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CLINICAL RESEARCH

Contemporary Drug Treatment of Chronic Heart Failure With Reduced Ejection Fraction

The CHECK-HF Registry

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ABSTRACT

OBJECTIVES This study investigated adherence to drug therapy guidelines in heart failure (HF) with reduced left-ventricular ejection fraction (LVEF) of <40% (heart failure with reduced ejection fraction [HFrEF]), in which evidence-based treatment has been established.

BACKGROUND Despite previous surveys of HF, important uncertainties remain regarding guideline adherence in a representative real-world population.

METHODS A cross-sectional registry in 34 Dutch HF outpatient clinics that included 10,910 patients with the diagnosis of HF was examined. Of that number, 8,360 patients had LVEF <50% (72 ± 12 years of age; 64% male) and were divided into HFrEF (n = 5,701), HF with mid-range LVEF (HFmrEF) with LVEF 40% to 49% (n = 1,574), and those with semiquantitatively measured LVEF but <50% (n = 1,085).

RESULTS In the HFrEF group, 81% of the patients were treated with loop diuretics, 84% with renin-angiotensin-system (RAS) inhibitors, 86% with β-blockers, 56% with mineralocorticoid-receptor antagonists (MRA), and 5% with I_f-channel inhibition. Differences in medication use were minor among the 3 groups but were significant among centers. Inability to tolerate the medications was recorded in 9.4% patients taking RAS inhibitors, 3.3% taking β-blockers, and 5.4% taking MRAs. Median loop diuretic dose was 40 mg of furosemide equivalent, RAS inhibitor dose 50% of target, β-blocker dose 25% of target, and MRA dose 12.5 mg of spironolactone equivalent. Elderly patients were treated predominantly with diuretics and less often with RAS inhibitors, β-blockers, and MRAs.

CONCLUSIONS This large contemporary HF registry showed a relatively high use of evidence-based treatment, particularly in younger patients. However, the average dose of evidence-based medication was still lower than recommended by guidelines. Furthermore, the more recently introduced I_f-channel inhibition has hardly been adopted. There is ample room for improvement of HFrEF therapy, even more than 25 years after convincing evidence that HFrEF treatment leads to better outcome. (J Am Coll Cardiol HF 2019;7:13–21) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

HF = heart failure

HFmrEF = heart failure with mid-range ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEF = left-ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

RAS = renin-angiotensin system

Adherence to guideline-recommended therapy in heart failure (HF) remains challenging. Adoption of new treatment options requires many years, often decades. Thus, angiotensin-converting enzyme (ACE) inhibitors were shown in the early 1990s to be beneficial in patients with heart failure with reduced ejection fraction (HFrEF) (1,2). However, more than 10 years later, only 60% of those patients were treated with an ACE inhibitor, although treating physicians were aware of the drug's benefits (3). The adoption of β-blockers, introduced later, was significantly worse (i.e., <40%) (4), and even currently mineralocorticoid receptor antagonists (MRAs) are still underused (5,6). At the same time, physicians' adherence to treatment guidelines is a strong predictor of favorable outcome (7,8). There is large regional variation both in Europe and in the United States, and this pertains not only to the use of HF medication but also device therapy (9).

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Recent surveys found a higher prescription rate of evidence-based HF medication (8,10–12). Higher prescription rates were also reported in large treatment trials (13), but such patients are hardly representative of the general HF population, and inclusion requires evidence-based treatment. These patients are approximately 10 years younger than those in clinical practice, which also applies to some of the registries (8,12). Treatment uptake is lower in elderly patients, but guidelines recommend the use of HF medication regardless of age, despite the lack of clear evidence (14).

As shown in the recent U.S. CHAMP-HF (Change the Management of Patients With Heart Failure) registry (6) and in recent administrative data, the use of HF medication seems to be even lower in the real world than in recent surveys (8,10–12). Thus, patients included in these surveys were selected and were hardly representative of the general HF population. Moreover, registries often do not distinguish between patients with HFrEF and those with heart failure with preserved ejection fraction (HFpEF), although treatment recommendations to improve prognosis only apply to HFrEF patients (14). Also, many registries do not report the doses administered to patients (15). Although they are not well investigated, guidelines recommend using high doses of both renin-angiotensin-system (RAS) blockade and β blockade (14).

Because of these uncertainties, the present authors set up a cross-sectional registry of all patients seen in the outpatient clinic of 34 Dutch hospitals with the aim of investigating the quality of current HF management in the Netherlands. Because all patients treated by specialists in the Netherlands are seen in outpatient clinics of hospitals and not in private practices, this HF population was representative of patients seen by HF specialists.

METHODS

PATIENTS AND CLINICS. The methods of the CHECK-HF (Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry have been published previously (16). Briefly, HF or cardiology (if no specific HF clinic was present) outpatient clinics were invited to participate. Over a period of 3 years (2013 to 2016), 34 clinics (40%) of 86 centers in the Netherlands participated, of which 60 have an outpatient HF unit. Patients were included cross-sectionally based on the available records of these patients.

Diagnosis of HF was based on the most recent European guidelines for HF management available at the time (i.e., 2012) (17), but no further prerequisites were made regarding diagnostic and therapeutic decisions. Information included patients' characteristics, main cause of HF, basic echocardiographic and electrocardiographic measurements, medication, comorbidities, and relevant laboratory results. Patients' inability to tolerate and contraindication to the medication were recorded, as indicated by the treating physician. No predefined rules were applied to determine absolute contraindications. Ethical approval was provided for anonymously analyzing existing patient data by the Ethical Committee of the Maastricht University Medical Center, the Netherlands.

As part of the database, patients were divided based on left-ventricular ejection fraction (LVEF) into those with HFpEF with LVEF ≥50% and those with HF with

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LVEF <50%. In some patients, LVEF was only known semiquantitatively (using visual estimation) and divided into HFpEF versus HFrEF. In 283 (2.6%) of 10,910 patients, recording in the database was insufficient to classify patients according to their LVEF, and they were excluded from this analysis. Patients with no LVEF <50% were considered to have HFpEF (n = 2,267; 21.3% of the remaining patients). They were not considered for this analysis. Patients with LVEF <50% were divided based on the most recent European guidelines (18) into HFrEF (i.e., LVEF <40%), HF with mid-range LVEF (HFmrEF, i.e., LVEF 40% to 49%), and those with only semiquantitatively measured LVEF but whose LVEF was <50%.

STATISTICAL ANALYSIS. Results are frequencies (%), mean ± SD, or median (interquartile range [IQR]), as appropriate. Between-group comparisons were performed using one-way analysis of variance (ANOVA), Kruskal-Wallis H test, or Pearson chi-square test, as appropriate. For multiple comparisons, the significance level was adjusted using a Bonferroni correction. Multivariate predictors of use of medication were sought, using multivariate logistic regression analysis, using the stepwise forward procedure. All predictors of medication use in univariate analysis (data not shown) at a p value of <0.10 were included in the multivariate regression analysis. Results of logistic expression are presented as odds ratio (OR) and level of significance.

A 2-sided p value of 0.05 was considered statistically significant. All calculations were performed using SPSS version 25.0 software (IBM, Armonk, New York).

RESULTS

Of the 10,910 patients included in the CHECK-HF registry, 8,360 patients (76.6%) with LVEF <50% were included in this analysis. Of these patients, 5,701 (68.2%) had HFrEF, 1,574 (18.8%) had HFmrEF, and 1,085 (13.0%) had only semiquantitatively estimated LVEF <50%.

Baseline characteristics of these patients are shown in **Table 1**. Patients were on average 72 years of age, and almost two-thirds were male. Most patients were in New York Heart Association (NYHA) functional class II, and only very few were in NYHA functional class IV. Coronary artery disease was the most common cause of HF, and most patients had relevant co-morbidities. HF had been diagnosed in most patients at least 1 year before inclusion. As shown in **Table 1**, there were some differences among patients with HFrEF, HFmrEF, and semiquantitatively measured LVEF. Most characteristics of the last group were somewhere between those of HFrEF and HFmrEF, suggesting a combination between the other 2 groups.

DRUG TREATMENT. As shown in **Figure 1**, approximately 80% of the patients were treated with loop diuretics in all 3 groups (median dose of 40 mg furosemide equivalent; IQR: 20 to 80 mg). A similar proportion received a RAS inhibitor and a β-blocker. In HFrEF, 1.4% received a β-blocker not recommended by guidelines (1.0% received atenolol, 0.3% received propranolol, and 0.1% received labetolol 0.1%): 1.9% in the HFmrEF group and 1.6% in the semiquantitatively measured LVEF group, respectively. Sacubitril and valsartan were available only during the last couple of months of data collection and were given in only 0.4% of the patients (0.5% in HFrEF, 0.1% in the other 2 groups [analyses are included in RAS inhibitor results]). MRAs were prescribed to approximately one-half of the patients. Interestingly, an I_f channel inhibitor (ivabradine) was prescribed in <5% of the cases and was also low in those with LVEF <40% and with sinus rhythm (7.4%). Treatment significantly differed among the 3 groups for most medications. However, the absolute differences were relatively small. The combination of a RAS inhibitor and a β-blocker was given in 68.6%, 60.6%, and 63.1% in patients with HFrEF, HFmrEF, and those with semiquantitatively measured LVEF, respectively ($p < 0.001$). The combination of RAS blockade, β-blockade, and MRA was given in 39.2%, 27.3%, and 29.0% of patients, respectively ($p < 0.001$).

Patients who had had HFrEF diagnosed at least 1 year prior to inclusion, compared to those who had received their diagnosis within the same year, received loop diuretics less often (80.3% vs. 86.2%, respectively; $p < 0.001$), thiazides more often (2.9% vs. 1.4%, respectively; $p = 0.03$), equal percentages of β-blockers (80.7% vs. 83.6%, respectively; $p = 0.09$) and RAS inhibitors (82.6% vs. 83.2%, respectively; $p = 0.63$), MRAs less often (55.1% vs. 65.6%, respectively; $p < 0.001$), and equal percentages of ivabradine (5.2% vs. 6.8%, respectively; $p = 0.10$). Other drugs did not differ between the 2 groups. There was no specific pattern regarding these differences among the 3 groups (data not shown).

ACE inhibitors and angiotensin receptor blockers (ARB) were recorded as contraindicated in 9.4% of patients, with a wide range between centers from 0% to 36%. In 3.3% of the patients, β-blockers were recorded as contraindicated (range between centers of 0% to 27%), and in 5.4% of patients MRAs were contraindicated (range between centers of 0% to 22%). Thus, if this percentage is added to the prescription rates, 92.6% of the patients had either an ACE inhibitor or an ARB or were unable to tolerate

TABLE 1 Baseline Characteristics of Patients With HFrEF, With HFmrEF, and With Only Semiquantitatively Measured LVEF

	Overall	HFrEF (n = 5,701)	HFmrEF (n = 1,574)	Semiquantitatively Measured (n = 1,085)
Age, yrs (n = 8,351)	72.3 ± 11.8	71.4 ± 11.8	73.7 ± 11.7*	74.8 ± 11.2*†
Males (n = 8,323)	5,320 (63.9)	3,767 (66.4)	917 (58.4)*	636 (59.2)*
BMI, kg/m^2 (n = 7,671)	27.2 ± 5.2	27.2 ± 5.1	27.5 ± 5.4	26.8 ± 5.2†
Edema (n = 6,286)	840 (13.4)	499 (12.2)	209 (18.0)*	132 (12.7)†
Euvolemic (n = 5,582)	5,097 (91.3)	3,272 (91.4)	911 (89.6)	914 (92.6)
NYHA functional class (n = 8,262)				
I	1,313 (15.9)	839 (14.9)	284 (18.2)*	190 (17.9)*
II	4,692 (56.8)	3,244 (57.5)	854 (54.8)	584 (56.0)
III	2,108 (25.5)	1,449 (25.7)	392 (25.2)	267 (25.2)
IV	149 (1.8)	111 (2.0)	28 (1.8)	10 (0.9)
Systolic BP, mm Hg (n = 8,246)	125.7 ± 20.7	124.4 ± 20.2	129.5 ± 21.6*	126.6 ± 21.1*†
Diastolic BP, mm Hg (n = 8,252)	71.2 ± 11.4	71.2 ± 11.3	71.8 ± 12.0	70.3 ± 11.0†
Heart rate, beats/min (n = 8,248)	72.0 ± 13.9	71.9 ± 13.8	72.5 ± 14.3	71.8 ± 13.3
Rhythm (n = 8,253)				
SR	4,901 (59.4)	3,432 (61.0)	857 (55.0)*	612 (57.2)*†
AF	2,109 (25.6)	1,258 (22.4)	534 (34.3)	317 (29.7)
PM	1,141 (13.8)	850 (15.1)	155 (9.9)	136 (12.7)
Ectopic	102 (1.2)	85 (1.5)	13 (0.8)	4 (0.4)
LBBB (n = 8,360)	1,414 (16.9)	1,050 (18.4)	216 (13.7)*	148 (13.6)*
QRS, ms (n = 6,921)	125 ± 34	128 ± 34	117 ± 31*	120 ± 34*
HF diagnosis ≥1 yr prior to inclusion (n = 8,325)	7,436 (89.3)	5,021 (88.4)	1,398 (89.4)	1,017 (93.8)*†
Ischemic cause of HF (n = 8,094)	4,182 (51.7)	2,945 (53.5)	691 (45.4)*	546 (51.1)†
Nonischemic DCM (n = 8,094)	1,180 (14.6)	910 (16.5)	149 (9,8)*	121 (11.3)*
Hypertensive HD (n = 8,094)	386 (4.8)	229 (4.2)	99 (6.5)*	58 (5.4)
Valvular HD (n = 8,094)	1,210 (14.9)	808 (14.7)	276 (18.1)*	126 (11.8)*†
Other cause (n = 8,094)	1,136 (14.0)	613 (11.1)	306 (20.1)*	217 (20.3)*
No comorbidity (n = 7,488)	1,308 (17.5)	987 (19.5)	176 (12.4)*	145 (14.5)*
Hypertension	2,978 (39.8)	1,944 (38.3)	619 (43.7)*	415 (41.6)
Diabetes type 1 (n = 7,488)	271 (3.6)	193 (3.8)	38 (2.7)	40 (4.0)
Diabetes type 2 (n = 7,488)	1,904 (25.4)	1,289 (25.4)	359 (25.3)	256 (25.7)
COPD (n = 7,488)	1,381 (18.4)	900 (17.7)	291 (20.5)*	190 (19.0)
OSAS (n = 7,488)	495 (6.6)	320 (6.3)	116 (8.2)*	59 (5.9)
Thyroid disease (n = 7,488)	560 (7.5)	369 (7.3)	113 (8.0)	78 (7.8)
Renal failure	3,950 (56.3)	2,741 (54.8)	745 (60.9)*	464 (59.2)*
eGFR (n = 6,731)				
<30	802 (11.9)	528 (11.0)	165 (13.9)*	109 (14.5)
30-59	3,026 (45.0)	2,130 (44.4)	560 (47.3)	336 (44.7)
≥60	2,903 (43.1)	2,137 (44.6)	459 (38.8)	307 (40.8)
eGFR, ml/min/1.73 m^2 (n = 6,077)	56.2 ± 22.5	57.1 ± 22.5	53.3 ± 21.9*	54.7 ± 22.8*
Potassium (n = 6,814)	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.3 ± 0.5

Values are mean ± SD or n (%). *p < 0.05 vs. HFrEF. †p < 0.05 vs. HFmrEF.

AF = atrial fibrillation; BMI = body mass index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; DCM = dilated cardiomyopathy; eGFR = estimated glomerular filtration rate; HD = heart disease; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction (i.e., 40% to 49%); HFrEF = heart failure with reduced ejection fraction (i.e., <40%); LBBB = left-bundle branch block; NYHA = New York Heart Association; OSAS = obstructive sleep apnea syndrome; PM = pacemaker; renal failure = either renal failure in medical history or eGFR <60 ml/min/1.73 m^2; SR = sinus rhythm.

them. The corresponding numbers were 84.3% for β-blockers (additionally 5.3% received sotalol), and 61.8% for MRAs. Because there were no major differences among the 3 groups based on LVEF, only numbers in HFrEF patients are given.

Prescription rates in HFrEF patients differed significantly (all p < 0.001) among the different centers (**Figure 2A**). Thus, all patients received loop diuretics in one center but only 63% in another. The largest differences were seen for MRAs, in which the prescription rates ranged between 34% and almost 90%. Also, the range for triple therapy was large, from 16% to 76%. Results in HFmrEF patients were even more pronounced (Online Figure S1).

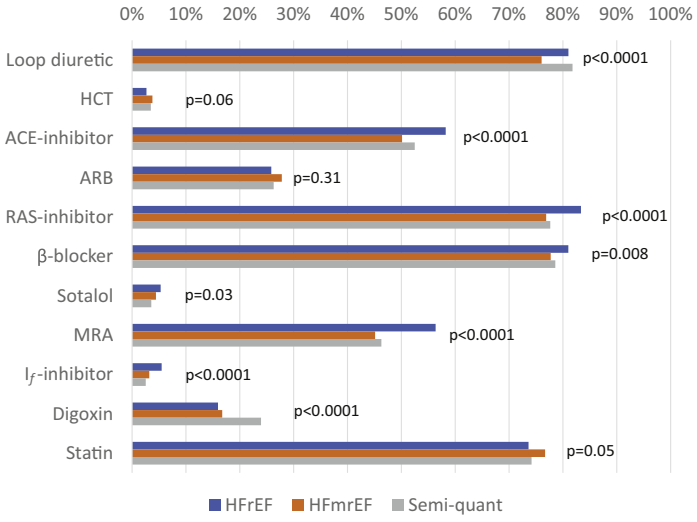
Age significantly influenced the prescription rate in HFrEF patients as shown in **Figure 3**. Loop diuretics

were more often prescribed to more elderly patients, whereas the opposite was the case for RAS inhibitors, β-blockers, and MRAs. Taking all patients into consideration did not change these results (data not shown).

HF MEDICATION PREDICTIONS. Multivariate predictors of the use of HF medication are shown in **Table 2**. Only patients with complete information were included in the analysis (n = 4,043). Patients not considered for multivariate analyses due to lack of some data were somewhat less symptomatic (NYHA functional class I was observed in 21% vs. 12%, respectively; NYHA functional class II in 52% vs. 61%, respectively; remainder were the same), less often no co-morbidity (10% vs. 22%, respectively), and more often had LVEF that was only semiquantitatively measured (18% vs. 9%, respectively) or HFmrEF (21% vs. 17%, respectively), but furthermore did not differ in a clinically meaningful way from those included. Age and body mass index had influences on the prescription of all investigated drugs. As expected, LVEF influenced the prescription rate significantly. Finally, co-morbidity had some impact on prescription rate. The presence of coronary artery disease as underlying cause of HF did not influence the prescription rate (**Table 2**).

Target dose (for definitions see Online Table 1) and use of RAS inhibitors, β-blockers, and MRAs in patients with HFrEF are shown in **Figure 2B**: on average, MRAs and RAS inhibitors were given in higher doses than β-blockers. Still, approximately one-half of the HFrEF patients taking the prescribed medication were receiving less than the target dose of MRAs and RAS inhibitors. Considering all 3 groups based on LVEF, statistically significant but still relatively small differences regarding doses were seen (Online Figure 2). In all 3 groups, more than two-third of the patients received loop diuretics of 40 mg furosemide equivalent or less. Very high doses (i.e., >160 mg furosemide equivalent) were given in <5% of the patients.

FIGURE 1 Medications



Medications in patients with HFrEF and with HFmrEF, and patients with only semi-quantitatively measured LVEF (semi-quant). ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HCT = hematocrit; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid-receptor antagonists; RAS = renin-angiotensin-system; Semi-quant = measured semiquantitatively.

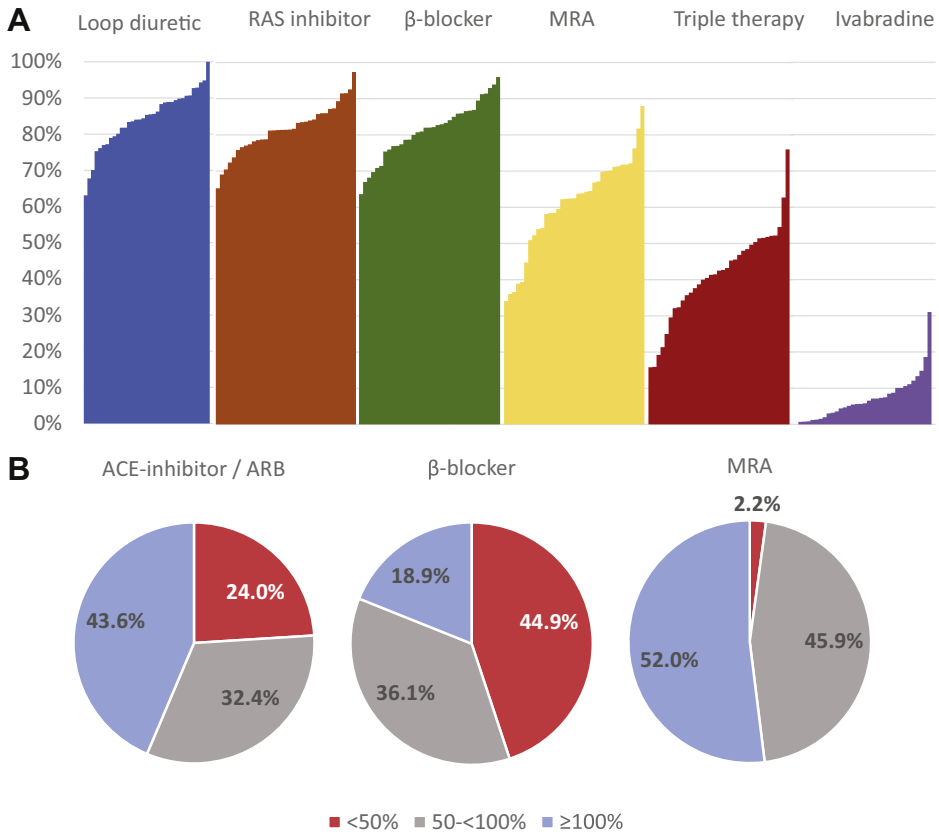
DISCUSSION

A survey of this large, contemporary registry of HFrEF patients in a representative number of centers in the Netherland showed a high use of evidence-based HF treatment. This was particularly true in younger patients but significantly less in more elderly patients who were treated predominantly with diuretics; yet, the average doses used for both RAS inhibitors and particularly β-blockers are still much lower than those recommended by the guidelines (14,18). MRAs were less used, and more recently introduced treatment such as I_f channel inhibition (19) was hardly adopted.

There was a large variation in the use of evidence-based therapy among different centers; medications not recommended by guidelines were used (e.g., sotalol, atenolol); and LVEF was only semi-quantitatively estimated in several patients. Therefore, and in line with the recent U.S. CHAMP-HF registry (6), there is still room for improvement of HFrEF therapy, despite the abundance of evidence for how to manage HFrEF patients.

A report by the Institute of Medicine suggested that it takes on average 17 years before new knowledge generated in randomized trials is incorporated into practice and even then acceptance varies considerably among centers (20). The difficulty in efficiently adopting new treatment has recently been confirmed by the Get-With-the-Guidelines Heart Failure registry for the introduction of sacubitril/valsartan (21) and even more impressively by the very recent CHAMP-HF registry (6). Better adoption of recommended therapy could theoretically result in a substantial reduction in HF deaths (22), as adherence to guideline-recommended medical therapy resulted in better outcome independent of device therapy (23). Also, a recent registry showed better short-term outcome with adherence to good general guidelines (8). Our data suggest that contemporary use of evidence-based treatment in HF is also reasonable in

FIGURE 2 Prescription Rates per Participating Center



(A) Prescription rates per participating center regarding the most important heart failure medication in HFrEF patients (ordered by percent of prescription; p values univariate chi-square test). **(B)** Proportion of eligible patients with available dosage data treated with <50% target dose, 50% to <100% target dose, or ≥100% target dose for medications known to improve prognosis. ACE = angiotensin-converting enzyme; other abbreviations as in Figure 1.

a real-world setting, but significant further improvement is required (6). Still, it is difficult to understand how such improvement can be achieved (20). Reasons for the limited adoption of not only new but also established therapy and the variation in practice are hardly understood. It is only relatively recently that the absolute number of recommended therapies as well as the possible reasons for not using such treatments have been investigated. However, usually such assessments are based on subjective opinion by the treating physician, as in our study. It is well recognized that reasons for not giving certain drugs may vary significantly among physicians and that drugs may be perceived as contraindicated even if they are not (24). Therefore, it is not surprising that not only did the prescription rates vary significantly but also the patients' recorded inability to tolerate the drugs. This highlights the need to also assess reasons for changing therapy in more detail, as was done in the CHAMP-HF registry (20). Various factors for not making optimal use of medication could be identified, and some of them represent accepted side effects (6). However, many factors were identified that were not

FIGURE 3 Prescription Rate of Medication in Different Age Groups in HFrEF Patients

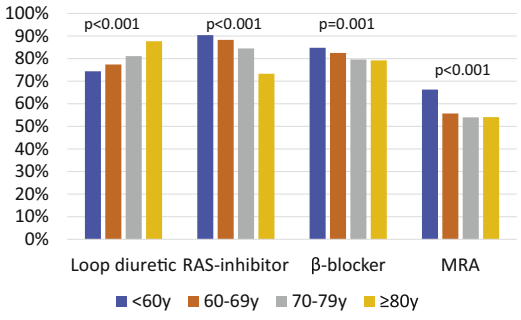


TABLE 2 Multivariate Predictors of the Use of Heart Failure Medication

	Loop Diuretic		RAS Blocker		β-Blocker		MRA	
	OR	p Value	OR	p Value	OR	p Value	OR	p Value
Females	–	–	–	–	1.20	0.03		
Age, per 10 yrs	1.10	0.03	0.86	0.002	0.81	<0.001	0.87	<0.001
BMI, per kg/m^2	1.05	<0.001	1.03	<0.001	1.02	0.05	1.02	0.002
Systolic BP, per 10 mm Hg	0.85	<0.001	–	–	–	–	0.84	<0.001
NYHA functional class, per class	1.76	<0.001	0.75	<0.001	–	–	1.28	<0.001
Heart rate, per 10 beats/min	1.09	0.01	0.85	<0.001	–	–	–	–
QRS, per 10 ms	–	–	0.98	0.05	0.97	0.009	1.03	0.003
eGFR	0.86	<0.001	1.18	<0.001	0.92	<0.001	–	–
Ischemic HF	–	–	–	–	–	–	–	–
Hypertension	–	–	1.24	0.02	1.22	0.01	1.14	0.05
Diabetes type 2	1.31	0.02	–	–	–	–	–	–
COPD	1.28	0.04	–	–	–	–	–	–
Renal failure	1.63	0.001	–	–	–	–	1.28	0.001
LVEF	–	–						
HFmrEF			0.64	<0.001	0.73	0.003	0.73	0.001
Semiquantitatively measured			0.56	<0.001	0.71	0.007	0.61	<0.001

OR = odds ratio; other abbreviations as in Table 1.

considered reasonable for underuse. It would be important to record not only specific instances of the inability to tolerate a drug but also to independently evaluate the individual decisions for not following guidelines. As far as these authors are aware, such an approach has not yet been followed. Although this kind of investigation is very time consuming, it would help to understand the real motivation for not strictly following the guidelines. A better understanding of health care provider and patient barriers to adoption of evidence-based therapies into routine clinical practice would have tremendous public health implications by designing effective quality improvement interventions.

Another possibility to improve adherence to therapy recommendations is benchmarking between different institutions and/or caregivers. This may result in in-depth reflection of therapeutic decision making and in sharing shortcomings and possible solutions. This is one of the important aims of the CHECK-HF registry (16). Indeed, the present authors found interesting and quite large differences among the participating centers, which will be fed back to all centers individually. Because the start of a Dutch national registry for HF has been planned for the near future, the impact of such feedback to adopt best clinical practice can be tested in the future.

To some extent, prescription of medication that does not accord with the guidelines is related to patient age. This may be seen as justified, at least to some extent, as in large randomized clinical trials, patients older than 75 years of age were rare with few exceptions (25). Thus, the positive effects in the very elderly patients and those with significant co-morbidities have not yet been sufficiently investigated. Although medication prescription was significantly influenced by age in multivariate analysis, it was much less influenced by co-morbidities. Also, given the large variations among the centers, it is unlikely that consideration of patient age is the main reason for not following the current guidelines.

Interestingly, treatment of patients with HFmrEF did not differ much from that in patients with HFrEF. This is in line with a recent report from the European Society of Cardiology Heart Failure Long-Term Registry in a population that was younger than that in this registry (26). In a recent report of a biomarker-guided trial including an older population, differences in baseline treatment between HFrEF and HFmrEF patients were also in a similar range (27). Differences were smaller than the variations in treatment seen among participating centers in this study. Therefore, indications for treatment in HFmrEF seem to be little different than that in HFrEF, although there is little support from prospective studies. Still, very recently, there is some evidence from a post-hoc analysis of the CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) trial that ARB has an effect in HFmrEF that is similar to that HFrEF (28). A subgroup analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study suggested that MRAs are beneficial in patients with slightly reduced LVEF (i.e., in the range of

HFmrEF) but less or not in patients with fully preserved LVEF (29). These 2 post hoc analyses provide some support that the assumption of similar treatment responses in HFrEF and HFmrEF may be correct. However, this needs to be tested prospectively. In this regard, it is important that LVEF is precisely determined and not only semiquantitatively as done in some patients in this registry, which may contribute to a large variability in the evaluation of LVEF (30). Also, other therapies such as implantable cardioverter-defibrillator insertion are dependent on exact measurements of LVEF (14,18).

STUDY LIMITATIONS. No follow-up data are available; therefore, it is possible that some patients were still in the uptitration phase, and final use of recommended therapy could have been closer to the guidelines than reported in this study. However, time of diagnosis did not influence the use of medication significantly. In addition, only approximately one-half of the centers with an outpatient HF clinic and 1 of 8 university centers participated. Still, this percentage is much higher than in most previous registries. Therefore, the reported data may reasonably reflect the current situation in the Netherlands.

Moreover, data were reported at the discretion of the participating centers, recorded based on existing patient files, and some data are therefore missing. We cannot exclude the possibility that this might have influenced our results. However, differences among patient characteristics did not differ in a clinically meaningful way among patients where information was available and where it was not. Moreover, differences among centers cannot be explained by missing values. Furthermore, this registry included only patients seen in secondary but not in primary care. This may explain why some of the characteristics were not fully in line with unselected populations. Still, our population represents an older population than that in many other registries and is a large and representative sample of Dutch HF patients in secondary care. In addition, patient selection by the necessity to obtain informed consent is absent, which is an important strength of this registry, improving the reflection of real-world information. Interestingly, the results of this registry are in many ways in line with the very recent CHAMP-HF registry in the United States that also included a representative HF population (6). Still, the overall use of medication and the doses used in CHAMP-HF were slightly lower than those in CHECK-HF. In contrast to CHAMP-HF, hardly any information is available for the use of sacubitril/valsartan since it was approved in the Netherlands only in June 2016. Also, the use of isordil/hydralazine is so low in the Netherlands that the information was not collected. From the American and European perspectives, both of the large registries CHAMP-HF (6,20) and CHECK-HF indicate the continuing need for optimizing guideline adherence and the importance of understanding reasons for nonadherence.

CONCLUSIONS

In a contemporary cohort of HF patients with reduced and mid-range LVEF, most patients received guideline-recommended medication but at doses lower than recommended. Moreover, ivabradine, which was introduced more recently was prescribed less. Patient age influenced prescription rates of medication significantly. Importantly, there was a large variation among centers, which could not be explained by differences in patients' characteristics. Medication in HFmrEF patients did not differ much from that in HFrEF patients, and LVEF was not precisely measured in a substantial number of patients. Therefore, there is still significant room for (further) improvement of treatment of patients with reduced LVEF, even 30 years after the first study showing that prognosis can be improved in HFrEF (31).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Results of this registry indicate that much more effort should be placed to understand the incomplete adoption of guideline recommendations in clinical practice.

TRANSLATIONAL OUTLOOK: Only if the effective measures are understood can they be taken to improve outcome. Such measures may include new means to educate healthcare professionals and to effectively involve patients in the treatment process, but also research on a more personalized approach of treating HF patients to more specifically target treatment to the needs of individual patients.

REFERENCES

1. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.

2. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669–77.

3. Cleland JG, Cohen-Solal A, Aguilar JC, et al. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. Lancet 2002;360:1631–9.

4. Komajda M, Follath F, Swedberg K, et al. The EuroHeart Failure Survey programme–a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J 2003;24:464–74.

5. Savarese G, Carrero JJ, Pitt B, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. Eur J Heart Fail 2018;20:1326–34.

6. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. J Am Coll Cardiol 2018;72:351–66.

7. Komajda M, Lapuerta P, Hermans N, et al. Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey. Eur Heart J 2005;26:1653–9.

8. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail 2017;19:1414–23.

9. Shah B, Hernandez AF, Liang L, et al. Hospital variation and characteristics of implantable cardioverter-defibrillator use in patients with heart failure: data from the GWTG-HF (Get With The Guidelines-Heart Failure) registry. J Am Coll Cardiol 2009;53:416–22.

10. Maggioni AP, Dahlstrom U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013;15:808–17.

11. Maggioni AP, Anker SD, Dahlstrom U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173–84.

12. Crespo-Leiro MG, Anker SD, Maggioni AP, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail 2016;18:613–25.

13. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.

14. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776–803.

15. Jonsson A, Edner M, Alehagen U, Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. Eur J Heart Fail 2010;12:25–31.

16. Brugts JJ, Linssen G, Hoes AW, Brunner-La Rocca HP, for the investigators C-H. Real-world heart failure management in 10,910 patients with chronic heart failure in the Netherlands: design and rationale of the Chronic Heart failure ESC-guideline based Cardiology practice Quality project (CHECK-HF) registry. Neth Heart J 2018;26:272–9.

17. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

18. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

19. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875–85.

20. DeVore AD, Thomas L, Albert NM, et al. Change the management of patients with heart failure: rationale and design of the CHAMP-HF registry. Am Heart J 2017;189:177–83.

21. Luo N, Fonarow GC, Lippmann SJ, et al. Early adoption of sacubitril/valsartan for patients with heart failure with reduced ejection fraction: insights from Get With the Guidelines-Heart Failure (GWTG-HF). J Am Coll Cardiol HF 2017;5:305–9.

22. Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J 2011;161:1024–30.

23. Roth GA, Poole JE, Zaha R, Zhou W, Skinner J, Morden NE. Use of guideline-directed medications for heart failure before cardioverter-defibrillator implantation. J Am Coll Cardiol 2016;67:1062–9.

24. Remme WJ, McMurray JJ, Hobbs FD, et al. Awareness and perception of heart failure among European cardiologists, internists, geriatricians, and primary care physicians. Eur Heart J 2008;29:1739–52.

25. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215–25.

26. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19:1574–85.

27. Rickenbacher P, Kaufmann BA, Maeder MT, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Eur J Heart Fail 2017;19:1586–96.

28. Lund LH, Claggett B, Liu J, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail 2018 Aug;20(8):1230–9.

29. Solomon SD, Claggett B, Lewis EF, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37:455–62.

30. Kaufmann BA, Min SY, Goetschalckx K, et al. How reliable are left ventricular ejection fraction cut offs assessed by echocardiography for clinical decision making in patients with heart failure? Int J Cardiovasc Imaging 2013;29:581–8.

31. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.