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ORIGINAL ARTICLE

Impact of adherence to guideline-directed therapy on risk of death in HF patients across an ejection fraction spectrum

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Abstract

Aims How different degrees of adherence to guideline-directed medical therapy (GDMT) affect mortality risk in patients with heart failure (HF) in a real-world clinical setting is poorly understood. This study sought to investigate how different levels of adherence to GDMT were associated with the risk of all-cause mortality in patients with HF across a spectrum of left ventricular ejection fractions (LVEFs) in a real-world clinical setting.

Methods and results A total of 64 610 HF patients with no missing value of LVEF from the Swedish Heart Failure Registry were included in the study. Patients were divided according to different LVEFs (<30%, 30–39%, 40–49%, and≥50%) and stratified by an adherence score (good, moderate, or poor) according to the triple, double, and single one usage of GDMT: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists. The outcome is time to all-cause mortality. The mean age of the whole cohort was 73.9 ± 12.1 years, and the proportion of patients in LVEF < 30%, 30–39%, 40–49%, and≥50% groups was 27.6%, 26.9%, 22.1%, and 23.3%, respectively. Patients with LVEF < 30% had the highest mortality rate, almost 20% higher than those with LVEF ≥ 50% {hazard ratio [HR] [95% confidence interval (CI)]: 0.80 [0.71–0.90], $P < 0.001$}. After treatment of GDMT with good adherence, patients with LVEF < 30% had similar mortality to those with LVEF ≥ 50% [HR (95% CI): 0.97 (0.86–1.10), $P = 0.664$]. However, the percentage of moderate or poor GDMT was alarmingly high, with good adherence only in 20% of the patients.

Conclusions Good adherence to GDMT works best in patients with LVEF < 50%, whereas moderate adherence to GDMT varies in efficacy depending on the components of the drug combinations.

Keywords Heart failure; Left ventricular ejection fraction; Guideline-directed medical therapy; All-cause mortality

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Introduction

Guideline-directed medical therapy (GDMT) for patients with heart failure (HF) with reduced ejection fraction (HFrEF) includes angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs), which all proved to be associated with a significant reduction in mortality and morbidity in large clinical randomized controlled trials.[1] However, there are virtually no evidence-based recommendations in patients with HF and left ventricular ejection fraction (LVEF) > 40%.

Regarding the clinical implementation of GDMT, there are still knowledge gaps in understanding whether different degrees of adherence to GDMT have similar efficacy from the patient's perspective and whether this adherence–effect relationship of GDMT differs across the LVEF spectrum. No prospective trial has been conducted in patients with HF with mid-range ejection fraction (HFmrEF) from 40% to 49%. All analyses and related recommendations are based on post hoc analyses from HFrEF or trials with HF with preserved

ejection fraction (HFpEF) patients, with inclusion criteria now classified as HFmrEF. For instance, according to a clinical practice update on HF in 2021, GDMT may be considered in HF patients with LVEF 40–49%.[1,2] However, no data are available about whether the adherence–effect relationship of GDMT is the same across different ejection fraction (EF) spectrums.[3,4] The adherence to GDMT and its relation to the treatment effect are relevant today as patient-centred individualized care has received increasing attention.

Thus far, the trial population has been younger than in the real world; moreover, women have usually been underrepresented in all HF clinical trials.[5,6] Therefore, in this study, we studied how different levels of adherence to GDMT affect the risk of mortality in patients with HF across the LVEF spectrum in a real-world clinical setting.

Methods

Database

This study was based on a database from the Swedish Heart Failure Registry (SwedeHF).[7] In brief, the SwedeHF has been an ongoing nationwide quality registry enrolling patients from primary and secondary care clinics in Sweden since 11 May 2000. The inclusion criterion to be registered in the SwedeHF is clinician-judged HF. Approximately 80 baseline variables are recorded at discharge from the hospital or after an outpatient visit when patients entered the registry. The protocol, registration form, and annual reports are available on the website: http://www.rikssvikt.se. The registry conforms to the Declaration of Helsinki. A multi-site ethics committee approved the SwedeHF and the present study. Individual patient consent is not required or obtained, but patients are informed of being entered into national registries and can withdraw at any time. The SwedeHF is an ongoing nationwide registry. Our database is a secondary database that contains output of registry data from the SwedeHF and moreover linked with several national administrative databases (National Patient Register, Drug Prescription Register, and Cause of Death Register) by using a unique Swedish personal identity number, which is an identity designation that a Swedish citizen retain whole life. By doing so, all the patients registered in the SwedeHF were able to be followed until death or the final dates of aforementioned administrative databases that cover.

Study population

Patients included in the SwedeHF from 11 May 2000 to 31 December 2017 were entered into this study. Patients with a missing value of LVEF were excluded.

Determination of optimal and suboptimal adherence to guideline-directed medical therapy

Optimal and suboptimal adherence to GDMT was based on a global guideline adherence score ranging from 0 (poor), 0.05 (moderate), and 1 (good). The adherence score was the ratio of the treatment prescribed compared with what should theoretically have been prescribed in all guideline-recommended foundational HF therapy, including ACEI/ARB/ARNI, BB, and MRA. Three levels of adherence were defined: good adherence (use of three indicated medications, score = 1), moderate adherence (use of more than half of the indicated medications, score $>$ 0.5), and poor adherence (use of less than half of the indicated medications, score $>$ 0.5).[8,9] We further divided all patients into three subgroups according to this score.

Subgroup division

1) Group division based on LVEF reporting:

In our database, the LVEFs were reported as $<$30%, 30–39%, 40–49%, and $\geq$50%. Therefore, all LVEFs were categorized into intervals of 10% in width for all HF patients in our study: $<$30%, 30–39%, 40–49%, and $\geq$50%.

2) Age was dichotomized at $\geq$75 years.

Data source (baseline and outcome)

Baseline data on patient demographics, baseline characteristics, medical history, clinical presentation, and laboratory test results were collected. The use of ACEI, ARB, ARNI, BB, MRA, digoxin, diuretic, nitrate, antiplatelet, anticoagulant, and statin, as well as device therapy were obtained from the SwedeHF and linked with the Swedish Drug Prescription Register.

The outcome of this study is all-cause mortality, which was obtained from the Cause of Death Register for all Swedish residents, irrespective of citizenship, which is linked to the database from the SwedeHF.

Statistical analysis

Baseline patient characteristics and clinical outcomes were reported for the study cohort according to LVEF categories. Continuous variables are described as mean ± standard deviation (SD) and compared by an analysis of variance (ANOVA) for normally distributed variables and the Kruskal–Wallis test for skewed variables. Categorical variables are represented by percentages and compared using the χ^2 test. The incidence rate of the outcome (all-cause mortality) was calculated for each LVEF category and GDMT adherence groups by sex and age and expressed as a rate per 1000 patient-years. Cumulative incidences of all-cause mortality were assessed by the Kaplan–Meier estimates, and significance

levels were compared using the log-rank test. To compare the risk of all-cause mortality between the different EF categories and medical adherence groups, we used Cox proportional hazards models and fixed baseline confounders, including age, sex, heart rate, smoking, body mass index (BMI), hypertension, diabetes, atrial fibrillation, and estimated glomerular filtration rate (eGFR).

A P value of <0.05 was considered statistically significant. All tests were two-sided. Analyses were performed with Stata software Version 14.1 (StataCorp LP, College Station, TX, USA).

Results

We studied 76 506 patients in the SwedeHF from 11 May 2000 to 31 December 2017. We excluded patients with a missing value of LVEF (n = 11 896). The final sample comprised 64 610 patients: 17 851 (27.6%) with LVEF $<$ 30%, 17 403 (26.9%) with LVEF 30–39%, 14 295 (22.1%) with LVEF 40–49%, and 15 061 (23.3%) with LVEF $\geq$ 50%. The mean age of the whole cohort was 73.9 ± 12.1 years, with 40 537 (62.7%) males. The median follow-up time was 1014 days.

Baseline characteristics in different ejection fraction categories

Table 1 describes baseline characteristics by different LVEF categories. Patients in the lower LVEF categories were younger, more likely to be males, and had lower systolic blood pressure and BMI and higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), eGFR, haemoglobin, and potassium, as well as a wider QRS duration. In addition, patients with lower LVEF were less likely to have a history of hypertension, atrial fibrillation, diabetes, valve disease, lung disease, and malignant diseases but more likely to have dilated heart disease and coronary artery disease (*Figure 1*).

Risk of mortality in different left ventricular ejection fraction categories

The median follow-up duration was 1014 days (interquartile range, 334–1942 days). A total of 39 958 patients (52.2%) died during the follow-up. As shown in *Table 2*, patients with LVEF $<$ 30% had the highest mortality rate, almost 20% higher than those with LVEF $\geq$ 50% {adjusted hazard ratio [aHR] [95% confidence interval (CI)]: 0.80 [0.71–0.90], $P < 0.001$}. After optimal treatment of GDMT with good adherence, patients with LVEF $<$ 30% had similar mortality to those with LVEF $>$ 50% [aHR (95% CI): 0.97 (0.86–1.10), P = 0.664] (*Figure 2*).

Adherence of guideline-directed medical therapy in different left ventricular ejection fraction categories

Based on the global medical adherence score, the percentages of good, moderate, and poor adherence were 20.1, 56.9, and 23.0, respectively, in the overall HF population. A good adherence score was highest in patients with LVEF $<$ 30%, whereas a poor adherence score was highest in those with LVEF $\geq$ 50%. Patients with a lower LVEF were more likely to be treated with GDMT, including ACEIs/ARBs/ARNIs, BBs, MRAs, and implantable cardiac devices (cardiac resynchronization therapy or implantable defibrillator) (*Table 1*).

Clinical outcome in different left ventricular ejection fractions stratified by degrees of adherence

As detailed in *Table 3*, GDMT with good adherence works best only in patients with an LVEF of $<$50%. For moderate adherence to GDMT, only those combinations of BB + ACEI/ARB were associated with a risk reduction in mortality across the entire spectrum of LVEFs. As seen in *Table 3*, in those patients with only double treatment, 33 053 (90.0%) were treated with ACEI/ARB/ARNI and BB, 1481 (4.0%) with ACEI/ARB/ARNI and MRA, and 2208 (6.0%) with BB and MRA. The combination of ACEI/ARB/ARNI and BB had the lowest risk of all-cause mortality in the entire LVEF spectrum, whereas a combination of ACEI/ARB/ARNI and MRA or BB and MRA appeared not to work at all (*Figure 3*).

Clinical outcome in different left ventricular ejection fraction categories and adherence groups specified by age and sex

According to *Table 4*, patients $>$75 years with a good adherence score had a lower risk of outcome if LVEF was $<$50% compared with those with a poor adherence score. On the other hand, patients $<$75 years with good adherence function best when LVEF is $<$40%. No significant difference was found between men and women with good adherence to GDMT. Both sexes work best when LVEF is $<$40%. However, a tendency to a higher risk reduction of 17% was found in female HF patients with HFmrEF (*Figure 1*).

Discussion

With access to a large cohort of real-world HF patients, we could show an alarmingly high proportion of HF patients treated suboptimally according to recommended GDMT in patients with HFrEF. We also found that GDMT with good ad-

Table 1 Baseline characteristics of patients with different left ventricular ejection fraction (LVEF) categories

	LVEF < 30% (*n* = 17 851)	LVEF 30–39% (*n* = 17 403)	LVEF 40–49% (*n* = 14 295)	LVEF ≥ 50% (*n* = 15 061)	*P* value
Clinical characteristics					
Age	70.6 ± 12.6	73.2 ± 11.7	74.5 ± 11.9	77.8 ± 10.7	<0.001
Sex, male	13 142 (73.6)	11 829 (68.0)	8711 (60.9)	6855 (45.5)	<0.001
Smoking					<0.001
Current	2459 (17.0)	1813 (13.0)	1245 (11.1)	1004 (9.1)	
Previous	6433 (44.5)	6197 (44.5)	4870 (43.4)	4420 (39.9)	
Never	5555 (38.5)	5917 (42.5)	5106 (45.5)	5667 (51.1)	
Body mass index, kg/m^2	26.4 ± 6.1	27.0 ± 7.3	27.4 ± 8.7	27.7 ± 6.4	<0.001
NYHA class					
II (%)	5692 (42.3)	6327 (50.8)	5343 (53.9)	4058 (45.7)	<0.001
III (%)	5993 (44.5)	4320 (34.7)	2794 (28.2)	3092 (34.8)	
IV (%)	859 (6.4)	369 (3.0)	246 (2.5)	371 (4.2)	
LBBB	4487 (29.4)	2865 (19.2)	1678 (13.9)	1026 (8.1)	<0.001
Medical history					
Hypertension	9594 (53.7)	10 821 (62.2)	9602 (67.2)	11 290 (75.0)	<0.001
Atrial fibrillation	8719 (48.8)	9142 (52.5)	8263 (57.8)	9666 (64.2)	<0.001
Diabetes mellitus	4711 (26.4)	4727 (27.2)	3854 (27.0)	4384 (29.1)	<0.001
Valve disease	3442 (19.3)	3279 (18.8)	2953 (20.7)	4183 (27.8)	<0.001
Dilated heart disease	4132 (23.1)	1536 (8.8)	718 (5.0)	374 (2.5)	<0.001
Coronary heart disease	8988 (50.4)	7390 (42.5)	6450 (45.1)	6917 (45.9)	<0.001
Stroke/TIA	2324 (13.0)	2432 (14.0)	2092 (14.6)	2545 (16.9)	<0.001
Lung disease	3185 (17.8)	3301 (19.0)	2913 (20.4)	3761 (25.0)	<0.001
Renal disease	1014 (5.7)	959 (5.5)	770 (5.4)	998 (6.6)	<0.001
Malignant diseases	1670 (9.4)	1852 (10.6)	1570 (11)	1796 (11.9)	<0.001
Heart rate, b.p.m.	76.3 ± 16.8	73.4 ± 16.2	73.4 ± 15.8	74.8 ± 16.2	<0.001
SBP, mmHg	121.1 ± 19.9	127.4 ± 24.4	130.4 ± 20.9	132.8 ± 22.0	<0.001
DBP, mmHg	72.9 ± 12.5	73.9 ± 12.2	73.8 ± 12.2	72.9 ± 13.4	<0.001
Laboratory findings					
NT-proBNP, pg/mL	6823.5 ± 88 565.9	4820.9 ± 6828.3	4242.9 ± 6631.2	3958.3 ± 6150.4	<0.001
eGFR, mL/min	63.6 ± 23.6	63.0 ± 23.4	61.9 ± 23.4	57.5 ± 22.7	<0.001
Haemoglobin, g/L	135.6 ± 17.5	133.2 ± 17.3	131.5 ± 17.5	127.3 ± 17.2	<0.001
Potassium, mmol/L	4.2 ± 0.45	4.18 ± 0.4	4.17 ± 0.4	4.12 ± 0.5	<0.001
QRS width	121.4 ± 31.1	113.4 ± 28.6	107.6 ± 26.5	102.1 ± 25.1	<0.001
Treatment					
Adherence score					
Poor	2098 (11.7)	2675 (25.3)	3206 (22.4)	5024 (33.4)	<0.001
Moderate	9676 (54.2)	10 552 (60.6)	86 878 (60.8)	7827 (52.0)	<0.001
Good	6077 (34.0)	4176 (24.0)	2402 (16.8)	2210 (14.7)	<0.001
ACEI/ARB/ARNI	16 152 (90.5)	15 336 (88.1)	11 806 (82.6)	10 554 (70.1)	<0.001
Beta-blocker	16 228 (91.4)	15 590 (89.9)	12 181 (85.6)	11 814 (79.0)	<0.001
MRA	6921 (39.2)	5042 (29.2)	3354 (23.7)	4007 (26.9)	<0.001
Digoxin	3103 (17.5)	2335 (13.5)	1964 (13.8)	2358 (15.7)	<0.001
Diuretic	14 440 (81.8)	12 535 (72.6)	10 080 (71.4)	12 310 (83.2)	<0.001
Nitrate	2149 (12.1)	2637 (15.2)	2122 (14.9)	2489 (16.6)	<0.001
Anticoagulant	7596 (42.8)	6895 (39.8)	5928 (41.7)	6456 (43.2)	<0.001
Antiplatelet	8027 (45.7)	8916 (52.2)	6730 (47.8)	6096 (41.2)	<0.001
Statins	8019 (45.2)	8973 (51.8)	6926 (48.7)	5935 (39.6)	<0.001
Device therapy					<0.001
ICD	604 (3.4)	430 (2.5)	178 (1.3)	84 (0.6)	
CRT	391 (2.2)	208 (1.2)	91 (0.7)	45 (0.3)	
CRT-D	540 (3.1)	212 (1.2)	62 (0.4)	35 (0.2)	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack.

herence works best in patients with LVEF < 50%, whereas the efficacy of moderate adherence to GDMT varies depending on the components of the drug combination.

LVEF is commonly used to categorize HF.[10] ARNI/ACEI/ARB, BB, and MRA are the cornerstones of GDMT for HFrEF patients based on solid evidence to improve prognosis. In contrast, no specific recommendations have been made for HFmrEF or HFrEF patients because of a lack of evidence. Our findings reaffirm that adherence to GDMT is associated with better outcome in HFrEF patients, which is in line with network meta-analysis reviewing 30 years of evidence on the efficacy of drugs for HFrEF (LVEF < 45%).[11,12] However,

Figure 1 Distribution of different left ventricular ejection fraction (LVEF) categories and guideline adherence scores in heart failure (HF) patients by age and sex.

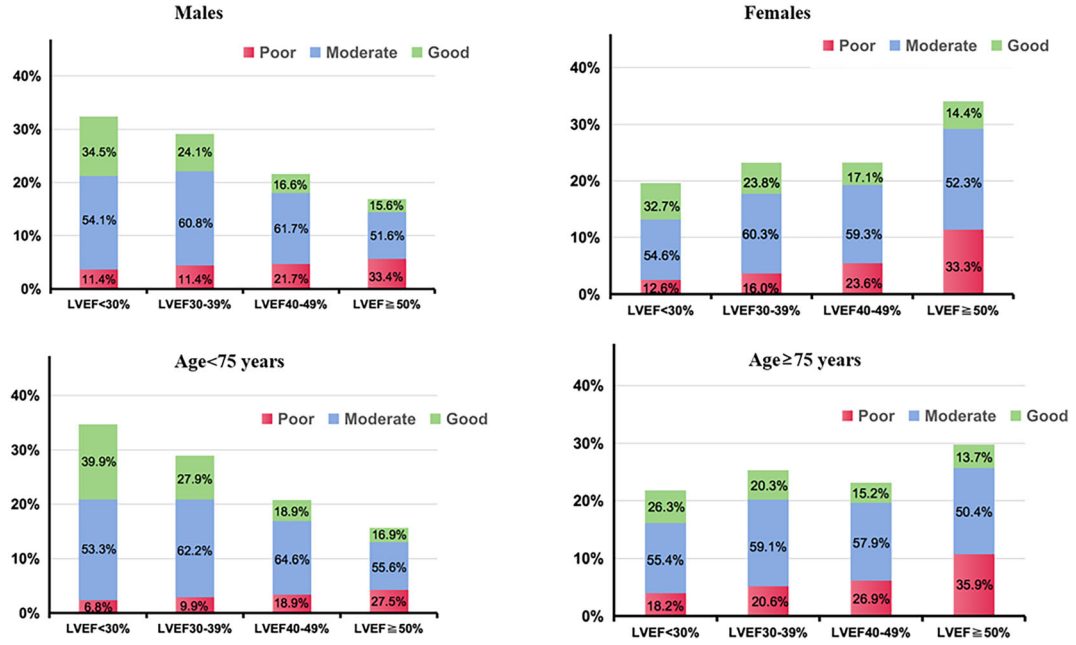


Table 2 Comparison of all-cause mortality according to different left ventricular ejection fraction (LVEF) categories in overall and different guideline-directed medical therapy (GDMT) adherence groups

	Overall		Poor	
All-cause mortality	No. at risk (event rate/1000 py)	Adjusted HR (95% CI) *P* value	No. at risk (event rate/1000 py)	Adjusted HR (95% CI) *P* value
LVEF < 30%	8309 (127)	1 (ref)	1300 (257)	1 (ref)
LVEF 30–39%	7749 (120)	0.85 (0.80–0.89) <0.001	1575 (204)	0.87 (0.76–0.99) 0.045
LVEF 40–49%	6469 (127)	0.82 (0.78–0.87) <0.001	1759 (187)	0.79 (0.69–0.89) <0.001
LVEF ≥ 50%	7985 (164)	0.93 (0.88–0.99) 0.015	2890 (198)	0.80 (0.71–0.90) <0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; py, person years; ref, reference.

Table 2 (continued)

	Moderate		Good	
All-cause mortality	No. at risk (event rate/1000 py)	Adjusted HR (95% CI) *P* value	No. at risk (event rate/1000 py)	Adjusted HR (95% CI) *P* value
LVEF < 30%	4470 (120)	1 (ref)	2539 (109)	1 (ref)
LVEF 30–39%	4470 (106)	0.83 (0.78–0.89) <0.001	1704 (113)	0.85 (0.77–0.9.4) 0.001
LVEF 40–49%	3578 (107)	0.79 (0.74–0.85) <0.001	1132 (135)	0.87 (0.77–0.98) 0.019
LVEF ≥ 50%	3984 (149)	0.92 (0.86–1.00) 0.045	1111 (154)	0.97 (0.86–1.10) 0.664

Abbreviations: CI, confidence interval; HR, hazard ratio; py, person years; ref, reference.

two issues need to be considered in the clinical implementation of GDMT: (i) Varying degrees of adherence to GDMT might affect the expected efficacy as tolerability of GDMT is highly individual, and (ii) efficacy of GDMT might differ in different categories of LVEF as GDMT was mainly studied in HF populations with HFrEF.

Figure 2 Comparison of all-cause mortality in different left ventricular ejection fraction (LVEF) categories by different guideline adherence scores.

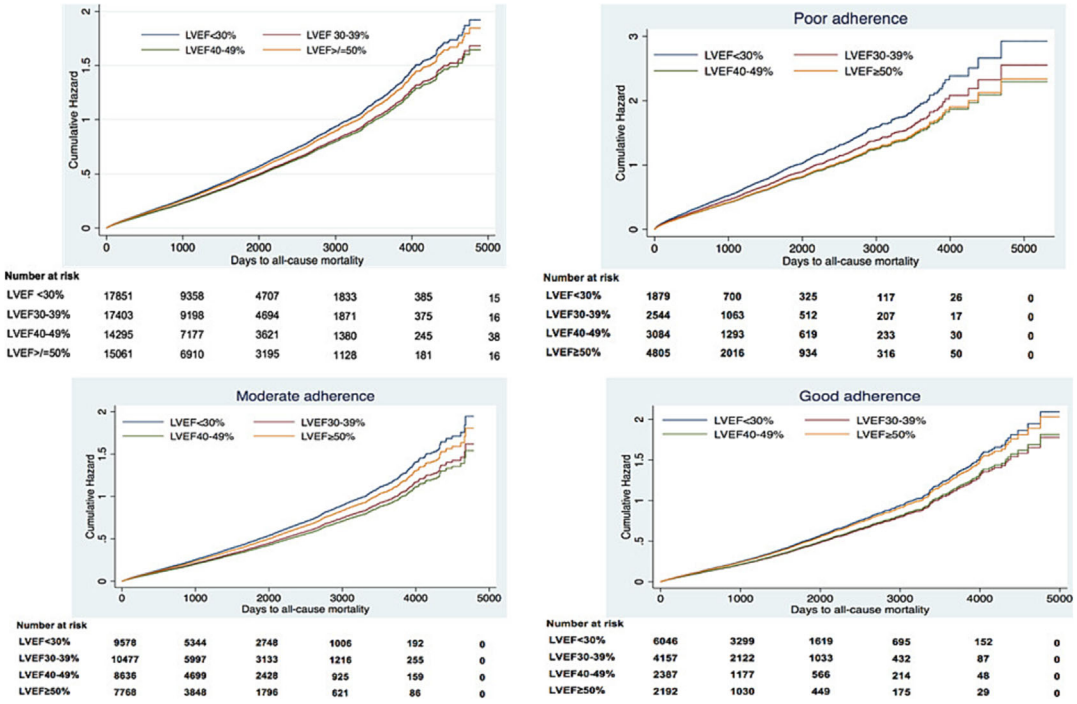


Table 3 Explorative analysis of all-cause mortality according to different drug combinations across the left ventricular ejection fraction (LVEF) spectrum

All-cause mortality		Overall		LVEF < 30%	
		No. at risk (event rate/1000 py)	HR (95% CI) *P* value	No. at risk (event rate/1000 py)	HR (95% CI) *P* value
Poor		7524 (205)	1 (ref)	1300 (257)	1 (ref)
Moderate	ACEI/ARB/ARNI + BB	14 098 (109)	0.69 (0.65–0.72) <0.001	3956 (113)	0.62 (0.55–0.69) <0.001
	ACEI/ARB/ARNI + MRA	922 (202)	1.16 (1.03–1.31) 0.014	245 (201)	0.96 (0.74–1.24) 0.766
	BB + MRA	1482 (281)	1.24 (1.13–1.37) <0.001	269 (346)	1.38 (1.08–1.75) 0.009
Good		6486 (120)	0.85 (0.80–0.90) <0.001	2539 (109)	0.72 (0.64–0.81) <0.001

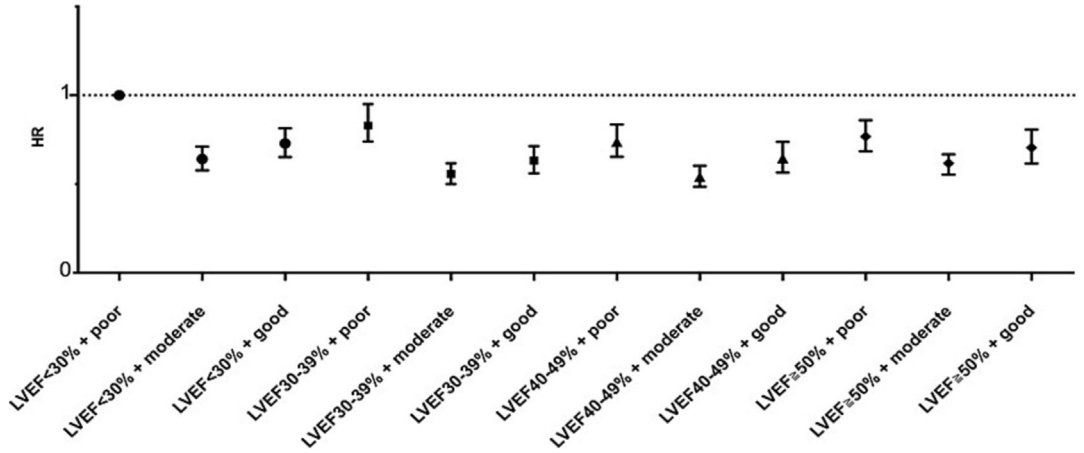
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; py, person years; ref, reference.

Table 3 (continued)

All-cause mortality	LVEF 30–39%		LVEF 40–49%		LVEF ≥ 50	
	No. at risk (event rate/1000 py)	HR (95% CI) *P* value	No. at risk (event rate/1000 py)	HR (95% CI) *P* value	No. at risk (event rate/1000 py)	HR (95% CI) *P* value
Poor	1575 (204)	1 (ref)	1759 (187)	1 (ref)	2890 (198)	1 (ref)
Moderate	3991 (100)	0.64 (0.57–0.70) <0.001	3070 (99)	0.67 (0.60–0.74) <0.001	3081 (133)	0.76 (0.69–0.83) <0.001
	196 (179)	1.17 (0.91–1.51) 0.219	186 (186)	1.26 (0.97–1.64) 0.083	295 (235)	1.17 (0.94–1.45) 0.163
	283 (295)	1.10 (0.87–1.39) 0.441	322 (278)	1.19 (0.95–1.48) 0.126	608 (256)	1.27 (1.10–1.48) 0.002
Good	1704 (113)	0.75 (0.67–0.85) <0.001	1132 (135)	0.86 (0.76–0.98) 0.024	1111 (154)	0.95 (0.84–1.07) 0.420

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; py, person years; ref, reference.

Figure 3 Different left ventricular ejection fraction (LVEF) categories and guideline adherence score hazard ratios (HRs) for all-cause mortality.



Our findings confirm that GDMT with good adherence (triple treatment with BB, ACEI/ARB, and MRA) works best in patients with HFrEF or HFmrEF, that is, those with LVEF $<$ 50% (patients with HFmrEF had quite similar clinical features as those with HFrEF). Thus, these findings add supporting evidence to the recommendation by clinical practice update on HF in 2021, in which GDMT may be considered in HF patients with LVEF 40–49%.[2] This is in line with several post hoc analyses in the HFmrEF population.[13–15] For instance, a patient-level pooled analysis on hospitalized HFmrEF (LVEF 40–49%) patients from the KorHF and KorAHF registries demonstrated that the use of BB or renin-angiotensin system blockers was associated with a reduced risk of all-cause mortality.[16] In addition, post hoc analysis of CHARM and TOPCAT trials suggests that candesartan and spironolactone, respectively, could improve outcomes in patients with HFmrEF.[17,18]

Our results clearly show that GDMT with good adherence (triple treatment with BB, ACRI/ARB, and MRA) did not work in patients with HFpEF, that is, LVEF $\geq$ 50%. This observation concurs with all neutral results from several clinical trials in HFpEF.[19–22] Alternatively, these patients with HFpEF were not well informed about their HF; therefore, they are not motivated to take their medications regularly.

Whereas good adherence to GDMT is expected to be best in patients with LVEF $<$ 50%, the efficacy of moderate adherence to GDMT varies depending on the components of the combination of GDMT (BB + ACEI/ARB, ACEI/ARB + MRA, or BB + MRA). The different GDMT combinations were shown to have varying efficacies. Only those combinations containing BB + ACEI/ARB are associated with a risk reduction in mortality across the entire spectrum of LVEFs. The ACEI/ARB + BB was the most efficacious strategy in any LVEF category. This finding is consistent with the network meta-analysis in which ACEI + BB + MRA [hazard ratio (HR) = 0.44] and ACEI + BB (HR = 0.47) had similar efficacies in HFrEF patients.[12] However, our study indicates that MRA's effectiveness might have sizeable individual variation. This could be true as previous subgroup analyses of the TOPCAT trial showed that not all patients respond to MRA treatment.[23–25] Device therapy has been suboptimal for a long time in Sweden because of fragmented HF care, leading to general practitioners seldom sending a referral to hospital specialists for consideration of device therapy.

Despite the dramatic differences in aetiology, pathophysiology, and pharmacokinetics, current guidelines recommend uniform therapy, regardless of the patient's age or sex. Females and elderly HF patients are underrepresented in HF trials, and with the underuse of GDMT in the real world,[26,27] the positive effect of GDMT in these HF populations is not yet fully understood. Recently, there has been an increasing interest in exploring optimal therapy. The BIOSTAT-CHF study found striking sex and age differences in optimal dose levels of ACEI/ARB and BB in HFrEF patients, in which females had the lowest risk of death or hospitalization for HF at half the guideline-recommended doses compared with males.[13] Achieving higher doses of BB was associated with improved outcome, which was only found in patients $<$70 years.[28] Despite the lack of dosage of GDMT, the present study was consistent with some post hoc analyses of HF trials and registries and supported the position that the beneficial effect of the use of GDMT in improving outcomes in patients with HFrEF and HFpEF was independent of age and sex.[14,15,29,30] In HFmrEF, however, age- and sex-based differences were observed in patients sharing characteristics with HFrEF and HFpEF. Female patients with HFmrEF and aged $\geq$75 years resembled HFrEF patients and could benefit from GDMT; male patients with HFmrEF and aged $<$75 years behaved more like patients with HFpEF and indicated no mortality risk reduction from good GDMT. Such a result reemphasizes the heterogeneous nature of the 'grey zone' of HF.

Table 4 Comparison of all-cause mortality according to different guideline-directed medical therapy (GDMT) groups across the spectrum of left ventricular ejection fraction (LVEF) by age and sex subgroup

		LVEF < 30%		LVEF 30–39%		LVEF 40–49%		LVEF ≥ 50	
All-cause mortality		No. at risk (event rate/ 1000 py)	Adjusted HR (95% CI) *P* value	No. at risk (event rate/ 1000 py)	Adjusted HR (95% CI) *P* value	No. at risk (event rate/ 1000 py)	Adjusted HR (95% CI) *P* value	No. at risk (event rate/ 1000 py)	Adjusted HR (95% CI) *P* value
Age < 75	Poor	313 (117)	1 (ref)	290 (83)	1 (ref)	305 (73)	1 (ref)	459 (84)	1 (ref)
	Moderate	1722 (69)	0.70 (0.56–0.87) 0.001	1342 (53)	0.74 (0.52–0.78) <0.001	974 (53)	0.73 (0.59–0.90) <0.001	849 (74)	0.82 (0.68–0.99) 0.039
	Good	1321 (76)	0.80 (0.65–0.99) 0.043	681 (70)	0.74 (0.59–0.93) 0.009	389 (81)	0.93 (0.73–1.19) 0.580	270 (86)	0.90 (0.71–1.15) 0.404
Age ≥ 75	Poor	987 (413)	1 (ref)	1285 (303)	1 (ref)	1454 (279)	1 (ref)	2431 (266)	1 (ref)
	Moderate	2748 (225)	0.65 (0.56–0.74) <0.001	3128 (189)	0.67 (0.60–0.75) <0.001	2604 (175)	0.73 (0.65–082) <0.001	3135 (204)	0.83 (0.75–0.91) <0.001
	Good	1218 (207)	0.70 (0.60–0.82) <0.001	1023 (193)	0.74 (0.65–0.86) <0.001	743 (206)	0.84 (0.72–0.98) 0.029	841 (207)	0.97 (0.84–1.11) 0.613
Male	Poor	948 (257)	1 (ref)	1051 (204)	1 (ref)	996 (175)	1 (ref)	1302 (193)	1 (ref)
	Moderate	3289 (119)	0.62 (0.55–0.71) <0.001	2980 (102)	0.66 (0.59–0.75) <0.001	2140 (102)	0.78 (0.68–0.88) <0.001	1732 (139)	0.83 (0.73–0.94) 0.004
	Good	193 (110)	0.70 (0.61–0.81) <0.001	1128 (109)	0.77 (0.67–0.89) <0.001	672 (130)	0.88 (0.75–1.04) 0.142	495 (146)	0.97 (0.81–1.15) 0.693
Female	Poor	352 (257)	1 (ref)	524 (203)	1 (ref)	763 (205)	1 (ref)	1588 (203)	1 (ref)
	Moderate	1181 (124)	0.72 (0.57–0.91) 0.005	1490 (116)	0.66 (0.55–0.80) <0.001	1436 (118)	0.62 (0.52–0.72) <0.001	2252 (157)	0.83 (0.73–0.93) 0.002
	Good	626 (105)	0.76 (0.59–0.97) 0.027	576 (121)	0.73 (0.59–0.90) 0.004	460 (142)	0.83 (0.68–1.01) 0.065	616 (162)	0.95 (0.80–1.11) 0.505

Abbreviations: CI, confidence interval; HR, hazard ratio; py, person years; ref, reference.

Conclusions

The optimal adherence to GDMT works best in patients with LVEF $< 50\%$, whereas moderate adherence to GDMT varies in efficacy depending on the drug combination components.

Limitations

This study has several limitations. The nonrandomized nature of registry data could introduce selection bias. The described drug prescriptions were prescribed mainly by specialists and based only on the occasion of registration. Furthermore, the data about possible EF changing after initiation of GDMT were not available. The clinical decision about choice of GDMT and subsequent uptitration was entirely the physician's judgement. Although we performed various risk adjustments for potential confounding factors, potential residual confounding for unmeasured variables cannot be ruled out. Finally, adherence to GDMT was only assessed by the number of medications without dosage information, as well as the unknown long-term adherence to GDMT due to the nature of registry study, which may affect the outcome.[31]

Conflict of interest

Dr Dahlström reports grants outside the present work from Boehringer Ingelheim, AstraZeneca, Pfizer, Vifor, Boston Scientific, and Roche Diagnostics and consultancies from Amgen and Novartis and speaker fees from AstraZeneca outside the submitted work. Xiaojing Chen, Yu Kang, and Michael Fu declare no conflict of interest.

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