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Contemporary Outcome in Patients with Idiopathic Dilated Cardiomyopathy

Running title: Outcome in Dilated Cardiomyopathy

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ABSTRACT

Outcome is better in patients with idiopathic dilated cardiomyopathy (IDC) than in ischemic heart failure (HF), but morbidity and mortality are nevertheless presumed to be substantial. Most data on the prognosis in IDC stem from research performed prior to the widespread use of current evidence based treatment, including implantable devices. We report outcome data from a cohort of patients with IDC treated according to current HF guidelines and compare our results with previous figures: 102 consecutive patients referred to our tertiary care hospital with idiopathic IDC and a left ventricular ejection fraction (LVEF) < 40 % were included in a prospective cohort study. After extensive baseline work-up, follow-up was performed after 6 and 13 months. Vital status and heart transplantation were recorded. Over the first year of follow-up, the patients were on optimal pharmacological treatment, and 24 patients received implantable devices. LVEF increased from 26 ± 10 % to 41 ± 11 %, peak oxygen consumption increased from 19.5 ± 7.1 to 23.4 ± 7.8 ml/kg/min, and functional class improved substantially (all p-values < 0.001). After a median follow up of 3.6 years, 4 patients were dead, and heart transplantations had been performed in 9 patients. According to our literature search, there survival in patients with IDC has improved substantially over the last decades. In conclusion, patients with IDC have a better outcome than previously reported when treated according to current guidelines.

Keywords: Cardiomyopathy, dilated; cohort studies; outcome studies; left ventricular remodeling

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Approximately 50 % of people diagnosed with HF die within 5 years.[1] The outcome is strongly related to left ventricular (LV) function.[2,3] Approximately 10 % of HF cases are due to idiopathic dilated cardiomyopathy (IDC).[4] Its prognosis is generally better than in patients with ischemic HF.[5,6] The 5-year mortality is substantial, however, ranging from > 50 % in early accounts[7] to approximately 25 % in more recent reports.[6,8] Reported survival varies due to different inclusion criteria in different trials. In addition, there has probably been a real improvement in outcome as treatment for HF has advanced over the last 3 decades.[9] A number of studies have shown that LV function often improves considerably in patients recently diagnosed with IDC.[3,10-12] The reason for this improvement, which is beyond what is observed after the initiation of treatment in patients with HF of ischemic etiology,[11,13] is poorly understood. Also, this improvement is by no means uniform and can be difficult to predict. We present outcome data from a contemporary cohort of patients with IDC treated according to current guidelines.[14] We hypothesized that in a meticulously assessed and well treated, contemporary cohort of patients with IDC, LV reverse remodeling and functional improvement would be substantial, and that the long-term prognosis would compare favorably with what has been reported previously.

METHODS

This is a prospective cohort study performed at our tertiary care university hospital. The trial complies with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics South East. The results are reported according to the STROBE guidelines. All patients provided written, informed consent.

Patients aged 18 or above, admitted to our cardiology department with suspected IDC, were eligible for participation. Inclusion criteria were a dilated left ventricle (end diastolic internal diameter ≥ 6.5 cm or an indexed value of > 3.2 cm/m^2), and a left ventricular ejection fraction (LVEF) ≤ 40 %. Ischemic, hypertensive and primary valvular heart disease were excluded by patient history, clinical examination, echocardiography, and coronary angiography (N = 101) or computer tomography angiography (N = 1) prior to inclusion. Other exclusion criteria were: A known or suspected cause of cardiomyopathy, including acute or prior myocarditis; inotropic or mechanical support at admittance; an implantable cardiac device (pacemaker, intra cardiac defibrillator and/or biventricular pacemaker); and significant concomitant disease such as chronic infections, connective tissue disease, severe pulmonary disease, cancer, serious psychiatric disease, life threatening ventricular arrhythmias, severe kidney failure or severe hepatic failure. As we are the only center in Norway to perform orthotopic heart transplantation, patients referred specifically for heart transplant evaluation were excluded to avoid outcome selection bias. Patients who were referred for diagnostic work-up, and were later found to be in need of heart transplantation, were not excluded. Atrial fibrillation was not an exclusion criterion, provided the ventricular rate had been well controlled (i.e an average resting heart rate < 100 beats per minute) over the last 4 weeks. As we are a tertiary care hospital, all patients had been admitted to their local hospitals initially, and unless the patients were in need of immediate mechanical support or urgent evaluation for heart transplantation, we usually awaited the effect of pharmacological intervention before the patients were transferred to our centre.

At baseline, the study participants underwent physical examination; blood tests including screening for known monogenic causes of IDC; echocardiography; cardiac magnetic resonance imaging (CMR); exercise testing with measurement of peak oxygen uptake; 24-hour electrocardiogram (ECG); and right-sided cardiac catheterization with endomyocardial biopsy. Follow-up was performed after 6 months and 1 year. Patients were later followed through the Norwegian National Population Register and our national heart transplant database for mortality and heart transplantation, respectively. Patient records were acquired from local hospitals for adjudication of events.

Echocardiography was performed with Vivid 7 or E9 ultrasound scanners (GE Vingmed Ultrasound, Horten, Norway), using phased array transducers. Three heart beats were recorded for each registration. Cine loops

were digitally stored and later analyzed off-line using Echo-Pac (GE Vingmed Ultrasound). Individual exams were de-identified and randomized, and image analysis was performed blinded to patient characteristics and to whether the exam was performed at baseline or follow-up. Two-dimensional parameters and conventional Doppler parameters were measured according to current recommendations.[15,16] Left ventricular ejection fraction was measured by Simpson's biplane method.

Exercise testing was performed on a bicycle ergo meter using an individualized, stepwise protocol, with the load incrementally increased every minute. Based on the patient's age, gender, size, physical shape and symptoms, an expected maximum load was estimated for each patient, and the test was designed to reach this load after approximately 10 minutes. Simultaneous hemodynamic monitoring and gas exchange analysis were performed (Cardiovit CS-200, Schiller, Baar, Switzerland and Ganshorn PowerCube, Ganshorn, Niederlauer, Germany). We calculated the peak oxygen consumption per kg/min, and expressed the result as a percentage of the age and gender adjusted reference values as recommended by Wasserman and colleagues.[17]

Values are presented as mean ± standard deviation, median (interquartile range) or number (%) depending on the distribution. Differences across subgroups were assessed by Student's t-tests for normally distributed values, Mann-Whitney U tests for skewed parameters and χ^2 tests for categorical data. Changes in values from baseline to follow-up were calculated by paired Student's t-tests for normally distributed values, or by Wilcoxon's signed rank tests for continuous, skewed parameters. We used Friedman's test to assess changes in New York Heart Association (NYHA) functional class. *Post hoc* Wilcoxon's signed ranks tests were performed.

Associations between baseline parameters and 1) the LVEF and 2) the age and gender adjusted peak oxygen consumption at one year follow-up were assessed by univariate and multiple linear regression. Skewed parameters were log-transformed prior to regression analyses. To avoid over-fitting, rather than feeding a large number of potential risk factors into an automated statistical algorithm, we a priori selected risk factors which have previously been shown to be associated with outcome in HF (age; symptom severity; duration of symptoms; heart rate and rhythm; blood pressure; LV volume and ejection fraction; peak oxygen consumption; QRS-width; pulmonary capillary wedge pressure and N-terminal-pro-B-type natriuretic peptide [NT-proBNP]). Associations between baseline values and the time to death due to HF or heart transplantation were assessed by Cox regression. P-values < 0.05 were considered significant. All statistical analyses were performed in SPSS version 21.0.

We performed a PubMed search using the search string [(dilated cardiomyopathy) and (mortality or survival) and (cohort studies or cohort or longitudinal or follow-up or "follow up" or prospective or retrospective)], and restricted our search to reports in English concerning adult, human patients. In addition, we used "snowballing" to identify additional reports pertaining to mortality in IDC.

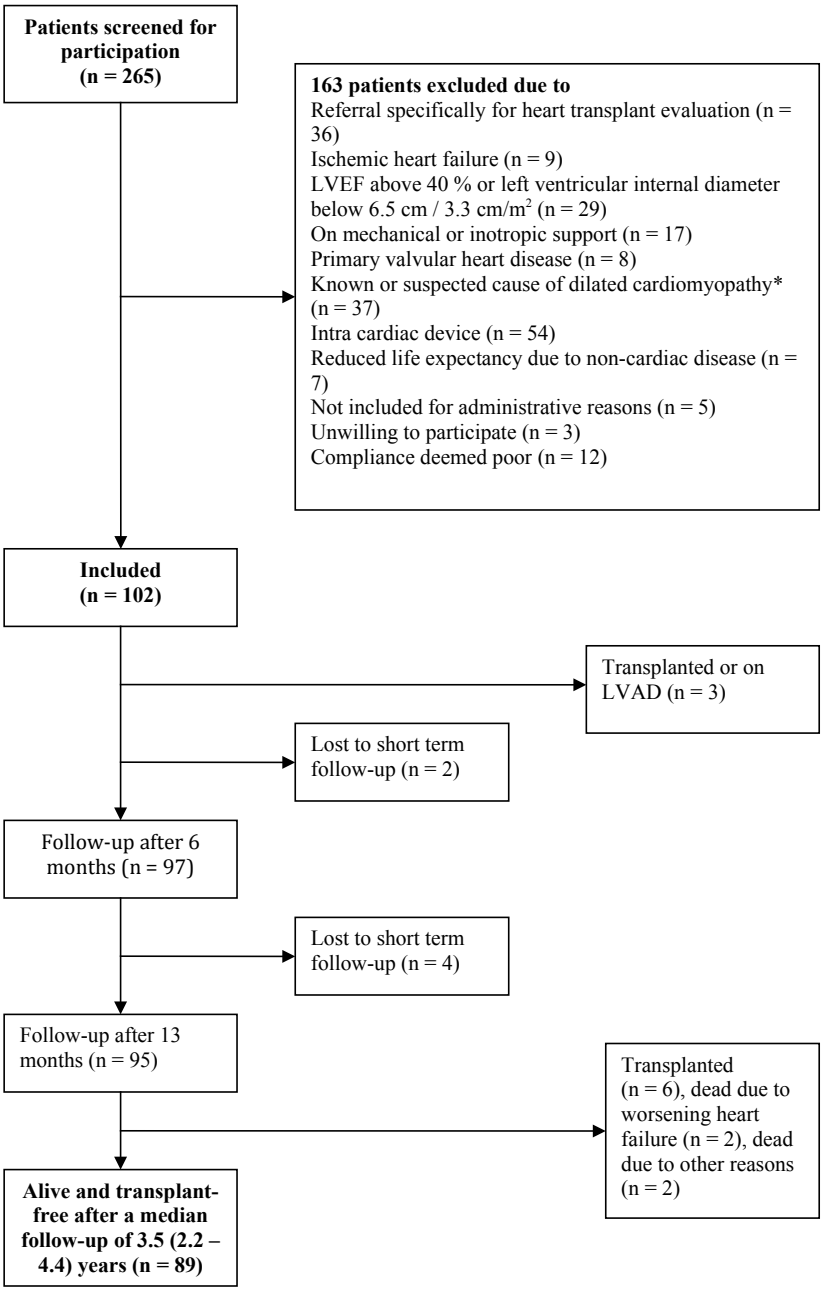

Figure 1: Patient selection and follow-up
*This category included 10 patients with suspected tachyarrhythmia, 9 treated for cancer with cardiotoxic cytostatics and/or trans-thoracic irradiation, 7 patients with hypertensive disease and 11 others. LVAD = left ventricular assist device.

RESULTS

Patient recruitment and follow-up are summarized in Figure 1. From the 13th of October 2008 to the 16th of November 2012, a total of 265 consecutive patients were evaluated for participation. One hundred and fifty five patients did not fulfill the inclusion criteria, 3 patients were unwilling to participate, and 5 patients were not included for administrative reasons. One hundred and two patients were thus included in the current study. Their baseline data are presented in Table 1.

Table 1: Population characteristics at inclusion

Variable	Value
Age (years)	51 ± 14
Male	74 (73 %)
Body mass index (kg/m^2)	28 ± 5
Systolic blood pressure (mm Hg)	116 ± 20
Diastolic blood pressure (mm Hg)	71 ± 12
Heart rate (beats/minute)	75 ± 16
Atrial fibrillation	18 (18 %)
NYHA class (I/II/III/IV)	15/61/20/6
Smokers	24 (24 %)
Hypertension (by history)	18 (18 %)
Diabetes mellitus	4 (4 %)
Duration of symptoms (months)	7 (3 – 16)
NYHA class at peak symptom severity (I/II/III/IV)	4/15/25/58
QRS-duration (ms)	110 (99 – 134)
Left bundle branch block	21 (21 %)
Hemoglobin (g/dl)	14.4 ± 1.5
Creatinine (mmol/l) [mg/dl]	86 ± 21 [0.97 ± 0.24]
N-terminal pro-B-type natriuretic peptide (pg/ml)	1332 (584 – 2903)
Echocardiogram	
Left ventricular ejection fraction (%)	26 ± 10
Left ventricular end diastolic diameter (cm)	7.1 ± 0.8
Left ventricular end diastolic internal volume (ml)	267 (216 – 328)
Cardiac output (l/min)	4.9 ± 1.4
Cardiac magnetic resonance imaging (88 patients)	
Left ventricular ejection fraction (%)	28 ± 11
Left ventricular end diastolic internal volume (ml)	273 (214 – 356)
Left ventricular myocardial volume (ml)	212 ± 62
Gadolinium late enhancement	29 (35 %)
Exercise testing (96 patients)	
Maximum work load (Watts)	133 ± 56
Peak heart rate (beats per minute)	151 ± 25
Peak oxygen uptake (ml/kg/min)	19.7 ± 7
Peak oxygen uptake as percentage of expected value	69 ± 22
Cardiac catheterization (97 patients)	
Right atrial (mmHg)	6 (4-10)
Mean pulmonary artery pressure (mmHg)	24 ± 10
Pulmonary capillary wedge pressure (mmHg)	15 ± 8
Cardiac output (l/min)	4.9 ± 1.5
24-hour electrocardiogram (89 patients)	
Average heart rate (beats per minute)	76 ± 13
Minimum heart rate (beats per minute)	49 ± 10
Maximum heart rate (beats per minute)	142 ± 28
Ventricular tachycardia	25 (28 %)

By design, all patients were diagnosed with IDC prior to inclusion. Extensive work-up led to a definitive etiological diagnosis in 14 patients: In 9 patients, a probable disease-causing mutation was discovered; 2 patients had inflammatory myocardial disease as diagnosed by CMR and/or endomyocardial biopsy; 1 patient had transthyretin amyloidosis as determined by endomyocardial biopsy, and 2 patients had non-compaction cardiomyopathy detected by CMR. Pharmacological treatment and device implantations are presented in Table 2. By design, no patients had implantable devices at inclusion.

Table 2: Treatment during first year of follow-up

Variable	Baseline	Six months	13 months
Medication			
Angiotensin converting enzyme inhibitor and/or anginotensin II receptor blocker	99 (97 %)	95 (98 %)	93 (98 %)
Angiotensin converting enzyme inhibitor and/or anginotensin II receptor blocker (% of optimal daily dose)	74	90	92
Beta blocker	95 (93 %)	96 (99 %)	94 (99 %)
Beta blocker (% of optimal daily dose)	47	72	74
Aldosterone antagonist	22 (22 %)	30 (29 %)	31 (33 %)
Diuretic	72 (71 %)	61 (63 %)	52 (55 %)
Digoxin or digitoxin	30 (29 %)	15 (15 %)	13 (14 %)
Implantable devices and heart transplantations			
Cardioverter defibrillator	0	19 (20 %)	20 (21 %)
Cardiac resynchronization therapy	0	9 (9 %)	9 (9 %)
Cardiac resynchronization therapy defibrillator	0	5 (5 %)	5 (5 %)
Left ventricular assist device*	0	1 (1 %)	0
Heart transplantation	0	2 (2 %)	3 (3 %)

*Left ventricular assist devices were used as bridge to transplantation.

At 6 months' follow-up, 97 patients were re-examined. One patient was on an LV assist device awaiting heart transplantation, 2 patients had received cardiac allografts, and 2 patients did not appear for their scheduled appointments. At 13 (12-16) months, 95 patients were re-examined: In addition to the 3 heart transplant recipients, 4 patients did not appear for their appointments. One of these patients did not show up for either of the 2 scheduled follow-up appointments and was thus lost to short-term follow-up (Figure 1).

Prior to treatment initiation, the large majority of patients were severely symptomatic. During follow-up, there was a highly significant change in NYHA classification over-all ($\chi^2[3] = 200.7$; $p < 0.001$), most of which occurred shortly after treatment initiation (Figure 2).

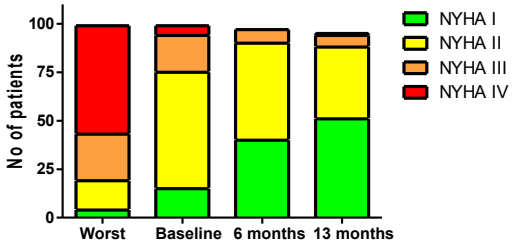

Figure 2 NYHA class development
Symptom burden by New York Heart Association (NYHA) functional class at peak symptom severity (worst), inclusion, after 6 months follow-up and after 13 months follow-up. There was a highly significant improvement in NYHA class throughout the follow-up period ($\chi^2[3] = 200.7$; $p < 0.001$).

A substantial increase in LVEF was observed in transplant-free survivors throughout the first year of follow-up (Table 3 and Figure 3). From baseline to 13 months, 69 patients experienced an increase in LVEF by ≥ 5 percentage points, 7 patients had a decrease in LVEF by ≥ 5 percentage points, and in 19 patients, there was no change (between -5 and 5 percentage points change). After 13 months, 22 patients (22 %) had achieved complete LV recovery, defined as an LVEF > 50 %, 11 of whom also had a normal NT-proBNP value at this time point. Most of the improvement in LVEF took place shortly after presentation, and after 6 months, it had increased to 37 ± 9 %. On univariate analyses, the duration of symptoms prior to inclusion; QRS-width; and LV end diastolic volume on presentation were associated with LVEF 1 year later. Left ventricular ejection fraction at baseline was not associated with LVEF at follow-up. Only LV end diastolic volume and the duration of symptoms on presentation remained independent predictors of 1 year LVEF in the multivariate model (Table 4). The duration of symptoms in patients who recovered by more than 10 LVEF points was 5 (2 – 8) months vs 12 (7 – 35) months in patients who did not recover ($p < 0.001$). Of note, neither viral persistence as examined by polymerase chain reaction in myocardial biopsies ($p = 0.63$), a monogenic etiology ($p = 0.44$), nor Gadolinium late enhancement ($p = 0.82$) at baseline were associated with LVEF at follow-up.

Table 3: Changes in key parameters over the first year of follow-up

Variable	Baseline	13 months	Mean change*	p-value
Systolic blood pressure (mm Hg)	116 ± 20	122 ± 18	6 (2 – 10)	0.002
Diastolic blood pressure (mm Hg)	71 ± 12	70 ± 11	0 (-2 – 3)	0.70
Resting heart rate (beats/minute)	75 ± 16	66 ± 14	-9 (-12 – -5)	<0.001
New York Heart Association class I/II/III/IV	15/61/20/6	51/37/6/1	-	<0.001
Left ventricular end diastolic volume (ml)	267 (216 – 328)	186 (154 – 244)	-81 (-96 – -65)	<0.001
Left ventricular ejection fraction (ml)	26 ± 10	40 ± 11	13 (11 – 16)	<0.001
Cardiac output at rest (l/min)	4.9 ± 1.4	4.9 ± 1.0	0 (-0.3 – 0.3)	0.97
Laboratory values				
Creatinine (mmol/l)	86 ± 21	86 ± 29	0 (-6 – 5)	0.97
C-reactive protein (mg/l)	3.0 (1.1 – 7.6)	2.1 (0.9 – 4.4)	-4.8 (-8.8 – -1.2)†	0.01
N-terminal pro-B-type natriuretic peptide (pg/dl)	1332 (583 – 2903)	330 (127 – 706)	-1182 (-1756 – -611)†	<0.001
Exercise testing				
Peak heart rate (beats per minute)	151 ± 25	150 ± 25	-3 (-2 – 8)	0.29
Peak load (Watts)	133 ± 56	153 ± 59	19 (10 – 28)	<0.001
Peak oxygen consumption (ml/kg/min)	19.5 ± 7.1	23.4 ± 7.8	3.7 (2.5 – 4.9)	<0.001
Peak oxygen consumption (% of expected value)	69 ± 22	84 ± 23	14 (10 – 18)	<0.001

Values are presented as mean ± standard deviation or median (interquartile range) depending on the distribution.
*This column contains the population average change and the 95 % confidence interval of this mean. †These confidence intervals were estimated by bootstrapping.

During the first 13 months, peak oxygen uptake in transplant free survivors increased by more than 1 metabolic unit (Table 3 and Figure 3). Parameters reflecting the severity of HF were associated with peak oxygen consumption at baseline as well as at follow-up. Peak oxygen consumption at follow-up correlated strongly with peak oxygen consumption at baseline ($r = 0.67$, $p < 0.001$), but was only weakly correlated with other baseline parameters (data not shown). The improvement in peak oxygen consumption from baseline to follow-up was associated with the improvement in LVEF ($r = 0.45$; $p < 0.001$).

After a median of 3.5 (2.2 – 4.4) years follow-up, 4 patients were dead. Two patients died from worsening HF, 1 died from a traumatic subdural hematoma, and 1 patient died a sudden, unexplained death more than 3 years after inclusion. Nine patients had received cardiac allografts, 1 of whom later died from acute allograft rejection. Overall survival at 5 years was 93 %, and transplant-free survival was 84 % (Supplementary figure 1).

The number of deaths and heart transplantations was too limited to allow for reliable multiple variable analyses. However, the 11 patients who died due to worsening HF or needed heart transplantation had on average more severe symptoms and more advanced HF at baseline. Compared with transplant-free survivors, they were on average younger (age at inclusion 41 vs 53 years; $p = 0.005$); their baseline LVEF was lower (18 vs. 28 %; $p < 0.001$); their pulmonary capillary wedge pressure was higher (25 vs. 14 mm Hg; $p < 0.001$); their relative exercise capacity was lower (50 vs. 71 % of the age and gender adjusted expected value; $p = 0.004$) and their systolic blood pressure was lower (103 vs. 118 mm Hg; $p = 0.02$).

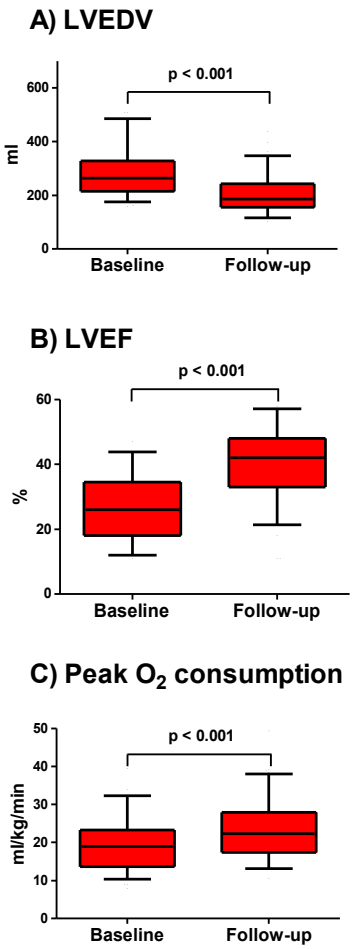

Figure 3 Key outcome parameters
Baseline and follow-up values for A) left ventricular end diastolic volume (LVEDV); B) left ventricular ejection fraction (LVEF), and C) peak oxygen consumption. Follow-up was performed after 13 (12 – 15) months.

Table 4: Baseline predictors of left ventricular ejection fraction after 13 months

Variable	Univariate r	p-value	Multivariate β	p-value
Age	-0.07	0.48	0.04	0.75
Duration of symptoms*	-0.46	<0.001	-0.55	<0.001
New York Heart Association class II			0.23	0.11
New York Heart Association class III	-	0.09†	0.08	0.61
New York Heart Association class IV			-0.11	0.38
Atrial fibrillation	-	0.11†	-0.06	0.59
Systolic blood pressure	0.14	0.18	0.14	0.23
Left ventricular ejection fraction	0.18	0.19	-0.10	0.52
Left ventricular end diastolic volume	-0.29	0.004	-0.41	0.006
Peak oxygen consumption (% of expected)	0.15	0.15	-0.05	0.73
Pulmonary capillary wedge pressure	-0.08	0.43	0.04	0.73
QRS width	-0.22	0.03	-0.16	0.21
N-terminal pro-B-type natriuretic peptide*	-0.12	0.23	0.04	0.77

*Skewed variables were log-transformed prior to analysis. †The differences in the change in left ventricular ejection fraction across groups were analyzed using ANOVA.

The PubMed search produced 1052 hits as of Jan 7th 2015. Among these reports, we identified 176 reports including > 50 patients with IDC who had been followed for > 1 year, and where survival data were reported, or studies with a mixed population of patients with HF where survival data for the subset of patients with IDC were reported specifically.

Inclusion criteria, population characteristics, follow-up time and the way the survival data were presented varied considerably, making direct comparison difficult. Overall, there was a strong trend towards improved outcome with time. In Table 5, we have listed 2 representative reports from each of the last decades for comparison with our own results.

Table 5: Survival in patients with dilated cardiomyopathy

Author	Pub. year	No of patients	Age (years)	Baseline LVEF	Follow-up (years)	Survival
Fuster[18]	1981	104	49 (median)	Not reported	11 (range 6-20)	35 % at 5 years
Diaz[19]	1987	169	39 ± 14	29 ± 13 %	5.5 ± 4.2	43 % at 5 years
Komajda[20]	1990	201	48 ± 11	31 ± 12	4.8 ± 2.4	77 % at 5 years
Di Lenarda[21]	1998	586	~44 (mean)	~28 ± 9 %	4.3 ± 2.7	~75 % at 5 years*
Felker[5]	2000	616	49 ± 14	Not reported	4.4 (mean)	~75 % at 5 years
Bardy[6]	2005	1211†	Not reported	< 35 %	3.8 (median)	72 % / 79% at 5 years‡
McNamara[22]	2012	373	45 ± 14	24 ± 8 %	2.2 ± 1.4	88 % at 4 years
Broch et al	2014	102	51 ± 14	26 ± 10 %	3.5 (2.2 – 4.4)	93 % at 5 years¶

*70 % in the 411 patients not receiving β-receptor antagonists at the beginning of the study, and 87 % in patients receiving β-receptor antagonists. †Number of patients in the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial with non-ischaemic heart failure. ‡Five year survival 72 % in patients assigned to optimal pharmacological treatment + placebo, and 79 % in patients assigned to optimal medical therapy + ICD. ¶The 5 year transplant-free survival in our patients was 84 %.

DISCUSSION

In our cohort of patients with IDC, considerable improvements in LVEF, functional status and peak oxygen consumption were observed over the first year of follow-up. Most of this improvement in occurred soon after the onset of therapy. Transplant free survival after a median of 3.5 years of follow-up was higher than previously reported. These results must be interpreted against a background of a relatively short median duration of symptoms, a thorough diagnostic evaluation, tailored treatment and a high level of adherence to current treatment guidelines.

In most patients, a substantial LV reverse remodeling took place, with an average 30 % reduction in LV end diastolic volume and a 13 percentage points' increase in LVEF. A short duration of symptoms and a relatively small LV size on presentation were independently associated with a favorable LV function at follow-up. These parameters are indicators of short disease duration. Possibly, these variables are also surrogate markers of an acute, at least partly reversible, pathogenic process. However, despite an extensive baseline work-up, a definitive diagnosis was made in a limited number of patients only, none of whom had primary myocarditis. Moreover, we found that even in patients with a probable monogenic (and thus presumably non-reversible) etiology, the LVEF improved considerably. It is therefore possible that other, co-pathogenic factors are at play that can be partly reversed in recently symptomatic dilated cardiomyopathy, irrespective of the etiology.

Whereas an irreversible loss of myocardial tissue lies at the core of the pathogenesis in ischemic HF, the myocardium is not necessarily irretrievably damaged in IDC. Therefore, patients with IDC might retain a potential for almost complete recovery, given that the drivers of the pathogenic processes can be reversed, be it through spontaneous improvement or optimal therapy. Our patients received optimal treatment as evident from the high adherence to recommended pharmacological treatment and the high number of implanted devices.

The term "myocardial recovery" has been coined to denote the normalization of LV structure and function and the freedom from future HF events.[23] Twenty-two percent of our patients experienced myocardial remission defined as an LVEF > 50 %. However, NT-proBNP remained above our laboratory reference values in half of these patients, meaning that only 11 patients had a normal cardiac function 13 months after inclusion. Incidentally, 2 of these patients subsequently died, 1 suddenly and unexplained, and 1 from worsening HF. Thus, the normalization of LV systolic function in patients with IDC does not necessarily signify the absence of pathology,[24] and we do not recommend cessation of medical therapy in patients with myocardial remission.

Prognosis in HF is linked to LV size and function,[2,25,26] and reverse remodeling is associated with a favorable outcome.[27-29] In accordance with the substantial increase in LVEF that we observed over the first year of follow-up, the transplant free and overall survival in our patients was fair, and better than previously described. There are many possible explanations for this. The referral practice to tertiary centers may have become more liberal with time, which might influence the results.[30] On the other hand, our patients had advanced disease as demonstrated by the large LV volumes, low LVEF and high pulmonary capillary wedge pressures at baseline. It is thus tempting to assume that the favorable prognosis observed in our patients is due to the tight adherence to current HF therapy guidelines. Ninety-eight percent of our patients received inhibitors of the renin-angiotensin axis, and 99 % received beta blocker therapy at a mean dose equipotent to that obtained in the MERIT-HF trial, i.e. approximately 75 % of the evidence-based target dose. We implanted cardiac devices according to current guidelines, but many of our patients improved rapidly and the indications for device implantation were no longer fulfilled. Only 1 of our patients died suddenly.

We present data from a well characterized, thoroughly examined, prospective cohort subjected to meticulous follow-up and little loss of data. The limited number of patients and strict inclusion criteria, including the exclusion of patients on inotropic or mechanical support at enrolment, must be acknowledged before broad generalizations to an unselected population of patients with IDC are made. The label "dilated cardiomyopathy" covers a very heterogeneous group of diseases, as far as both etiology and clinical

manifestations are concerned. Thus, a very fastidious characterization and reporting of the actual sample at hand is required for the results to be reproducible, and a direct comparison with historic cohorts must be made with care.

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Conflict of interest
None

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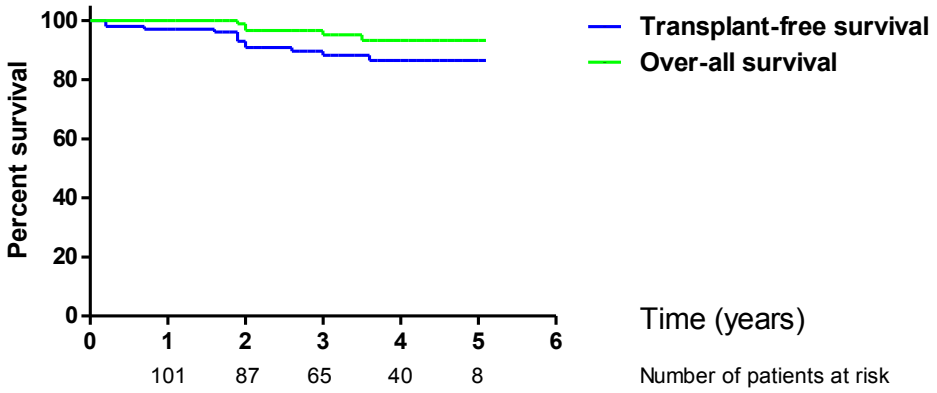

Supplementary Figure 1 Survival
Kaplan Meyer plot depicting over-all survival and survival free from heart transplantation