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ORIGINAL ARTICLE

Prognostic differences in long-standing vs. recent-onset dilated cardiomyopathy

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Abstract

Aims This study aimed to evaluate the outcome and prognostic factors in patients with dilated cardiomyopathy (DCM) and long-standing heart failure (LDCM) vs. recent-onset heart failure (RODCM).

Methods and results We compared 2019 patients with RODCM (duration <6 months, mean age 58.6 years, 70.7% male) with 1714 patients with LDCM (duration ≥6 months, median duration 3.5 years, mean age 62.5 years, 73.7% male) included in the Swedish Heart Failure Registry in the years 2003–16. Outcome measures were all-cause, cardiovascular (CV), and non-CV death and hospitalizations; heart transplantation; and a combined outcome of all-cause death, heart transplantation, or heart failure (HF) hospitalization. Multivariable risk factor analyses were performed for the combined endpoint. All outcomes were more frequent in LDCM than in RODCM. The multivariable-adjusted hazard ratios (HRs) (95% confidence interval) for LDCM vs. RODCM were 1.56 (1.34–1.82), $P < 0.0001$, for all-cause death over a median follow-up of 4.2 and 5.0 years, respectively; 1.67 (1.36–2.05), $P < 0.0001$, for CV death; 2.12 (1.14–3.91), $P < 0.0001$, for heart transplantation; 1.36 (1.21–1.53), $P < 0.0001$, for HF hospitalization; and 1.37 (1.24–1.52), $P < 0.0001$, for the combined outcome. A propensity score-matched analysis yielded similar results. CV death was the main cause of mortality in LDCM and was higher in LDCM than in RODCM ($P < 0.0001$). Almost all co-morbidities were significantly more frequent in LDCM than in RODCM, and the mean number of co-morbidities increased significantly with increased duration of disease, also after age adjustment. Age, New York Heart Association functional class, ejection fraction, and left bundle branch block were prognostically adverse. The only co-morbidity associated with the combined outcome regardless of HF duration was diabetes, in LDCM [HR 1.34 (1.15–1.56), $P = 0.0002$] and in RODCM [HR 1.29 (1.04–1.59), $P = 0.018$]. Male sex [HR 1.38 (1.18–1.63), $P < 0.0001$] and aspirin use [HR 1.33 (1.14–1.55), $P = 0.0004$] carried increased risk only in RODCM. Heart rate ≥75 b.p.m. [HR 1.20 (1.04–1.37), $P = 0.01$], atrial fibrillation [HR 1.24 (1.08–1.42), $P = 0.0024$], musculoskeletal or connective tissue disorder [HR 1.36 (1.13–1.63), $P = 0.0014$], and diuretic therapy [HR 1.40 (1.17–1.67), $P = 0.0002$] were prognostically adverse only in LDCM.

Conclusions This nationwide study of patients with DCM demonstrates that longer disease duration is associated with worse prognosis. Co-morbidities are more common in long-standing HF than in recent-onset HF and are associated with worse outcome. With the increased survival seen in the last decades, our results highlight the importance of careful attention to co-morbid conditions in patients with DCM.

Keywords Dilated cardiomyopathy; Heart failure; Systolic; MortalityHospitalizationCo-morbidity; Duration of therapy

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Introduction

Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic impairment.[1] DCM represents a major proportion of non-ischaemic heart failure (HF) with reduced left ventricular ejection fraction (HFrEF)[2,3] and is the leading reason for heart transplantation.[4]

The reported mortality in non-ischaemic HFrEF and DCM has decreased over the years. Studies published in the last decade report 1 year mortality of 5.4–21%[5–7] and mortality event rates of <5% per 100 person-years.[3,8] Long-term studies of DCM have shown a less severe phenotype and gradually declining mortality over the last decades, despite an older population, likely due to more extensive diagnostic work-up, earlier diagnosis, and better treatment.[8,9]

In tandem with increased survival, the risk for patients to develop co-morbidities increases. In addition, HF itself may increase the incidence of diabetes.[10] To date, the prognostic importance of ischaemic aetiology in HFrEF has been studied with conflicting conclusions,[2,5,6,11–13] but concomitant coronary artery disease *per se* appeared not to increase risk in DCM over a mean follow-up 36.3 months.[14] The association between common co-morbidities and outcome in patients with DCM is inadequately studied, and to what extent HF duration affects the prognosis in a contemporary DCM cohort remains unclear.

In this study of patients with DCM, we sought to compare the outcomes and the prognostic risk factors in long-standing HF, with recent-onset HF, by using the Swedish Heart Failure Registry (SwedeHF).

Methods

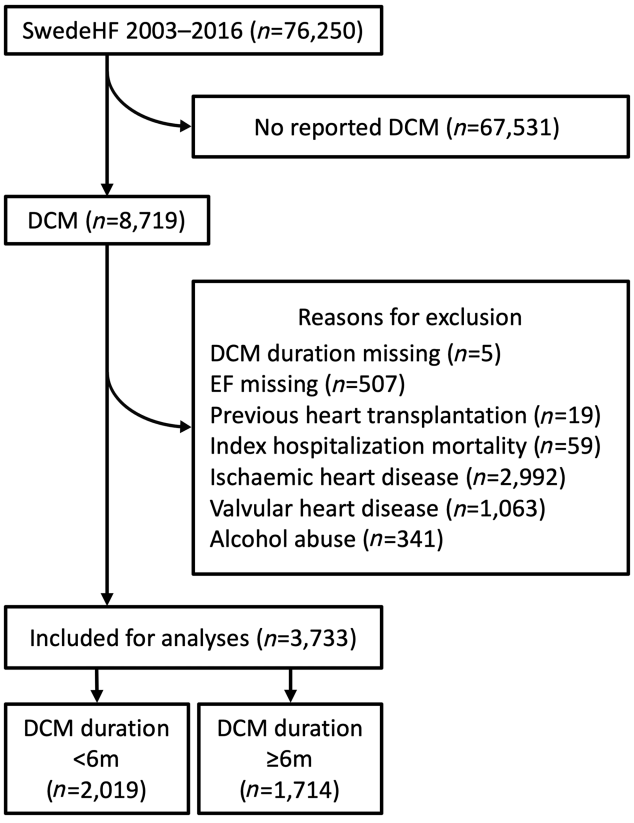
The Swedish Heart Failure Registry and data collection

The Swedish Heart Failure Registry is a nationwide HF registry implemented in 2003, further described elsewhere.[15,16] The annual reports, protocol, and registration form are available at http://www.swedehf.se. Individual written consent is not required for registration in national registries, but patients are informed and allowed to opt out. The registration index date in SwedeHF is defined as the date of visit for outpatients or the date of discharge after in-hospital care. All data are gathered at registration. Left ventricular ejection fraction (EF) is only available categorized as <30%, 30–39%, and ≥40%. Additional data regarding co-morbidities were obtained from the Swedish National Patient Register (NPR). The diagnoses are registered according to the International Classification of Diseases, Tenth Revision (ICD-10). Mortality data were obtained from the Swedish Cause of Death Register (http://www.socialstyrelsen.se). Information regarding income and level of education was obtained from the longitudinal integrated database for health insurance and labour market studies (http://www.scb.se/en/LISA). The establishment of the registry, and analysis of the data, was approved by a multisite ethics committee (2012/285-31, 2013/302-32, and 2017/510-32). The registry and this study are conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.[17]

Patient selection and group definitions

All 76 250 patients registered in SwedeHF between 1 January 2003 and 31 December 2016 were eligible for inclusion. The inclusion criterion was the documentation of DCM in SwedeHF or a diagnosis of DCM (ICD-10 Code I42.0) in the NPR. Patients lacking data regarding DCM duration or EF were excluded. Patients with pre-index heart transplantation or in-hospital death during the index hospitalization were excluded. DCM does not exclude concomitant coronary artery disease, but as SwedeHF does not contain information of coronary angiograms, misclassification of ischaemic HF could not be ruled out and patients with the variable 'ischaemic heart disease' were excluded, as were patients with SwedeHF information of haemodynamically significant valvular disease or previous valve intervention. Additionally, patients with advanced alcohol abuse were excluded. An inclusion/exclusion flow chart is depicted in *Figure 1*. Details of exclusion are presented in Supporting Information, *Table S1*.

Figure 1 Inclusion/exclusion flow chart. DCM, dilated cardiomyopathy; EF, ejection fraction; SwedeHF, Swedish Heart Failure Registry.



At registration in SwedeHF, duration of DCM is specified as more or less than 6 months, based on registered data or clinical history. Patients with SwedeHF data of DCM duration of $<$6 months without previous diagnosis of DCM in the NPR were classified as recent-onset DCM (RODCM). Patients with DCM duration of $\geq$6 months in either dataset were classified as long-standing DCM (LDCM).

Outcomes

Outcome information relies on the main ICD-10 diagnosis in the NPR. The following outcomes, occurring after the index date until the end of follow-up (31 December 2016), were analysed: all-cause, cardiovascular (CV), and non-CV death; heart transplantation; all-cause death or heart transplantation; all-cause, CV, and HF hospitalizations; and a combined primary outcome of all-cause death, heart transplantation, and HF hospitalization. Outcome definition details are presented in Supporting Information, *Table S1*.

Statistical analyses

For the baseline data, continuous variables are presented as mean and standard deviation, or median and inter-quartile range (IQR) as appropriate, and categorical variables are presented as percentages. When comparing the differences in characteristics between groups, Fisher's exact test was used for dichotomous variables, Mantel–Haenszel χ^2 trend test for ordered categorical variables, χ^2 test for non-ordered categorical variables, and Mann–Whitney *U* test for continuous variables. The Jonckheere–Terpstra test was used to compare a trend of continuous variables for different categories of DCM duration.

The unadjusted cumulative incidence of outcomes over the entire follow-up was estimated using the Kaplan–Meier method. Non-CV death and all-cause death, respectively, were handled as competing risk when depicting CV death and hospitalizations. The cumulative incidence curves for hospitalization handled all-cause death as competing risk. Crude, and age-adjusted and sex-adjusted event rates for mortality and hospitalization were calculated as the number of events per 100 person-years [Poisson-based 95% confidence interval (CI)]. Multivariable-adjusted Cox regression analyses of time to event for each endpoint, and a propensity score-matched analysis as sensitivity analysis on all-cause death and the combined outcome, LDCM vs. RODCM, were performed.

Cox regression analyses were used to describe the prognostic value of baseline variables on the combined outcome (all-cause mortality, heart transplantation, or HF hospitalization), separately for LDCM and RODCM. Hazard ratios (HRs) with (95% CI) are presented. A multivariable model was selected using stepwise regression. Categorical variables with more than 1% missing data were handled as 'unknown category' in the multivariable models. The proportional hazards assumption for each baseline variable was assessed by studying interaction between that variable and log(follow-up time) and reviewing log(−log(survival)) vs. log(follow-up time) plots. All tests were two sided, and $P < 0.05$ was considered significant. Eklund–Seeger's algorithm was used for estimation of upper limit of false significances. Further details on statistical methods are available in Supporting Information, *Appendix S1*. Statistical analyses were performed using SAS software (Version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

After exclusion, 3733 patients remained for analyses. Of these, 2019 were classified as RODCM and 1714 as LDCM (*Figure 1*).

Clinical characteristics and co-morbidities

The baseline characteristics of the patients are presented in *Table 1*. RODCM patients were significantly younger, and the prevalence of 11 of the 13 studied co-morbidities was significantly lower in RODCM than in LDCM. The use of renin–angiotensin system blockade and beta-blockers was significantly higher in RODCM than in LDCM, while the opposite was true for mineralocorticoid receptor antagonists (MRAs) and devices.

The mean age and mean number of co-morbidities increased significantly with increased duration, when comparing RODCM and LDCM with HF duration below the median 3.5 years (IQR 0.7–7.4) and LDCM with HF duration above the median (*Table 2*). Age alone explained 11% of the variability in the number of co-morbidities in the population, while duration category alone explained 7%.

Outcomes

All outcomes were significantly less common in RODCM than in LDCM. The cumulative unadjusted incidences of all-cause death/heart transplantation and hospitalizations are shown in *Figure 2*. The cumulative incidence of the combined outcome is shown in *Figure 3*.

The cumulative incidences and event rates for all outcomes are shown in *Table 3*. In LDCM, cardiovascular death (62%) was the main cause of mortality, $P < 0.0001$. In RODCM, CV mortality (53%) was similar to non-CV death. Age-adjusted CV mortality was higher in LDCM than in RODCM, $P < 0.0001$. Among survivors, there was no differ-

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Table 1 Baseline characteristics at index date by DCM duration

	RODCM (n = 2019)	LDCM (n = 1714)	P-value
Disease duration (years)		3.5 (0.7–7.4)	
Age (years)	58.6 (13.2)	62.5 (13.9)	<0.0001
Male sex	70.7%	73.7%	0.041
Disposable income (thousand Swedish crowns)	2155 (1616)	2039 (2791)	<0.0001
Highest level of education			
Compulsory school	31.7%	35.3%	
Secondary school	45.8%	44.1%	
University	22.5%	20.6%	0.024
Follow-up at heart failure unit	74.4%	55.1%	<0.0001
Inpatient location for inclusion	41.1%	34.0%	<0.0001
Physical examination			
Weight (kg)	85.1 (20.1)	85.2 (20.7)	0.99
Systolic blood pressure (mmHg)	122.2 (20.4)	121.3 (20.4)	0.37
Diastolic blood pressure (mmHg)	76.5 (12.9)	73.5 (12.3)	<0.0001
Heart rate (b.p.m.)	75.4 (16.1)	72.5 (14.4)	<0.0001
ECG			
Sinus rhythm	77.3%	60.2%	
Atrial fibrillation/flutter	20.0%	26.4%	
Pacemaker/other rhythm	2.8%	13.5%	<0.0001
Left bundle branch block	26.4%	29.8%	0.040
Left ventricular ejection fraction			
<30%	69.7%	50.7%	
30–39%	21.0%	24.1%	
≥40%	9.3%	25.2%	<0.0001
New York Heart Association functional class			
I	15.5%	14.4%	
II	55.8%	48.5%	
III	27.0%	34.2%	
IV	1.6%	2.9%	<0.0001
Laboratory tests			
Haemoglobin (g/L)	142.8 (15.6)	139.2 (16.1)	<0.0001
Estimated glomerular filtration rate (mL/min/1.73 m^2)	79.9 (20.1)	73.3 (27.1)	<0.0001
Medical history in SwedeHF or National Patient Register			
Smoking			
Never	40.1%	45.5%	
Former	40.6%	38.6%	
Current	19.4%	15.8%	0.0006
Hypertension	35.8%	46.1%	<0.0001
Diabetes	11.0%	20.8%	<0.0001
Atrial fibrillation	26.9%	44.1%	<0.0001
Lung disease	11.8%	15.9%	0.0004
Stroke/transient ischaemic attack	4.4%	9.8%	<0.0001
Liver disease	1.7%	2.7%	0.047
Renal disease	1.7%	3.7%	0.0002
Dialysis	0.1%	0.5%	0.081
Non-coronary vascular disease	1.7%	3.2%	0.0046
Sleep apnoea	3.2%	6.9%	<0.0001
Cancer within the last 3 years	7.0%	8.6%	0.090
Musculoskeletal or connective tissue disorder within the last 3 years	8.8%	12.6%	0.0002
Medical treatment at index registration			
ACEIs	82.6%	69.5%	<0.0001
ARBs	16.0%	30.9%	<0.0001
ACEIs and/or ARBs	96.8%	94.7%	0.0015
Beta-blockers	94.0%	91.5%	0.0038
Mineralocorticoid receptor antagonists	38.5%	46.1%	<0.0001
Digoxin	12.5%	19.1%	<0.0001
Statins	22.4%	28.3%	<0.0001
Diuretics	70.0%	71.2%	0.47
Anticoagulants	35.6%	42.6%	<0.0001
Acetylsalicylic acid	25.7%	25.1%	0.70
Long-acting nitrates	1.0%	2.6%	0.0003
Device treatment			
None/pacemaker	96.4%	81.4%	
ICD	2.1%	6.9%	
CRT-P	0.4%	4.5%	
CRT-D	1.1%	7.2%	<0.0001

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CRT-D, cardiac resynchronization therapy with implantable cardioverter defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; DCM, dilated cardiomyopathy; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; IQR, inter-quartile range; LDCM, dilated cardiomyopathy with long-standing heart failure; RODCM, dilated cardiomyopathy with recent-onset heart failure; SD, standard deviation; SwedeHF, Swedish Heart Failure Registry.

For continuous variables, mean (SD) or median (IQR) is presented. For categorical variables, % is presented.

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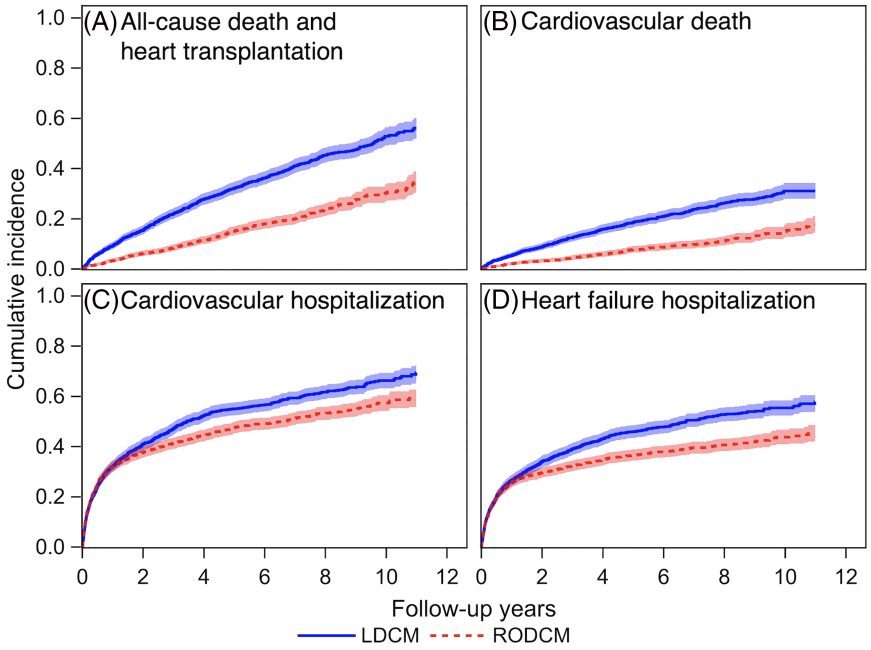
Table 2 Age and number of co-morbidities by DCM duration

	RODCM Duration <6 months (*n* = 2019)	LDCM Duration 6 months to 3.5 years (*n* = 863)	LDCM Duration >3.5 years (*n* = 851)	*P*-value
Age (years)	58.6 (13.2)	61.5 (14.4)	63.6 (13.2)	<0.0001
Number of co-morbidities at index visit	1.14 (1.05)	1.57 (1.26)	1.92 (1.36)	<0.0001
Number of co-morbidities at index visit, age adjusted	1.19 (1.15–1.24)	1.52 (1.49–1.56)	1.85 (1.78–1.92)	<0.0001

DCM, dilated cardiomyopathy; IQR, inter-quartile range; LDCM, dilated cardiomyopathy with long-standing heart failure; RODCM, dilated cardiomyopathy with recent-onset heart failure; SD, standard deviation.
For age and number of co-morbidities at index visit, raw data mean (SD) is presented. For age-adjusted number of co-morbidities at index visit, least squares mean (95% confidence interval) is presented. For comparison between groups, the Jonckheere–Terpstra trend test was used for age and number of co-morbidities at index visit. The age-adjusted model was performed using multivariable linear regression.

Figure 2 Cumulative incidence of outcomes: (A) all-cause death or heart transplantation; (B) cardiovascular death, non-cardiovascular death as competing risk; (C) cardiovascular hospitalization, death as competing risk; and (D) heart failure hospitalization, death as competing risk. LDCM, long-standing dilated cardiomyopathy; RODCM, recent-onset dilated cardiomyopathy.



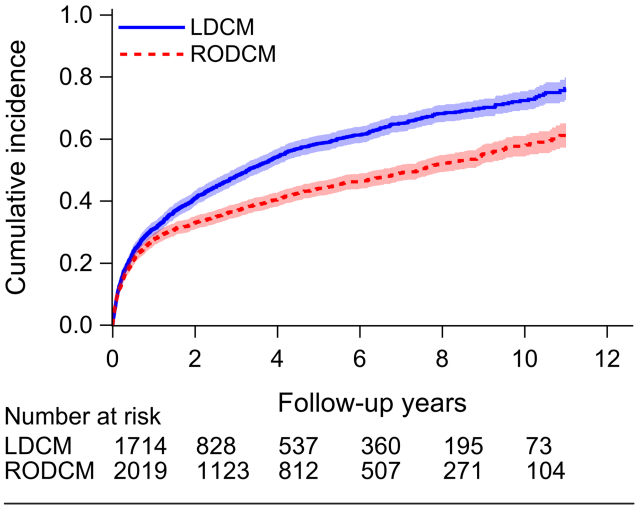
ence in median follow-up time between groups: LDCM 5.3 years (IQR 2.2–8.4) vs. RODCM 5.3 years (IQR 2.7–7.9), $P = 0.93$. HF was the dominating reason for hospitalization in both RODCM (63%) and LDCM (70%), $P < 0.0001$ for both. The results from the multivariable-adjusted Cox regression analyses comparing time to event for LDCM with RODCM, for all outcomes, are shown in *Table 3*. The assumption of proportional hazards was violated in the analyses of all outcomes including heart transplantation and hospitalizations, mainly explained by similar risk during the first year (illustrated in *Figures 2* and *3*), and HRs were interpreted as the mean relative risk over the studied follow-up time.

From each group, 922 patients were included in the propensity score-matched analysis. The groups were well balanced with respect to matched variables (Supporting Information, *Table S2*). The analyses yielded similar HRs for all-cause death and for the combined endpoint as the multivariable-adjusted regression analyses of the non-matched cohort: for the propensity score matched, 1.57 (95% CI: 1.31–1.87), $P < 0.0001$, and 1.33 (1.18–1.51), $P < 0.0001$; for the non-matched cohort, 1.56 (1.34–1.82), $P < 0.0001$, and 1.37 (1.24–1.52), $P < 0.0001$, respectively.

Association between baseline variables and outcome

As shown in *Figure 4*, several factors were independently associated with higher risk for the combined outcome in both groups: higher age (above the median), lower systolic blood

Figure 3 Cumulative incidence of the combined outcome: all-cause death, heart transplantation, or heart failure hospitalization. LDCM, long-standing dilated cardiomyopathy; RODCM, recent-onset dilated cardiomyopathy.



pressure (below the median), increased functional limitation, lower EF, left bundle branch block, and diabetes. In RODCM, increased risk was associated with male sex, lower haemoglobin, and the use of acetylsalicylic acid, whereas lower risk was associated with use of statins. Overall, co-morbidities had a greater impact for LDCM patients.

Discussion

In this nationwide DCM patient cohort study, we have found substantially higher event rates for all-cause, CV, and non-CV mortality; heart transplantation; and cause-specific hospitalizations in LDCM than in RODCM. While HF duration appears to be the main adverse factor, co-morbidity is associated with worse prognosis also after age adjustment.

Clinical characteristics

The prevalence of nearly all studied co-morbidities was significantly higher in LDCM than in RODCM, and the number of co-morbidities increased with the duration of disease. Despite similar mean body weight and a mere 3.9 year gap in mean age, the prevalence of diabetes was almost doubled in LDCM compared with RODCM. The prevalence of pharmacologically treated diabetes in Sweden in the year 2013 was 6.8% in all adults and 15.6% in patients >65 years of age.[18] Considering these numbers, the prevalence of 20.8% in LDCM appears high but in line with the 24.6–26.6% in previously studied DCM cohorts.[2,19] Given a reported 48% risk increase of incident diabetes associated with prevalent HF,[10] the aetiological interplay remains a topic for future studies.

While the degree of baseline medical treatment initiation was high regardless of disease duration, the proportion of patients with optimized doses would likely be higher in LDCM, and the higher EF in this group may be a result of treatment-related reverse remodelling. Still, the functional capacity was lower in the LDCM group, maybe due to older age and accumulated co-morbidity. The less frequent use of MRA and device in RODCM was expected as being second-line treatment. Among LDCM patients with EF < 30% and left bundle branch block, 13.4% were treated with cardiac resynchronization therapy, and 16.6% of patients with EF < 30% had received an implantable cardioverter defibrillator. Changed treatment recommendations during the study period may in part explain the low number of patients receiving devices, but previous analyses of SwedeHF have reported underuse of device treatment in a broad group of patients with HFrEF, not only in DCM.[20,21]

Dilated cardiomyopathy duration and prognosis

In our study, HF duration was a considerable factor for all outcomes also after multivariable adjustment of baseline characteristics. When the LDCM group was split by the median duration, we found significant trends both for increasing age and for increasing number of co-morbidities at baseline. Importantly, the significant trend of increasing number of co-morbidities with increasing disease duration remained also after adjustment for age.

It is noteworthy to mention that the all-cause mortality in LDCM was similar to the conservatively treated patients in the DANISH study[3] but lower than reported in the ESC Heart Failure Long-Term Registry.[6] In RODCM, the mortality was almost half of that seen in LDCM, but comparable with the 1 year mortality of 5.4% in DCM patients with duration <6 months reported by Teeter *et al*.[5] In a recent publication by Merlo *et al*., the mortality event rate in idiopathic DCM was only 1.1 per 100 person-years for the time period 2005–15.[8] Our study, however, included a broader range of DCM patients, and even if aetiology *per se* may affect prognosis,[8,11] cohorts of varying aetiologies differ in several aspects. The mean age of patients with chemotherapy-induced DCM is higher than in idiopathic or genetically determined DCM.[8] Exclusion of older patients results in cohorts less burdened with co-morbidities, which we have shown is of significant importance for prognosis. Still, the unadjusted transplantation rate of 0.5 per 100 person-years in LDCM in our study seems similar to the transplantation/ventricular assist device rate of 0.34 reported by Merlo *et al*.[8]

Table 3 Outcomes by DCM duration

Endpoint	RODCM				LDCM				LDCM vs. RODCM Hazard ratio (95% CI)[b] Multivariable adjusted
	Events *n* (%)	Median follow-up (years) (IQR)	Event rate per 100 person-years (95% CI)[a] Unadjusted	Age and sex adjusted	Events *n* (%)	Median follow-up (years) (IQR)	Event rate per 100 person-years (95% CI)[a] Unadjusted	Age and sex adjusted	
All-cause death	327 (16.2)	5.0 (2.4–7.6)	3.1 (2.8–3.5)	2.9 (2.6–3.2)	577 (33.7)	4.2 (1.6–7.6)	7.0 (6.5–7.6)	5.5 (5.0–6.0)	1.56**** (1.34–1.82)
CV death	173 (8.6)	5.0 (2.4–7.6)	1.7 (1.4–1.9)	1.5 (1.2–1.7)	356 (20.8)	4.2 (1.6–7.6)	4.3 (3.9–4.8)	3.2 (2.8–3.6)	1.67**** (1.36–2.05)
Non-CV death	154 (7.6)	5.0 (2.4–7.6)	1.5 (1.2–1.7)	1.4 (1.2–1.7)	221 (12.9)	4.2 (1.6–7.6)	2.7 (2.4–3.1)	2.3 (2.0–2.6)	1.42** (1.13–1.79)
Heart Tx	22 (1.1)	4.9 (2.4–7.6)	0.2 (0.1–0.3)	0.1 (0.1–0.2)	43 (2.5)	4.0 (1.6–7.5)	0.5 (0.4–0.7)	0.3 (0.2–0.5)	2.12**** (1.14–3.91)
All-cause death or heart Tx	348 (17.2)	4.9 (2.4–7.6)	3.4 (3.0–3.7)	3.3 (2.9–3.6)	616 (35.9)	4.0 (1.6–7.5)	7.7 (7.1–8.3)	6.5 (6.0–7.1)	1.63**** (1.41–1.90)
All-cause hospitalization	1158 (57.4)	1.5 (0.3–4.4)	21.1 (19.9–22.4)	21.8 (20.6–23.1)	1101 (64.2)	1.2 (0.3–3.5)	27.0 (25.4–28.7)	26.7 (25.2–28.3)	1.17*** (1.06–1.28)
CV hospitalization	940 (46.6)	1.9 (0.4–5.2)	14.8 (13.9–15.8)	15.2 (14.3–16.2)	923 (53.9)	1.5 (0.3–4.2)	19.6 (18.3–20.9)	19.3 (18.1–20.6)	1.19*** (1.07–1.32)
HF hospitalization	727 (36.0)	2.7 (0.6–6.0)	10.0 (9.2–10.7)	10.2 (9.5–10.9)	776 (45.3)	1.9 (0.4–5.1)	14.5 (13.5–15.5)	14.4 (13.4–15.4)	1.36**** (1.21–1.53)
All-cause death, heart Tx, or HF hospitalization	893 (44.2)	2.7 (0.6–6.0)	12.2 (11.4–13.1)	12.5 (11.7–13.3)	989 (57.7)	1.9 (0.4–5.1)	18.4 (17.3–19.6)	18.0 (16.9–19.1)	1.37**** (1.24–1.52)

CI, confidence interval; CV, cardiovascular; DCM, dilated cardiomyopathy; HF, heart failure; IQR, inter-quartile range; IQR, inter-quartile range; LDCM, dilated cardiomyopathy with long-standing heart failure; RODCM, dilated cardiomyopathy with recent-onset heart failure; Tx, transplantation.

[a]95% CI computed by using exact Poisson limits.

[b]By Cox regression analyses adjusting for index age, sex, location for registration, systolic blood pressure, heart rate, New York Heart Association functional class, left ventricular ejection fraction, left bundle branch block, haemoglobin, estimated glomerular filtration rate, acetylsalicylic acid, statins, diuretics, device, hypertension, diabetes, atrial fibrillation, lung disease, stroke/transient ischaemic attack, liver disease, renal disease, dialysis, non-coronary vascular disease, sleep apnoea, cancer within the last 3 years, and musculoskeletal or connective tissue disorder within the last 3 years.

$^{**}P < 0.01$.

$^{***}P < 0.001$.

$^{****}P < 0.0001$.

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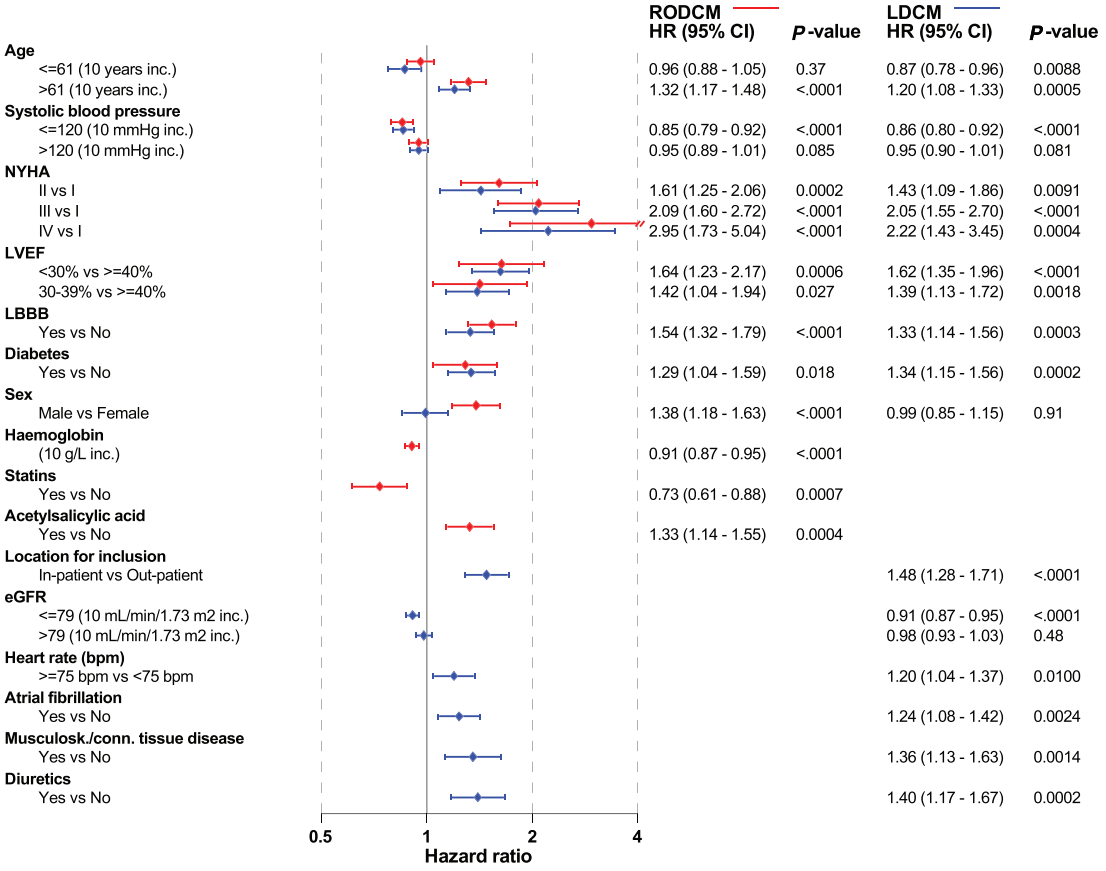
Figure 4 Cox proportional multivariable hazard analysis of predictors for the combined outcome of all-cause death, heart transplantation, or heart failure hospitalization, by dilated cardiomyopathy duration. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LBBB, left bundle branch block; LDCM, long-standing dilated cardiomyopathy; LVEF, left ventricular ejection fraction; Musculosk./conn. tissue disease, musculoskeletal or connective tissue disorder within last 3 years; NYHA, New York Heart Association functional class; RODCM, recent-onset dilated cardiomyopathy.



Co-morbidity and prognosis

As expected, several factors were associated with worse outcome regardless of DCM duration. However, in this study, we have shown that not only are co-morbidities more prevalent in LDCM, but also that the prognostic impact of co-morbidities differs between RODCM and LDCM and that the increased co-morbid burden is associated with increased mortality and need of transplantation.

The effect of sex on outcome in DCM is not consistent, but adverse impact of male sex in recent-onset DCM has been reported.[8,11,22,23] Cardiac-related events predominate the adverse outcomes in the early phase of symptomatic HF. Over time, the increasing impact of age and co-morbidities may attenuate the sex-related risk, possibly explaining the increased risk for men only in RODCM.

Patients with diabetes had an increased risk for the combined outcome of ~30% regardless of DCM duration. In the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction trial (DAPA-HF), two-thirds of the non-diabetic patient had prediabetes, resulting in >80% of the patients having abnormal glucose regulation.[24,25] The high prevalence of diabetes in non-ischaemic HF, the worse prognosis, and the results from DAPA-HF emphasize the significance of glucose metabolism in HF.

The association of diuretic therapy with worse outcome in HF is established.[26,27] The initial need of diuretics in HF is common, but the recurring need of treatment often occurs with progressive disease. We believe that the increased risk for the combined outcome associated with diuretics in LDCM reflects the combination of more advanced HF and increased co-morbidity, despite similar use of diuretics in the two groups. One-fourth of the patients in both groups were treated with acetylsalicylic acid. While we cannot evaluate the reasons for treatment, the worse prognosis in RODCM emphasizes the importance of correct treatment indication. In conformity with results from previous analyses of SwedeHF data and randomized trials,[28,29] statin treatment did not affect outcome in LDCM. In the present study, however, statins were associated with a considerable risk reduction in RODCM.

Limitations

Being an observational study, we report associations only. Although our registry contains a large number of unique patients with extensive baseline variables, we cannot validate individual data, and selection bias, recording inaccuracies, and the impact of residual or unmeasured confounders cannot be ruled out. The accuracy of CV death in the studied populations is not validated. We lack data of DCM aetiology and magnetic resonance imaging. The only echocardiographic information available is EF in the presented categories. N-terminal pro-B-type natriuretic peptide was missing in 51% and removed from analyses. Index date treatment is presented as medication type, before optimization, which especially in case of RODCM likely would affect the use of MRA. While our selection minimized the inclusion of patients misclassified as DCM, we acknowledge the possible exclusion of patients with limited coronary artery disease and severe secondary valvular disease. Outpatient registration in SwedeHF may take place shortly after hospitalization, possibly reducing the differences with regard to location for inclusion. In the multivariable regression models for the combined outcome, age, systolic blood pressure, and EF did not fulfil the assumption of proportional hazards in either group nor did location for registration, in LDCM, thus limiting the interpretation of HRs for the complete follow-up period.

Conclusions

This nationwide study of patients with DCM demonstrates that longer disease duration is associated with worse prognosis. Co-morbidities are more common in long-standing HF than in recent-onset HF and are associated with worse outcome also after adjustment for age. Diabetes was the only co-morbidity independently associated with worse prognosis regardless of HF duration. With the increased survival seen in the last decades, our results highlight the importance of careful attention to optimal treatment of co-morbid conditions in patients with DCM.

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Conflict of interest

M.F. reports unrelated modest consulting fee from Novartis, Pfizer, Boehringer Ingelheim, Vifor Pharma, and AstraZeneca. U.D. reports unrelated research funding/honoraria from AstraZeneca, Novartis, Amgen, Pfizer, Boehringer Ingelheim, Roche Diagnostics, Vifor Pharma, and Boston Scientific. No other conflict of interest, or relationship with the industry, was declared.

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Supporting information

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

Appendix S1. Supporting Information.
Table S1. Excluded variable details and outcome definitions.
Table S2. Baseline characteristics by DCM duration, propensity score matched individuals.

References

1. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008; **29**: 270–276.
2. Balmforth C, Simpson J, Shen L, Jhund PS, Lefkowitz M, Rizkala AR, Rouleau JL, Shi V, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJV. Outcomes and effect of treatment according to etiology in HFrEF: an analysis of PARADIGM-HF. *JACC Heart Failure* 2019; **7**: 457–465.
3. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016; **375**: 1221–1230.
4. Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes D Jr, Kucheryavaya

AY, Levvey BJ, Meiser B, Rossano JW, Stehlik J. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult heart transplantation report—2018; focus theme: multiorgan transplantation. *J Heart Lung Transplant* 2018; **37**: 1155–1168.
5. Teeter WA, Thibodeau JT, Rao K, Brickner ME, Toto KH, Nelson LL, Mishkin JD, Ayers CR, Miller JG, Mammen PP, Patel PC, Markham DW, Drazner MH. The natural history of new-onset heart failure with a severely depressed left ventricular ejection fraction: implications for timing of implantable cardioverter-defibrillator implantation. *Am Heart J* 2012; **164**: 358–364.
6. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **19**: 1574–1585.
7. Pecini R, Moller DV, Torp-Pedersen C, Hassager C, Kober L. Heart failure etiology impacts survival of patients with heart failure. *Int J Cardiol* 2011; **149**: 211–215.
8. Merlo M, Cannatà A, Pio Loco C, Stolfo D, Barbati G, Artico J, Gentile P, De Paris V, Ramani F, Zecchin M, Gigli M, Pinamonti B, Korcova R, Di Lenarda A, Giacca M, Mestroni L, Camici PG, Sinagra G. Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2020; **22**: 1111–1121.
9. Sjoland H, Silverdal J, Bollano E, Pivodic A, Dahlstrom U, Fu M. Temporal trends in outcome and patient characteristics in dilated cardiomyopathy, data from the Swedish Heart Failure Registry 2003–2015. *BMC Cardiovasc Disord* 2021; **21**: 307. https://doi.org/10.1186/s12872-021-02124-0
10. Nichols GA, Moler EJ. Cardiovascular disease, heart failure, chronic kidney disease and depression independently increase the risk of incident diabetes. *Diabetologia* 2011; **54**: 523–526.
11. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000; **342**: 1077–1084.
12. Silverdal J, Sjoland H, Bollano E, Pivodic A, Dahlstrom U, Fu M. Prognostic impact over time of ischaemic heart disease vs. non-ischaemic heart disease in heart failure. *ESC Heart Fail* 2020; **7**: 265–274. https://doi.org/10.1002/ehf2.12568
13. Mentz RJ, Allen BD, Kwasny MJ, Konstam MA, Udelson JE, Ambrosy AP, Fought AJ, Vaduganathan M, O'Connor CM, Zannad F, Maggioni AP, Swedberg K, Bonow RO, Gheorghiade M. Influence of documented history of coronary artery disease on outcomes in patients admitted for worsening heart failure with reduced ejection fraction in the EVEREST trial. *Eur J Heart Fail* 2013; **15**: 61–68.
14. Frankenstein L, Hees H, Taeger T, Froehlich H, Dosch A, Cebola R, Zugck C, Katus HA. Clinical characteristics, morbidity, and prognostic value of concomitant coronary artery disease in idiopathic dilated cardiomyopathy. *Clin Res Cardiol* 2013; **102**: 771–780.
15. Jonsson A, Edner M, Alehagen U, Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail* 2010; **12**: 25–31.
16. Savarese G, Vasko P, Jonsson Å, Edner M, Dahlström U, Lund LH. The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure. *Ups J Med Sci* 2019; **124**: 65–69.
17. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191–2194.
18. Andersson T, Ahlbom A, Carlsson S. Diabetes prevalence in Sweden at present and projections for year 2050. *PLoS One* 2015; **10**: e0143084.
19. Bertoni AG, Tsai A, Kasper EK, Brancati FL. Diabetes and idiopathic cardiomyopathy: a nationwide case-control study. *Diabetes Care* 2003; **26**: 2791–2795.
20. Lund LH, Braunschweig F, Benson L, Ståhlberg M, Dahlström U, Linde C. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: results from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2017; **19**: 1270–1279.
21. Schrage B, Uijl A, Benson L, Westermann D, Ståhlberg M, Stolfo D, Dahlström U, Linde C, Braunschweig F, Savarese G. Association between use of primary-prevention implantable cardioverter-defibrillators and mortality in patients with heart failure: a prospective propensity score-matched analysis from the Swedish Heart Failure Registry. *Circulation* 2019; **140**: 1530–1539.
22. McNamara DM, Starling RC, Cooper LT, Boehmer JP, Mather PJ, Janosko KM, Gorcsan J 3rd, Kip KE, Dec GW. Clinical and demographic predictors of outcomes in recent onset dilated cardiomyopathy: results of the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy)-2 study. *J Am Coll Cardiol* 2011; **58**: 1112–1118.
23. Halliday BP, Gulati A, Ali A, Newsome S, Lota A, Tayal U, Vassiliou VS, Arzanauskaite M, Izgi C, Krishnathasan K, Singhal A, Chiew K, Gregson J, Frenneaux MP, Cook SA, Pennell DJ, Collins P, Cleland JGF, Prasad SK. Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy. *Eur J Heart Fail* 2018; **20**: 1392–1400.
24. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, on behalf of the DAPA-HF Committees and Investigators. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. *Eur J Heart Fail* 2019; **21**: 1402–1411.
25. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381**: 1995–2008.
26. Kapelios CJ, Bonou M, Malliaras K, Athanasiadi E, Vakrou S, Skouloudi M, Masoura C, Barbetseas J. Association of loop diuretics use and dose with outcomes in outpatients with heart failure: a systematic review and meta-analysis of observational studies involving 96,959 patients. *Heart Fail Rev* 2020; **27**: 147–161.
27. Paren P, Dahlstrom U, Edner M, Lappas G, Rosengren A, Schaufelberger M. Association of diuretic treatment at hospital discharge in patients with heart failure with all-cause short- and long-term mortality: a propensity score-matched analysis from SwedeHF. *Int J Cardiol* 2018; **257**: 118–124.
28. Alehagen U, Benson L, Edner M, Dahlström U, Lund LH. Association between use of statins and outcomes in heart failure with reduced ejection fraction: prospective propensity score matched cohort study of 21 864 patients in the Swedish Heart Failure Registry. *Circ Heart Fail* 2015; **8**: 252–260.
29. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**: 1231–1239.