related to LV hypertrophy, interstitial fibrosis, fiber disarray, and subendocardial ischemia. LV systolic function is usually preserved.

SD constitutes the major risk (children 1–2 % / year; adults 0,5–1 % / year). HF is present in 5–10 % of cases and is an important cause of death and HTx. ICD placement to prevent SD is recommended for patients with HCM with prior documented cardiac arrest or life-threatening arrhythmias. The indication is reasonable for patients with HCM with unexpected SD in first-degree relatives, in those with a maximum LV wall thickness ≥ 30 mm, with unexplained syncopal episodes. In selected patients with non-sustained ventricular tachycardia or abnormal blood pressure response with exercise, the risk of SD may be increased by concomitant presence of LV outflow tract obstruction, late gadolinium enhancement as a marker of myocardial fibrosis or scarring, LV apical aneurysm, and possibly some genetic mutations. Multiple risk markers in individual patients would intuitively suggest greater risk for SD; however, the vast majority of patients with ≥ 1 risk marker will not experience SD.

In the Trieste Heart Muscle Disease Registry we consecutively enrolled 157 HCM patients to analyze long-term prognostic implications of symptoms and echocardiographic progression to LV systolic and diastolic dysfunctions (7,8). A familial history of HCM was found in 27 % of the cases. During a median follow-up of 102 months, asymptomatic cases (47 %) as well as those with symptoms of chest pain (15 %) showed a significantly lower rate of CV death or HTx (< 1 % / year) in comparison with patients symptomatic for HF or arrhythmias (respectively 17 % and 22 %, CV death or HTx 3–5 % / year) (7).

A further analysis was performed on 101 HCM patients with systematic Echo Doppler evaluation at enrollment and during follow-up (66 men, 65 %; mean age 43 ± 19 years, follow-up 109 ± 67 months) to analyze the presence of restrictive

Tab. 1. Main baseline clinical characteristics of the study population with HCM (8).

Variables	Baseline (n=101)
Asymptomatic patients (%)	28
NYHA class II-IV (%)	39
Syncopal epysodes (%)	7
Ventricular arrhythmias (%)	11
Supraventricular tachycardia / atrial fibrillation (%)	24 / 5
LV end diastolic diameter indexed (cm / m²)	2,5 ± 0,4
LV maximal thickness (cm)	2,2 ± 0,5
LV ejection fraction (%)	65 ± 11
LV ejection fraction < 50 % (%)	7
Left atrial area indexed (cm² / m²)	15 ± 5
LV systolic pressure gradient > 30 mmHg (%)	28,3
LV abnormal relaxation (%)	36
LV Restrictive Filling Pattern (%)	15
Beta-blockers / Verapamil (%)	37 / 25
Amiodarone (%)	19
ACE-inhibitors / Diuretics (%)	9 / 1

filling pattern (RFP) and LV systolic dysfunction as markers of worse clinical status, elevated LV filling pressure, and poor prognosis (Table.1) (8).

At enrollment, 17 % of patients showed RFP and / or left ventricular systolic dysfunction (LVEF < 50 %), while at follow-up, LV systolic and / or diastolic dysfunctions persisted or developed in 44 patients (44 %). From the clinical point of view, patients who maintained or developed LV RFP and / or systolic dysfunctions presented a more serious clinical status and more severe echocardiographic abnormalities, both upon enrollment and during the follow-up.

The only risk factor at enrollment for development of diastolic and / or systolic

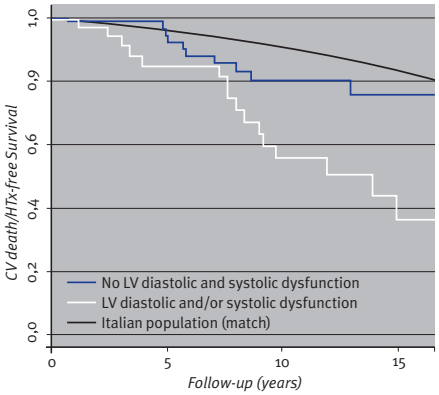

Fig. 1. Survival curves of 101 HCM patients according to the presence of LV diastolic and / or systolic dysfunctions at presentation or during follow-up compared with patients without left ventricular dysfunctions and age- and sex-matched italian population (modified from ref. 8).

dysfunction was a higher indexed LV end diastolic diameter; on the other hand, a higher indexed left atrial area predicted the development of RFP, while a lower LV ejection fraction at enrolment would predict the evolution in LV systolic dysfunction. During follow-up, CV death / HTx was demonstrated in 27 patients (27 %). HTx-free survival independently correlated with NYHA classes III–IV and with left ventricular systolic and / or diastolic dysfunctions at baseline or during follow-up (Fig. 1). The short-term revaluation showed a significant incremental prognostic value when compared to the baseline evaluation.

For underwriting, in presence of LV systolic and / or diastolic dysfunction, the MR ranges from 200–300 % in the first 2 years to 400–700 % from 5 to 10 years of cover. Otherwise in absence of LV dysfunctions (and other major risk factors for SD), the candidates could meet criteria for life insurance with a MR ranging from 150–200 % in the first two years to 200–300 % from 5 to 10 years of cover indicating an extramortality from + 50 % to + 200 % for a maximal cover of 10 years.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is a primary myocardial disease predominantly involving the right ventricle (RV). It may lead to life-threatening ventricular arrhythmias and HF (ref. 9,10). ARVC is a genetic disease (in most cases autosomal dominant with

incomplete penetrance) with an estimated prevalence of 1:5000 and a familial trait in 30–50 % of cases. Several desmosomal mutations are considered to be responsible for the progressive loss of ventricular myocytes, and their replacement with fibro-adipose tissue, the pathologic landmark of the disease.

Major arrhythmic events and SD can occur in both early 'concealed' phase (characterized by little or no evidence of heart disease) and in the overt stage of disease (characterized by fibro-fatty replacement of the myocardium). The progressive myocyte loss and replacement with fibro-fatty tissue, due to intrinsic genetically determined structural pathology and stress, are also responsible for the gradual dilation and functional RV and LV impairment that eventually result in progressive HF.

Tab. 2. Main baseline clinical characteristics of the study population with ARVC (10).

Variables	Baseline (n=96)
Asymptomatic patients (%)	27
NYHA class II-IV (%)	17
Syncopal epysodes (%)	15
Non sustained ventricular tachycardia (%)	34
Supraventricular tachycardia / atrial fibrillation (%)	19 / 4
ECG abnormalities (%)	78
RV dilatation (%)	79
RV systolic dysfunction (%)	64
Moderate-severe tricuspid regurgitation (%)	15
LV dilation (%)	14
LV wall motion abnormalities / systolic dysfunction (%)	45 / 26
Antiarrhythmics (%)	54
Amiodarone (%)	24
Beta-blockers / Sotalol (%)	20 / 19
ACE-inhibitors / Diuretics (%)	17 / 17
ACE-inhibitors / Diuretics (%)	9 / 1

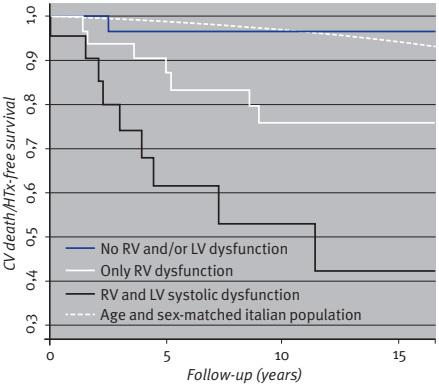

Fig. 2. Survival curves of 96 ARVC patients classified according to the «ordinal ventricular dysfunction» (solid line = no ventricular dysfunction; dashed line = right ventricular dysfunction; dotted line = biventricular dysfunction) compared with age- and sex-matched italian population (modified from ref. 10).

We analyzed the clinical presentation, natural history and long-term echocardiographic prognostic predictors in 96 patients with ARVC consecutively enrolled in our Registry (68 % men, mean age 35 ± 15 years, follow-up 128 ± 92 months) (Table 2) (9). A familial history of ARVC was found in 46 % of the cases.

During follow-up, the 20 patients who reached the primary endpoint of CV death or HTx showed a more severe clinical presentation, characterized by more frequent HF as well as RV and LV systolic dysfunctions, atrial enlargement and significant tricuspid regurgitation.

On Cox multivariate analysis, the 3 significant independent predictors of CV death / HTx were ordinal dysfunction (0= no RV or LV systolic dysfunction; 1=RV systolic dysfunction, 2=RV and / or LV systolic dysfunction) along with significant tricuspid regurgitation and amiodarone treatment. A progressive increase of CV death and HTx rate was observed in the presence of RV and biventricular dysfunction, respectively (Figure 2).

For underwriting, in absence of RV and LV systolic dysfunction, the MR ranges from 100–200 % in the first 2 years to 200–300 % from 5 to 10 years of coverage, indicating a mortality from standard to an extramortality of + 200 %. Otherwise, candidates should be considered unsuitable for life insurance.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by a contractility reduction and LV or biventricular dilation and constitutes a relevant mortality and morbidity factor, as well as a frequent indication to HTx. The estimated prevalence is 1:500 and at least 30 % to 50 % of DCM cases are familial, suggesting a relevant genetic background (more than 40 genes involved, different modes of inheritance with incomplete and age-dependent penetrance). After adjustment for the clinical stage of the disease, the overall outcome of familial cases is similar to that of sporadic ones.

The combined influence of a progressively earlier diagnosis (also due to systematic familial screening) and efficacy of HF interventions were associated to a significant improvement in DCM prognosis with < 2 / 100 patients / year of major events and 8-year HTx-free survival of 87 % in the last decade (ref. 11). The improvement of LV function and remodelling overtime on tailored medical treatment is relatively frequent and sustained over the years, while complete normalization of LV is possible but relatively uncommon. In spite of this significant advance, DCM patients are at present unlikely accepted for life insurance.

We prospectively enrolled 577 DCM patients in our Registry (75 % males, mean age 45 ± 14 years, median follow-up 8 years) to compare the long-term all-cause death or HTx with background Italian population, taking into account

Tab. 3. Main baseline clinical characteristics of the study population with DCM (4).

Variables	Baseline (n=577)
NYHA class I-II (%)	75
HF duration (months)	12
Atrial fibrillation (%)	10
LV EF (%)	31
Beta-blockers (%)	82
ACE / Angiotensin II-inhibitors (%)	93

demographic characteristics and 'reverse remodelling'of LV after the first two years of optimal medical treatment (Tab. 3) (4).

Reverse remodelling (RR) was defined in presence of a LVEF improvement of at least 10 points, or normalization (LVEF> 50 %) and a left ventricular end diastolic diameter (LVEDD) decrease of at least 10 %, or normalization (indexed LVEDD < 3,3 cm / m²) after 12–24 months of optimal medical therapy. During the study period, 178 patients died or underwent HTx (3,8 % pts / year). Fifty-five patients (9,5 %) were treated with ICD for primary prevention of SD.

At 2 years from enrollment, 389 patients had available data to evaluate their clinical status. Among them, 140 (36 %) were defined to have RR. Most of the RR patients were asymptomatic (NYHA I 80 % in RR vs 47 % in not RR, p=0,001), with LVEF > 45 % (RR 68 % vs not RR 22 %, p=0,001).

In comparison with the matched Italian population, DCM patients showed a relative survival ranging between 0,91 and 0,73 for males (at 2 and 10 years) and between 0,95 and 0,79 for females. Relative survival rates also confirmed the significant worse condition of males, as emerging in many clinical studies. With a global 5-year survival of only 78 % (males) to 87 % (females), DCM patients would appear to be uninsurable at a first glance with MR ranging from 500 % to more than 800 %, fairly equivalent in both sexes, showing values incompatible with life insurance suitability.

Instead, by considering reverse remodelling within the first 2 years of follow-up, percentage of survival at 5 and 10 years of such patients showed a highly significant improvement with a MR ranging from 200 % to 400 %, so that they could be considered acceptable life insurance candidates by defining an extramortality ranging from + 100 % to + 300 % depending on the entity of clinical improvement on optimal medical treatment (complete normalization of LV dimension and function vs persistent mild to moderate impairment), the length of the cover (up to 10 years) and the age of candidates (over 50 years old candidates with RR showed a better relative situation compared to younger patients) (fig.3).

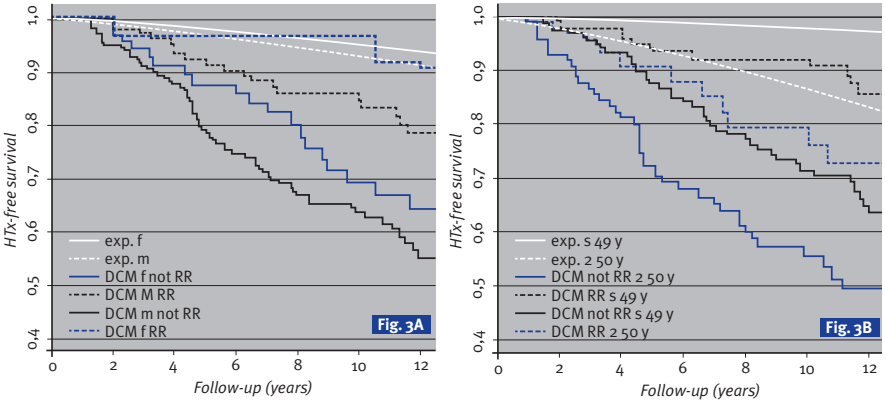

Fig. 3. Survival curves of 389 DCM patients, by gender (m=male, f=female) (fig. 3A) and by age groups (fig. 3B) and reverse remodelling (RR=reverse remodelling, not RR=not reverse remodelling) compared with age- and sex-matched italian population (from ref. 4).

The relatively high rate of events during the first years after diagnosis (ref. 11) highlights the importance for the insurance company to evaluate the candidates after at least 1 to 2 years of follow-up on tailored medical treatment in order to guarantee an adequate risk stratification and underwriting.

Myocarditis

Active myocarditis (AM) is an inflammatory disease of the myocardium, diagnosed by established histological, immunological and immunohistochemical criteria. Heterogeneity of clinical manifestation is a peculiar feature of AM, which may variably present itself with recent onset HF, arrhythmias, chest pain or a concurrence of these elements. Similarly, natural history of AM is highly variable, ranging from full recovery with excellent mid-term outcome to development of DCM or SD.

Our study consecutively enrolled 82 patients in the Trieste Heart Muscle Disease Registry (70% males, mean age 38±16 years, median follow-up 147±107 months) with biopsy-proven AM to describe the long-term natural history and early pre-

dictors of long-term prognosis (ref. 12). Beyond HF tailored medical treatment, 56 % of patients received immunosuppressive therapy (prednisone and azathioprine) for a 6-month period on the basis of absence of genome of cardiotropic viruses in endomyocardial biopsies with evidence of immune activation at immunohistochemical analysis and persistent severe symptoms of HF or LV dysfunction and / or otherwise unexplained life-threatening ventricular arrhythmias.

Patients were categorized in three groups according to the main pattern of disease onset: 65 % of patients presented with HF and / or LVEF < 50 %, 24 % with electrocardiographic evidence of bradyarrhythmias or tachyarrhythmias and 11 % with chest pain (Table 4). Among the three groups, patients with HF more frequently presented LV dysfunction and enlarged left atrium and ventricle.

Tab. 4. Main baseline characteristics of the study population with Acute Myocarditis according to clinical presentation (12).

Variables	Heart Failure (N=53,65 %)	Arrhythmias (N=20,24 %)	Chest Pain (N=9, 11 %)	p value
NYHA functional classes III-IV (%)	68	15	0	<0,001
Left bundle branch block (%)	19	10	0	0,407
Non sustained ventricular tachycardia (%)	40	11	0	0,007
Left atrial diameter indexed (cm/m)	2,5 ± 4	2,0 ± 3	2,0 ± 3	<0,001
LV end diastolic diameter indexed (cm/m)	39[35–42]	30[28–33]	31[29–33]	<0,001
LV ejection fraction (%)	28[21–32]	57[49–64]	56[53–64]	<0,001
LV ejection fraction < 50 % (%)	100	25	11	<0,001
LV Restrictive filling pattern %	61,5	8	33	0,003
Moderate-severe mitral regurgitation (%)	25	10	0	0,146
ACE / Angiotensin II-inhibitors (%)	57	25	22	0,018
Beta-blockers (%)	49	30	11	0,058
Diuretics (%)	85	0	11	<0,001
Amiodarone (%)	28	15	0	0,130
Immunosoppressants-no. (%)	66	40	33	0,043

During follow-up, 23 (28 %) patients died and 7 (9 %) underwent HTx; 9 (11 %) patients received an ICD. Long-term HTx-free survival was significantly different among groups according to the pattern of disease onset, with the poorest outcome being for HF patients. Upon multivariable analysis, the independent predictors of long-term HTx-free survival were the left atrium enlargement and the presence of LV systolic dysfunction at enrollment. These patients represent a high risk subgroup and require further reevaluations under optimal medical treatment in order to improve the prognostic stratification and guide a tailored global management. In contrast, AM patients with preserved LVEF at disease onset (also in presence of symptoms as chest pain) present an excellent long-term prognosis and should be treated conservatively. The only exception may be related to patients with AM presenting with arrhythmias, in which the rhythm instability may indicate a diffuse myocardial involvement and possibly risk of late events.

Early improvement or normality of LVEF (defined as LVEF increase > 20 percentage points or LVEF ≥ 50 %) was observed in 53 % of our patients at 6 months. In the high-risk subgroup of patients with LVEF< 50 %, tailored medical therapy for HF with ACE inhibitors and beta-blockers was the only variable independently associated with LV function recovery. More recent data from the literature suggest that the absence of late gadolinium enhancement on cardiac magnetic resonance may further improve our prediction of recovery of LV function.

Persistence of NYHA III-IV classes, left atrium dilatation and improvement or normality of LVEF at 6 months were independent predictors of long-term outcome in our study. The prompt improvement or normality of LVEF were independently associated with excellent long-term outcome on multivariable analysis, regardless of LV function at disease onset (fig. 4). For underwriting, in the presence of improvement or normality of LVEF at 6 months, MR range from 100–200 % during the first 10 years of cover, indicating a mortality from standard to an extramortality of + 100 %. Otherwise, the candidates should be considered unsuitable for life insurance.

This information underscores the importance of clinical and echocardio-

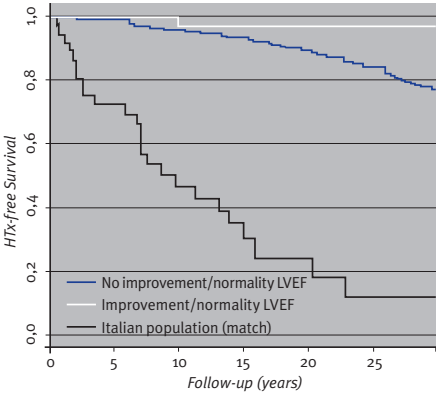

Fig. 4. Survival curves of 82 patients with acute myocarditis according to the improvement or normality of LVEF after 6 months of optimal medical treatment compared with age- and sex-matched italian population.

graphic early reevaluation in AM patients to increment the prognostic accuracy of long-term risk stratification. Nevertheless, it needs to be underlined that, although a fair prognosis is consistent with the spontaneous or therapeutically-induced reversibility of the pathological substrate, AM may recur, evolve to dilated cardiomyopathy, or complicate with life-threatening arrhythmias consistently with its complex and not yet fully understood pathophysiology.

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