Treatment of Heart Failure in Real-World Clinical Practice: Findings From the REFLECT-HF Registry in Patients With NYHA Class II Symptoms and a Reduced Ejection Fraction

Address for correspondence:
Prof. Dr. Michael Böhm
Saarland University
Medical Center Internal Medicine
Clinic III Kirrberger Strasse 66424
Homburg/Saar, Germany
michael.boehm@uks.eu

Michael Böhm, MD; Carsten Tschöpe, MD; Jost Henner Wirtz, MD; Jan Lokies, MD; Eva Turgonyi, MD; Peter Bramlage, MD; Katharina Lins, PhD; Anke M. Strunz, PhD; Ulrich Tebbe, MD

Internal Medicine Clinic III (Böhm), Saarland University Medical Center, Homburg/Saar, Germany; Medical Clinic II, Department of Cardiology and Pulmonology (Tschöpe), Charité–Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany; Cardiology Group Practice (Wirtz), Dinslaken, Germany; Eickhoff Lokies Cardiology Group Practice (Lokies), Berlin, Germany; Medical Department Pfizer Ltd. (Turgonyi, Lins), Tadworth, Surrey, England, United Kingdom; Institute for Pharmacology und Preventive Medicine (Bramlage), Mahlow, Germany; Medical Department Pfizer Pharma GmbH (Strunz), Berlin, Germany; Department of Cardiology, Angiology and Intensive Care Medicine (Tebbe), Lippe-Detmold Clinic, Detmold, Germany

ABSTRACT

Background: Optimal medical therapy (OMT) for patients with chronic heart failure and a reduced ejection fraction (HF-REF) includes angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and mineralocorticoid receptor antagonists, plus a diuretic.

Hypothesis: We hypothesized that OMT is less often prescribed in HF-REF patients (≤35%) with New York Heart Association (NYHA) class II symptoms compared with those with NYHA class III/IV symptoms.

Methods: This was a cross-sectional, observational, multicenter survey of hospital-based cardiologists, office-based cardiologists, and general practitioners in Germany.

Results: Out of a total of 384 patients enrolled, 144 had REF ≤35%. Patients with REF had NYHA class II symptoms in 39.6% (n = 57) and NYHA class III/IV symptoms in 60.4% (n = 87). The REF/NYHA class II group had a higher proportion of males than the REF/NYHA class III/IV group. For angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers, prescription rates were high and comparable between groups. However, prescription rates for mineralocorticoid receptor antagonists were lower compared with other guideline-recommended treatments. Multivariate analyses indicated that OMT prescription was reduced for older patients and increased for patients cared for by an office-based cardiologist.

Conclusions: Given the high proportion of patients with reduced left ventricular systolic function but only minor symptoms, HF-REF appears to be underdiagnosed, and a higher proportion of patients than are currently recognized could potentially be candidates for OMT.

Steering Committee: Michael Böhm (Homburg/Saar), Carsten Tschöpe (Berlin), Ulrich Tebbe (Detmold), Jost Henner Wirtz (Dinslaken), Jan Lokies (Berlin), Peter Bramlage (Mahlow).

Investigators: Ulrich Tebbe (Detmold), Stefan Blankenberg (Hamburg), Stefan Störk (Würzburg), Bernd-Dieter Gonska (Karlsruhe), Günter Piske (Berlin), Gunter Stenzel (Riesa), Clemens Bauknecht (Rottweil), Heribert Brück (Erkelenz), Peter Bosiljanoff (Munich), Jens Taggeselle (Markkleeberg), Gunter Seidel (Detmold), Sinisa Miketic (Detmold), Torsten Figura (Rinteln), Susanne Backhaus (Buchholz), Dag-Alexander Keilhau (Hamburg), Jens Beermann (Wedel), Behrus Subin (Hamburg), Wilhelm Josef Mieseler (Höchberg), Claus Günthert (Höchberg), Michael Dobler (Karlstadt), Heinrich Bechtold (Schrozberg), Matthias Salefsky (Aschaffenburg), Ulrich Staedt (Speyer), Thomas Dieterle (Ettlingen), Sabine Raulin (Karlsruhe), Mustafa Durak (Heidelberg), Petra Lange-Braun (Berlin), Andreas Förster (Berlin), Rene Oliver (Berlin), Claudia Zemmrich (Berlin), Werner Rieker (Berlin), Heike Stenzel (Riesa), Peter Kindermann (Riesa), Jan Nimetschik (Gröditz), Petra Bauer (Bad Liebenwerda), Andreas Hagenow (Elsterwerda), Ottmar Banning (Waldmössing), Klaus Götz (Bad Dürrheim), Johannes Guhl (Villingen-Schwenningen), Karl Stuff (Donaueschingen), Helmut Hermanns (Erkelenz), Franz-Josef Geffers (Erkelenz), Ulrich Arendt (Mönchengladbach), Alexandra

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Haupt-Pichler (Munich), Cornelia Groos-März (Munich), Constanze Schmidt (Borna), Thomas Theuner (Markkleeberg), Astrid Meier (Markkleeberg), Cornelia Schlott (Zwenkau).
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Introduction

Heart failure (HF) with reduced left ventricular ejection fraction (HF-REF) may become clinically apparent with moderate to severe symptoms (classified as New York Heart Association [NYHA] class III or IV) or rather mild symptoms (NYHA class I or II). Because of the lack of overt disease in patients with mild symptoms, it is reasonable to expect that HF may frequently remain undiagnosed and often undertreated.

To date, the major clinical trials for the treatment of HF have primarily included patients with REF (left ventricular ejection fraction [LVEF] $\leq$35%).[1] There is broad evidence to support the use of 3 classes of neurohumoral antagonists: angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists (MRAs), in patients with HF-REF and NYHA class III/IV symptoms.[2] More recent evidence suggests that neurohumoral antagonists are also beneficial for patients with HF-REF and NYHA class II symptoms.[3–9] This has been incorporated into the 2012 version of the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure, which state that optimal medical therapy (OMT) for patients with HF-REF and a NYHA class $\geq$ II should include all 3 classes of neurohumoral antagonists (ie, ACEI/ARB, β-blocker, and MRA) plus a diuretic.[10]

The Registry in Germany Focusing on Level-Specific and Evidence-Based Decision Finding in the Treatment of Heart Failure (REFLECT-HF) survey was a cross-sectional, observational, multicenter survey of treatment patterns of hospital-based cardiologists (HBCs), office-based cardiologists (OBCs), and general practitioners (GPs). The aim of the present analysis was to assess the use of OMT in patients with REF but mild symptoms.

Methods

The REFLECT-HF survey was conducted in 10 regional clusters across Germany, in which either an HBC (n = 5) or an OBC (n = 5) served as a main center, with 5 satellites per center that were either OBCs (when the center was an HBC) or GPs (when the center was an OBC) in the respective area. In the end, a total of 384 patients were included at 5 HBCs, 26 OBCs, and 18 GPs. Physicians received a compensation of €100 per patient for the complete documentation of their patients.

The recruitment target was consecutive patients (age $\geq$18 years) with a documented history of chronic HF, with 20 patients for each HBC, 10 for each OBC, and 5 for each GP. Patients were required to have a NYHA class of $\geq$ II, and/or a LVEF <50%. Patients who were unable to complete the questionnaires because of psychiatric reasons, dementia, or other neurological diseases were excluded.

Information was collected on each participating physician, on patient demographics, the diagnosis of heart failure (NYHA class, LVEF), medical history, device and pharmacological treatments (drug classes were recorded, but not specific compounds or dose levels), quality of life (using the Minnesota Living With Heart Failure [MLHF] questionnaire), hospitalization-related parameters, electrocardiography (rhythm, branch blocks, heart rate, and QRS interval), and laboratory values.

The study protocol was approved by the International Ethics Committee in Freiburg, Germany, on September 26, 2011. All patients provided written informed consent.

Statistical Analysis

Quantitative data (eg, patient age) in the tables and figures are presented by using either mean ± SD or 95% confidence intervals, and qualitative data (eg, patient sex) are expressed as respective proportions. Group differences were evaluated by applying χ^2 tests for qualitative and Wilcoxon tests for quantitative data; *P* values for the latter were derived from the 2-sided test situation.

Simple and multiple logistic regression models were also performed. For models accounting for multiple variables, stepwise selection was applied based on the *P* values of the parameter estimates: Only such variables remained in the final model where respective *P* values of the Wald statistic were <0.1. Variables with a large amount of missing values were not included into the model-selection process to reach a high number of evaluable patients for the model calculation. Other possible reasons for variables not being included were lack of variability or collinearity issues. Results of the logistic regression models are presented in terms of estimated odds ratio and corresponding 95% confidence intervals. All statistical analyses were carried out using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Patient Characteristics

The REFLECT-HF survey included a total of 384 patients documented at 48 physicians between January 16 and August 30, 2012. This analysis includes data from 364

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Table 1. Patient Characteristics

	All Patients With LVEF ≤35% by NYHA Class			All Patients by NYHA Class		
	NYHA II + LVEF ≤35%, n = 57	NYHA III/IV + LVEF ≤35%, n = 87	*P* Value	NYHA II, n = 202	NYHA III/IV, n = 162	*P* Value
Age, y	64.2 ± 12.8	66.5 ± 11.7	0.3588	67.9 ± 12.3	69.7 ± 11.0	0.3120
Female sex	8.8	28.7	0.0039	24.3	33.3	0.0561
BMI, kg/m²	28.4 ± 4.5	28.5 ± 5.7	0.7116	28.8 ± 4.3	28.9 ± 5.7	0.4331
Cr, mg/dL	1.3 ± 0.5	1.3 ± 0.4	0.7760	1.3 ± 0.6	1.3 ± 0.4	0.6216
eGFR, mL/min/1.73 m²	67.5 ± 29.5	64.8 ± 22.6	0.9738	64.8 ± 25.1	61.1 ± 22.3	0.3449
<30	6.3	6.3	1.0000	6.3	5.9	0.9347
K^+, mmol/L	4.3 ± 0.3	4.4 ± 0.5	0.6233	4.4 ± 0.5	4.4 ± 0.5	0.7375
>5.5	0.0	2.9	0.5022	0.0	1.5	0.3556
NT-proBNP, pg/mL	629.2 ± 665.4	976.0 ± 856.2	0.3977	554.7 ± 532.6	872.9 ± 772.1	0.1040
≥125	20.0	14.3	0.7503	26.3	14.3	0.3037
Heart rate, bpm[a]	75.8 ± 16.2	73.7 ± 9.5	0.9917	72.0 ± 11.9	72.1 ± 11.3	0.7031
Rhythm[b]			0.3386			0.0930
Sinus rhythm	76.2	69.2		76.8	65.6	
AF	23.8	26.2		21.8	30.4	
Other	0.0	4.6		1.4	4.0	
LBBB	34.9	32.8	0.8244	30.4	28.7	0.7680
QRS >130 msec	42.9	32.8	0.3272	31.0	31.7	0.9110
Ischemic etiology of HF	56.1	60.9	0.5685	57.9	60.5	0.6198
Prior MI	45.6	42.5	0.7151	38.1	38.3	0.9762
Hypertensive heart disease	22.8	26.4	0.6228	32.2	26.5	0.2422
MLHF summary score	27.2 ± 20.4	42.5 ± 19.3	<0.0001	28.5 ± 18.4	42.4 ± 19.0	<0.0001
Physical dimension	13.3 ± 9.2	20.9 ± 8.0	<0.0001	14.3 ± 8.9	21.0 ± 8.3	<0.0001
Emotional dimension	4.2 ± 5.0	7.4 ± 6.0	0.0004	4.7 ± 5.0	7.3 ± 5.9	<0.0001

Abbreviations: AF, atrial fibrillation; BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate; HF, heart failure; K+, potassium; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MLHF, Minnesota Living With Heart Failure Questionnaire; NT-proBNP, N-terminal pro–brain natriuretic peptide; NYHA, New York Heart Association; QRS, QRS interval; SD, standard deviation.
Data are presented as mean ± SD or %.
[a]Only patients with sinus rhythm. [b]Patients with pacemaker excluded from this analysis.

patients with HF who displayed NYHA class II–IV symptoms with LVEF <50%.

Out of 364 patients considered valid for this analysis, 144 had both a REF (defined as LVEF ≤35%) and either NYHA class II (n = 57; 39.6%) or NYHA class III/IV (n = 87; 60.4%). REF/NYHA class II patients were less often females (8.8% vs 28.7% with REF/NYHA class III/IV; $P = 0.0039$; Table 1), which had a similar trend in analyses disregarding the LVEF and only considering the NYHA class (24.3% vs 33.3%; $P = 0.0561$).

Patients with REF/NYHA class II also had a lesser score on the MLHF questionnaire (27.2 ± 20.4 vs 42.5 ± 19.3; $P < 0.0001$), reflecting better quality of life in those with NYHA class II symptoms. The difference in MLHF scores was also observed for NYHA class II vs NYHA class III/IV ($P < 0.0001$), irrespective of actual LVEF.

As depicted in Figure 1A, the majority of patients seen by HBCs had NYHA class III/IV (70.0% vs 30.0%), whereas OBCs and GPs saw a greater proportion of patients with NYHA class II (60.8% and 59.8%, respectively) compared with NYHA class III/IV (39.2% and 40.2%, respectively; $P < 0.0001$ for NYHA class II vs III/IV, all 3 physician groups). For the REF/NYHA class II and REF/NYHA class III/IV group, HBCs and GPs primarily saw patients with class III/IV symptoms (83.9% and 66.7%, respectively), whereas OBCs saw a similar proportion of patients with class II (48.4%) and class III/IV (51.6%) symptoms ($P = 0.0052$ for REF/NYHA class II vs REF/NYHA class III/IV, all 3 physician groups).

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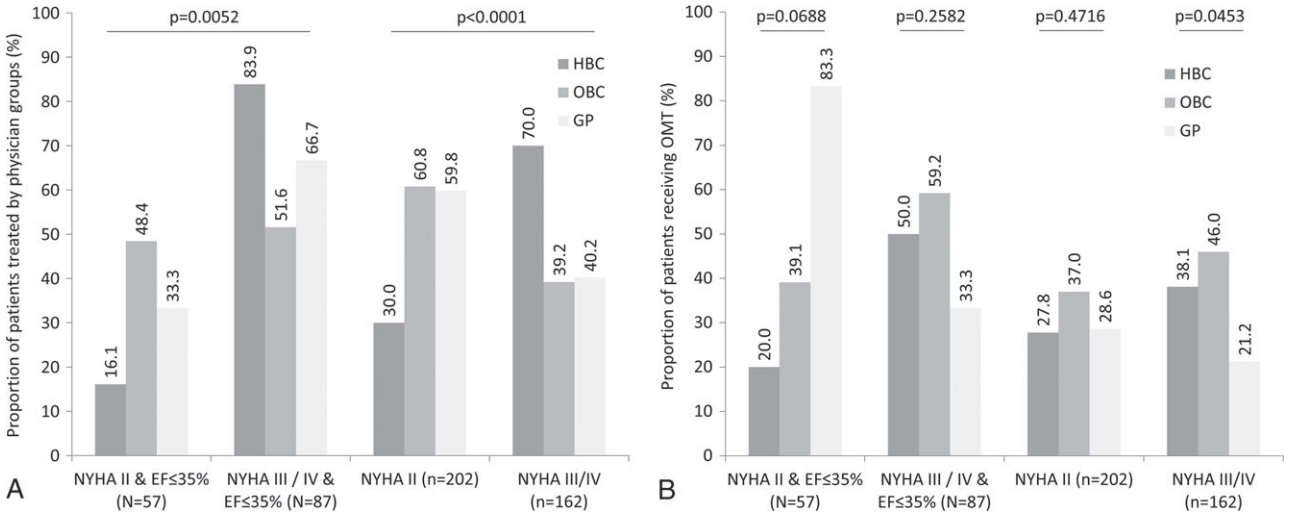

Figure 1. (A) Percentages of patients who were cared for by each type of physician according to NYHA class, with or without consideration of LVEF. (B) Percentages of patients who received OMT by the type of physician, and by NYHA class, LVEF, and NYHA class and LVEF. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; GP, general practitioner; HBC, hospital-based cardiologist; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OBC, office-based cardiologist; OMT, optimal medical therapy (treatment with ACEI/ARB, β-blocker, MRA, and diuretic).

Treatment Patterns

The majority of patients with REF received ACEIs and/or ARBs (94.7% in NYHA class II vs 92.0% in NYHA class III/IV), β-blockers (93.0% vs 92.0%, respectively), and diuretics (80.7% vs 88.5%, respectively), with no significant differences between the REF/NYHA class II and REF/NYHA class III/IV groups (Table 2). There were, however, nominal differences for the proportion of patients receiving diuretics (80.7% and 88.5%), MRAs (54.4% and 64.4%), anticoagulants (38.6% and 51.7%), and for implantable cardioverter-defibrillators (ICD; 0.0% and 8.3%). Ivabradine was administered to 0.0% and 10.3% of patients in the REF/NYHA class II and REF/NYHA class III/IV groups, respectively, but this difference only reached borderline significance ($P = 0.0524$).

Regardless of LVEF, administration of diuretics, MRAs, and ivabradine was more frequent in the NYHA class III/IV group ($P = 0.0102$, 0.0229, and 0.0362, respectively), whereas β-blockers were more commonly prescribed in the NYHA class II group ($P = 0.0048$). The proportion of patients receiving OMT did not differ between either the NYHA class II and the NYHA class III/IV groups or the REF/NYHA class II and REF/NYHA class III/IV groups.

Factors Associated With Optimal Medical Therapy

The frequency at which OMT was prescribed was greater for patients with NYHA class III/IV symptoms who saw an OBC, as compared with an HBC or a GP ($P = 0.0453$). No other significant differences were observed in the frequency of OMT prescription when assessed by physician group (Figure 1B).

For patients with REF and either NYHA class II or class III/IV symptoms, there were no notable differences in the prescription of OMT with respect to physician sex, their working experience, the type of physician (HBC, OBC, or GP), the number of HF patients treated per day, patient sex, or the patient's estimated glomerular filtration rate. On the other hand, in the NYHA class III/IV group, the REF group, as well as the REF/NYHA class II and REF/NYHA class III/IV groups, older patients (> median vs ≤ median) had a reduced likelihood of receiving OMT (Table 3). Similarly, irrespective of LVEF, physicians with a long work experience (> median vs ≤ median) were less likely to prescribe OMT to patients with NYHA class III/IV symptoms, as were GPs vs OBCs.

Factors Associated With Being New York Heart Association Class II Despite Left Ventricular Ejection Fraction ≤35%

Univariate analyses for being NYHA class II with REF were performed using the following 6 variables: age (> median), female sex, body mass index (> median), ischemic origin of HF or prior myocardial infarction, hypertensive heart disease, and heart rate (> median). The only one of these 6 variables that influenced the probability of being NYHA II with REF was female sex, which was a negative correlation. Multivariate analyses demonstrated that female sex was independently associated with a reduced likelihood of being NYHA class II despite REF (Table 4).

Discussion

The present subanalysis extends the initial findings of the REFLECT-HF survey[11] by investigating the differences in treatment patterns for patients with reduced LVEF (defined as ≤35%) and either NYHA class II or NYHA class III/IV symptoms. Because patients defined as having NYHA class II heart function have only mild symptoms, both the diagnosis and treatment of these patients is potentially more challenging than for those with overt disease. Based on recent evidence from clinical trials, the 2012 version of

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Table 2. Pharmacotherapy/Device Use

	All Patients With LVEF ≤35% by NYHA Class			All Patients by NYHA Class		
	NYHA II + LVEF ≤35%, n = 57	NYHA III/IV + LVEF ≤35%, n = 87	*P* Value	NYHA II, n = 202	NYHA III/IV, n = 162	*P* Value
	%	%		%	%	
ACEIs	77.2	69.0	0.2811	68.8	64.8	0.4201
ARBs	21.1	27.6	0.3759	26.7	28.4	0.7240
ACEIs and/or ARBs	94.7	92.0	0.5206	93.1	88.9	0.1616
β-Blockers	93.0	92.0	0.8203	94.1	85.2	0.0048
Diuretics	80.7	88.5	0.1944	81.2	90.7	0.0102
MRAs	54.4	64.4	0.2310	43.6	55.6	0.0229
Ivabradine	0.0	10.3	0.0524	3.9	11.0	0.0362
Anticoagulants	38.6	51.7	0.1225	39.6	46.9	0.1614
CRT	12.5	14.9	0.7125	9.0	8.6	0.884
ICD	0.0	8.3	0.5035	0.0	7.7	0.2398
ACEI/ARBs, β-blockers, diuretics, and MRAs combined	42.1	52.9	0.2061	34.2	38.9	0.3508

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Table 3. Univariable Predictors of OMT (% of Patients Receiving ACEI/ARB, β-Blocker, Diuretic, and MRAs)

	NYHA II + LVEF ≤35%, n = 57, OR (95% CI)	NYHA III/IV + LVEF ≤35%, n = 87, OR (95% CI)	NYHA II, n = 202, OR (95% CI)	NYHA III/IV, n = 162, OR (95% CI)
Physician sex, F vs M	0.32 (0.03–3.02)	0.88 (0.26–2.96)	0.58 (0.27–1.27)	0.61 (0.25–1.50)
Physician working experience > median vs ≤ median	0.74 (0.25–2.23)	0.40 (0.16–1.00)	0.58 (0.32–1.07)	0.37 (0.19–0.73)
GP vs OBC	7.78 (0.84–72.13)	0.34 (0.09–1.31)	0.68 (0.33–1.39)	0.32 (0.12–0.81)
GP vs HBC	20.00 (0.93–429.90)	0.50 (0.12–2.08)	1.04 (0.31–3.46)	0.44 (0.15–1.24)
OBC vs HBC	2.57 (0.27–24.89)	1.45 (0.56–3.78)	1.53 (0.51–4.54)	1.38 (0.65–2.93)
No. of HF patients treated/d > median vs ≤ median	0.70 (0.24–2.03)	1.82 (0.72–4.56)	1.14 (0.63–2.07)	1.84 (0.93–3.64)
Patient sex, F vs M	0.32 (0.03–3.02)	0.95 (0.38–2.41)	0.91 (0.46–1.81)	1.00 (0.51–1.95)
Patient age > median vs ≤ median	0.28 (0.08–0.93)	0.31 (0.13–0.75)	0.65 (0.36–1.18)	0.29 (0.15–0.56)
Patient eGFR <30 vs ≥30	0.56 (0.02–17.92)	1.00 (0.06–17.51)	1.23 (0.10–14.78)	0.68 (0.07–6.96)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; F, female; GP, general practitioner; HBC, hospital-based cardiologist; HF, heart failure; LVEF, left ventricular ejection fraction; M, male; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OBC, office-based cardiologist; OMT, optimal medical therapy; OR, odds ratio.

the ESC guidelines for the treatment of HF included new recommendations, in particular on the use of all 3 classes of neurohumoral antagonists for patients with REF and NYHA class II–IV symptoms.[10]

Patient Characteristics

The present subanalysis of the REFLECT-HF study demonstrates that patient demographics vary according to the degree of left ventricular dysfunction and NYHA class. The NYHA class II group comprised a higher proportion of males than females, and the mean age tended to be lower than that of patients with NYHA class III/IV symptoms. Accordingly, compared with the REF/NYHA class III/IV group, the REF/NYHA class II group was characterized by a significantly higher proportion of males and a slightly lower mean age. This sex-specific difference was emphasized by the results of multivariate modeling for predictors of being NYHA class II and having REF—the only factor that was identified was female sex, and this was a negative correlation. Thus, the characteristics of patients in this study were consistent with the published literature, which suggests that HF with preserved LVEF (≥50%) is more

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Table 4. Multivariable Predictors of Being NYHA II Despite LVEF ≤35% (Stepwise Multivariable Regression Analysis)

	No.	Simple OR (95% CI)	Multiple OR (95% CI)
Age > median	144	0.83 (0.42–1.64)	—
Female sex	144	0.24 (0.09–0.67)	0.24 (0.09–0.67)[a]
BMI > median	144	0.80 (0.40–1.56)	—
Ischemic origin of HF or prior MI	144	0.80 (0.40–1.58)	—
Hypertensive heart disease	144	0.82 (0.38–1.80)	—
Heart rate > median	144	1.14 (0.58–2.22)	—

Abbreviations: CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; OR, odds ratio.
[a]Final multiple model is equivalent to simple model.

commonly observed in females and older patients.[10,12,13] Of note in this survey, approximately 40% of all patients with REF had mild, NYHA class II symptoms.

Guideline Adherence

For the 3 classes of well-established drugs for the treatment of heart failure (ACEIs/ARBs, β-blockers, and diuretics), rates of administration were high, with no significant differences between the REF/NYHA class II and REF/NYHA class III/IV groups. These figures are in line with the recommendations of both the 2012 version of the ESC guidelines[10] for the treatment of heart failure, as well as regional guidelines, such as the German Society of General Practitioners guidelines.[14]

In contrast, for MRAs, the prescription rate was much lower, at 54% and 64% for the REF/NYHA class II and REF/NYHA class III/IV groups, respectively. When considering older versions of the ESC guidelines,[15] as well as regional guidelines (which had not been updated at the time the REFLECT-HF survey was conducted), a lower rate of prescription of MRAs relative to the other 3 drug classes may be expected. Prior to the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) clinical trial, MRAs were only indicated for patients with NYHA class III/IV symptoms. However, the 2012 ESC guidelines were revised to reflect the findings related to the use of MRAs in patients with NYHA class II symptoms.[10,16] Even accounting for the use of the older ESC guidelines or regional guidelines, MRAs appear to be underprescribed, with up to 35% of patients in the REF/NYHA class III/IV group being eligible for, but not receiving, this drug class. Furthermore, the 2012 ESC guidelines recommend that the combination of an ACEI/ARB, a β-blocker, and an MRA should be initiated as soon as possible following the diagnosis of HF-REF with NYHA class II symptoms.[10,17] Thus, a considerable subset of patients in the REF/NYHA class II group would be eligible for, but did not receive, an MRA. In the present subanalysis, the probability of receiving all 3 classes of neurohumoral antagonists was highest for NYHA class III/IV patients who were treated by an OBC. Data from the primary REFLECT-HF analysis, which included an evaluation of the rate of prescription of each drug class according to physician type, indicate that MRAs were more frequently prescribed by OBCs than HBCs and GPs. Interestingly, the REFLECT-HF analysis also demonstrated that the proportion of patients who were eligible for an MRA but did not receive treatment was greater for those who saw an HBC or an OBC than for those who saw a GP.[11]

Another noteworthy finding of this subanalysis was the lack of administration of ivabradine to patients in the REF/NYHA class II group, despite a high mean heart rate. This is especially pertinent in the context of the finding of a significantly higher heart rate in patients with REF vs those with LVEF >35%. The 2012 version of the ESC guidelines (but not the previous version) advocates the use of ivabradine as an add-on treatment for patients with an REF and NYHA class II or higher who have a resting heart rate >70 bpm, despite receiving an ACEI/ARB, a β-blocker, an MRA, and a diuretic. Although rates of administration of both ivabradine and β-blockers were similar in the REF and the LVEF >35% group, significant differences were observed when comparing the NYHA class II group with the NYHA class III/IV group. Use of β-blockers was significantly more frequent in the NYHA class II group, whereas use of ivabradine was significantly more frequent in the NYHA class III/IV group. Based on the recommendations of clinical guidelines, it would be expected that β-blockers are the first-line drug for the reduction of heart rate. Thus, it appears likely that the combination of β-blockers and ivabradine was used more frequently in patients with NYHA class III/IV symptoms than in patients with NYHA class II symptoms. Estimates suggest that in real-life clinical practice, only 30% to 35% of patients attain the therapeutic target dose of β-blockers, and, in addition, even in patients who receive optimal dose levels, an elevated heart rate is often observed.[18] Given that a high heart rate has been identified as an independent predictor of cardiovascular events in patients with HF, increased use of the combination of β-blockers and ivabradine may confer survival benefits.[18–21]

Finally, the use of the nonsurgical devices (ICDs and cardiac resynchronization therapy [CRT]) has also been demonstrated to be beneficial for patients with HF-REF and mild symptoms. Results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-CRT indicated that the addition of ICD or CRT to pharmacological treatment improved survival in this patient population.[6,11] Analyses of registries and hospital claims data suggest that only 20% to 50% of eligible patients receive ICD or CRT.[22–24] Our own rates are at the lower end of this estimate, with 14.9% of patients with REF and NYHA group III/IV having a CRT and 8.3% an ICD. Rates were even lower for those with only mild symptoms (12.5% CRT) or in those with LVEF >35%. This may reflect the inclusion of HF patients at office-based physicians (cardiologists and GPs) rather than in hospitals only, which was the case for the majority of other registries.

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Our results are certainly relevant for the German setting, but they need to be put into perspective with European data. The ESC-HF Long-Term registry,[25,26] which is a prospective, observational study involving 211 cardiology centers in 21 European and Mediterranean countries, enrolled 7401 patients with chronic HF from May 2011 to April 2013. The median LVEF was 35% (range, 28%–45%), and 74.7% had either NYHA class I or II symptoms. Among the subpopulation of patients with LVEF ≤45% (n = 4792), the rates of prescription of diuretics were 84.3%, ACEIs 70.7%, ARBs 23.5%, β-blockers 92.7%, MRAs 67.0%, and ivabradine 10.5%. However, data on the subpopulation of patients with REF and NYHA class I or II symptoms were not available at the time of publication,[25] making a direct comparison with our data difficult.

Factors Predictive of Receiving Optimal Medical Therapy

The frequency of patients in the present subanalysis who were receiving OMT was highest in the REF/NYHA class III/IV group (53%) and lowest in the LVEF >35% subgroup (30%), with an intermediate value for the REF/NYHA class II group (42%). Because the rate of prescription of the 3 well-established drug classes for HF was high and relatively uniform across groups, the less-than-adequate administration of OMT appears to be primarily associated with the underuse of MRAs. In the case of older patients, physicians may be less willing to prescribe MRAs, possibly because of the presence of risk factors such as reduced renal function. A survey performed in France also indicated that underprescription of OMT was more frequent among older patients, as well as those with renal dysfunction.[27] In addition, a recently published study highlighted the requirement for better adherence to guidelines for monitoring creatinine and potassium levels in patients with HF following the initiation of an MRA.[28] Improvements in monitoring of renal function in patients receiving MRAs would allow dosage modifications or discontinuation of treatment, potentially resulting in fewer adverse events and this class of drug being associated with a better benefit-risk profile.

With regard to the increased likelihood of receiving OMT for patients who saw an OBC, this may in part be reflective of differences in the patient population at each type of clinical setting. For example, the REFLECT-HF analysis indicated that patients cared for by GPs were more often females, and tended to be older, with reduced renal function and a lower NYHA class. The frequency of patients with atrial fibrillation was also higher for GPs. Furthermore, it may be expected that patients who require treatment in a hospital setting have greater morbidity than those who visit OBCs or GPs. In the present subanalysis, differences were also observed in the patient population seen by each physician type, with HBCs caring predominantly for patients with NYHA class III/IV symptoms. The patient population seen by each type of physician may contribute to variations in the implementation of guidelines for 2 reasons: (1) the inherent characteristics of a patient may preclude treatment with a particular agent (ie, patients may have other comorbidities or contraindications that complicate drug prescription); and (2) the relative experience of each type of physician with particular patient populations.

Study Limitations

Although the REFLECT-HF survey comprised data from the 3 main groups of physicians who treat patients with HF in Germany, and is thus reflective of real-world clinical practice, the study has some limitations. In particular, because REFLECT-HF was a cross-sectional study, data on the time since diagnosis of HF, as well as morbidity and mortality rates, were not obtained. Other limitations of this study have already been discussed in the primary publication of the REFLECT-HF survey.[11] These include a change of guideline recommendations recommending the use of MRAs in patients with NYHA class II HF and REF. Finally, though the findings may apply to the German health care system, they should be validated in different health care systems.

Clinical Implications

Using OMT is associated with an improved prognosis, even in those patients with only moderate, NYHA class II symptoms. The reluctance to intensify treatment, based on a lack of clinical consequences and a fear of treatment-associated side effects, but improved prognosis, should be overcome by a closer cooperation and exchange of different physician groups caring for the HF patient.

Conclusion

Given the high proportion of patients with a reduced left ventricular systolic function but only minor symptoms, HF-REF appears to be underdiagnosed, and a higher proportion of patients than are currently recognized could potentially be candidates for OMT.

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