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RESEARCH ARTICL

Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy

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Aim Contemporary survival trends in dilated cardiomyopathy (DCM) are largely unknown. The aim of this study is to investigate clinical descriptors, survival trends and the prognostic impact of aetiological characterization in DCM patients.

Methods and results Dilated cardiomyopathy patients were consecutively enrolled and divided into four groups according to the period of enrolment (1978–1984; 1985–1994; 1995–2004; and 2005–2015). A subset of patients with DCM of specific aetiology, enrolled from 2005 to 2015, was also analysed. Over a mean follow-up of 12 ± 8 years, 1284 DCM patients (52 in the 1978–1984 group, 326 in the 1985–1994 group, 379 in the 1995–2004 group, and 527 in the 2005–2015 group) were evaluated. Despite older age (mean age 51 ± 15, 43 ± 15, 45 ± 14, and 52 ± 15 years for the 1978–1984, 1985–1994, 1995–2004, and 2005–2015 groups, respectively; $P < 0.001$), most of the baseline clinical characteristics improved in the 2005–2015 group, suggesting a less advanced disease stage at diagnosis. Similarly, at competing risk analysis, the annual incidence of all outcome parameters progressively decreased over time (global $P < 0.001$). At multivariable analysis, the last period of enrolment emerged as independently associated with a reduction in all-cause mortality/heart transplantation (HTx)/ventricular assist device (VAD) implantation (1.46 events/100 patients/year), cardiovascular death/HTx/VAD implantation (0.82 events/100 patients/year) and sudden cardiac death (0.15 events/100 patients/year). Lastly, in 287 patients with DCM of specific aetiology, patients with environmental, toxic, or removable factors appeared to have different phenotypes and prognosis compared to those with genetic, post-myocarditis, or idiopathic DCM ($P < 0.001$).

Conclusions Contemporary survival trends in DCM significantly improved, mainly due to a reduction of cardiovascular events. Appropriate aetiological characterization might help in prognostication of DCM patients.

Keywords Dilated cardiomyopathy • Heart failure • Long-term prognosis • Contemporary survival

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Introduction

Epidemiology and prognosis of cardiovascular diseases have significantly changed alongside the increased lifespan of individuals.[1] However, contemporary survival trends in specific settings are lacking, and prognostic hypothesis can only be derived from dated analyses.

Dilated cardiomyopathy (DCM) is characterized by phenotypic heterogeneity in heart failure, usually affecting relatively young patients without relevant comorbidities. In fact, modes of death of DCM patients are mainly driven by cardiovascular events and the disease remains one of the leading causes of heart transplantation (HTx) in the western world.[2,3] Although the long-term prognosis progressively improved over the past decades,[4–7] survival rates of DCM patients in the last vs. previous decades as well as the different prognosis according to specific aetiologies have not been yet reported.

Thus, the aims of the present study were: (i) to investigate the changes in survival rates in a large cohort of DCM patients enrolled over the past 40 years; (ii) to evaluate the evolution of clinical prognostic descriptors in these patients, and (iii) to conduct a preliminary analysis to assess the role of aetiological characterization in the stratification of DCM patients.

Methods

Study population and definitions

All DCM patients consecutively enrolled from the 1 January 1978 to 31 December 2015 in the Heart Muscle Disease Registry of Trieste, Italy, were considered eligible for this study and retrospectively analysed. Patients might have been referred from peripheral centres; therefore, the date of enrolment was considered as the first evaluation at our centre, and the time frame between symptom onset and enrolment was calculated as referral time. Patients were referred to our centre from across the entire country (Italy) throughout the enrolment period. The referral protocol and the referral areas remained constant over time.

Dilated cardiomyopathy was defined as left ventricular (LV) systolic dysfunction [i.e. LV ejection fraction (LVEF) <50%], in the absence of other conditions, including significant coronary artery disease (>50% obstruction of any major coronary artery branch) or abnormal loading conditions (history of blood pressure >160/100 mmHg or significant organic valve disease). Excessive alcohol intake, previous chemotherapy, an advanced systemic disease affecting short-term prognosis, pericardial diseases, congenital heart diseases, cor pulmonale, persistent supraventricular tachyarrhythmias and active myocarditis,[4,8] were considered exclusion criteria from the main analysis.

After baseline evaluation, patients received guideline-directed medical therapy [i.e. systematic use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) since 1985 and beta-blockers since 1988] up-titrated to the highest tolerated dose.[9] Since 2005, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) were systematically introduced. All patients were re-evaluated over the long term through a structured follow-up comprehensive of clinical and non-invasive examinations at regularly scheduled time points until 24 months from enrolment and then every 2 years, or earlier, according to specific clinical needs. Indications for ICD/CRT were re-evaluated during the entire follow-up in all patients, according to international guidelines.[9]

For the purpose of the study, patients were divided into four groups, according to the period of enrolment: 1978 to 1984, 1985 to 1994, 1995 to 2004, and 2005 to 2015.

To investigate the aetiological characterization in the current management of DCM, a distinct subset of patients enrolled between 2005 and 2015, with an available deep aetiological characterization (i.e. genetic testing or endomyocardial biopsy) or with known external triggers of LV dysfunction, was analysed. DCM due to a specific aetiology [i.e. genetically determined, post-lymphocytic myocarditis (on autoimmune basis), alcohol-induced, chemotherapy-induced, and tachycardia-induced] or idiopathic DCM were considered (see online supplementary *Methods S1* for specific definitions).[10]

All patients gave written consent, and the institutional ethics review board approved the study. The study complied with the Declaration of Helsinki.

Characterization of patients

Clinical history and examination, electrocardiogram (ECG), Holter ECG monitoring, and echocardiography were performed at baseline and during follow-up. Coronary angiography or computed tomography was performed in all patients older than 35 years and/or with cardiovascular risk factors.

On echocardiography, LV dimensions and function were assessed according to international guidelines.[11] LV volumes and LVEF were calculated using the Simpson's biplane method, if available. Transmitral flow velocities were measured using pulsed-wave Doppler at the level of the mitral leaflet tips. The LV filling pattern was defined as restrictive (RFP) when the E-wave deceleration time was <120 ms, or if the E/A ratio was ≥2 associated with E-wave deceleration time ≤150 ms. Right ventricular (RV) dysfunction was defined as a RV fractional area change <35%. Mitral regurgitation (MR), assessed using a multiparametric approach, was considered significant if moderate to severe.[11,12]

From 1995 endomyocardial biopsy was performed in selected patients with high suspicion of inflammatory cardiomyopathy, according to international statements.[13,14] Patients with findings compatible with acute, active myocarditis were excluded from the main analysis.

Long-term outcome

Pre-defined main outcome parameters included the following: (i) a composite of all-cause mortality, HTx, or ventricular assist device (VAD) implantation as destination therapy; (ii) a composite of cardiovascular death, HTx and VAD implantation as destination therapy; (iii) the occurrence of sudden cardiac death (SCD). Furthermore, a composite of pump failure death, HTx, VAD implantation as destination therapy and all-cause mortality were considered as secondary outcome measures. All the HTx procedures were performed due to refractory heart failure. SCD was defined as sudden death or death occurred within 1 h of symptom onset, or as death occurred during sleep in clinically stable patients with New York Heart Association (NYHA) class I–III.

Information regarding outcomes was obtained either directly from the patients, their family, or the medical records, or from national and local registers of death. Protocols of coroner referral and post-mortem analysis were constant over time. An internal committee reviewed and adjudicated each event reported.

Table 1 Baseline characteristics of the dilated cardiomyopathy population according to the enrolment period

	1978–1984 (*n* = 52)	1985–1994 (*n* = 326)	1995–2004 (*n* = 379)	2005–2015 (*n* = 527)	*P*-value
Age, years (mean ± SD)	51 ± 15	43 ± 15	45 ± 14	52 ± 15	<**0.001**
Male sex, *n* (%)	40 (77)	238 (73)	272 (72)	360 (69)	**0.33**
Family history of DCM[a], *n* (%)	10 (19)	69 (21)	81 (22)	103 (20)	0.84
SBP, mmHg (mean ± SD)	127 ± 14	123 ± 16	128 ± 18	126 ± 20	**0.02**
NYHA class III/IV, *n* (%)	21 (40)	88 (27)	80 (22)	110 (23)	**0.01**
History of syncope, *n* (%)	2 (9)	30 (10)	26 (7)	47 (9)	0.60
Referral time, months[b], median [IQR]	4 [1–31]	3 [0–3]	2 [0–8]	1 [0–6]	<**0.001**
Sinus rhythm, *n* (%)	42 (84)	287 (80)	333 (89)	449 (88)	0.69
LBBB, *n* (%)	16 (32)	93 (20)	122 (33)	159 (31)	0.66
LVEF, % (mean ± SD)	–	31 ± 12	33 ± 11	34 ± 11	**0.001***
LVEDVI, mL/m^2 (mean ± SD)	–	108 ± 43	98 ± 38	85 ± 29	<**0.001***
LAAI, mm/m^2 (mean ± SD)	–	14 ± 5	14 ± 4	14 ± 4	0.89*
RFP, *n* (%)	–	165 (51)	79 (21)	123 (24)	<**0.001***
RV dysfunction, *n* (%)	–	67 (21)	70 (19)	128 (25)	0.09*
Moderate to severe MR, *n* (%)	–	27 (9)	33 (10)	59 (12)	0.31*
ACEi/ARB, *n* (%)	21 (40)	287 (88)	364 (96)	489 (93)	<**0.001**
Beta-blockers, *n* (%)	11 (24)	247 (77)	314 (84)	462 (89)	<**0.001**
MRA, *n* (%)	8 (17)	30 (9)	50 (13)	202 (39)	<**0.001**
Digoxin, *n* (%)	39 (85)	261 (82)	226 (61)	87 (17)	<**0.001**
ICD implantation during follow-up, *n* (%)	0 (0)	54 (17)	73 (19)	146 (28)	<**0.001**
CRT implantation during follow-up, *n* (%)	0 (0)	23 (7)	34 (9)	67 (13)	**0.003**
Genetic testing, *n* (%)	2 (3)	35 (11)	60 (16)	144 (28)	<**0.001**
Genetic testing for family screening, *n* (%)	1 (50)	21 (60)	22 (37)	51 (35)	**0.13**

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LAAI, left atrial area index; LBBB, left bundle branch block; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RFP, restrictive filling pattern; RV, right ventricular; SBP, systolic blood pressure; SD, standard deviation.

[a]Family history of DCM was defined as the presence of one or more relatives affected by DCM or a relative of a DCM patient with unexplained sudden death before the age of 35 years.

[b]Referral time was considered as the timeframe from symptom onset to the first evaluation in our centre.

*The *P*-value is calculated after excluding the 1978–1984 cohort.

Statistical analysis

All statistical analyses were performed using IBM-SPSS and R statistical packages. The results are reported as per indications of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15] Comparisons between groups were made by the analysis of variance (ANOVA) test for continuous variables, using the Brown–Forsythe statistic if the assumption of equal variances did not hold, or by the non-parametric Kruskal–Wallis test, as appropriate; the Chi-square test was calculated for categorical variables. Kaplan–Meier curves for the composite outcome measure of all-cause mortality, HTx, or VAD implantation were estimated and compared between groups by means of the log-rank test. Cumulative incidence curves for the composite outcome measure of cardiovascular death, HTx, or VAD implantation and the occurrence of SCD were estimated and compared by enrolment cohort or aetiology, taking into account competing risks of death for other causes, and the appropriate statistical test suitable for competing risks.[16] Since more than two groups were compared, Bonferroni correction was applied in all group analyses reported.

Univariable and cause-specific multivariable Cox models were estimated, and variables were selected for each specific outcome using clinically relevant variables without significant missing values (i.e. <5%) to univariable analyses (i.e. those with a *P*-value ≤0.1) in a full-model approach, considering an event-per-variable ratio threshold of ≥10. ICD implantation and CRT were considered as time-dependent covariates in both univariable and multivariable models. Given that before 1985, routine echocardiographic measurements were based on M-mode analysis, LVEF, LV end-diastolic volume (LVEDV), LV end-diastolic volume index (LVEDVI), left atrial area index, RFP, RV dysfunction and MR were not routinely evaluated in the 1978–1984 group. Thus, univariable and multivariable analyses were performed after excluding the 1978–1984 group.

Results

Baseline characteristics

The study population included 1284 DCM patients followed for a mean of 12 ± 8 years. Each recruitment interval comprised 52, 326, 379 and 527 patients, respectively. Baseline clinical characteristics of the population according to the period of enrolment are summarized in *Table 1*.

Mean age at enrolment was 51 ± 15 years for the 1978–1984 group, 43 ± 15 years for the 1985–1994 group, 45 ± 14 years for the 1995–2004 group, and 52 ± 15 years for the 2005–2015 group ($P < 0.001$).

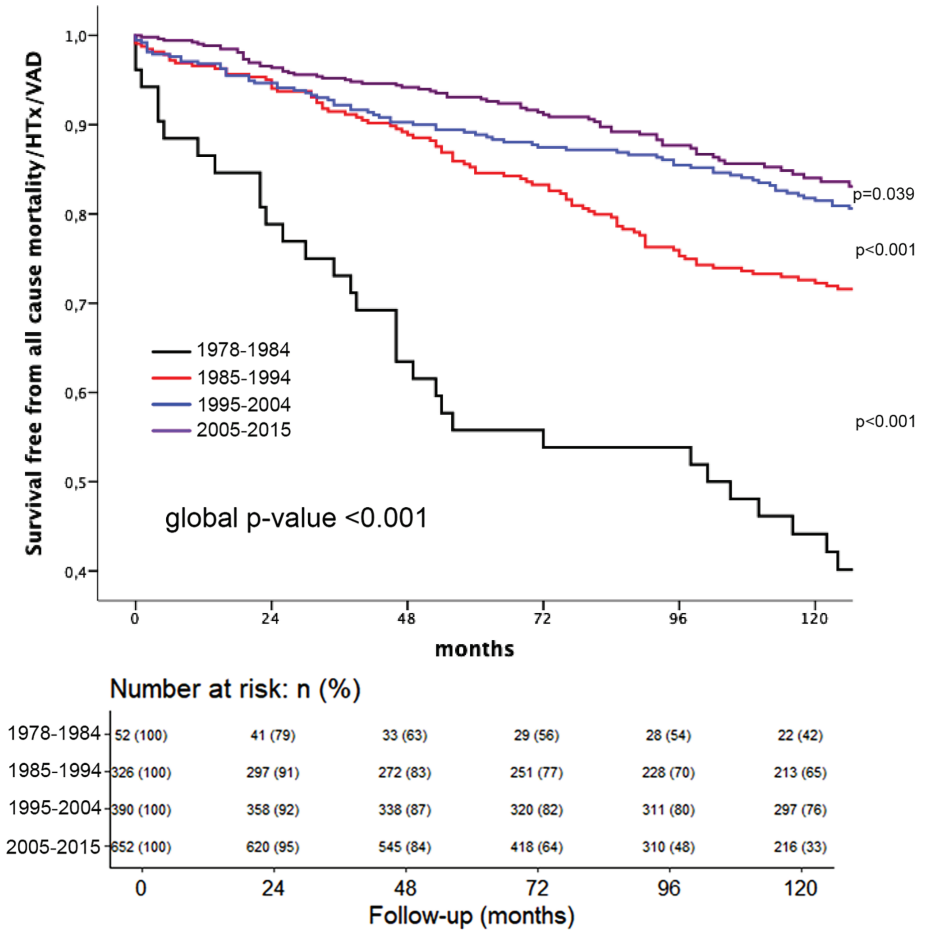

Figure 1 Kaplan–Meier curves for all-cause mortality/heart transplantation (HTx)/ventricular assist device (VAD) implantation, according to the enrolment period. Survival free from all-cause mortality/HTx/VAD implantation at 2, 4, 6, 8 and 10 years was 79%, 63%, 54%, 53%, 42%, respectively, in the 1978–1984 period vs. 90%, 83%, 77%, 69%, 65% in the 1985–1994 period vs. 92%, 86%, 82%, 78%, 76% in the 1995–2004 period vs. 95%, 91%, 87%, 83%, 79% in the 2005–2015 period (global $P < 0.001$). The table below shows the absolute numbers of patients at risk at different follow-up times, with percentage in brackets calculated with respect to the initial size of each group. According to Bonferroni correction for multiple tests, *P*-value significance is set at 0.02.

Clinical phenotypes of the disease reflected earlier diagnosis throughout the period of enrolment: patients of the 2005–2015 group were referred after a median of 1 month [interquartile range (IQR) 0–6 months] from symptom onset, slightly earlier than the 1978–1984 group (median referral time: 4 months, IQR 1–31) ($P < 0.001$). Furthermore, fewer patients in the 2005–2015 group presented with NYHA class III or IV compared to those in the 1978–1984 group (23% vs. 40.4%; $P = 0.021$). LVEDVI was progressively lower at diagnosis (85 ± 29 mL/m^2 in the 2005–2015 group vs. 108 ± 43 mL/m^2 in the 1985–1994 group; $P < 0.001$), together with slightly higher LVEF (34 ± 11% in the 2005–2015 group vs. 31 ± 12% in the 1985–1994 group; $P = 0.001$) and a lower incidence of RFP (23% in the 2005–2015 group vs. 51% in the 1985–1994 group; $P < 0.001$). On the other hand, the incidence of RV dysfunction and MR was comparable across groups ($P = 0.093$ and $P = 0.308$, respectively). Moreover, at ECG, the incidence of left bundle branch block and sinus rhythm at diagnosis was similar across the four enrolment periods. Genetic testing was performed in patients recruited in all the four study periods, although the rate of genetic testing increased significantly over time ($P < 0.001$) (*Table 1*). Among those, approximately 40% ($n = 95$) were identified on the basis of family screening. All patients received optimal medical treatment, according to time-specific international guidelines. Indeed, ACEi/ARBs and beta-blockers were prescribed in >80% of patients starting from the 1985–1994 group onwards. On the other hand, mineralocorticoid receptor antagonists (MRAs), ICD and CRT were progressively implemented across the decades, being mostly administered in the last recruitment interval.

Long-term outcome

Patients enrolled more recently, i.e. between 2005 and 2015, had the most favourable outcome compared to those enrolled earlier (*Figure 1*). At 8-year follow-up, the rates of all-cause mortality/HTx/VAD implantation decreased significantly over time

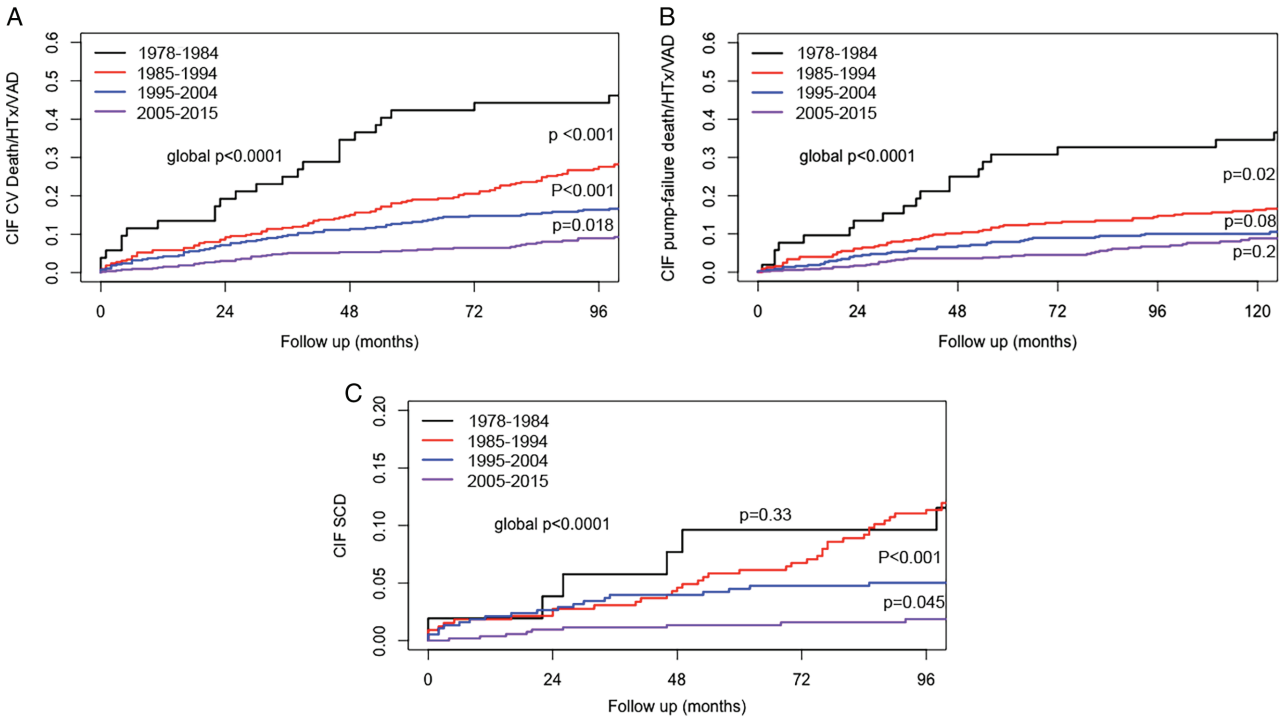

Figure 2 Cumulative incidence curves for cardiovascular (CV) death/heart transplantation (HTx)/ventricular assist device (VAD) implantation (*A*), pump failure death/HTx/VAD implantation (*B*), and sudden cardiac death (SCD) (*C*), according to the enrolment period. CIF, cumulative incidence function. According to Bonferroni correction for multiple tests, *P*-value significance is set at 0.02.

(48% in the 1978–1984 group, 30% in the 1985–1994 group, 21% in the 1995–2004 group, and 17% in the 2005–2015 group, global $P < 0.001$; *Figure 1*). The survival improvement appeared to be driven mainly by a reduction of all cardiovascular events over time (global $P < 0.001$; *Figure 2A*) and, particularly, of SCD (global $P < 0.001$; *Figure 2C*). Overall survival as well as pump failure-related events were improved significantly over time (global $P < 0.001$; *Figure 2B* and online supplementary *Figure S1*), although no significant differences were found between the last two periods. Noteworthy, the average annual incidence rates of all pre-specified composite or single outcome parameters progressively reduced over time (*Table 2* and *Figure 3*). Interestingly, only annual rates of non-cardiac deaths were increased in the last periods, probably reflecting competing causes of death occurring at an older age in adequately treated patients (*Table 2* and *Figure 3*).

At multivariable analysis, the 2005–2015 period of enrolment emerged as independently associated with very low event rates of all-cause mortality/HTx/VAD implantation [1.46 events/100 patients/year; hazard ratio (HR) 0.69; 95% confidence interval (CI) 0.49–0.96; $P = 0.029$ vs. the 1995–2004 period], cardiovascular death/HTx/VAD implantation (0.82 events/100 patients/year; HR 0.55; 95% CI 0.37–0.82; $P = 0.003$ vs. the 1995–2004 period), and SCD (0.15 events/100 patients/year; HR 0.33; 95% CI 0.14–0.74; $P = 0.008$ vs. the 1995–2004 period). Notably, other than the period of enrolment, LVEF, male sex and ICD implantation during follow-up were independently associated with all the three main outcome parameters (*Table 3*).

Aetiological characterization

The DCM cohort used for the analysis on aetiological characterization consisted of 287 patients, with DCM due to a specific cause in 199 (genetically determined in 51, post-myocarditis in 23, alcohol-induced in 27, chemotherapy-induced in 49, and tachycardia-induced in 49) whilst in the remaining 88 patients DCM was idiopathic. Specific genetic background in patients with genetically determined DCM is shown in online supplementary *Figure S2*. Clinical characteristics showed heterogeneity in age, gender and disease severity among groups (*Table 4*). In general, patients with idiopathic, genetically determined or post-myocarditis DCM were younger and with a more advanced phenotype compared with the other subgroups. Similarly, event rates in subgroups significantly differed, with chemotherapy-induced DCM being the worst case scenario and tachycardia-induced DCM the best one (global $P < 0.001$; *Figure 4*).

Discussion

This is the first study to analyse the contemporary survival trends in a large cohort of patients with DCM enrolled across the last 40 years and followed up for a mean of 12 ± 8 years. To date,

Table 2 Incidence of events as number/100 patients/year

	1978–1984 (*n* = 52)	1985–1994 (*n* = 326)	1995–2004 (*n* = 379)	2005–2015 (*n* = 527)
Cumulative follow-up (months)	148 ± 98 (12.33 years)			
Mean follow-up (months)	145 ± 155	200 ± 127	175 ± 83	94 ± 43
All-cause mortality	6.55 (42)	3.83 (154)	2.08 (97)	1.12 (73)
All-cause mortality/HTx/VAD implantation	6.86 (44)	5 (201)	2.87 (134)	1.46 (95)
All-cause mortality/HTx/VAD implantation/MVA[a]	6.95 (44)	5.32 (211)	3.32 (153)	2.14 (137)
CV death/HTx/VAD implantation	5.93 (38)	3.86 (155)	2.01 (94)	0.82 (53)
CV death/HTx/VAD implantation /MVA	6 (38)	4.26 (169)	2.47 (114)	1.57 (101)
SCD	2.03 (13)	1.54 (62)	0.53 (25)	0.15 (10)
SCD/MVA	2.05 (13)	2.07 (82)	1.13 (52)	0.97 (62)
Pump failure death/HTx/VAD implantation	3.74 (24)	2.11 (85)	1.44 (58)	0.60 (39)
Non-cardiac death	0 (0)	0.17 (7)	0.34 (16)	0.37 (24)
Unknown cause of death	0.94 (6)	1.02 (41)	0.51 (24)	0.29 (19)
Appropriate ICD intervention	–	0.49 (20)	0.59 (28)	0.80 (52)

CV, cardiovascular; HTx, heart transplantation; ICD, implantable cardioverter-defibrillator; MVA, major ventricular arrhythmia; SCD, sudden cardiac death; VAD, ventricular assist device.
In brackets the absolute number of events.
[a]MVA was defined as ventricular fibrillation or flutter, sustained ventricular tachycardia, appropriate ICD interventions for ventricular fibrillation or sustained ventricular tachycardia >185 bpm.

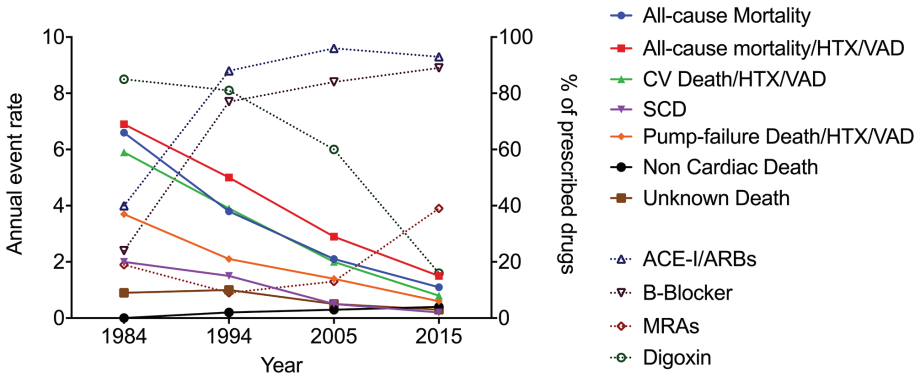

Figure 3 Progressive declining risk of events in dilated cardiomyopathy patients over time. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; HTx, heart transplantation; MRA, mineralocorticoid receptor antagonist; VAD, ventricular assist device.

long-term changing survival rates are mainly based on surveys performed over a decade ago or older, and contemporary data are largely missing.[5–7] Indeed, although several prognostic factors, including male sex, have previously been identified for patients with DCM,[17–19] all analyses focused on specific timeframes. Our analysis provides novel insights into the contemporary prognosis of DCM patients, showing a constant improvement over time. Nowadays, receiving a diagnosis of DCM appears to be associated with very low annual event rates (i.e. <1.5 major events/100 patients/year), likely mainly driven by a reduction of adverse cardiovascular events. In fact, a significantly longer survival free from major cardiovascular events (<1 event/100 patients/year) was observed in patients enrolled from 2005 to 2015, independently of other known Umprognostic predictors (namely duration of heart failure, LV size and function, functional capacity and medical Umtherapy).

The reasons for survival improvement

The introduction of neurohormonal blockers and, in the 2000s, of device therapy (i.e. ICD and CRT) dramatically improved the natural history of heart failure with reduced ejection fraction and, specifically, of DCM patients.[5–7] However, this study provides a quantification of the effectiveness of management strategies in terms of current survival rates. At present, being diagnosed with DCM is associated with more favourable outcomes compared to the past, although patients tend to be slightly older at the time of diagnosis. The increasing specialization and structured network in medical care over time might have prompted an

Table 3 Univariable and multivariable analyses

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
All-cause death/HTx/VAD implantation						
Age at enrolment[a]	1.02	1.01–1.03	<0.001	1.01	1.00–1.02	0.025
Male sex	**1.53**	**1.22–1.92**	**<0.001**	**1.41**	**1.08–1.86**	**0.012**
SBP[a]	0.99	0.98–1.00	<0.001	0.99	0.99–1.00	0.039
Duration of HF[a]	1.01	1.00–1.01	<0.001	1.01	1.00–1.01	<0.001
NYHA class III/IV	2.26	1.85–2.77	<0.001	1.42	1.09–1.85	0.009
Sinus rhythm	0.59	0.45–0.76	<0.001	0.62	0.44–0.86	0.012
Heart rate[a]	1.01	1.01–1.02	<0.001	1.00	0.99–1.01	0.687
LVEF[a]	**0.95**	**0.94–0.96**	**<0.001**	**0.98**	**0.96–0.99**	**0.001**
LVEDVI[a]	1.01	1.01–1.01	<0.001	1.01	1.00–1.01	0.012
RFP	2.08	1.71–2.52	<0.001	1.33	1.02–1.73	0.018
RV dysfunction	1.70	1.37–2.10	<0.001	1.28	0.98–1.69	0.074
Moderate to severe MR	2.12	1.61–2.80	<0.001	1.21	0.86–1.71	0.275
ACEi/ARB	0.67	0.44–1.01	0.054	0.73	0.35–1.58	0.422
Beta-blockers	0.51	0.41–0.63	<0.001	0.42	0.31–0.57	<0.001
MRA	1.22	0.95–1.55	0.114			
ICD implantation	**0.51**	**0.40–0.65**	**<0.001**	**0.43**	**0.32–0.59**	**<0.001**
CRT implantation	0.50	0.36–0.70	<0.001	0.71	0.44–1.14	0.155
2005–2015 vs.1995–2004[b]	**0.82**	**0.62–1.07**	**0.143**	**0.54**	**0.38–0.77**	**0.001**
Cardiovascular death/HTx/VAD implantation						
Age at enrolment[a]	1.00	0.99–1.00	0.203			
Male sex	**1.59**	**1.21–2.09**	**0.001**	**1.52**	**1.10–2.11**	**0.011**
SBP[a]	0.98	0.98–0.99	<0.001	0.99	0.98–1.00	0.016
Duration of HF*	1.01	1.00–1.01	<0.001	1.01	1.00–1.01	0.003
NYHA class III/IV	2.58	2.04–3.26	<0.001	1.56	1.16–2.11	<0.001
Sinus rhythm	0.61	0.45–0.84	0.002	0.61	0.41–0.90	0.026
Heart rate[a]	1.02	1.01–1.02	<0.001	1.00	1.00–1.01	0.367
LVEF[a]	**0.95**	**0.94–0.96**	**<0.001**	**0.98**	**0.96–0.99**	**0.006**
LVEDVI[a]	1.01	1.01–1.02	<0.001	1.01	1.00–1.01	0.005
RFP	2.62	2.09–3.29	<0.001	1.42	1.04–1.93	0.008
RV dysfunction	2.03	1.59–2.60	<0.001	1.35	0.99–1.84	0.112
Moderate to severe MR	2.29	1.67–3.14	<0.001	1.07	0.73–1.58	0.725
ACEi/ARB	0.61	0.36–1.03	0.062	0.62	0.22–1.71	0.358
Beta-blockers	0.54	0.41–0.70	<0.001	0.45	0.32–0.65	<0.001
MRA	0.99	0.73–1.33	0.928			
ICD implantation	**0.41**	**0.32–0.54**	**<0.001**	**0.30**	**0.21–0.44**	**<0.001**
CRT implantation	0.42	0.28–0.61	<0.001	0.68	0.39–1.18	0.171
2005–2015 vs. 1995–2004[b]	**0.60**	**0.43–0.85**	**0.004**	**0.35**	**0.23–0.54**	**<0.001**
Sudden cardiac death						
Age at enrolment[a]	1.00	0.99–1.01	0.964			
Male sex	**1.77**	**1.07–2.93**	**0.025**	**1.85**	**1.03–3.33**	**0.039**
SBP[a]	0.99	0.98–1.00	0.068	1.00	0.99–1.02	0.578
Duration of HF[a]	1.01	1.00–1.01	0.037	1.01	1.00–1.01	0.085
NYHA class III/IV	2.13	1.40–3.25	<0.001	1.35	0.98–1.93	0.092
Sinus rhythm	0.90	0.48–1.69	0.744			
Heart rate[a]	1.01	1.00–1.02	0.052	1.00	0.98–1.01	0.584
LVEF[a]	**0.96**	**0.94–0.98**	**<0.001**	**0.95**	**0.93–0.97**	**0.001**
LVEDVI[a]	1.01	1.01–1.02	<0.001	1.00	1.00–1.01	0.609
RFP	1.65	1.09–2.50	0.017	0.51	0.29–0.99	0.057
RV dysfunction	2.13	1.39–3.25	0.001	2.55	1.55–4.21	0.001
Moderate to severe MR	0.81	0.35–1.86	0.62			
ACEi/ARB	0.51	0.19–1.39	0.188			
Beta-blockers	0.57	0.35–0.93	0.024	0.73	0.39–1.34	0.335
MRA	0.76	0.43–1.35	0.347			
ICD implantation	**0.35**	**0.13–0.95**	**0.039**	**0.14**	**0.05–0.38**	**0.001**
CRT implantation	0.35	0.13–0.95	0.039	0.38	0.05–2.89	0.351
2005–2015 vs. 1995–2004[b]	**0.40**	**0.19–0.84**	**0.015**	**0.33**	**0.14–0.74**	**0.008**

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CRT, cardiac resynchronization therapy; HF, heart failure; HR, hazard ratio; HTx, heart transplantation; ICD, implantable cardioverter-defibrillator; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RFP, restrictive filling pattern; RV, right ventricular; SBP, systolic blood pressure; VAD, ventricular assist device.

The 1978–1984 cohort was not included in univariable and multivariable analyses due to high percentage of missing data.

In bold significant variables at multivariable analyses in all pre-specified outcomes.

[a]For continuous variables, HR is considered for one unit increase.

[b]1995–2004 vs. 1985–1994, multivariable analysis: all-cause death/HTx/VAD implantation – HR 0.69; 95% CI 0.52–0.90; $P = 0.007$. Cardiovascular death/HTx/VAD implantation – HR 0.69; 95% CI 0.50–0.95; $P = 0.021$. SCD – HR 0.40; 95% CI 0.24–0.68; $P = 0.001$.

Table 4 Baseline characteristics according to different aetiologies

	Idiopathic DCM (*n* = 88)	Genetically determined DCM (*n* = 51)	Post-myocarditis DCM (*n* = 23)	Alcohol-induced DCM (*n* = 27)	Chemotherapy-induced DCM (*n* = 49)	Tachycardia-induced DCM (*n* = 49)	*P*-value
Age, years (mean ± SD)	45 ± 13	43 ± 13	46 ± 14	59 ± 9	57 ± 14	52 ± 14	<0.001
Male sex, *n* (%)	57 (65)	37 (72)	12 (52)	26 (96)	12 (25)	38 (78)	<0.001
NYHA class III/IV, *n* (%)	20 (23)	8 (16)	10 (46)	6 (22)	14 (29)	11 (23)	0.25
Sinus rhythm, *n* (%)	79 (91)	45 (92)	22 (96)	24 (89)	40 (87)	4 (9)	<0.001
LBBB, *n* (%)	28 (32)	7 (14)	5 (21)	6 (22)	16 (34)	1 (2)	0.002
LVEF, % (mean ± SD)	35 ± 12	35 ± 11	31 ± 10	30 ± 9	38 ± 13	35 ± 9	0.04
LVEF <35%, *n* (%)	42 (48)	27 (53)	15 (65)	19 (73)	20 (42)	23 (47)	0.13
LVEDVI, mL/m^2 (mean ± SD)	88 ± 32	87 ± 30	84 ± 24	89 ± 31	69 ± 26	64 ± 20	<0.001
RV dysfunction, *n* (%)	21 (24)	13 (25)	9 (39)	5 (18)	11 (22)	21 (43)	0.07
Moderate to severe MR, *n* (%)	7 (8)	5 (10)	4 (17)	3 (11)	4 (9)	2 (4)	0.50
ACEi/ARB, *n* (%)	82 (93)	47 (92)	22 (96)	27 (100)	47 (96)	37 (76)	0.001
Beta-blockers, *n* (%)	80 (92)	47 (92)	18 (81)	24 (89)	43 (88)	37 (76)	0.07
MRA, *n* (%)	34 (40)	22 (43)	12 (52)	13 (48)	17 (35)	14 (29)	0.43

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DCM, dilated cardiomyopathy; LBBB, left bundle branch block; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RV, right ventricular; SD, standard deviation.

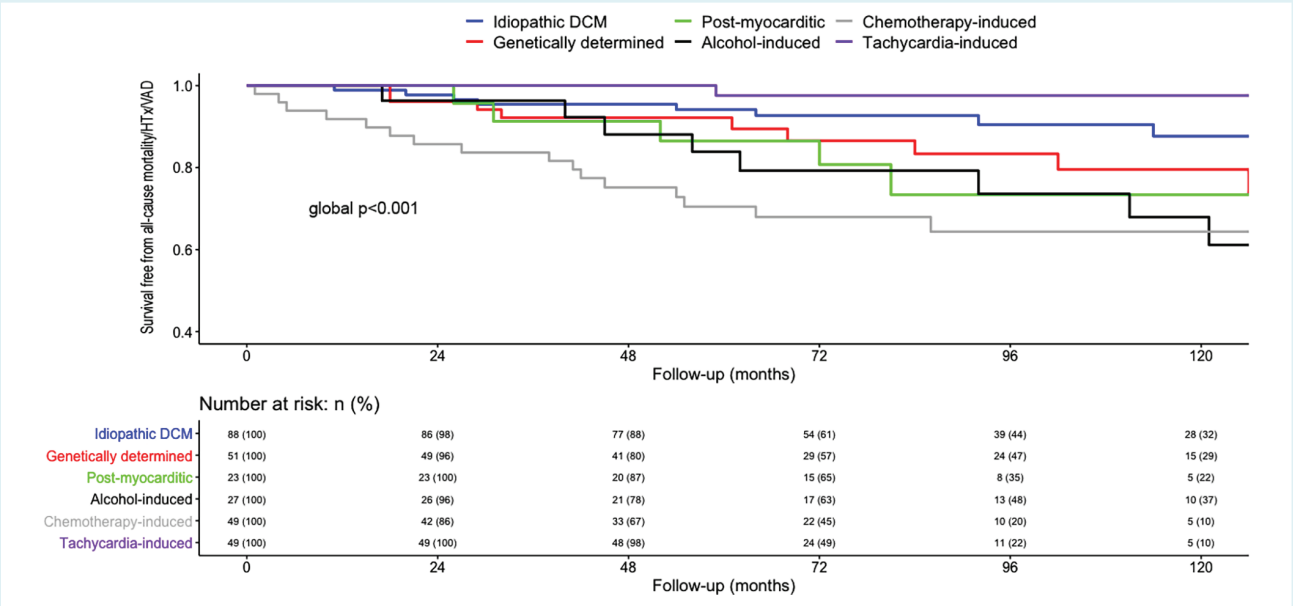

Figure 4 Kaplan–Meier curves for all-cause mortality/heart transplantation (HTx)/ventricular assist device (VAD) implantation, according to the specific aetiologies of dilated cardiomyopathy (DCM).

increased and more timely referral of DCM patients to tertiary centres. This might have led to treatment of milder cases of the disease, which might have remained unnoticed and untreated in previous decades. This might also explain, at least in part, the different baseline characteristics of each group, including older age of patients recruited in the later periods. Unfortunately, due to the intrinsic limitations of the retrospective study design, it is difficult to determine the impact over time of any changes in unmeasured confounders that were therefore grouped in the proxy period of enrolment.

Noteworthy, the occurrence of major cardiovascular events, particularly SCD, became reduced at a later stage, following the advent and implementation of ICD and CRT. Indeed, ICD implantation was an independent prognostic factor for all the three main outcomes considered. Our results highlight the overall prognostic value of ICD implantation in a highly selected DCM population, in

line with the results of recent studies.[20,21] The last two periods of enrolment showed comparable outcomes when overall survival as well as heart failure-related events were considered in the analysis, supporting the importance of reducing fatal arrhythmic events in this population. Alongside, non-cardiovascular adverse outcomes slightly increased over time in the whole population. This might be secondary to older age at diagnosis (>50 years in the 2005–2015 group) and to the occurrence of competing causes of death in patients who have survived prior cardiovascular events. Notably, the rate of unknown causes of death was minimal, reflecting the implementation of national and local registries, and the need for further joint projects to minimize missing information.

Finally, an integrated and multimodal diagnostic and prognostic approach and the implementation of evidence-based treatments (in particular with MRAs, ICD and CRT), more evident in the last decade, might have contributed to the better outcomes. Indeed, as recently highlighted, guideline-directed medical therapy ensures a long-term and possibly progressive benefit, while its discontinuation can reverse this benefit.[22] This comprehensive approach and a more personalized treatment might have played a substantial role in this regard. Furthermore, overall survival and cardiovascular outcomes of patients with heart failure significantly improved over time,[23] supporting our results in other settings. Further research focused on investigating the impact of single diagnostic and therapeutic interventions in this setting might be warranted.

The importance of appropriate aetiological characterization

Recent advances in medical knowledge and technology have shed light on the possibility of tailoring diagnostic pathways and treatment to improve outcomes of patients with specific disease subtypes. However, the importance of aetiological characterization has been seldom assessed in DCM. Besides the pioneering analysis performed by Felker *et al.* in the early 2000s,[24] this is the first report to provide insights into the aetiological characterization of patients with DCM, also focusing on genetic testing. Patients with possibly environmental removable factors or with history of toxic exposure (i.e. sustained supraventricular tachycardia, chemotherapy, or alcohol intake) appear to have different phenotypes and prognosis compared with those with an intrinsic cause of the disease (i.e. genetic or post-myocarditis). Appropriate aetiological characterization appears, therefore, important to stratify patients according to their specific risk of adverse events and might help clinicians to decide on treatment strategies and follow-up evaluation. Further studies are warranted to investigate the prognostic role of a better aetiological characterization (including different genetic backgrounds) in this setting and to determine the impact of specific aetiologies on the single components of adverse outcomes.

Arrhythmic events

Our results confirmed the well-known overall reduction in SCD rates over time[25] and proved a landmark rate of SCD in the DCM population that has declined to a yearly risk of 0.15%. This reinforces the need for larger population studies in the future to investigate possible useful tools in stratifying DCM patients for this specific important outcome. The reduction of SCD in patients enrolled between 2005 and 2015 was independent of LVEF and the use of beta-blockers. Therefore, integrated arrhythmic risk models might be warranted in the future to tailor patient risk of SCD and to reduce the risk of side effects of treatments or devices. In this setting, the integrated use of clinical data, echocardiography, cardiac magnetic resonance and, if applicable, genetic testing, should be encouraged in order to achieve deep insight into the specific characterization of every DCM patient.[26,27] Differentiating genetically determined DCMs from inflammatory cardiomyopathies, identifying possible mechanisms of correlation between genotype and environmental factors in the phenotype expression appears pivotal, also in the light of the application of precision medicine to DCM.[28]

Limitations

This single-centre retrospective analysis was conducted across a wide range of years. Therefore, information gathered on patients is not always complete, especially when the 1978–1984 patient cohort is considered, which was excluded from univariable and multivariable analyses.

This single-centre study was conducted in an Italian tertiary referral centre for cardiomyopathies. Patient characteristics and results reported might not be entirely representative of the entire DCM spectrum and might be of difficult application to a broader unselected DCM population. Therefore, these results should be applied only to patients with similar characteristics. Large multicentre international registries are advocated to overcome this limitation and to confirm our data.

Although the evaluation of the crude number of outpatient visits was out of the scope of this study, a similar structured follow-up strategy and protocol was carried out over time in our Department, resulting in a comparable number and type of outpatient evaluations for each patient.

Echocardiographic parameters might have been influenced to some extent by changes in technology over time. Cardiac magnetic resonance, biomarkers, advanced echocardiography and genetic testing data were not systematically available for all patients. Considering these variables in the analysis might introduce a selection bias. Therefore, this information was excluded. The investigation of the role of these factors is advocated in future large studies and was beyond the aim of the present study. Similarly, the variables considered in the analysis might slightly differ from previous reports[5] given the more detailed data collection over time.

Analyses on competing causes of death and on specific outcomes of patients with DCM of different aetiologies were out of the scope of this study. Further research is needed to confirm and expand these data in larger multicentre cohorts.

Lastly, although follow-up duration of the 2005–2015 cohort was shorter than that of earlier periods (on average 8 years), it appears to be adequate in order to obtain reliable outcome results.

Conclusions

The prognosis of patients affected by DCM has changed significantly over the last 40 years and progressively improved over time. A reduction in cardiovascular and, particularly, in fatal arrhythmic events was the main driver of the more favourable prognosis. Nowadays, the lower incidence of cardiovascular events and the longer event-free survival should warrant specific attention to competing risk of non-cardiac death in DCM patients over long-term follow-up. Finally, appropriate aetiological characterization might help in prognostication of DCM patients and should be expanded in future research.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Methods S1. Supplementary methods.
Figure S1. Survival free from all-cause mortality.
Figure S2. Genetically determined dilated cardiomyopathy.

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