



Left ventricular remodelling and prognosis after discharge in new-onset acute heart failure with reduced ejection fraction

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Abstract

Aims This study aimed to investigate the left ventricular (LV) remodelling and long-term prognosis of patients with new-onset acute heart failure (HF) with reduced ejection fraction who were pharmacologically managed and survived until hospital discharge. We compared patients with ischaemic and non-ischaemic aetiology.

Methods and results This cohort study consisted of 111 patients admitted with new-onset acute HF in the period 2008–2016 [62% non-ischaemic aetiology, 48% supported by inotropes, vasopressors, or short-term mechanical circulatory devices, and left ventricular ejection fraction (LVEF) at discharge 28% (interquartile range 22–34)]. LV dimensions, LVEF, and mitral valve regurgitation were used as markers for LV remodelling during up to 3 years of follow-up. Both patients with non-ischaemic and ischaemic HF had significant improvement in LVEF ($P < 0.001$ and $P = 0.004$, respectively) with significant higher improvement in those with non-ischaemic HF (17% vs. 6%, $P < 0.001$). Patients with non-ischaemic HF had reduction in LV end-diastolic and end-systolic diameters (6 and 10 mm, both $P < 0.001$), but this was not found in those with ischaemic HF [+3 mm ($P = 0.09$) and +2 mm ($P = 0.07$), respectively]. During a median follow-up of 4.6 years, 98 patients (88%) did not reach the composite endpoint of LV assist device implantation, heart transplantation, or all-cause mortality, with no difference between with ischaemic and non-ischaemic HF [hazard ratio 0.69 (95% confidence interval 0.19–2.45)].

Conclusions Patients with new-onset acute HF with reduced ejection fraction discharged on optimal medical treatment have a good prognosis. We observed a considerable LV remodelling with improvement in LV function and dimensions, starting already at 6 months in patients with non-ischaemic HF but not in their ischaemic counterparts.

Keywords HF rEF; LV remodelling; Prognosis; Optimal medical treatment

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Introduction

Hospitalization for new-onset heart failure (HF) often indicates a severe HF phenotype, in which introduction and titration of medication may be difficult and the response to treatment is influenced by the severity of ejection fraction impairment.¹ Less is known about the natural course of patients with new-onset acute HF with reduced

ejection fraction (HF rEF) who can be medically managed, but in whom the severity of left ventricular (LV) dysfunction raises the question whether advanced treatment is indicated. A too early decision for left ventricular assist device (LVAD) or heart transplantation (HT) in patients with first admission for new-onset HF rEF and who tolerate HF medication may have a heavy impact on the morbidity and mortality risks of the individual patients as well as on health

care resources, as LV function may recover in some of these patients.²

In the current study, we aimed to investigate the LV remodelling and long-term prognosis of patients with new-onset acute HFrEF who were pharmacologically managed and survived to hospital discharge. We designed this study in patients with new-onset acute HF in order to evaluate the effect of HF medication in a formerly non-exposed patient with HF. Because the remodelling is dependent on the HF aetiology, we compared the LV remodelling between patients with ischaemic and non-ischaemic aetiology of acute HFrEF.

Methods

Study population

This retrospective cohort study consisted of patients admitted with acute HF to the Erasmus Medical Center in the period January 2008 until December 2016. The inclusion criteria were (i) a diagnosis of acute HF at admission, (ii) no history of chronic HF or any other structural heart disease, and (iii) a left ventricular ejection fraction (LVEF) < 40% at admission. Patients were excluded if they received an LVAD, underwent HT, or died before discharge and in case of limited or no follow-up in our hospital.

Our hospital is a tertiary referral centre and serves as one of the national referral centres for patients with advanced HF with need for mechanical circulatory support or HT for a significant part of the Netherlands. This study was conducted in accordance to the Declaration of Helsinki.³ Our local research ethics committee has given approval for this study.

Data collection

We extracted the variables from patients' records and discharge letters. Data collection started at day of admission for new-onset acute HF. Follow-up was considered complete after approximately 3 years. Variables were collected during admission (i.e. baseline), at 6 months, and at 1, 2, and 3 years after admission (all ± 3 months). Data collection ended when patients died, received an LVAD, underwent HT, or moved to another hospital's outpatient clinic.

In addition to the variables age and sex, we collected body mass index, medical history, and aetiology of HF. At baseline and during follow-up moments, we gathered systolic and diastolic blood pressure, heart rate, rhythm on electrocardiogram, medical and device therapy, and a selection of laboratory parameters.

We also collected a number of echo parameters with transthoracic echocardiography. These included left ventricular end-diastolic (LVED) diameter, left ventricular end-systolic (LVES) diameter, and LVEF. The LVEF was determined by using

the Simpson method with software Image-Com 5.5 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). If available, we measured the following parameters of diastolic function: E/A ratio, mitral valve deceleration time, and E/e' ratio. The severity of mitral valve regurgitation and tricuspid valve regurgitation were classified into absent, mild, moderate, or severe. Mitral and tricuspid valve regurgitation was defined by using the qualitative and semiquantitative criteria as defined in the European Society of Cardiology guideline about valvular heart disease.⁴ Grading the severity of mitral and tricuspid valve regurgitation was performed according to the guidelines of the European Association of Echocardiography.⁵ Right ventricular function was quantified with the tricuspid annular plane systolic excursion. Lastly, we measured the inferior caval vein's diameter.

Definitions

We defined the recovery of the LV as an LVEF of at least 50% in a patient with previous HFrEF as this definition has been used in several other studies.^{6,7} Furthermore, in the TRED-HF trial on withdrawal of HF medication after recovery of dilated cardiomyopathy, an improvement of LVEF to 50% was required before withdrawal was attempted.⁸ Furthermore, we used an increase of >10% of LVEF as a measure of significant LV reverse remodelling.

Endpoint

The primary endpoint of our study was the LV remodelling during up to 3 years of follow-up. LVED diameter, LVES diameter, and LVEF were used as markers for LV remodelling. Next to those markers, we analysed the pattern of mitral valve regurgitation.

We also studied the patient's prognosis (up to 10 years) using the composite of all-cause mortality, HT, and LVAD implantation. We also analysed the HF rehospitalization according to aetiology. The Municipal Civil Registries were consulted to assess the survival status of the included patients.

Statistical analyses

Continuous variables were presented as median with interquartile range (IQR) and categorical variables as numbers and percentages. The Mann–Whitney *U* test and χ^2 test were used to compare continuous and categorical variables, respectively.

We used the Kaplan–Meier method in order to estimate the cumulative event rates. Cox proportional hazard models were applied to evaluate the difference in the composite endpoint between patients with ischaemic and

non-ischaemic HF. The results are presented as hazard ratio (HR) with their 95% confidence interval (95% CI).

Linear mixed-effects models were fitted for LVEF, LVED diameter, and LVES diameter (dependent) to assess remodelling. To compare remodelling between patients with ischaemic and non-ischaemic HF, we calculated the delta remodelling by subtracting the baseline measurement from the measurements taken at least 6 months after inclusion per patient, as we expected that most remodelling will have occurred within the first 6 months after admission. Subsequently, these deltas were used as dependent in the adjusted linear mixed-effects models. Lastly, Cox proportional hazard regression was used to relate the repeated LVEF, LVED, and LVES measurements to outcome. To avoid bias, parameters of the linear mixed-effects models and Cox regression models were combined in a joint model.

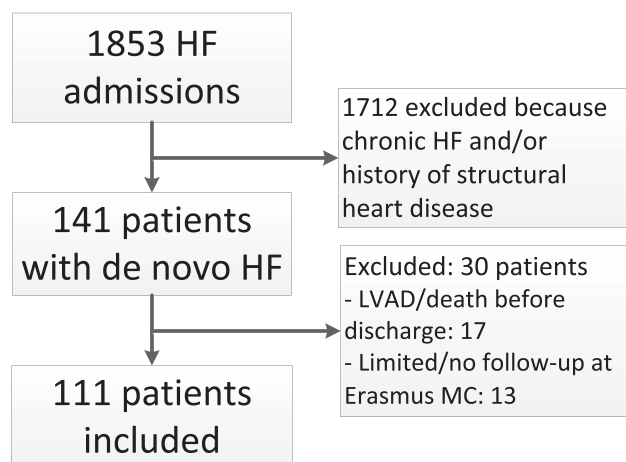
All tests were two-tailed, and $P < 0.05$ were considered as statistically significant. SPSS software (SPSS 24.0, IBM Corp., Armonk, NY, USA) was used for the descriptive statistical analyses and the survival analyses. R statistical software (Version 3.4.3) was used for the linear mixed-effects models and joint models, in particular the packages *nlme* and *JMbayes*.

Results

Baseline characteristics

During the inclusion period, 141 patients admitted with acute HF potentially qualified for inclusion. Of these, 17 patients were excluded because they died or received an LVAD before discharge, and 13 patients were excluded due to limited follow-up in our hospital. Consequently, we included 111 patients admitted with new-onset acute HF (Figure 1).

Figure 1 Flow chart of patient selection. HF, heart failure; LVAD, left ventricular assist device.



The included patients had a median age of 50.0 (IQR 38.6–60.3) years, almost half were men, and 38% of the patients had ischaemic HF (Table 1). Non-ischaemic HF was predominately diagnosed as idiopathic dilated cardiomyopathy ($n = 27$), toxic cardiomyopathy ($n = 13$), and myocarditis ($n = 11$). During admission, 48% of the patients required inotrope and/or vasopressor support, and 23% needed in addition short-term mechanical circulatory support by extracorporeal membrane oxygenation and/or intra-aortic balloon pump. Of the patients with ischaemic HF, 33 had a percutaneous coronary intervention and one underwent coronary artery bypass grafting during the initial hospitalization. At discharge, New York Heart Association class and HF treatment were comparable between patients with ischaemic and non-ischaemic HF.

Left ventricular remodelling

At discharge, both the LVED and LVES diameters were significantly larger in patients with non-ischaemic HF than in those with ischaemic HF (Table 2). In addition, patients with non-ischaemic HF had lower LVEF than patients with ischaemic HF [26% (IQR 21–33) and 32% (IQR 25–36), respectively]. The prevalence of poor LVEF (i.e. $LVEF \leq 30\%$) at discharge was higher in patients with non-ischaemic HF than in those with ischaemic HF (67% vs. 48%, $P = 0.047$). Furthermore, 44% of the patients exhibited moderate to severe mitral valve regurgitation, and 26% moderate to severe tricuspid valve regurgitation.

During 3 years of follow-up, LVEF recovered in 10% of the patients with ischaemic HF and in 39% of those with non-ischaemic HF ($P < 0.001$). Of the patients with LVEF recovery, recovery was already present in half of the patients during the echocardiographic assessment at 6 months after discharge. In total, 26% of the patients with ischaemic HF had a significant (at least 10%) improvement of LVEF, compared with 72% of those with non-ischaemic HF ($P < 0.001$). The LVEF recovery and significant improvement of LVEF were comparable between patients with an $LVEF \leq 30\%$ and $LVEF > 30\%$ ($P = 0.06$).

Figure 2 presents the time-dependent changes in LVED diameter, LVES diameter, and LVEF after discharge (see Supporting Information, Table S1 for fitting values). Both patients with non-ischaemic and ischaemic HF had significant improvement in LVEF ($P < 0.001$ and $P = 0.004$, respectively). This improvement was significant higher in those with non-ischaemic HF (17% vs. 6%, $P < 0.001$). Furthermore, while patients with non-ischaemic HF had a significant reduction in LVED and LVES diameters (6 and 10 mm, both $P < 0.001$), these diameters did not change in those with ischaemic HF [+3 mm ($P = 0.09$) and +2 mm ($P = 0.07$), respectively]. In addition to the aforementioned parameters of LV remodelling, we also found that the severity of mitral valve

Table 1 Baseline characteristics of patients with ischaemic and non-ischaemic heart failure

	Total population (n = 111)	Ischaemic HF (n = 42)	Non-ischaemic HF (n = 69)	P-value
Demographics				
Age	50.0 (38.6–60.3)	58.9 (50.3–64.9)	43.8 (32.9–54.7)	<0.001
Male	62 (56%)	26 (62%)	36 (52%)	0.32
Body mass index	24.9 (22.3–27.3)	24.9 (22.7–27.2)	24.9 (21.8–28.0)	0.91
Aetiology heart failure				
Ischaemic				<0.001
STEMI	31 (28%)	31 (74%)		
Non-STEMI	3 (3%)	3 (7%)		
Stable coronary artery disease	8 (7%)	8 (19%)		
Idiopathic dilated cardiomyopathy	27 (24%)		27 (39%)	
Non-compaction cardiomyopathy	5 (5%)		5 (7%)	
Hypertensive cardiomyopathy	5 (5%)		5 (7%)	
Immune-mediated cardiomyopathy	2 (2%)		2 (3%)	
Toxic cardiomyopathy	13 (12%)		13 (20%)	
Peripartum cardiomyopathy	4 (4%)		4 (6%)	
Myocarditis	11 (10%)		11 (16%)	
Tako-tsubo cardiomyopathy	2 (2%)		2 (3%)	
Medical history				
Atrial fibrillation	2 (2%)	1 (2%)	1 (1%)	1.00
Diabetes	8 (7%)	7 (17%)	1 (1%)	0.008
Hypertension	27 (24%)	19 (45%)	8 (12%)	<0.001
Hypercholesterolaemia	11 (10%)	9 (21%)	2 (3%)	0.007
Smoker				0.82
Current smoker	35 (32%)	16 (38%)	19 (28%)	
Former smoker	17 (15%)	7 (17%)	10 (15%)	
Renal dysfunction	3 (3%)	2 (5%)	1 (1%)	0.57
Anaemia	2 (2%)	0 (0%)	2 (3%)	0.51
Chronic obstructive pulmonary disease	2 (2%)	1 (2%)	1 (1%)	1.00
Malignancy	8 (7%)	1 (2%)	7 (10%)	0.13
Depression	5 (5%)	1 (2%)	4 (6%)	0.39
Advanced therapy during admission				
IABP treatment	24 (22%)	21 (50%)	3 (4%)	<0.001
ECMO treatment	3 (3%)	1 (2%)	2 (3%)	1.00
Inotrope/vasopressor support	53 (48%)	25 (60%)	28 (41%)	0.05
Characteristics at discharge				
Systolic blood pressure (mmHg)	103 (90–115)	105 (88–116)	103 (93–115)	0.53
Diastolic blood pressure (mmHg)	63 (55–75)	65 (55–75)	62 (56–75)	0.85
Heart rate (b.p.m.)	74 (65–83)	76 (69–84)	72 (63–82)	0.19
Sinus rhythm	101 (92%)	40 (95%)	61 (90%)	0.48
Bundle branch block				0.67
Left bundle branch block	5 (5%)	1 (2%)	4 (6%)	
Right bundle branch block	6 (5%)	2 (5%)	4 (6%)	
Therapy at discharge				
Beta-blocker	103 (93%)	36 (86%)	67 (97%)	0.05
ACE-inhibitor or ARB	106 (96%)	41 (98%)	65 (94%)	0.65
Mineralocorticoid receptor antagonist	67 (60%)	24 (57%)	43 (62%)	0.59
Diuretics	97 (87%)	36 (86%)	61 (88%)	0.68
Digoxin	55 (50%)	16 (38%)	39 (57%)	0.06
Statin	45 (41%)	39 (93%)	6 (9%)	<0.001
(Direct) oral anticoagulant	78 (70%)	27 (64%)	51 (74%)	0.28
Thrombocyte aggregation inhibitor	36 (32%)	30 (71%)	6 (9%)	<0.001
Pacemaker	1 (1%)	0 (0%)	1 (1%)	1.00
ICD	26 (23%)	7 (17%)	19 (28%)	0.19
CRT	4 (4%)	0 (0%)	4 (6%)	0.16
Laboratory values at discharge				
Creatinine (μmol/L)	91 (76–116)	94 (80–129)	89 (72–112)	0.22
eGFR (mL/min)	64 (54–83)	60 (48–80)	67 (56–86)	0.11
Sodium (mmol/L)	139 (137–141)	139 (137–141)	139 (137–141)	0.86
Potassium (mmol/L)	4.5 (4.2–4.8)	4.5 (4.2–4.8)	4.5 (4.2–4.8)	0.85
Urea (mmol/L)	9.2 (6.8–12.3)	9.3 (6.7–12.3)	9.2 (7.0–12.3)	0.82
ASAT (U/L)	29 (23–38)	26 (19–33)	31 (25–43)	0.06
ALAT (U/L)	35 (24–60)	26 (19–43)	39 (29–70)	0.02

(Continues)

Table 1 (continued)

	Total population (n = 111)	Ischaemic HF (n = 42)	Non-ischaemic HF (n = 69)	P-value
Haemoglobin (mmol/L)	7.6 (6.7–8.6)	7.0 (6.3–7.8)	8.2 (7.0–9.7)	<0.001
Haematocrit (L/L)	0.38 (0.33–0.41)	0.35 (0.31–0.38)	0.39 (0.36–0.43)	0.001
NT-proBNP (pmol/L)	251 (100–577)	577 (392–738)	234 (87–401)	0.02

ACE, angiotensin-converting enzyme; ALAT, alanine aminotransferase; ARB, angiotensin receptor blocker; ASAT, aspartate aminotransferase; CRT, cardiac resynchronization therapy; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HF, heart failure; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; STEMI, ST-elevated myocardial infarction. Results depicted as *N* (%) or median (interquartile range).

Table 2 Echocardiography parameters at discharge of patients with ischaemic and non-ischaemic heart failure

	Total population	Ischaemic HF	Non-ischaemic HF	P-value
LVED diameter (mm)	58 (53–66)	54 (52–62)	60 (56–68)	0.001
LVES diameter (mm)	48 (39–56)	43 (36–49)	52 (46–59)	<0.001
LVEF (%)	28 (22–34)	32 (25–36)	26 (21–33)	0.03
Mitral valve regurgitation				0.80
Absent	22 (21%)	10 (25%)	12 (18%)	
Mild	37 (35%)	12 (30%)	25 (37%)	
Moderate	24 (22%)	9 (23%)	15 (22%)	
Severe	24 (22%)	9 (23%)	15 (22%)	
E/A ratio	1.6 (1.0–2.3)	1.4 (0.9–2.2)	1.7 (1.1–2.3)	0.29
Deceleration time mitral valve (ms)	158 (123–190)	171 (136–201)	151 (113–181)	0.06
E/E'	14.7 (10.2–19.8)	13.9 (10.1–23.1)	14.7 (10.3–19.4)	0.70
Tricuspid valve regurgitation				0.95
Absent	44 (43%)	16 (41%)	28 (44%)	
Mild	32 (31%)	13 (33%)	19 (30%)	
Moderate	17 (17%)	7 (18%)	10 (16%)	
Severe	9 (9%)	3 (8%)	6 (10%)	
Tricuspid insufficiency gradient (mmHg)	27 (21–36)	36 (26–43)	25 (21–29)	0.002
Diameter inferior caval vein (mm)	16 (13–19)	17 (13–18)	16 (13–20)	0.79
TAPSE (mm)	18 (16–22)	19 (16–22)	18 (16–22)	0.59

HF, heart failure; LVED, left ventricular end-diastolic; LVEF, left ventricular ejection fraction; LVES, left ventricular end-systolic; TAPSE, tricuspid annular plane systolic excursion. Results depicted as *N* (%) or median (interquartile range).

regurgitation decreased during the first 6 months ($P = 0.02$) in patients with non-ischaemic HF but not in those with ischaemic HF (Figure 3). Furthermore, the N-terminal prohormone of brain natriuretic peptide levels decreased in both patients with ischaemic and non-ischaemic HF during follow-up, especially in the first 6 months (Table 3).

Because there was no consistent policy on the interval between the echocardiograms, we had missing values in LVED diameter, LVES diameter, LVEF, and mitral valve regurgitation during the 3 years of follow-up (Supporting Information, Table S2). Nevertheless, the median number of repeated measurements for LVED diameter, LVES diameter, and LVEF was 3 (IQR 2–4).

Prognosis

During a median follow-up time of 4.6 years, 13 patients (12%) reached the composite endpoint of all-cause mortality, HT, and LVAD implantation. Prognosis was comparable between patients with ischaemic and non-ischaemic HF [HR 0.69 (95% CI 0.19–2.45); Figure 4]. Eleven patients died

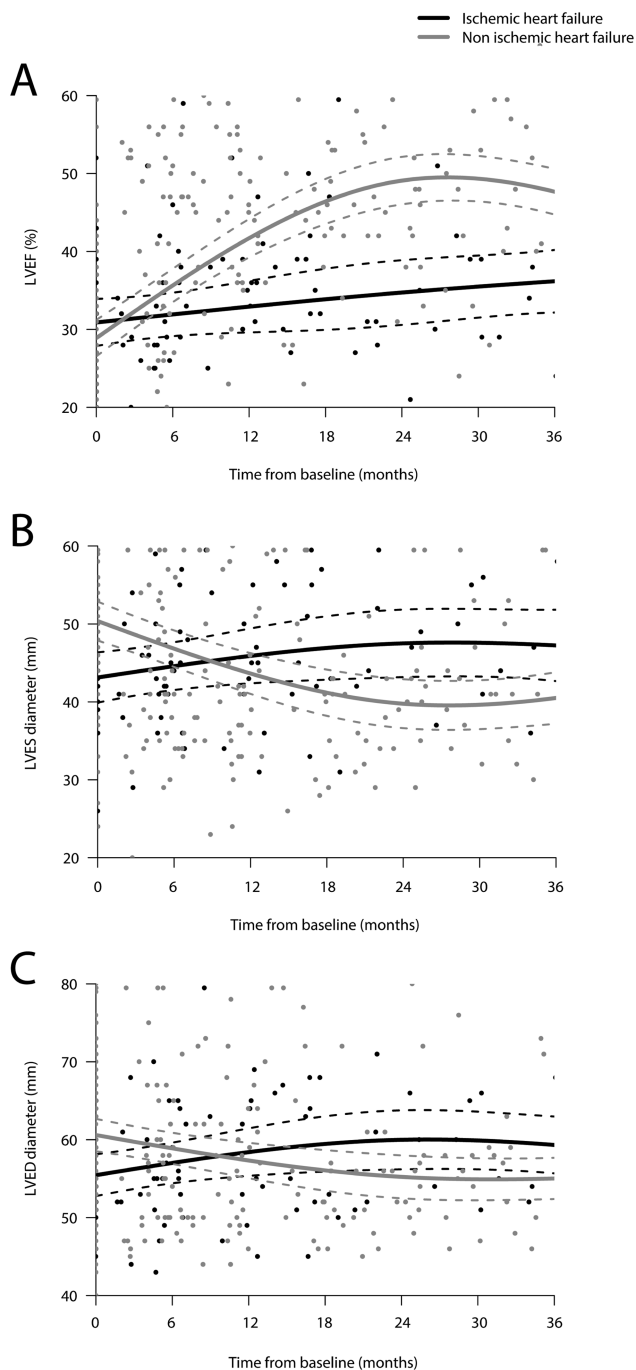
during follow-up; three patients received an LVAD, and two underwent HT. Thirteen patients (12%) needed rehospitalization for HF during the follow-up, with no difference between patients with and without ischaemic aetiology [HR 2.02 (95% CI 0.68–6.02)].

Furthermore, we found that higher increase in LVEF was associated with better prognosis [HR per 5% increase 1.13 (95% CI 1.10–1.43)]. In contrast, decreases in LVED diameter and LVES diameter were not associated with better outcome [HR per 1 mm decrease in LVED diameter 1.002 (95% CI 0.93–1.07) and HR per 1 mm decrease in LVES diameter 1.00 (95% CI 0.92–1.06)]. Adjustment for HF aetiology did not change these associations.

Among the patients with clinical follow-up until 3 years ($n = 58$), 28 patients received an implantable cardioverter defibrillator (ICD) and five patients of them a cardiac resynchronization therapy device. During up to 3 years of clinical follow-up, eight patients had nine shock events. Of these, four shocks were inappropriate.

After the initial hospitalization, four patients underwent cardiac surgery (three coronary artery bypass grafting and

Figure 2 Changes in LVEF (A), LVES diameter (B), and LVED diameter (C) over time in patients with ischaemic and non-ischaemic heart failure. LVED, left ventricular end-diastolic; LVEF, left ventricular ejection fraction; LVES, left ventricular end-systolic.



one mitral valve replacement) and eight patients received catheter-based therapy (eight percutaneous coronary interventions, one MitraClip implantation, and one transcatheter aortic valve implantation).

Discussion

This study describes the LV remodelling and long-term prognosis in a cohort of patients with new-onset severe HFrEF, who required admission and in many cases needed inotropes (48% of the patients) and short-term mechanical support (23% of the patients), but who were eventually successfully weaned from support and discharged with medication. The improvement in LVEF was already present at 6 months in the patients with non-ischaemic aetiology and increased exponentially up to 2 years of follow-up, which mirrored the decrease of LV diameters, both end-diastolic and end-systolic. Furthermore, in these patients, the severity of mitral regurgitation significantly decreased at 6 months. On the contrary, in their ischaemic counterparts, the LVEF modestly increased linearly during follow-up, while LV diameters and the severity of mitral regurgitation did not change. The prognosis of this subpopulation of patients discharged on medication after the first episode of severe acute HFrEF is much better as compared with other studies on large cohorts with acute decompensated HF.

Indeed, it is not very unique to study recovery of LVEF and its relation with prognosis.^{9–12} However, our study has some unique strengths. First, we included a less heterogenic population than others. Although other studies did not include patients with de novo HF specifically, in our opinion, LV remodelling should be studied in an early stage of HF because recovery of the LVEF takes place early. Further, compared with other studies, echocardiography in our study was repeated after a relatively short period. This enables us to say something about the trend in remodelling. Last, we included clinical variables that are missing from other studies.

Left ventricular remodelling

Improvement of LVEF in a minority of patients with dilated cardiomyopathy within 6 months and therefore deferral of listing for HT was already reported in 1994, before the introduction of beta-blocker therapy.¹³ However, after the introduction of beta-blockers and aldosterone antagonists in HF treatment, a significant improvement of LVEF was shown in one-third of patients with recently diagnosed HFrEF, and in half of them, this improvement already occurred at 6 months.¹⁴ More studies have investigated improvement of LVEF and prognosis in outpatients with recent onset dilated cardiomyopathy.¹⁵ To the best of our knowledge, our study is the first to investigate the LV remodelling in a subpopulation of severe new-onset HFrEF that required admission.

A large proportion of our patients received digoxin (57% of the patients with non-ischaemic HF). The beneficial properties of digoxin in acute HF syndromes have been attributed to the improvement of haemodynamics by attenuating tachycardia

Figure 3 Severity of mitral valve regurgitation in patients with ischaemic (A) and non-ischaemic (B) heart failure.

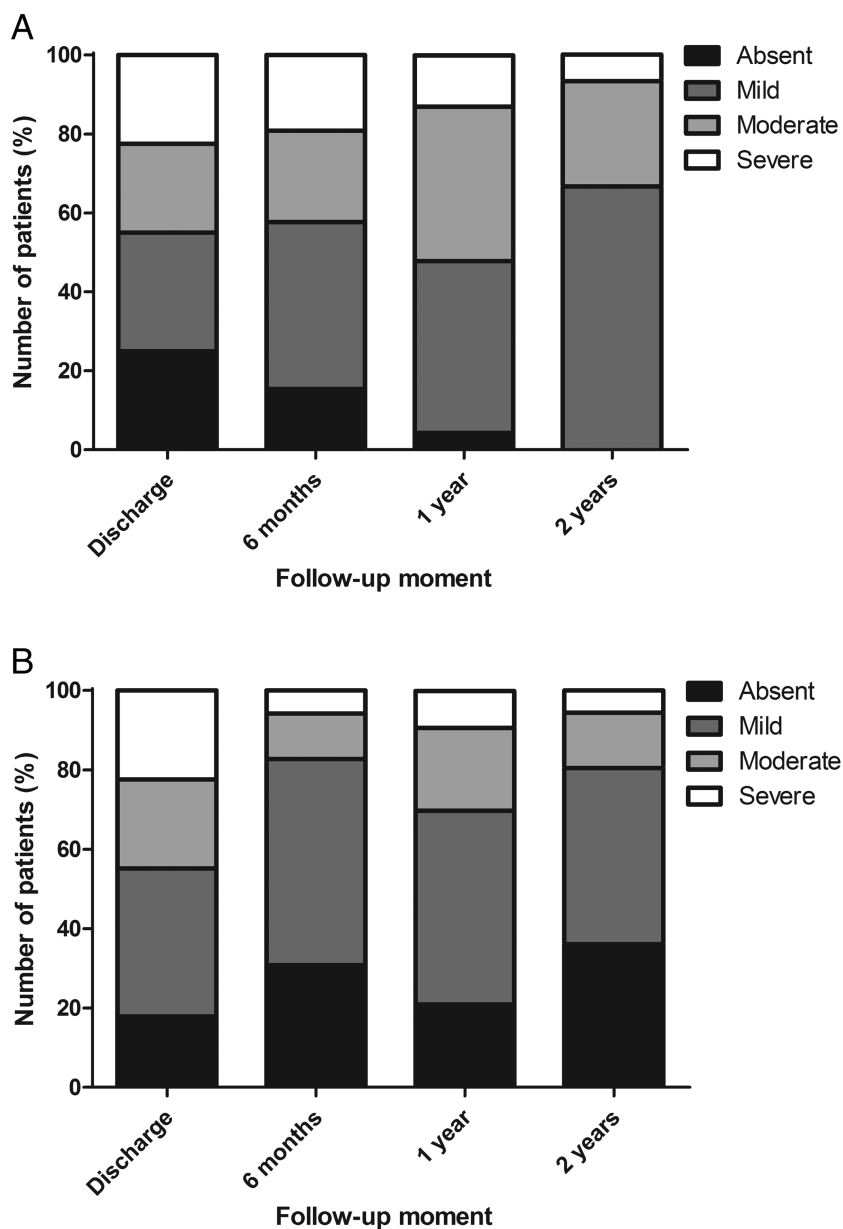


Table 3 N-terminal prohormone of brain natriuretic peptide during follow-up in patient with ischaemic and non-ischaemic heart failure

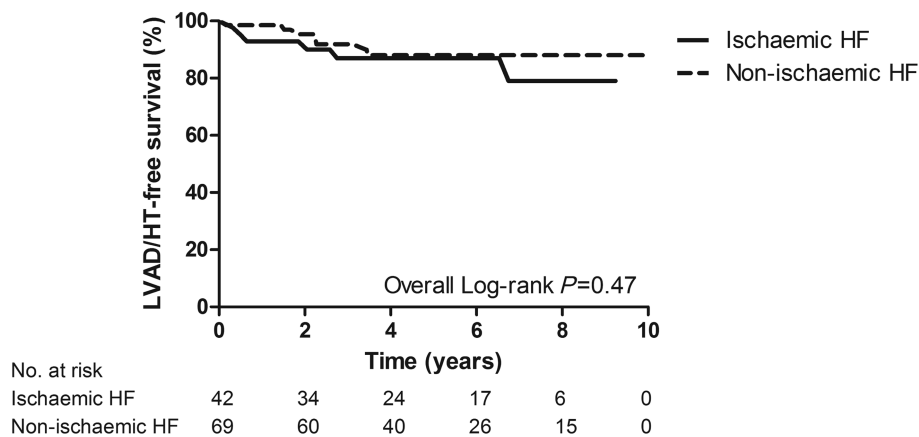
	Ischaemic HF	Non-ischaemic HF	P-value
Baseline	577 (392–738)	234 (87–401)	0.02
6 months	237 (101–514)	48 (22–114)	<0.001
1 year	170 (80–285)	38 (18–81)	0.004
2 years	137 (79–294)	22 (12–95)	0.008
3 years	74 (41–151)	16 (6–124)	0.17

HF, heart failure.

Results depicted as median (interquartile range).

without negative inotrope effects and to the absence of side effects at lower dosages.¹⁶ The inotropy-dependent low-output patients in our cohort could be immediately treated with digoxin, while introduction of beta-blocker was postponed until the relief of congestion and achievement of euvoaemia, according to a previously published protocol from our centre.¹ At discharge, >90% of patients were treated by beta-blockers in combination with ACE-inhibitors or angiotensin receptor blockers. The patients were followed weekly thereafter at our outpatient clinic, and the medication

Figure 4 LVAD/HT-free survival curve of patients with ischaemic and non-ischaemic HF. HF, heart failure; HT, heart transplantation; LVAD, left ventricular assist device.



has been up titrated till maximum tolerated dosage according to the European Society of Cardiology HF guidelines.¹⁷

We found a clear difference in LV remodelling between patients with non-ischaemic HF and those with ischaemic HF. This difference can primarily be explained by the aetiology of HF. To qualify for LV remodelling, there should be limited replacement fibrosis and enough viable myocardium.¹⁸ Patients with ischaemic HF are less potential to develop LV remodelling because ischaemic myocardium is more extensively and irreversibly damaged. In contrast, patients with non-ischaemic HF may have more viable myocytes.^{7,18} Indeed, it has been observed that some specific non-ischaemic causes like myocarditis and peripartum cardiomyopathy have a relatively high chance to recover.⁶ However, optimal HF treatment may be another explanation for LV remodelling. HF treatment and in particular neurohumoral blockers have been associated with LV remodelling.^{19,20} Optimal therapy with beta-blockers, ACE-inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists is of great importance.

In literature, several other factors, besides optimal medical treatment, have been found to be associated with LVEF improvement.^{9–12,14} In several studies, female sex has been associated with improvement of LV function.^{9–12} In our study, the distribution of sex was not different between the ischaemic and non-ischaemic HF, and we found no difference in the outcomes. However, the size of our cohort may be too small to assess the effect of sex on top of the medical treatment. The presence of hypertension and diabetes have also been correlated with LVEF changes. Furthermore, it has been reported that LVEF improvement was more common in patients with HF with non-ischaemic cause than in subjects with ischaemic HF. However, so far, the time-dependent evolution of LV remodelling including LVEF, LV dimensions, and mitral valve regurgitation has

never been compared in patients with ischaemic and non-ischaemic HF.

Further, we also found a decrease in severity of mitral valve regurgitation. Decrease in mitral valve regurgitation has found to be associated with better prognosis and symptom relieve.^{21,22} Our study showed that LV remodelling by medical treatment also leads to reduction of mitral valve regurgitation, which is consistent with other reports.^{21–23}

Prognosis

The prognosis of patients with acute HF has been studied extensively. Mortality rates of up to 35% at 1 year^{24–28} and up to 75% at 5 years of follow-up^{25,27} are reported. These cohorts included patients with acute HF of the whole broad range: both new-onset acute HF and decompensated chronic HF, with and without cardiac history, and patients admitted to secondary and tertiary hospitals. Notably, our patients had a more favourable prognosis with an LVAD/HT-free survival of 88% during a follow-up of up to 10 years. The better prognosis in our study can be explained by the specific inclusion of new-onset HF in patients without a history of HF or any structural heart disease and exclusion of patients who could not be weaned from advanced support and received a permanent LVAD or died in hospital. Furthermore, we included patients in a more recent era than previous studies, and, hence, our patients were treated with the broad range of guideline-based HF medication, including a large number of patients using beta-blocker therapy.

Furthermore, we found that improvement in LVEF was associated with a better prognosis. This was in accordance with a recent meta-analysis by Jorgensen *et al.*²⁹ who showed that patients in whom LVEF improved were found to have a better

prognosis consisting of both improved survival rate and lower risk of appropriate ICD shocks.

Implications for clinical practice

As already mentioned, patients with HFrEF should be treated according to the guidelines with optimal dosage of beta-blocker, renin angiotensin aldosterone system inhibition, and mineralocorticoid receptor antagonists.¹⁷ Recently, data from the PIONEER-HF trial show that introduction of angiotensin receptor neprilysin inhibitor (ARNI) during hospitalization for acute HF significantly improved the clinical outcome as compared with ACE-inhibitors.³⁰ Although not investigated in our study, replacing ACE-inhibitor by ARNI should be considered before discharge or at the outpatient clinic. Optimal medical treatment does not only carry prognostic benefit, but it may also contribute to the LV remodelling. Because we found that remodelling may occur until 2 years after the initial event mainly in non-ischaemic HF, clinicians should optimize medication and give time to remodel before concluding that LVAD or HT is necessary.²

Because almost half of our study patients needed inotrope and/or vasopressor support and almost a quarter of the patients received mechanical circulatory support, this indicates that we included very ill patients with HF. Despite this adverse clinical presentation, we found remodelling in a significant part of these patients. Because we included patients with severe HFrEF with or without cardiogenic shock at presentation, part of them may currently qualify for LVAD or HT. Indeed, LVAD therapy also leads to cardiac remodelling. However, LVAD therapy has several potential complications like stroke, pump thrombosis, bleeding, and infection.³¹ Therefore, we propose persuasion of the attempts to wean the support in patients with the first hospitalization for new-onset HFrEF during concomitant optimization of HF medication. Only under the condition that patients remain inotrope dependent, one should proceed to urgent LVAD or HT.

It still remains uncertain how patients with recovered LVEF should be treated in the long term. Indeed, patients with recovered LV function may have abnormal biomarker levels and may still have an adverse long-term prognosis.³² Recently, the TRED-HF trial has shown that withdrawal of pharmacological treatment negatively influenced the course of dilated cardiomyopathy.⁸ In our hospital, patients with completely recovered LVEF and without HF symptoms are continued to be treated with beta-blocker and ACE-inhibitor or angiotensin receptor blocker. Basuray and Fang⁶ also advocated continuation of HF medication after recovered LVEF in patients with several different aetiologies.

Limitations

Several study limitations should be acknowledged. First and foremost, the retrospective nature of this study resulted into a significant number of missing LVED diameters, LVES diameters, LVEF, mitral valve regurgitation, and N-terminal pro-hormone of brain natriuretic peptide measurements during follow-up. However, we used the delta remodelling in the linear mixed-effects models in order to make optimal use of all the available measurements. Secondly, despite the long inclusion period, we had a relatively small number of patients. This is suggesting that there are only a limited number of patients with severe new-onset HFrEF without any previous structural heart disease requiring hospitalization. Thirdly, because we are a tertiary referral centre, part of our patients initially presented in another hospital. Consequently, there may be a bias because a number of patients were not referred to our hospital, which may reduce the external validity. Next, we excluded patients who died or received an LVAD during the initial hospital admission, because we designed this study to investigate the LV remodelling in patients treated with medical HF therapy. However, this may have influenced the prognostic endpoint of this study. Furthermore, there were low implantation rates of ICD and cardiac resynchronization therapy. This could be explained by the LVEF improvement during follow-up and therefore the lack of indication for ICD. Also, the low number of events did not allow a proper multivariable analysis, because the event-per-variable ratio would lead to significant overfitting in the model and a high risk of statistical error. Lastly, we did not measure LV volumes, which could give additional information regarding LV remodelling.

We also acknowledge the lack of treatment with ARNIs and sodium-glucose co-transporter inhibitors, which were not available at the moment of our study but nevertheless may present a limitation for extrapolation of our results to the modern clinical practice.

Conclusions

This study investigated LV remodelling and prognosis in patients with new-onset acute severe HFrEF. There was no difference in prognosis between patients with ischaemic and non-ischaemic HF, although the LV remodelling differed considerably between these two patient groups. In contrast to those with ischaemic HF, patients with non-ischaemic HF showed significant LV remodelling already at 6 months, which progressed exponentially in the first 2 years of medical treatment. Hence, our study emphasizes the importance of optimal medical treatment at discharge, as this is a determinant of LV remodelling and a good long-term prognosis.

Conflict of interest

None 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.

Table S1. Fitting values belonging to Figure 2.

Table S2. Number of missing values.

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