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Longitudinal evaluation of ventricular ejection fraction and NT-proBNP across heart failure subgroups

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Running title: EF improvement with modern HF therapy

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Abstract

Objectives

Left ventricular ejection fraction (EF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are important surrogate markers of cardiac function and stress. Randomized trials of heart failure (HF) have shown improvements in survival in patients with reduced EF (<40%, HFrEF) but not with preserved EF (≥50%, HFpEF) or mid-range EF (40-49%, HFmrEF). Limited information is available on the trajectory of EF in contemporary heart failure management programs (HFMPs).

Design

201 HF patients consecutively enrolled 2010-2011 in the outpatient-based HFMP of Skåne University Hospital in Lund were included in the study. Probable etiology, EF, NT-proBNP and medications were assessed at baseline and 1 year after enrollment.

Results

HFrEF was the most common heart failure subgroup (78.1% of patients) in this HFMP, followed by HFmrEF (14.9%) and HFpEF (7.0%). The most common etiology was ischemic heart disease (IHD, 40.8%).

Complete recovery of EF (>50%) was rare; 14.1% of patients with HFrEF and 26.7% with HFmrEF, some degree of improvement was observed in 57.7% and 46.7% of patients. LVEF improved on average 9.1% in patients with HFrEF ($p<0.001$) and NT-proBNP decreased from 4,202 to 2,030 pg/ml ($p<0.001$). A similar trend was noticed for the HFmrEF group but was not statistically significant. The improvement in LVEF

was consistent across subgroups with HF attributable to IHD (6.2%), idiopathic dilated cardiomyopathy (7.1%) and tachycardia-induced HF (17.5%).

Conclusions

This study provides estimates of the improvement in LVEF and NT-proBNP that can be expected with contemporary management across subgroups of HF and different etiologies in a contemporary HFMP.

Introduction

The prognosis of heart failure (HF) has improved markedly during the last two decades, as has been reported from prospective cohort studies and nationwide registers (1-3). These observations likely reflect the introduction of several novel pharmacologic treatment alternatives in the last three decades and the implementation of treatment programs with well-documented effects on both morbidity and mortality (1,4-9). Clinical trials of new therapies such as beta-receptor blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and mineralocorticoid antagonists have typically included patients with reduced left ventricular ejection fraction (EF <40%, HFrEF). None of the handful of clinical trials performed to date for HF with preserved EF (EF≥50%, HFpEF) have found evidence of efficacy (10), and trials are currently lacking for patients with mid-range EF (40-49%) as recently acknowledged by the European Society of Cardiology (ESC) in the 2016 Clinical practice guidelines (11).

Improvements in EF and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have been shown to be associated with improved outcomes in patients with HFrEF, but the expected improvements in these parameters with modern therapy in the setting of a modern heart failure management program (HFMP) remain unclear, particularly for HFmrEF (12-15). A few recent studies have highlighted the greatly improved prognosis in patients who achieve complete recovery of EF (12,16).

HF consists of a heterogeneous group of etiologies, potentially with different propensity for treatment response. Limited information is available on the improvement after adequate therapy across etiologies.

The aim of the current study was therefore to investigate longitudinal trends in measures of ventricular function and use of evidence-based and guideline-recommended medical therapies in patients enrolled in a Swedish HFMP, both overall, across EF subgroups, and across a range of etiologies.

Material and Methods

All patients enrolled in the outpatient-based HFMP at the Department of Cardiology of Skåne University Hospital in Lund in 2010 and 2011 were screened and included if either echocardiography or NT-proBNP were available at the time of the baseline visit. The patient cohort enrolled at the HFMP was referred from secondary level care centers, primary care units and for follow-up after hospital admission. HF patients are generally referred to the HFMP early after HF diagnosis for titration of evidence-based medications and for diagnostic evaluation by a cardiologist (17-20). Transcripts of first patient visits were retrieved from administrative registers and clinical data was extracted retrospectively from medical records. The study was performed as part of an ethically approved clinical quality control program of the HFMP at Skåne University Hospital.

The HFMP of the Skåne University Hospital catchment area covered 320,000 inhabitants on December 31, 2010. At the baseline visit, the responsible cardiologist evaluates each patient regarding probable etiology and current medication. Guideline adherence was evaluated based on the European Society of Cardiology guidelines available at the time of the study and patients were stratified into HF with reduced, mid-range and preserved EF as described in the current guidelines (11). As the study was carried out before introduction of angiotensin receptor neprilysin inhibitors (21) these were not included in the current analysis. Baseline and follow-up echocardiograms were used to evaluate EF. Data on EF were extracted from these reports. Blood samples are routinely evaluated, including NT-proBNP. Dose titration and patient education is performed at follow-up visits to an experienced nurse specialized in heart failure, and a follow-up visit with a cardiologist is scheduled after

12 months. During the time period in the current study, patients also routinely underwent echocardiography and sampling of NT-proBNP both at the initial examination and at the time of the follow-up visit, the latter in large part for academic purposes.

Patients lost to follow-up were excluded from the longitudinal analysis. Follow-up echocardiographic data were missing in 38 subjects and NT-proBNP in 23 individuals, of which 21 individuals lacked both echocardiographic and NT-proBNP data at follow-up.

Patients were classified according to EF at the baseline visit as HFrEF, HFmrEF or HFpEF as outlined by the ESC 2016 Clinical practice guidelines (11). A diagnosis of heart failure in HFpEF and HFmrEF requires additional diagnostic criteria in addition to typical symptoms: elevated levels of natriuretic peptides and evidence of ventricular hypertrophy, atrial enlargement, or diastolic dysfunction (11). Information on the most probable etiology of HF was extracted through retrospective evaluation of medical files. Cases with uncertain or multiple potential etiologies were reviewed by one or two cardiologists (Ö.R. and J.G.S). Complete recovery of EF in patients with initial HFrEF or HFmrEF was considered with improvement to >50%, although improvement to >40% was also explored in HFrEF patients. Differences in clinical characteristics at baseline and follow-up visits were examined using non-parametric tests, with the Mann-Whitney U test or the Wilcoxon signed-rank test (used for changes in EF and NT-proBNP). One-way ANOVA was used to test improvements in EF and NT-proBNP across different etiologies. P-values <0.05 were

considered statistically significant. Statistical analyses were performed using IBM SPSS (version 24.0 IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

A total of 201 patients were enrolled in the study, of which 21 patients were lost to follow-up. 38 patients lacked a follow-up echocardiogram. The mean age at baseline was 66.2 years for patients with HFrEF, 63.7 for patients with HFmrEF and 64.4 years for patients with HFpEF, as shown in Table 1. A majority of patients were men across all subgroups, HFrEF (81.3%), HFpEF (58.3%), and HFmrEF (72.7%). The average time to the follow-up echocardiogram was 355 days, and 293 days to the follow-up NT-proBNP measurement. NYHA classification generally improved for patients with HFrEF (NYHA I and II 53.6% at baseline versus 70.6% at follow-up) and HFmrEF (NYHA I and II 47.1% versus 69.3%) during follow-up. In the group with preserved systolic function NYHA classification data were largely lacking at follow-up. In the HFrEF group, blood pressure and pulse rate did not differ between baseline and follow-up visits (126/78 versus 126/76 and 73.7 versus 71.3 respectively). For patients with HFmrEF and HFpEF lowered pulse rate were noted at follow-up (69.0 and 64.9 respectively) versus baseline (79.4 and 73.7 respectively) but there were no large differences between blood pressure measurements.

Improvement of EF and NT-proBNP

A total of 128 patients with HFrEF underwent serial echocardiograms. Patients with HFrEF had a mean baseline EF of 27.9%, which improved with an average of 9.1% to 37.0% at the follow-up visit (Table 1, $p<0.001$). Complete recovery of EF to >50% was observed in 22 patients (14.1%) and to 40-49% in 47 patients (30.1%). Some degree of improvement was observed in 57.7% of patients. At the baseline visit the

average NT-proBNP was 4,202 pg/ml, which decreased to 2,030 pg/ml at follow-up ($p<0.001$).

Patients with HFmrEF had a mean EF of 42.5% at baseline, which improved by an average of 4.0% to 46.5% at the follow-up visit, but the difference did not achieve statistical significance ($p=0.069$). Complete recovery to >50% was achieved in 8 patients (26.7%) and 14 patients (46.7%) experienced some degree of improvement. Similarly, a trend towards decreased NT-proBNP was observed but did not achieve statistical significance, from 2212 pg/ml to 1750 ($p=0.078$)

No significant changes were observed in the group with preserved LVEF, although a non-significant trend towards decreased pro-BNP was noted, from 3,512 to 2,589 pg/ml ($p=0.48$).

Impact of etiology

The most common etiology of HF in this study was ischemic heart disease (IHD, 40.8%), followed by idiopathic dilated cardiomyopathy (DCM, 26.4%), tachycardia-induced HF (TIC, 8.5%) and hypertension (6.0%) as shown in Table 2. IHD was the most prevalent etiology in all HF subtypes. TIC was more common in the HFmrEF group than the HFrEF and HFpEF groups. DCM, TIC and hypertension caused no cases of HFpEF, which had a heterogeneous background (IHD 28.6%, hypertrophic cardiomyopathy 28.6%, valvular disease 21.4%).

In longitudinal analyses for the major etiological subgroups (Table 3), the smallest improvement was observed for HF on the basis of IHD, with an improved EF from

30.0% to 36.2% (+6.2%, p<0.001) in this group. EF also improved in patients with DCM from 28.5% to 35.6% (+7.1%, p=0.001), more markedly in patients with TIC from 34.3% to 51.8% (+17.5%, p=0.001) and in patients with hypertensive HF from a baseline EF of 29.4% to 40.0% at follow-up (+10.6%, p=0.01). The improvement in EF for patients with TIC was significantly larger than for patients with IHD and DCM (p=0.007 and 0.016 respectively). Patients with TIC also more commonly had complete recovery of EF (53.3%) than other major etiologies. Functional grade, according to the NYHA classification, improved for all etiologies. Patients with hypertension had the smallest improvement in functional grade but were more commonly classified as NYHA I-II at baseline (NYHA I-II 66.7% versus 71.4%). There was no substantial difference in pulse rate or blood pressure at follow-up compared to baseline examination for IHD, DCM and TIC. Patients with hypertension as underlying etiology had lower blood pressure at follow-up (mean 123/75) compared to baseline (mean 134/81).

NT-proBNP decreased after enrollment in the HFMP for patients with ischemic heart disease, DCM and hypertension (Table 4). Patients with TIC had lower NT-proBNP at baseline and did not improve significantly from baseline to follow-up. Patients with DCM and hypertension exhibited the most pronounced differences for NT-proBNP, with a reduction of 2,597 and 3,742 pg/ml respectively.

Only 1 patient with TIC was treated with antiarrhythmic drugs (amiodarone) and 3 patients (20%) underwent electroconversion during follow-up. Rhythm control was rare, 66.7% (10) of patients with TIC had atrial fibrillation or flutter at baseline visit and 63.6% (7) had atrial arrhythmia at follow-up.

Medical therapy and adherence to guidelines

At baseline, the proportion of patients with guideline-recommended medications was low (Table 1). In the HFrEF group, 39.8% were treated with beta-blockers, 45.3% with either an ACE-inhibitor or ARB, and 16.4% with a mineralocorticoid antagonist (MRA). These proportions improved to 91.4%, 96.1% and 53.1%, respectively at the end of follow-up. At baseline, 11 (8.6%) patients with HFrEF were prescribed the target dose for beta-blockers and 15 (11.7%) target dose for ACE-inhibitors or ARBs. The proportions improved during follow-up to 17 (13.3%) and 52 (40.6%) respectively. Adherence to guidelines was somewhat better for patients with HFmrEF at baseline, where 54.2% had been prescribed beta-blockers, 41.7% ACE-inhibitors/ARBs and 33.3% MRAs. At the end of follow-up 83.3% were prescribed beta-blockers of which 12.5% reached target doses. The prescription of ACE-inhibitors/ARBs increased to 91.7%, of which 29.2% received the target dose. Use of MRAs increased to 50.0% in this patient cohort. For patients with preserved EF the proportion prescribed a beta-blocker increased from 63.6% to 81.8%, ACE-inhibitors/ARBs from 27.3% to 63.6%, and the prescription of mineralocorticoid antagonists remained the same at 18.2%.

18 patients were offered resynchronization therapy due to bundle branch block and persisting symptomatic HF. These patients had a mean EF of 27.4% at both baseline visit and follow-up, which likely contributed to the decision of resynchronization therapy. The most common etiology in these patients were DCM (8, 44.4%) and IHD (7, 38.9%).

Discussion

In the current study of heart failure, although complete recovery of EF was rare, we observed substantial improvements in EF and NT-proBNP across diverse etiologies for HF with reduced EF over the first year following enrollment in a HFMP. The largest improvement was not surprisingly observed for TIC, consistent with the view that rate control often can result in complete restitution of EF in TIC (22-23), 53.3% of patients with TIC had complete recovery of EF during follow-up, surprisingly without a substantial rate difference between baseline and follow-up. Likely, some manner of rate control had been achieved prior to enrollment in the HFMP. Rhythm control was seldom achieved and most patients with TIC had persistent atrial arrhythmia at follow-up. Interestingly, substantial improvement was also observed in HF with hypertension as the only identified potential etiology. Furthermore, in the small number of patients with HFpEF a non-significant trend towards reduced NT-proBNP was observed.

Patients with HFmrEF represent a subgroup that has not been well studied, as recently acknowledged by the definition of this group in the ESC guidelines (11). HFmrEF represented almost 15% of the population in this HFMP. Trends towards increased EF and decreased NT-proBNP at follow-up were noticed but these changes were not statistically significant, likely due to a lack of power as the study sample was small. Patients with HFmrEF were younger (63.7 years) than patients with HFrEF and HFpEF. Interestingly, numerically more cases were caused by TIC and less by IHD than in the other HF subgroups. It can be speculated that this group is likely to benefit from guideline-based treatment similarly to the HFrEF group, but larger, randomized studies are needed to establish the adequate treatment strategy in this cohort. Large

studies will also be needed to determine the optimal management in patients who achieve complete recovery of EF, which is characterized by a good prognosis (12,16,24-25). For patients with both HFrEF and HFmrEF enrollment in an HFMP was associated with improved functional classification, as would be expected.

The most common etiologies of HF in the present study were IHD, DCM, TIC and hypertension, which is overall in agreement with previous studies (26). However, the proportion of patients that had HFpEF and hypertensive HF were substantially lower than in reports of HF in the general population, in which HFpEF and HF with reduced EF are considered to be equally common, and hypertensive HF often presents with preserved EF (27). This is likely due to the fact that a majority of patients with preserved LVEF is older, have a large burden of comorbid diseases, and therefore are often treated in primary care or at nursing homes (27). This observation is also reflected in the heterogeneous etiology observed for these patients at our HFMP. Improved blood pressure control and, as a result, reduced afterload for patients with hypertension likely contributed to the improved EF reported for this patient cohort.

Patients with TIC had the most pronounced improvements in LVEF but their NT-proBNP levels remained similar. This could reflect the low proportion of patients with rhythm control in the current study as atrial arrhythmia is independently (and irrespectively of other markers of ventricular function) associated with an increase in NT-proBNP (28-29). Resynchronization therapy was not associated with a significant increase in ventricular function. This was likely caused by two contributing factors, the short follow-up after pacemaker implantation to follow-up echocardiogram (mean 3.2 months), and the patient population, which largely consisted of patients with heart

failure due to ischemic heart disease. Previous studies have shown that there is a time dependent improvement in LVEF (30) and that the benefit of resynchronization therapy is smaller for patients with ischemic heart disease (31) which could explain the findings.

Patients were often treatment-naïve at baseline, but the proportion with evidence-based medications and target doses increased during follow-up at the HFMP. Although the goals of the HFMP are to initiate and titrate such medications to as near recommended doses as possible, about 10% in this real-world population did not receive beta-blockers and ACE-inhibitors/ARB, illustrating the burden of compliance issues and side effects of medications in this population. These numbers are similar to other reported HFMPs (32) and substantially lower than in the Swedish primary care population (33). It seems likely that the improvements seen in the current study would be more pronounced if a larger percentage of patients would tolerate evidence-based treatment at target doses.

Limitations

The current study was retrospective and therefore suffers from the limitations inherent to such study designs. Specifically, procedures for echocardiography and management were not prespecified. However, the limited number of physicians, nurses and echocardiographers at our center provides conditions for relatively homogeneous estimates. Diastolic function was not assessed, which could have added important information on possible improvements in this parameter for patients with HFmrEF and HFpEF.

Conclusions

In summary, enrollment in a HFMP was associated with an improvement in measures of systolic function after 1 year of follow-up. This improvement was consistent across the range of major etiologies for heart failure with reduced EF and less pronounced in HFmrEF, although complete recovery of EF was more commonly observed for patients with HFmrEF. Our findings provide estimates of the improvements in EF and NT-proBNP that can be expected in contemporary heart failure management programs. Particularly striking improvements in EF were observed in patients with HF on the basis of tachyarrhythmia and hypertension.

Disclose of interest

The authors report no conflict of interests.

Authors' contributions

AM drafted the manuscript, performed statistical analysis and participated in the interpretation of the data. PO participated in the design of the study and performed data collection and statistical analysis. MBW performed data collection. ÖR conceived of the study and participated in the design of the study and drafting of the manuscript. JGS conceived of the study, participated in the study design and contributed to drafting of the manuscript. All authors read and approved the final manuscript.

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Table 1. Clinical characteristics at baseline and follow-up.

	HFrEF (<40%, N)			HFmrEF (40-49%, N)			HFpEF (≥50%, N)		
	Baseline	Follow-up	p	Baseline	Follow-up	p	Baseline	Follow-up	p
	128	128		24	24		11	11	
Age, mean (SD)	66.2 (10.2)			63.7 (14.7)			64.4 (19.9)		
Men, N (%)	104 (81.3)			14 (58.3)			8 (72.7)		
NYHA classification, N (%)									
I	19 (17.0)	21 (30.9)		2 (11.8)	5 (38.5)		1 (12.5)	0 (0)	
II	41 (36.6)	27 (39.7)		6 (35.3)	4 (30.8)		3 (37.5)	1 (33.3)	
IIIa	33 (29.5)	12 (17.6)		5 (29.4)	2 (15.4)		2 (25.0)	0 (0)	
IIIb	15 (13.4)	8 (11.8)		4 (23.5)	2 (15.4)		2 (25.0)	2 (66.7)	
IV	4 (3.6)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Pulse, mean (SD)	73.7 (16.0)	71.3 (15.0)		79.4 (12.4)	69.0 (10.2)		73.7 (14.2)	64.9 (8.5)	
Blood pressure, mean	126/78	126/76		124/74	130/75		131/75	127/72	
LVEF, mean % (SD)	27.9 (5.9)	37.0 (12.1)	<0.001	42.5 (3.4)	46.5 (9.5)	0.069	57.0 (4.0)	55.7 (8.7)	0.593
NT-proBNP, (N)	153	114		27	27		15	13	
NT-proBNP, mean pg/ml, (SD)	4,202 (5,397)	2,030 (3,067)	<0.001	2,212 (3,093)	1,750 (2,241)	0.078	3,512 (5,434)	2,589 (2,776)	0.480
ACE inhibitors, N (%)	33 (25.8)	82 (64.1)		6 (25.0)	15 (62.5)		3 (27.3)	6 (54.5)	
Angiotensin receptor blockers, N (%)	25 (19.5)	41 (32.0)		4 (16.7)	7 (29.2)		0 (0)	1 (9.1)	
ACEI/ARB target dose, N (%)	15 (11.7)	52 (40.6)		1 (4.2)	7 (29.2)		1 (9.1)	2 (18.2)	
Beta-blockers, N (%)	51 (39.8)	117 (91.4)		13 (54.2)	20 (83.3)		7 (63.6)	9 (81.8)	

Beta-blockers target dose, N (%)	11 (8.6)	17 (13.3)	3 (12.5)	3 (12.5)	2 (18.2)	1 (9.1)
Mineralocorticoid antagonists, N (%)	21 (16.4)	68 (53.1)	8 (33.3)	12 (50.0)	2 (18.2)	2 (18.2)
Diuretics, N (%)	39 (30.5)	73 (56.9)	10 (41.7)	11 (45.8)	5 (45.5)	6 (54.5)
Digoxin, N (%)	13 (10.2)	12 (9.4)	3 (12.5)	5 (20.8)	0 (0)	1 (9.1)

Clinical characteristics, including markers of ventricular function and medical therapy. Only patients with a follow-up echocardiogram is included in the baseline characteristics. Patients with serial NT-proBNP measurement without follow-up echocardiogram are included in the reported NT-proBNP values but excluded from the other baseline characteristics. Target dose refers to doses recommended by current practice guidelines from ESC.[17] LVEF, left ventricular ejection fraction. MRA, mineralocorticoid antagonist. SD, standard deviation.

Table 2. Probable etiology of HF for patients enrolled in a HFMP.

Etiology	Total	HFrEF	HFmrEF	HFpEF
Ischemic heart disease	82 (40.8)	70 (44.6)	8 (26.7)	4 (28.6)
Idiopathic dilated CM	53 (26.4)	46 (29.3)	7 (23.3)	0 (0)
Tachycardia-induced CM	17 (8.5)	12 (7.6)	5 (16.7)	0 (0)
Hypertension	12 (6.0)	10 (6.4)	2 (6.7)	0 (0)
Chemotherapy-induced CM	8 (4.0)	6 (3.3)	2 (6.7)	0 (0)
Valvular disease	6 (3.0)	1 (0.6)	2 (6.7)	3 (21.4)
Hypertrophic CM	5 (2.5)	1 (0.6)	0 (0)	4 (28.6)
Myocarditis	5 (2.5)	3 (1.9)	1 (3.3)	1 (7.1)
Alcohol-induced CM	2 (1.0)	2 (1.3)	0 (0)	0 (0)
Idiopathic diastolic dysfunction	2 (1.0)	0 (0)	1 (3.3)	1 (7.1)
Sarcoidosis	2 (1.0)	2 (1.3)	0 (0)	0 (0)
Amyloidosis	1 (0.5)	1 (0.6)	0 (0)	0 (0)
Connective tissue disease	1 (0.5)	1 (0.6)	0 (0)	0 (0)
Constrictive pericarditis	1 (0.5)	1 (0.6)	0 (0)	0 (0)
Drug-induced CM	1 (0.5)	0 (0)	1 (3.3)	0 (0)
Muscular dystrophy	1 (0.5)	1 (0.6)	0 (0)	0 (0)
Peripartum CM	1 (0.5)	0 (0)	1 (3.3)	0 (0)
Stress-induced CM	1 (0.5)	0 (0)	0 (0)	1 (7.1)

Shown are numbers and percentages within each subgroup of HF and across the combined subgroups. HF, heart failure. HFMP, heart failure management program. CM, cardiomyopathy.

Table 3. Improvement in EF for major etiologies.

	Ischemic heart disease	Idiopathic DCM	Tachycardia-induced CM	Hypertension
Baseline / follow -up (n)	77 / 57	53 / 44	17 / 15	12 / 11
EF at baseline (mean, SD)	30.0% (10.0)	28.5% (7.4)	34.3% (6.4)	29.4% (6.7)
EF at follow-up (mean, SD)	36.2% (11.1)	35.6% (12.1)	51.8% (9.0)	40.0% (7.1)
EF, improvement	6.2% (p<0.001)	7.1% (p=0.001)	17.5% (p=0.001)	10.6% (p=0.01)
Improved EF	66%	64%	87%	73%
Lowered EF	16%	20%	7%	9%
Complete recovery (EF >50%)	8 (14.0%)	7 (11.4%)	8 (53.3%)	1 (8.3%)
Partial recovery (EF >40%)	7 (12.3%)	5 (15.9%)	5 (33.3%)	4 (33.3%)
NYHA classification, N (%) at baseline and follow-up				
I	2 (4.0) – 5 (17.9)	8 (20.0) – 13 (44.8)	3 (27.3) – 2 (66.7)	4 (44.4) – 1 (14.3)
II	23 (46.0) – 12 (42.9)	13 (32.5) – 9 (31.0)	4 (36.4) – 1 (33.3)	2 (22.2) – 4 (57.1)
IIIa	13 (26.0) – 4 (14.3)	12 (30.0) – 4 (13.8)	4 (36.4) – 0 (0.0)	3 (33.3) – 2 (28.6)
IIIb	10 (20.0) – 7 (25.0)	5 (12.5) – 3 (10.3)	0 (0.0) - 0 (0.0)	0 (0.0) - 0 (0.0)
IV	2 (4.0) – 0 (0.0)	2 (5.0) – 0 (0.0)	0 (0.0) - 0 (0.0)	0 (0.0) - 0 (0.0)

Pulse, mean (SD)				
- Baseline	75.0 (15.2)	76.9 (16.0)	77.1 (22.7)	72.6 (9.2)
- Follow-up	75.5 (12.7)	71.3 (9.3)	75.9 (24.6)	73.3 (11.4)
Blood pressure, mean				
- Baseline	128/74	126/79	120/80	134/81
- Follow-up	127/75	128/78	127/77	123/75

Number of subjects with echocardiography at baseline and the follow-up exam for different etiologies and distribution of left ventricular ejection fraction (LVEF).

Table 4. Improvement in NT-proBNP for major etiologies.

	Ischemic heart disease	Idiopathic DCM	Tachycardia-induced CM	Hypertension
Baseline / follow-up (n)	78 / 70	52 / 49	16/ 14	12 / 11
NT-proBNP, baseline (mean, SD)	4,199 (4,432)	4,019 (5,895)	2,368 (2,918)	5,410 (9,591)
NT-proBNP, follow-up (mean, SD)	3,613 (4,061)	1,422 (1,669)	3,019 (5,927)	1,668 (1,811)
NT-proBNP, improvement	586 (p=0.034)	2,597 (p<0.001)	-651 (p=0.600)	3,742 (p=0.026)

Number of subjects with a baseline NT-proBNP and the follow-up exam for different etiologies and distribution of development of NT-proBNP.