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ORIGINAL ARTICLE

Treatment response in recent-onset heart failure with reduced ejection fraction: non-ischaemic vs. ischaemic aetiology

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Abstract

Aims In heart failure (HF) with reduced left ventricular ejection fraction (HFrEF), the prognosis appears better in non-ischaemic than in ischaemic aetiology. Infrequent diagnostic work-up for ischaemic heart disease (IHD) in HF is reported. In this study, we compared short-term response to initiated guideline-directed medical treatment (GDMT) in recent-onset HFrEF of non-ischaemic (non-IHF) vs. ischaemic (IHF) aetiology and evaluated the frequency of coronary investigation.

Methods and results Patients hospitalized with recent-onset HFrEF [left ventricular ejection fraction (LVEF) $<$ 40%] between 1 January 2016 and 31 December 2019 were included. Treatment response was determined by use of a hierarchical clinical composite outcome classifying each patient as worsened, improved, or unchanged based on hard outcomes (mortality, heart transplantation, and HF hospitalization) and soft outcomes (± ≥10 unit change in LVEF, ± ≥30% change in N-terminal pro-B-type natriuretic peptide, and ± ≥1 point change in New York Heart Association functional class) during 28 weeks of follow-up. The associations between baseline characteristics and composite changes were analysed with multiple logistic regression. Among the 364 patients analysed, 47 were not investigated for IHD. Comparing non-IHF (n = 203) vs. IHF (n = 114), patients were younger (mean age 61.0 vs. 69.4 years, $P < 0.001$) with lower mean LVEF (26% vs. 31%, $P < 0.001$), but with similar male predominance (70.4% vs. 75.4%, P = 0.363). For non-IHF vs. IHF, the composite outcomes were worsened (19.1% vs. 43.9%, $P < 0.001$) and improved (74.2% vs. 43.9%, $P < 0.001$). After multivariable adjustments, IHF was associated with increased odds for worsening [odds ratio (OR) 2.94; 95% confidence interval (CI) 1.51–5.74; P = 0.002] and decreased odds for improvement (OR 0.35; 95% CI 0.18–0.65; $P < 0.001$). In cases without previous IHD or new-onset myocardial infarction (n = 261), a decision for coronary investigation was made in 69.0%.

Conclusions In recent-onset HFrEF, patients with non-IHF responded better to GDMT than patients with IHF. Almost one-third of patients selected for follow-up at HF clinics were never investigated for IHD.

Keywords Heart failure; systolic; Ischaemic heart disease; Non-ischaemic heart failure; Recent-onset heart failure; Treatment response; Coronary investigation

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Introduction

The prognostic impact of ischaemic heart disease (IHD) on mortality in heart failure (HF) with reduced left ventricular ejection fraction (HFrEF) is incompletely elucidated. Two large randomized treatment trials of chronic HFrEF, the EVEREST (Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan) and PARADIGM-HF [Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor (ARNI) with Angiotensin-Converting Enzyme Inhibitor to

Determine Impact on Global Mortality and morbidity in Heart Failure] trials, failed to show any association between mortality and coronary artery disease (CAD), or ischaemic aetiology, respectively, after multivariable adjustments.[1,2] Several observational studies of HFrEF, however, have shown association between mortality and IHD[3–6] as well as with increasing severity of CAD.[3,7,8] Improved long-term prognosis after revascularization further supports an adverse prognostic impact of IHD in HFrEF.[9] Also, lesser left ventricular recovery during the early years of treatment has been shown for IHF compared with non-IHF.[10,11] Studies of new-onset HF report significant CAD or ischaemic aetiology in approximately 25–50% of patients[12–14]; however, American studies report that only a minority of patients with new-onset HFrEF seem to undergo diagnostic work-up for IHD.[15,16]

The concept of a clinical composite outcome was introduced as an alternative assessment of response to treatment.[17] By including changes in the patients' functional status among outcome measures, they are classified as worsened, improved, or unchanged in a hierarchical order. Thus, by taking clinically meaningful changes into account, positive or negative effects may be evaluated also in patients not experiencing hard endpoints. The clinical composite outcome has been used in several therapeutic trials and has detected favourable results in studies originally considered neutral.[18]

The aims of this study were, first, to compare the response to initiated guideline-directed medical treatment (GDMT) in a real-world cohort of patients with recent-onset HFrEF with ischaemic and non-ischaemic aetiology, using a clinical composite outcome, and, second, to evaluate the practice of aetiological work-up.

Methods

Data were extracted from a register of patients 16 to 85 years of age, hospitalized at the Sahlgrenska University Hospital, Gothenburg, Sweden, between 1 January 2016 and 31 December 2019, and discharged with a primary diagnosis code I42 or I 50, according to the International Classification of Diseases, Tenth Revision. Included for analyses were non-transplanted patients with recent-onset non-valvular HFrEF receiving outpatient follow-up at hospital-based HF units at Sahlgrenska University Hospital or Angered Hospital with the intention of GDMT optimization.[19]

Recent onset was defined by neither previous history or medical record of HF nor systolic dysfunction at previous imaging. HFrEF was defined by left ventricular ejection fraction (LVEF) $<$ 40% by any imaging modality. For cases with in-hospital diagnosis of HFrEF, the first recorded LVEF after admission and the last values of laboratory or anthropometric data before discharge were registered. The index date was defined as the date of discharge. Patients hospitalized without in-hospital evaluation of LVEF were included if a subsequent investigation within 6 months established HFrEF. Patients first diagnosed with HFrEF during outpatient investigations were included if they were hospitalized within 6 months thereafter, without previously initiated GDMT. For cases with outpatient HFrEF diagnosis, the index date was the date of HFrEF registration in the medical records, whereas the other variables were obtained at first visit after HFrEF diagnosis.

Measurements of LVEF presented as intervals including values $<$ 40% were included. Date of death was obtained from medical records or administrative software linked to the Swedish Tax Agency, the Swedish administrative authority registering deaths. Patients without evidence-based benefit of GDMT were not included (i.e. patients with amyloidosis, haemodialysis, or transient systolic LVEF reduction only). The registry and the study were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments[20] and approved by the local ethics committee (2013/709-13, 2017/T539-17, and 2021-01644).

Grouping

HFrEF aetiology was classified as *ischaemic (IHF)* when the extent of present CAD was judged sufficient to explain the myocardial dysfunction, that is, significant three-vessel disease or one- or two-vessel disease (proximal or mid-vessel) in a myocardial region of reduced contractility. Angiography data were collected from the medical records. If no angiography was performed or a previous angiogram was unavailable, patients with a record of previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting were classified as IHF. If no coronary work-up was performed at the time of HFrEF diagnosis, the aetiology was considered ischaemic if a later investigation during the data extraction period revealed either evidence of a previous myocardial infarction or CAD sufficiently explaining HFrEF. The decision for abstaining coronary investigation was made at the discretion of the treating physician. HF aetiology was considered *non-ischaemic (non-IHF)* if invasive or non-invasive coronary investigations were carried out without fulfilling prior criteria for IHF. If prior conclusive data were absent and no investigation for IHD was performed, the aetiology was considered *unknown*. Investigations carried out during the entire study period were used for aetiological classification.

Outcome

A clinical composite score based on hard and soft outcomes was constructed, classifying each patient as worsened, improved, or unchanged, hierarchically in that order. Hard outcomes were death, heart transplantation, or HF hospitaliza-

tion. Soft outcomes were composed by changes in LVEF, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and New York Heart Association (NYHA) that were judged clinically significant: a ± ≥10-unit change in LVEF, a ± ≥30% change in NT-proBNP, and a ± ≥1 point change in NYHA class, from baseline to follow-up within 28 weeks. Patients were classified as worsened if they experienced any hard outcome or an LVEF reduction of ≥10 units, an NT-proBNP increase of ≥30%, or an NYHA increase of ≥1 point without any clinically significant improvement of the others. Patients were classified as improved if they did not experience any hard outcome but an LVEF increase of ≥10 units, an NT-proBNP reduction of ≥30%, or an NYHA reduction of ≥1 point, without any clinically significant deterioration of the others. The remaining patients were classified as unchanged provided that any LVEF, NT-proBNP, or NYHA data were recorded within 28 weeks. 'Overall change' represents changes in the summarized clinical composite score. Patients without hard endpoints were excluded if changes of LVEF, NYHA, or NT-proBNP during follow-up were in opposition, that is, improvement in any variable and worsening of another. Predictors for composite improvement and worsening in all patients investigated for IHD were analysed after multivariable adjustments.

Patients were followed from index until 28 weeks. The frequency of LVEF recovery (using the JACC Scientific Expert Panel consensus definition for HF with recovered LVEF; improvement of ≥10 units to LVEF ≥ 40%)[21] and decisions for coronary investigation at the time of HFrEF diagnosis were analysed.

Statistics

Baseline characteristics are presented as mean and standard deviation, or median and the 25th and 75th percentiles, for continuous variables and as percentages for categorical variables. For analyses of overall differences between all three groups, we used χ^2 test for both dichotomous variables and for the overall analyses of the soft outcomes and the composite outcome. When comparing two groups, we used Student's *t*-test for continuous variables, Fisher's exact test for dichotomous variables and outcomes, and the Mantel–Haenszel χ^2 trend test for overall analyses of the soft outcomes and the composite outcome. The Kruskal–Wallis test was used for analyses of time to soft outcomes between groups. Predictors for composite improvement and worsening were analysed using logistic regression after adjustments for ischaemic aetiology and the following baseline variables: age, sex, atrial fibrillation/flutter (AF), diabetes, left bundle branch block (LBBB), systolic blood pressure (SBP), haemoglobin, estimated glomerular filtration rate, and LVEF. Due to considerable missing data on NYHA class and NT-proBNP at index, separate analyses were performed for these variables and age. Adjusted odds ratios (ORs) with 95% confidence interval (CI) are presented. All tests were two-sided, and a *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics for Macintosh, Version 28.0 (IBM Corp., Armonk, NY, USA).

Results

After applying the inclusion criteria, 395 patients were identified, of which 31 patients were lost to follow-up and excluded. Of the 364 patients remaining, 203 were classified as non-IHF, 114 as IHF, and 47 as unknown.

Baseline characteristics

Patients with non-IHF were younger compared with patients with IHF (61.0 vs. 69.4 years, $P < 0.001$) with lower mean LVEF (26% vs. 31%, $P < 0.001$). The male predominance was similar (70.4% vs. 75.4%, $P = 0.363$). The following conditions were less common in non-IHF than in IHF: hypertension ($P = 0.026$), diabetes ($P < 0.001$), cerebrovascular disease (CVD) ($P < 0.001$), and previous/current smoking ($P = 0.046$), whereas pulmonary disease ($P = 0.012$), LBBB ($P = 0.049$), and previous/current drug abuse ($P = 0.037$) were more common. The prevalence of both previous and new-onset AF was similar in both groups investigated for IHD ($P = 1.000$ and $P = 0.378$, respectively). One patient with non-IHF had previously received an implantable cardioverter defibrillator (ICD). Implantation of ICDs and devices for cardiac resynchronization therapy (CRT) at baseline were similar for non-IHF and IHF [ICD: non-IHF 4.9% vs. IHF 0.9% ($P = 0.105$), and CRT: non-IHF 3.0% vs. IHF 1.8% ($P = 0.716$)]. Baseline characteristics are presented in *Table 1*.

Hard and soft outcomes

Eleven patients died and one was transplanted, with no significant differences between groups, but HF hospitalizations were less common in non-IHF than in IHF (*Figure 1*). HF was a common reason for hospitalization in all groups (in non-IHF 55.0%, in IHF 60.0%, and in unknown aetiology 62.5% of all hospitalizations). The overall changes in NYHA class, from index to the latest registered value, were similar between groups. The overall changes of NT-proBNP and LVEF differed significantly and were more favourable for non-IHF than for IHF. LVEF recovery was approximately twice as frequent in non-IHF as in IHF. The median time to the latest registered LVEF, NYHA score, and NT-proBNP was similar between groups (*Table 2*). The proportions of patients with follow-up recordings of NYHA and NT-proBNP were larger in non-IHF than in IHF (*Table 3*).

Table 1 Baseline characteristics

	Missing	Non-IHF $n = 203$	Missing	IHF $n = 114$	Missing	Unknown $n = 47$
Age at index, years		61.0 (11.8)		69.4 (9.2)		76.2 (9.7)
Male sex		70.4		75.4		57.4
Ischaemic heart disease		14.3		100.0		—
Atrial fibrillation/flutter		39.4		35.1		61.7
New-onset atrial fibrillation/flutter		21.2		16.7		29.8
Hypertension		42.9		56.1		51.1
Diabetes mellitus		10.8		28.1		19.1
Cerebrovascular disease		6.9		20.2		12.8
Rheumatic disease		5.4		4.4		6.4
Chronic liver disease		0.5		0		0
Pulmonary disease		13.8		4.4		19.1
Smoking, previous and current		48.3		60.5		27.7
Alcohol overconsumption, previous and current		10.4		7.0		4.3
Drug abuse, previous and current		7.4		1.8		0
New York Heart Association functional class	13.8%		32.5%		14.9%	
NYHA I		2.3		1.3		0
NYHA II		16.6		9.1		7.5
NYHA III		80.6		88.3		80.0
NYHA IV		0.6		1.3		12.5
Body mass index, kg/m^2		27.2 (5.6)		26.4 (4.5)		26.5 (5.8)
Systolic blood pressure, mmHg		124 (22)		123 (20)		129 (19)
Diastolic blood pressure, mmHg		78 (15)		74 (12)		79 (15)
Echocardiography						
Left ventricular end-diastolic diameter, mm	12.8%	63 (7)	19.3%	59 (8)	25.5%	59 (7)
Left ventricular ejection fraction, %		26 (7)		31 (6)		27 (7)
Electrocardiography						
Sinus rhythm		70.0		79.8		36.2
Atrial fibrillation/flutter		26.1		16.7		53.2
Pacemaker rhythm		3.9		3.5		10.6
Left bundle branch block		21.2		12.3		14.9
Haemoglobin, g/L		142 (16)		127 (18)		135 (19)
N-terminal pro-B-type natriuretic peptide, ng/L	8.9%	3490 (1480;6140)	21.2%	4680 (2290;8690)	12.8%	9280 (5140;14 900)
Estimated glomerular filtration rate, mL/min/1.73 m^2		73 (20)		71 (19)		61 (18)
Implantable cardioverter defibrillator		4.9		0.9		0
Cardiac resynchronization therapy		3.0		1.8		0

IHF, ischaemic aetiology; Non-IHF, non-ischaemic aetiology; Unknown, no coronary investigation performed.
For continuous variables, mean (SD) or median (25% quartile;75% quartile) is presented. For categorical variables, % is presented.

Clinical composite outcome

Thirteen patients lacking soft outcome registrations and five with soft outcome changes in opposition were excluded from the clinical composite outcome analysis, with no overall differences between groups ($P = 0.790$). There were overall significant differences in the composite outcome between non-IHF and IHF. In non-IHF, three-quarters improved, whereas worsening was as frequent as improvement in IHF (*Figure 2*, *Table 2*). In addition, in patients who did not worsen, the proportion who improved vs. remained unchanged was larger in non-IHF than in IHF (91.7% vs. 78.3%, $P = 0.010$). Adjusted predictor analyses showed significant association between composite worsening and IHF (OR 2.94; 95% CI 1.51–5.74; $P = 0.002$) and SBP +10 mmHg (OR 0.87; 95% CI 0.76–1.00; $P = 0.049$) and between composite improvement and IHF (OR 0.35; 95% CI 0.18–0.65; $P < 0.001$) and LVEF (OR 0.96; 95% CI 0.92–1.00; $P = 0.047$). Neither NYHA nor NT-proBNP at index was associated with composite changes.

Investigation of ischaemic aetiology

Of the 62 patients experiencing a type-1 myocardial infarction at index, 60 (96.8%) were investigated for CAD. Of the 39 patients with previous IHD without myocardial infarction at presentation, a decision for investigation was made in 28 (71.8%). Two of the 263 patients without previous IHD or new-onset myocardial infarction were coronary investigated earlier the same or previous year and not repeatedly investigated. In the remaining 261 cases, a decision for coronary investigation was made in 180 (69.0%).

Figure 1 Death, heart transplantation, or heart failure hospitalization (hard outcomes), by heart failure aetiology.

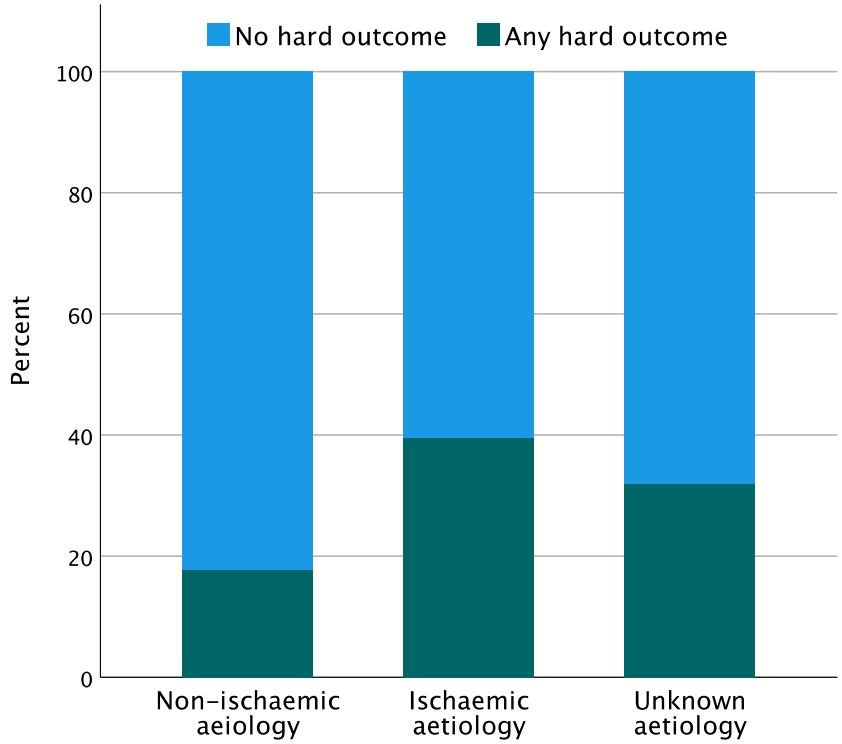


Table 2 Outcomes, by heart failure aetiology

	Non-IHF *n* = 203	IHF *n* = 114	*P* value Non-IHF vs. IHF	Unknown *n* = 47	Overall *P* value
Composite clinical outcome	*n* = 194	*n* = 107	<0.001	*n* = 45	<0.001
Worsened	19.1	43.9	<0.001	33.3	
Unchanged	6.7	12.1		13.3	
Improved	74.2	43.9	<0.001	53.3	
Hard outcomes	*n* = 203	*n* = 114		*n* = 47	
Any hard outcome	17.7	39.5	<0.001	31.9	*<0.001*
Death within 28 weeks	2.0	5.3		2.1	*0.228*
Heart Tx within 28 weeks	0	0.9		0	*0.442*
HF hospitalization within 6 months	16.3	36.8	<0.001	31.9	<0.001
LVEF	*n* = 150	*n* = 73	<0.001	*n* = 16	<0.001
Worsened ≥10 units	0	6.8		6.3	
Unchanged	30.0	57.5		31.3	
Improved ≥10 units	70.0	35.6		62.5	
LVEF recovery ≥ 10 units to ≥40%	50.7	26.0	<0.001	50.0	*0.002*
Time to latest LVEF, weeks	17.9 (12.7;24.1)	18.1 (13.0;22.5)		12.8 (10.0;25.5)	*0.523*
NYHA	*n* = 162	*n* = 66		*n* = 36	*0.302*
Worsened ≥1 point	0.6	0		0	
Unchanged	29.6	43.9		30.6	
Improved ≥1 point	69.8	56.1		69.4	
Improvement to NYHA I	(*n* = 159) 32.1	(*n* = 66) 24.2		(*n* = 36) 16.7	*0.137*
Time to latest NYHA, weeks	23.8 (20.0;26.3)	23.4 (20.0;25.5)		23.5 (13.9;26.4)	*0.427*
NT-proBNP	*n* = 161	*n* = 63	*0.001*	*n* = 30	*0.018*
Worsened ≥30%	7.5	19.0		13.3	
Unchanged	12.4	22.2		20.0	
Improved ≥30%	80.1	58.7		66.7	
Time to latest NT-proBNP, weeks	20.9 (13.4;25.8)	21.1 (14.1;24.9)		18.2 (5.9;24.4)	*0.221*

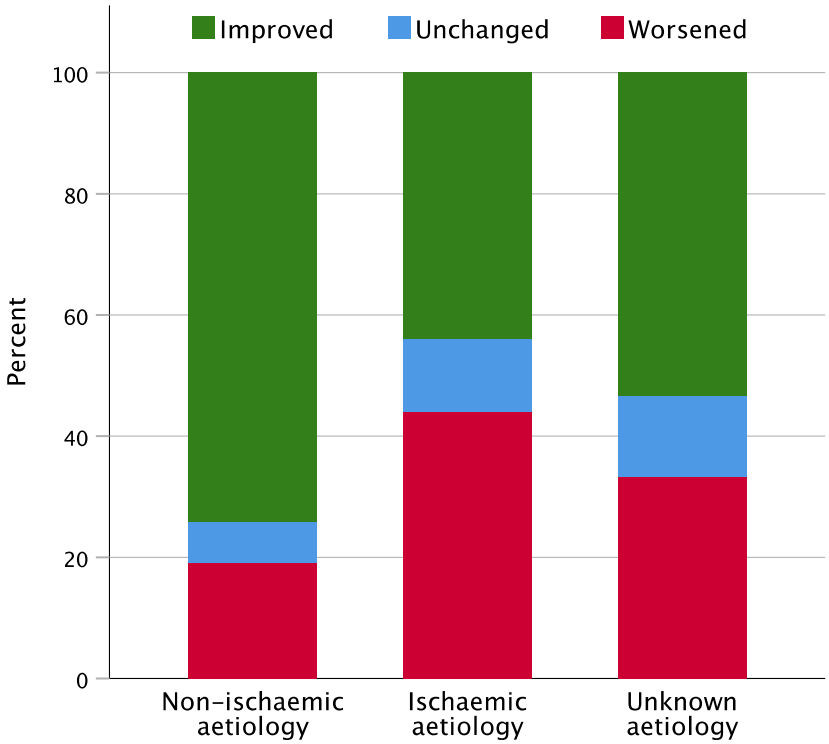
Heart Tx, heart transplantation; HF, heart failure; IHF, ischaemic aetiology; LVEF, left ventricular ejection fraction; Non-IHF, non-ischaemic aetiology; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; Unknown, no coronary investigation performed.
For categorical variables, % is presented. For continuous variables, median (25% quartile;75% quartile) is presented. Overall *P* values are presented in italics.

Table 3 Follow-up recordings

Follow-up recordings	Non-IHF *n* = 203	IHF *n* = 114	Unknown *n* = 47	*P* value Non-IHF vs. IHF
Left ventricular ejection fraction	73.9	64.0	34.0	0.073
New York Heart Association functional class	79.8	57.9	76.6	<0.001
N-terminal pro-B-type natriuretic peptide	79.3	55.3	63.8	<0.001

IHF, ischaemic aetiology; Non-IHF, non-ischaemic aetiology; Unknown, no coronary investigation performed.
Frequencies of recordings during follow-up are presented as percentages.

Figure 2 Clinical composite outcome, by heart failure aetiology.



Treatment at 6 months

The overall use of renin-angiotensin blockers did not differ between non-IHF and IHF, although treatment with an ARNI was more frequent in non-IHF (18.5% vs. 7.5%, *P* = 0.011). The mean doses of renin-angiotensin blockers (including ARNI) and mineralocorticoid receptor antagonists (MRA) were significantly higher in patients in non-IHF than in IHF (77.6% vs. 65.7%, *P* = 0.002, and 57.9% vs. 50.4%, *P* = 0.025, respectively). The overall number of patients treated with devices during the 28 week follow-up did not differ between non-IHF and IHF (*Table 4*).

Discussion

In this retrospective single-centre study of patients hospitalized for recent-onset HFrEF, the short-term response to initiated GDMT was considerably better in non-IHF than in IHF. The incidence of HF hospitalization in non-IHF was half of that seen in IHF, and a hierarchical clinical composite outcome showed that patients with non-IHF improved more often than patients with IHF.

The patients in the group of unknown aetiology were more often women and overall older, with intermediate prevalence

Table 4 Treatment at 6 months, non-transplanted survivors

Treatment	Non-IHF $n = 200$	IHF $n = 107$	Unknown $n = 46$	*P* value Non-IHF vs. IHF
Angiotensin-converting enzyme inhibitors (ACEIs)	54.0	61.7	58.7	0.227
Angiotensin receptor blockers (ARBs)	27.0	29.9	28.3	0.596
Angiotensin receptor-neprilysin inhibitor (ARNI)	18.5	7.5	4.3	**0.011**
ACEIs, ARBs, or ARNI	99.5	99.1	91.3	1.000
Mean dose, percentage of GDMT target dose	77.6	65.7	58.0	**0.002**
Beta-blockers	99.0	98.1	93.5	0.613
Mean dose, percentage of GDMT target dose	71.5	65.7	59.3	0.172
Mineralocorticoid receptor antagonists	64.5	53.3	39.1	0.066
Mean dose, percentage of GDMT target dose	57.9	50.4	51.6	**0.025**
Sodium-glucose cotransporter-2 inhibitors	3.0	3.7	0	0.743
Ivabradine	1.0	0.9	0	1.000
Digoxin	9.0	1.9	21.7	**0.015**
Daily loop diuretics	83.5	87.9	69.6	0.402
Thiazide diuretics	4.0	3.7	0	1.000
Oral anticoagulants	45.5	36.4	69.6	0.146
Amiodarone	8.5	3.7	4.3	0.155
Statins	30.0	86.9	32.6	**<0.001**
Implantable cardioverter defibrillator, within 28 weeks	6.4	5.3	0	0.808
Cardiac resynchronization therapy, within 28 weeks	5.4	2.6	1	0.393

GDMT, guideline-directed medical treatment; IHF, ischaemic aetiology; Non-IHF, non-ischaemic aetiology; Unknown, no coronary investigation performed.
Frequencies of treatment are presented as percentages. Significant differences, IHF vs. no-IHF, are in bold.

of hypertension, diabetes, and CVD relative to the groups investigated for IHD. The high prevalence of new-onset AF may have constituted part of the decision to abstain from diagnostic coronary work-up.

Non-ischaemic HF vs. ischaemic HF

The patients with non-IHF were younger, with lower prevalence of traditional risk factors for IHD, but with higher prevalence of pulmonary disease, current/previous drug abuse, and LBBB compared with patients with IHF. The groups investigated for IHD were overall younger and with lower prevalence of common comorbidities compared with other studies of recent-onset HF.[4,16]

Applying the clinical outcome for evaluating the treatment response in HFrEF of different aetiologies, we found statistically and clinically significant changes in the composite outcome demonstrating a more favourable clinical course in non-IHF. Compared with IHF, a smaller proportion in non-IHF worsened. Further, the proportion of patients who improved vs. remained unchanged was higher in non-IHF than in IHF, adding to existing data supporting the worse prognosis in HFrEF of ischaemic aetiology. The overall 28 week mortality of 3.2%, similar between groups, compares well to a recently published study by McGuinn *et al.*, reporting a 1 year mortality of 9% in patient with new-onset HFrEF investigated for IHD, despite the exclusion of patients dying within 90 days of inclusion.[16] Ventricular arrhythmia is more frequent in IHF than in non-IHF,[22] but the use of ICDs in the present study was low, similar between groups, and not likely a factor of importance for the outcomes. In the study by McGuinn *et al.*, patients who were re-hospitalized within 90 days were also excluded, which may explain the low 1 year HF hospitalization rate of 17% compared with 24% over 6 months in our study. HF hospitalization constituted the overwhelming share of hard endpoints for all groups and was the major reason for composite worsening, although significantly less frequent in non-IHF than in IHF. The inclusion of biomarkers or measures of cardiac function in the clinical composite outcome has previously been questioned in therapeutic trials due to uncertainty of clinical significance[18]; however, increasing evidence of prognostic value has been gained. LVEF improvement has been associated with both non-IHF and better prognosis compared with patients with persistently reduced LVEF.[23–25] Also, in-hospital reduction of NT-proBNP in acute decompensated HFrEF associates with better prognosis,[26] and the initiation of ARNI in acute HFrEF reduces both NT-proBNP and early HF re-hospitalization compared with the angiotensin-converting enzyme inhibitor enalapril,[27] supporting the significance of early reduction. The majority of patients improved similarly in NYHA class, regardless of HF aetiology, and the better composite improvement seen in non-IHF was due to a comparably greater decrease in NT-proBNP and better improvement in LVEF. Half of the patients in the non-IHF group with follow-up evaluations showed LVEF recovery by ≥10 units to an LVEF ≥ 40%, twice as often as the patients in the IHF group. Little is published regarding LVEF recovery in various aetiologies shortly after initiated treatment. In a study by Lupón *et al.*, patients with non-ischaemic aetiologies showed better improvement of LVEF than patients with ischaemic aetiologies after 1 year of GDMT.[10] In our study, the median time to last evaluation of LVEF was 18 weeks for both groups,

suggesting that the differences in LVEF recovery between aetiologies occur earlier than previously reported.

Multivariable adjusted analyses of patient characteristics showed that IHF was significantly associated with increased odds for composite worsening and reduced odds for improvement, and the only variable considerably affecting the treatment response. LVEF and SBP were associated with composite changes, but with small effect sizes and borderline statistical significance. No other variable of known adverse prognostic importance was associated with composite changes in our study, possibly due to the short duration of follow-up and limited number of patients.

At 6 months post index, virtually all patients were treated with renin-angiotensin blockers and beta-blockers, and the use of MRA was balanced between groups. Treatment with ARNI differed, but the overall low usage is in part explained by the treatment first being approved in Sweden in 2016. The use of CRT was similar between groups, but as expected due to the limited follow-up period, device treatment was infrequent and unlikely to impact the outcomes.

Some explanations for the superior outcome after treatment in non-IHF may be proposed. In our study, 83% of the patients with IHF suffered from acute or previous myocardial infarctions and the permanent loss of contractile tissue after infarctions may contribute to the worse treatment response in IHF. In contrast, non-IHF comprises several causes with varying pathophysiology and may include cases with reversible causes of systolic dysfunction such as myocarditis and AF. Left ventricular recovery is better in non-IHF than in IHF after AF ablation,[28,29] and even though the number of patients with AF in the present study was similar between groups, different distribution of persistent vs. permanent AF may contribute to the differences in outcomes. Although the proportions of patients receiving recommended treatment were similar between groups, with the exception of ARNI, the doses of renin-angiotensin blockers (including ARNI) and MRA were significantly lower in IHF. Older age and increased comorbidity in IHF may reduce the tolerance for treatment, explain the differences in treatment dosage, and possibly contribute to the worse treatment response in IHF.

Investigation of ischaemic aetiology

In patients with new-onset HF, underlying CAD should be considered. The recommended modality of investigation depends on overt ischaemic symptoms and suitability for revascularization[30] but the purpose of evaluation is, however, not restricted to revascularization assessment. In significant CAD, medication is recommended to reduce future events,[31] and patients undergoing diagnostic evaluation are more likely to receive preventive medication.[31,32] Previous American studies of new-onset HF reported that a minority of patients with HFrEF underwent coronary investigation[15,16]; however, in our study, almost 70% of the patients without acute myocardial infarction were referred for investigation at the time of HFrEF diagnosis. Interestingly, the degree of coronary investigation was similar in patients with and without known IHD at baseline. One may speculate that concurrent non-coronary vascular disease justifying antiplatelet therapy and statins would reduce the propensity for coronary investigation in patients not suitable for revascularization, but the reasons for abstaining investigation were seldom described.

Only patients followed at HF units were included, and patient selection is likely to explain the differences in baseline characteristics and, in part, the higher degree of investigation for IHD than previously reported. Nevertheless, also in this well-treated selected patient cohort, there were clinically important findings suggesting better early response to GDMT in non-IHF compared with IHF.

Limitations

The study is retrospective and reports associations only. Ejection fraction data are obtained from the first examination whereas NYHA and NT-proBNP are collected near discharge. In cases of longer hospital stays with early start of treatment, initially elevated NT-proBNP values may have decreased significantly, reducing the difference vs. follow-up data compared with patients with shorter stays or no repeated measurements. In cases of non-reported NYHA class, patients were assigned an NYHA class after record examination by the first author (JS) when symptoms and function were sufficiently described; however, available data were limited, leading to 20% missing data. Patients with HFrEF due to myocardial infarctions were included only if they were re-hospitalized for HF during the period of data extraction. We acknowledge that the patients in the IHF group of this study may be more affected than patients not re-hospitalized. Patients referred to primary care within 6 months without assured treatment optimization and soft outcome follow-up were excluded.

Conclusions

Among patients hospitalized with recent-onset non-valvular HFrEF, patients with non-IHF responded better to GDMT than patients with IHF. In non-IHF, the HF hospitalization rate was lower and improvement in variables of prognostic importance was considerably more frequent than in IHF. Almost one-third of patients selected for follow-up at HF clinics were never investigated for IHD.

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Conflicts of interest

Michael Fu reports unrelated modest consulting fee from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer, Vifor Fresenius Medical Care Renal Pharma, and Vifor Pharma. Carmen Basic reports unrelated personal fees from Boehringer Ingelheim. No other conflict of interest, or relationship with the industry, was declared.

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