Conflicting gender-related differences in the natural history of patients with Idiopathic Dilated Cardiomyopathy

Vitali-Serdoz Laura [1], Lutman Cristina [1], Cadamuro Elena [1], Barbati Giulia [1], Zecchin Massimo [1], Merlo Marco [1], Puggia Ilaria [1], Pinamonti Bruno [1], Di Lenarda Andrea [2], Sinagra Gianfranco [1]

(1) Cardiovascular Department, Ospedali Riuniti and University of Trieste, Italy
(2) Cardiovascular Center, Azienda per i Servizi Sanitari n° 1 of Trieste, Italy

CORRESPONDING AUTHOR: *Laura Vitali-Serdoz, MD, Polo Cardiologico, S.C. di Cardiologia, Azienda Ospedaliero-Universitaria "Ospedali Riuniti di Trieste", Ospedale di Cattinara (via Valdoni, 7), 34129 Trieste, Italy; Tel + 39 040 399 4828; FAX + 39 040 399 4878; e-mail: lauravitaliserdoz@gmail.com*

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ABSTRACT

Objective: To evaluated possible clinical and instrumental, natural history and prognostic divergences in women and men with idiopathic dilated cardiomyopathy (IDCM).
Patients and Methods: From 1988 to 2012, we evaluated 803 consecutive patients with IDCM recorded in the Heart Muscle Disease Registry of Trieste (Italy). All patients had serial follow-up evaluations at 6, 12, and 24 months, and subsequently every two years, or more frequently if clinically indicated.
Results: Two hundred and twenty-seven patients (28%) were female. At first evaluation women were significantly older (48 vs. 45 years old, p = 0.008); presented more frequently left bundle branch block at ECG (38% vs. 28%, p = 0.01), smaller left ventricular end-diastolic indexed volume at echocardiography (85 vs. 93 ml/m2, p <0.002) and more frequently moderate to severe mitral regurgitation at Doppler (43% vs. 33%, p = 0.015). No differences in NYHA class, medical treatment and device implantation rates were found. During a median of 108 months follow-up, women showed a significantly lower ten-year total mortality/heart transplantation (20% vs. 32% respectively, p = 0.001) and cardiovascular mortality rates (9% vs. 15%, p = 0.024) despite a less marked clinical and echocardiographic improvement.
Conclusion: In our population of patients with IDCM, women showed a better long-term prognosis notwithstanding a presentation with a more advanced disease and a lower clinical-instrumental improvement on optimal medical therapy compared to men.

Key words: natural history of idiopathic dilated cardiomyopathy, epidemiology, gender, women, prognosis

INTRODUCTION

Several gender differences exist in normal heart anatomy and physiology. In fact men have an increased left ventricle (LV) indexed mass, but female myocardial mass is better preserved with aging [1]; coronary vessels are smaller and LV ejection fraction (LVEF) is higher in women compared to men. Moreover, premenopausal

women have lower blood pressure, faster resting heart rate and longer QTc interval than men [2].

Clinical and experimental evidence suggests that the pathogenesis and prognosis of many cardiovascular diseases differ between genders.

Idiopathic dilated cardiomyopathy (IDCM) can be considered the most genetically heterogeneous cardiac disease, with mutations in more than 50 single genes encoding cytoskeletal, nuclear skeletal, mitochondrial, and calcium-handling proteins [3,4]. Most of the genes implicated are autosomal, with primarily dominant transmission. However, other causes of IDCM (i.e. inflammatory or autoimmune) exist and preliminary data suggest that gender-related variations may account for some differences in epidemiology, left ventricular recovery, and survival between men and women with post-myocarditis IDCM, highlighting knowledge gaps in management of women with acute IDCM [3].

IDCM has a slight greater prevalence in men than in women; recent trials and registries report a female/male ratio between 1:1.3 and 1:1.5 [3,4], anyway there are few information about clinical-instrumental and prognostic gender differences in this specific setting.

The present investigation wanted to provide an insight into clinical, laboratory, echocardiographic, long-term evolution and prognostic divergences in the natural history of women and men with IDCM.

METHODS

Study population

In our study we evaluated patients with IDCM enrolled in the Heart Muscle Disease Registry of Trieste (Italy) from January 1st 1988 to December 31st, 2012. Although data were retrospectively analysed, patients were prospectively included in the Registry.

We considered patients referred to our Center in both acute instable clinical condition and stable clinical status.

At enrolment, a physical examination, 12-lead electrocardiogram (ECG), transthoracic echocardiogram and 24-hour Holter-ECG monitoring were performed. All patients >35 years old underwent coronary angiography to exclude a significant coronary artery stenosis (>50% in a major vessel). Until 1996, patients routinely underwent endomyocardial biopsy in order to exclude an active myocarditis. Thereafter, biopsies were performed only in those patients presenting with recent (<6 months) onset of heart failure and/or clinical history and instrumental findings suggesting active myocarditis, severe LV dysfunction without significant ventricular remodeling on echocardiography or left bundle branch block at ECG, and/or idiopathic major ventricular arrhythmias at presentation.

IDCM diagnosis was defined according to the World Health Organization criteria. Enrolled patients presented left ventricular (LV) ejection fraction <50% at baseline evaluation in absence of any of the following conditions: history of blood pressure >160/100 mmHg, obstruction >50% of a major coronary artery branch (at coronary angiography), alcohol intake >100 g/day, advanced systemic disease affecting short-term prognosis, pericardial diseases, congenital heart diseases, cor pulmonale, active myocarditis, aortic valve disease and organic mitral valve disease . Persistent high-rate supraventricular arrhythmias were considered an exclusion criteria when documented in the six months before the enrolment.

All familial IDCM cases fulfilled the published criteria(4).

Since 1988, after careful stabilization on optimal dose of ACE-inhibitors, besides digitalis and diuretics, patients were treated with beta-blockers (metoprolol tartrate, carvedilol or bisoprolol).

Medical treatment for IDCM was considered optimal when the maximal tolerated dose of beta-blockers and ACE-inhibitors was administered: in order to achieve this condition, low doses of beta-blockers and ACE-inhibitors were tested and slowly up-titrated to the highest dosage tolerated within 2-3 months. The daily dosages of ACE-inhibitors and beta-blockers were reported as enalapril and carvedilol-equivalents, respectively [5] . Anti-aldosterone agents were given only for potassium sparing intent and, after the publication of the Randomized Aldactone Evaluation Study (RALES) [6] to patients with persisting severe heart failure despite the optimization of medical treatment. Amiodarone was administered in the presence of frequent and/or symptomatic ventricular or supraventricular arrhythmias. No other antiarrhythmic drugs were given.

From 1998 all high-risk patients with IDCM were treated with an implantable cardioverter defibrillator (ICD) for primary prevention adding cardiac resyncronization therapy (CRT) according to the current guidelines at the time of enrolment or follow-up. A CRT device was routinely implanted in our patients after 2005. Patients had serial follow-up evaluations at the Heart Failure Outpatient Clinic of the Cardiology Department of Trieste at 6, 12, and 24 months, and subsequently every two years, or more frequently if clinically indicated.

We considered and compared some clinical, laboratory, electrocardiographic and echocardiographic characteristics between men and women at baseline, and then we evaluated the longitudinal changes of the most relevant parameters in different steps during follow-up.

The primary measurement of outcome of the study was long-term total death/ heart transplantation (D/HTx) and the secondary endpoints were cardiovascular death (CVD), heart failure death, unexpected sudden cardiac death and unexpected sudden cardiac death/ major ventricular arrhythmias/appropriate ICD interventions (SD/MVA/AII).

Urgent heart transplantation was considered for

patients with refractory heart failure requiring inotropic treatment and/or mechanical support.

SD was defined as an immediate death or a death occurring within 1 hour after the onset of symptoms or during sleep in stable NYHA I-III functional class patients.

Statistical Analysis

Study design, data analysis and reporting were performed according to the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines [7]. This study was performed in accordance with the guidelines set by the Declaration of Helsinki [8] and with the local legal requirements. Descriptive statistics of clinical and instrumental parameters are reported as median and interquartile range or number and percentages, respectively for continuous and discrete variables. To investigate for gender differences, both at baseline and cross-sectionally at different follow up visits, continuous parameters were compared by means of the ANOVA test if Gaussian distributed or the non parametric Median test if not; the Chi-square or Fisher exact test were applied for discrete parameters. Variations in repeated measures in each group were evaluated for continuous parameters by means of paired t-test if Gaussian distributed or the non parametric Friedman test if not; the Mc Nemar test was used for binary parameters.

Survival curves were calculated according to the Kaplan Meier method and the comparison between groups was carried out with the Log Rank test. We also estimated the cumulative incidence functions of two specific competing risk (sudden cardiac death/major ventricular arrhythmias/ appropriate ICD intervention vs pump failure death/heart transplant) and tested for differences between males and females. All results were considered as statistically significant when the p value was <0.05. The entire analysis was performed using the SPSS package, version 13.0 (SPSS Inc., Chicago, Illinois, USA) and the R package version 3.01 package cmprsk.

RESULTS

Baseline characteristics

Study population counted 803 consecutive patients with IDCM. Of these 227 (28 %) were women. The baseline clinical and instrumental characteristics of the overall population are shown in Table 1.

At enrolment, women resulted significantly older compared to men [48 (37-58) vs. 45 (34-55) years old respectively,p=0.008], with lower haemoglobin values [12.9 (12.1-13.9) vs. 14.6 (13.8-15.4) g/dL, p<0.001] and lower glomerular filtration rate [66 (56-75)vs.115 (93-139) mL/min, p<0.001].

Regarding ECG evaluation, women presented more frequently with left bundle branch block (38% vs. 28%, p=0.01).

Considering echocardiographic measurements women showed a significantly greater left ventricular end-diastolic indexed diameter [36 (33-40) vs. 34 (31-38) mm/m2; p<0.001], but a slight smaller end-diastolic volume index [85 (67-111) vs. 93 (75-120) ml/m2; p=0.002], and more frequently a moderate to severe mitral regurgitation at Doppler (43% vs. 33%; p=0.015).

No significant differences were observed in baseline NYHA class, duration of heart failure and pharmacological treatment after first evaluation and device implantation during follow-up: 88% of women and 92% of men received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (p=0.054) and 80% of women and 81% of men received beta-blockers (p= ns); 13% of women and 18% of men received an ICD (p=ns), and 8% of women and 5% of men a CRT device (p=ns).

Long-term follow-up trends

In the first 6 months of follow-up, a higher percentage of men compared to women improved clinically gaining NYHA class I, whereas more women maintained a NYHA classes III-IV (see trends in Supplementary Table 1). The NYHA class improvement among men was maintained stable up to the 72 months follow-up, but subsequently a significant worsening was observed (p<0.001). Conversely, women showed no significant variation in NYHA class during the entire follow-up (Figure 1).

Considering echocardiographic parameters, a higher quota of women showed a significant mitral regurgitation and a restrictive pattern during the first 24 months of follow-up; subsequently a similar trend was observed for the frequency of these parameters in both genders. Women showed a larger index diastolic diameter during the whole long-term follow-up (Figure 1). Considering the evolution of LVEF, a significant improvement was observed in both genders at 12 months (p<0.001); thereafter, a further improvement at 24 months was documented only in men (p=0.011), followed by a worsening after 72 months. Conversely, LVEF remained stable in women at long-term follow-up. (see trends in Supplementary Table 1 and Supplementary Table 2).

Both total mortality/heart transplantation and cardiovascular mortality at 20 years resulted significantly lower in women than in men (20% vs. 32% p=0.001 and 9% vs. 15% p=0.024, respectively). Considering heart failure mortality, unexpected sudden cardiac death and unexpected sudden cardiac death/major ventricular arrhythmias/appropriate ICD intervention, there was a trend of a lower rate of events in women (Table 2, Figures 2,3) Moreover the appropriate test in order to compare the cumulative incidence of a competing risk showed no

TABLE 1. Baseline clinical instrumental characteristics of patients

Variable	All (N=803)	Males (N= 576, 72%)	Females (N=227, 28%)	P value
Age (y)	45	45 (34-55)	48 (37-58)	0.008
Weight (kg)	74 (65-84)	78 (70-87)	64 (56-71)	< 0.001
Height (cm)	171 (165-178)	174 (170-180)	163 (160-168)	< 0.001
Body mass index (kg/m^2)	25.3 (22.7-27.9)	25.7 (23.3-28.0)	24.0 (21.6-26.8)	< 0.001
Body surface area (m^2)	1.9 (1.8-2.0)	1.9 (1.8-2.1)	1.7 (1.6-1.8)	< 0.001
Family history	14 (18%)	98 17%	43 19%	ns
Heart rate at rest (beats/min)	75 (68-87)	75 (68-85)	76 (70-90)	ns
Systolic blood pressure (mmHg)	120 (110-135)	125 (110-135)	120 (110-140)	ns
NYHA I	277 (34.6%)	209 (36%)	68 (30%)	
II	327 (41%)	231 (40%)	96 (42%)	ns
III	152 (19%)	103 (18%)	49 (22%)	
IV	44 (5.5%)	31 (5%)	13 (6%)	
NYHA III-IV	196 (24.5%)	134 (23.3%)	62 (27.4%)	ns
Heart Failure duration (y)	1 (0-7)	1 (0-7)	1 (0-8.5)	ns
Laboratory findings				
Haemoglobin (mg/dL)	14 (13-15)	14.6 (13.8-15.4)	12.9 (12.1-13.9)	< 0.001
GFR (ml/min)	102 (76-130)	115 (93-139)	66 (56-75)	< 0.001
Potassium (mEq /L)	4.2 (4-4.5)	4.2 (4.0-4.5)	4.2 (3.9-4.5)	ns
Creatinine (mg/dL)	1.1 (0.9-1.2)	1.1 (1.0-1.2)	0.9 (0.8-1.1)	<0.001
Diabetes mellitus	51 (6%)	39 (7%)	12 (5 %)	ns
Electrocardiographic findings				
Sinus rhythm	697 (89.5 %)	489 (87.5 %)	208 (94.5 %)	0.004
RBBB	136 (17.6 %)	88 (15.9%)	48 (21.7%)	0.055
LBBB	242 (31.2%)	158 (28.5%)	84 (38%)	0.01
QRS duration (msec)	90 (80-100)	80 (80-100)	100 (80-130)	ns
QTC (msec)	437 (403-468)	433 (400-466)	440 (411-476)	ns
QT (msec)	400 (360-420)	400 (360-420)	400 (360-440)	ns
VEB/ 24h monitoring	19 (1-101)	21 (1-103)	16 (1-93)	ns
Ventricular Couplets/ 24h	1,2 (0.0-1.5)	0.1 (0-1.6)	0,1 (0-1.4)	ns
Ventricular tachycardias / 24h	0,0 (0.0-0.1)	0 (0-0.1)	0 (0-0.1)	ns
Echocardiographic findings				
LVEF (%)	32 (24-39)	32 (24-39)	31 (24-41)	ns
LVEF < 30	324 (45 %)	229 (44 %)	95 (46,8 %)	ns
LVEF < 35	445 (61.6 %)	318 (61.3 %)	127 (62.6 %)	ns
Indexed LVEDD (mm/m^2)	35 (30-41)	34 (31-38)	36 (33-40)	< 0.001
Indexed LVESD (mm/m^2)	29 (23-34)	29 (24-33)	29 (26-33)	0.05
Restrictive filling pattern	184 (28 %)	140 (29 %)	44 (25.4 %)	ns
Moderate-severe MR	271 (36 %)	180 (33.5 %)	91 (42.9 %)	0.015
Indexed LVEDV (mL/m^2)	91 (72-117)	93 (75-120)	85 (67-111)	0.002
Indexed LVESV (mL/m^2)	63 (44-86)	64 (46-89)	57 (40-81)	0.008
Indexed Left atrium diameter (mm/m^2)	19 (15-23)	19 (15-23)	20 (13-24)	ns
Indexed left atrium area (cm^2/m^2)	13 (10-16)	13 (10-16)	13 (11-16)	ns
Drug therapy				
Enalapril equivalent dosage (mg/day)	18 (10-20)	20 (10-20)	13 (10-20)	ns
Carvedilol equivalent dosage (mg/day)	25 (20-75)	37.5 (20-75)	25 (20-50)	ns
Anti-arrhythmics	156 (19.4 %)	117 (20.3%)	39 (17.2%)	ns
Diuretics	393 (49 %)	283 (49%)	110 (48.5%)	ns
Potassium-sparing diuretics	47 (6.1 %)	36 (6.5%)	11 (5%)	ns
Beta-blockers	653 (81.2 %)	470 (81.5%)	183 (80.6%)	ns
ACE inhibitors	730 (91 %)	531 (92%)	199 (87.7%)	ns
Digoxin	451 (56.1%)	332 (57.5%)	119 (52.4%)	ns
Devices				
CRT	49 (6.1%)	30 (5.2%)	19 (8.4%)	ns
ICD	132 (16.4%)	102 (17.7%)	30 (13.2%)	ns

NYHA, New York Heart Association class; GFR, Glomerular filtration rate; LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end-diastolic diameter; LVESD, Left ventricular end-systolic diameter; MR, mitral regurgitation; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RBBB, Right bundle branch block; LBBB, Left bundle branch block; CRT Cardiac resynchronization therapy; ICD Implantable cardiac defibrillator.

FIGURE 1. Longitudinal trends during follow-up. Red lines are for females and black lines are for males. NYHA: New York Heart Association class; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; MR: mitral regurgitation; RFP: restrictive filling pattern.

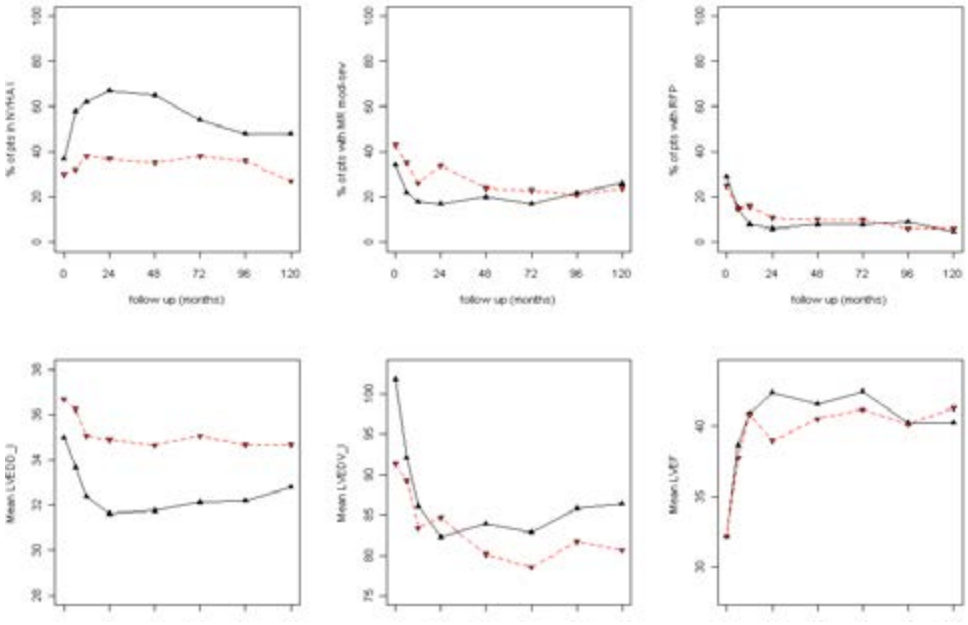


TABLE 2. Events

	All (N = 803)	Males (N= 576, 72 %)	Females (N=227, 28%)	P value (Kaplan- Meier)
Mean follow-up (months)	108	108	108	
All cause mortality/heart transplant n(%)	233 (29%)	187 (32.5%)	46 (20.3%)	0.001
Heart transplant n (%)	69 (8.6%)	54 (9.4%)	15 (6.6%)	ns
Cardiovascular death n (%)	110(13.7%)	89 (15.4%)	21 (9.3%)	0.014
Pump failure death n (%)	47 (5.8%)	37 (6.4%)	10 (4.4%)	ns
Unexpected sudden death n (%)	68 (8.5%)	55 (9.5%)	13 (5.7%)	ns
Unknown cause death n (%)	29 (3.6%)	24 (4.2%)	5 (2.2%)	ns
Appropriate intervention of ICD N=40 N (% of implanted patients 132: 102 men, 30 women)	40 (30%)	29/102 (28%)	11/30 (37%)	ns

FIGURE 2. Total death/ heart transplantation free survival.

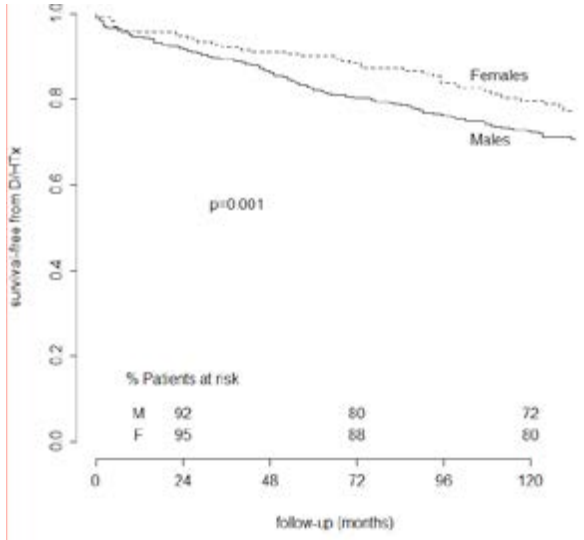
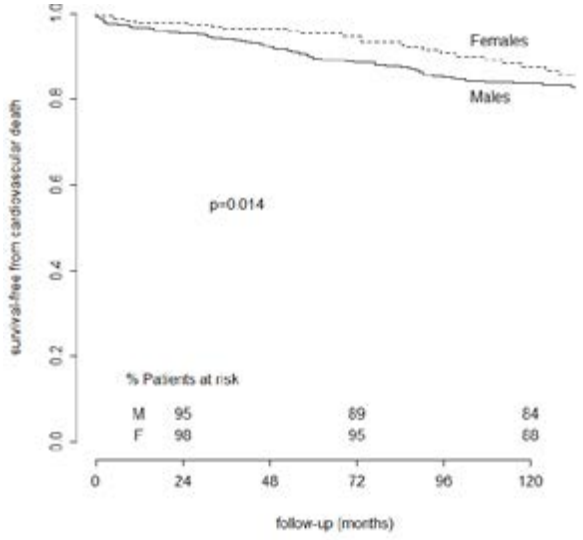


FIGURE 3. Cardiovascular death free survival.



significant differences between genders (for SD/MVA/All p=0,10; for pump failure death/HTx p=0,286) (Supplementary figure 4).

In order to understand the role of fully optimized medical therapy, including anti-aldosterone and the progressive use of device therapy that increased in the last decade, we analyzed the long-term results before and after 1998: women maintain a survival benefit compared to men in both periods (Supplementary figure 5).

DISCUSSION

This study analysed a single-center, large, well delineated population of patients affected by IDCM who were enrolled in the Heart Muscle Disease Registry of Trieste and regularly followed since 1988. Our data confirmed the epidemiological higher prevalence of male gender in IDCM and newly demonstrated that, even if male patients showed more frequently than women a clinical and echocardiographic improvement, they have a worse long-term evolution of the disease in terms of left ventricular impairment and total and cardiovascular mortality.

Gender differences have been described in different heart failure populations in clinical trials and registries [9-13]; aetiology is different with a prevalence of ischemic heart disease and IDCM in men whereas hypertension and valvular heart disease are frequent risk factors in women. Women with heart failure (HF) present more often with preserved or mildly depressed systolic function than men, notwithstanding, women have a lower quality of life with a more pronounced functional capacity impairment, comorbidities and depressed mental status [14-17] . Nevertheless, women with HF have a better survival but the reason still remains unclear; some authors suggest that it might be related to sex differences in aetiology and in pathophysiology, pointing out neuro-hormonal and inflammation divergences between genders [16,18].

Anyway, aetiology has not been confirmed as a gender-specific prognostic risk factor. In fact, in the analysis of CHARM trial, which compared the outcomes of 2400 women to 5199 men randomized to candesartan therapy, women had a better survival than men, independently from the cause of heart failure, age and LVEF [19]. In addition, the MADIT-CRT study demonstrated a striking difference in survival between men and women, the latter presenting with a better reverse cardiac remodelling and prognosis; these results have been interpreted as probably due to the higher prevalence of IDCM and to the more frequent left bundle branch block in women. Even in the subset of MADIT-CRT patients with LBBB, females had a more relevant benefit with respect to males after adjustment for covariates [20].

From a public health and management point of view, large series of patients with HF show greater underutilisation of guideline based HF therapy in women [21]; in our population medical therapy uptitration was equally performed in both sexes, that allowed us to avoid any gender discrimination in our analysis.

At the best of our knowledge this is the largest study that analysed gender differences in an homogeneous population with IDCM.

There are only few and aged studies that consider the specific setting of gender differences in IDCM. Two decades ago, De Maria et al., reporting data from 303 patients with IDCM, concluded that women had a longer duration of disease before diagnosis and consequently presented with a more advanced phase of cardiomyopathy with a greater LV dilatation, but did not have a different prognosis than men [22].

Further information came from the IMAC-2 study (Intervention in Myocarditis and Acute Cardiomyopathy), which investigated new clinical and demographic predictors of outcome for subjects with recent onset dilated cardiomyopathy. In that study, women demonstrated a more favourable prognosis; however the Authors drove their attention to racial rather than to gender differences, underlining that recovery and survival were poorer in black subjects [23].

Recently published results from our group in a selected cohort of patients with IDCM and at least 10 years of follow-up identified the male gender as a predictor of adverse outcome and identified the absence of LBBB and a higher blood pressure as features predictive for left ventricular reverse remodeling [24].

Interestingly, in our population women presented more often with left bundle branch block, that could suggest a more pronounced electrical and myocardial disease, anyway, women demonstrated a better prognosis than men during follow-up. In our population we have found also interesting data regarding left ventricular shape, in fact women presented a larger indexed diameter and smaller indexed volumes: these apparently conflicting results may be expression of a different left ventricular remodeling and reshaping in women with IDCM and be another explanation for the better natural history of this disease in female gender.

A possible interpretation for different gender-related prognosis in heart failure can be found in the sex-related differences in the inflammatory and biochemical remodeling process. A recent study by Meyer et al. investigated a cohort of 567 patients enrolled in the COACH (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure) with heart failure (ischemic aetiology in 41% of patients) and evaluated serum biomarkers related to inflammation, extracellular matrix remodelling, cardiomyocyte stretch, angiogenesis and oxidative stress. Interestingly, female patients had a better prognosis and their levels of biomarkers related to inflammation and remodeling were significantly lower [25]. Several animal models and some human studies

on myocardial injury, as well as on pressure and volume overload, demonstrated that female gender is reliably associated with a slowed and attenuated development of adverse cardiac remodelling and heart failure [26-28]. In particular, men are more prone to remodel with LV dilatation and fibrosis, while women more frequently remodel with marked concentric hypertrophy and smaller cavity volumes [29]. These findings could suggest an explanation for the prevalence of heart failure with preserved EF in women. Moreover, sex-differences in inflammatory and remodelling process can be attributed also to the effects of sexual hormones, in particular oestrogens/progesterone balance, on the corresponding pathophysiological pathways. According to recent studies, sex hormones seem to be correlated to the subsequent risk of chronic dilated cardiomyopathy after heart injury [3]. Sex steroid hormones are able to directly affect cardiac function, endothelial cell function, and vascular tone through genomic and non-genomic effects of the androgen and oestrogen receptors, which are present on vascular endothelial and smooth muscle cells as well as on cardiac fibroblasts, myocytes, and platelets with a different distribution according to gender [30]. These underlying sex differences in cardiac function and physiology may influence the immune response to inflammation and injury in the heart. The role of neuro-hormonal pattern has not yet been investigated in the specific subset of IDCM; notwithstanding that we could argue that sex-differences in clinical response, echocardiographic reverse remodelling and outcome in IDCM could be influenced by neuro-hormonal status translating results from heart failure models and ischemic heart disease remodelling.

Our results confirmed the previous information about gender differences in heart failure demonstrating the better prognosis of women also in the IDCM subset. IDCM usually affect young people with few comorbidities, so it delineates an ideal model of heart failure. In this context, further studies evaluating genetic and molecular differences between genders might be important to understand the different clinical behavior and prognosis between men and women.

Study Limitations

The observational studies on long-term registries usually suffer from the common bias of different protocols and treatment. However, different therapeutic strategies in presence of the same inclusion criteria overtime at the same institution could represent an advantage for the present analysis. Moreover, the current study population was enrolled in a tertiary referral center for cardiomyopathies and heart failure, thus imposing a selection bias with respect to the characteristics of IDCM in the general population. We included heart transplantation in the composite end-point even if it is not a fatal event. In our opinion, it remains a major event in the natural history of IDCM, which has the same impact of death in the prognostic evaluation of the disease, especially considering that only urgent heart transplantation were included.

Interesting information in order to understand gender differences could arise from cardiac magnetic resonance imaging or from laboratory data (i.e. BNP and genotypic characterizations) that has not been systematically performed in all our populations considering that the enrollment started in 1988. These additional evaluations should be assessed in future dedicated prospective investigation.

Finally, our population included only patients with IDCM: the results therefore should not be extended to patients with other causes of impaired LVEF, such as hypertension or ischemic heart disease.

CONCLUSIONS

In our population, women with ICDM presented at enrollment a clinical and instrumental severity of the disease comparable to men and remain stable during follow-up in optimal medical treatment or device therapy, whereas men demonstrated a better response in terms of clinical features and echocardiographic LVRR but a worse prognosis regarding long-term total and cardiovascular mortality.

To the best of our knowledge this is the first epidemiological study that analyses sex-differences in a large homogeneous population of patients with IDCM enrolled in a tertiary center and followed up to more than two decades. Further studies are required to confirm our data on larger multicentric patient populations in order to assess the mechanisms underlying the natural history and prognostic gender-related differences.

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