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ORIGINAL INVESTIGATIONS

Medical Therapy for Heart Failure With Reduced Ejection Fraction

The CHAMP-HF Registry

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ABSTRACT

BACKGROUND Guidelines strongly recommend patients with heart failure with reduced ejection fraction (HFrEF) be treated with multiple medications proven to improve clinical outcomes, as tolerated. The degree to which gaps in medication use and dosing persist in contemporary outpatient practice is unclear.

OBJECTIVES This study sought to characterize patterns and factors associated with use and dose of HFrEF medications in current practice.

METHODS The CHAMP-HF (Change the Management of Patients with Heart Failure) registry included outpatients in the United States with chronic HFrEF receiving at least 1 oral medication for management of HF. Patients were characterized by baseline use and dose of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB), angiotensin receptor neprilysin inhibitor (ARNI), beta-blocker, and mineralocorticoid receptor antagonist (MRA). Patient-level factors associated with medication use were examined.

RESULTS Overall, 3,518 patients from 150 primary care and cardiology practices were included. Mean age was 66 ± 13 years, 29% were female, and mean EF was 29 ± 8%. Among eligible patients, 27%, 33%, and 67% were not prescribed ACEI/ARB/ARNI, beta-blocker, and MRA therapy, respectively. When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%), whereas most patients were receiving target doses of MRA therapy (77%). Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA. In adjusted models, older age, lower blood pressure, more severe functional class, renal insufficiency, and recent HF hospitalization generally favored lower medication utilization or dose. Social and economic characteristics were not independently associated with medication use or dose.

CONCLUSIONS In this contemporary outpatient HFrEF registry, significant gaps in use and dose of guideline-directed medical therapy remain. Multiple clinical factors were associated with medication use and dose prescribed. Strategies to improve guideline-directed use of HFrEF medications remain urgently needed, and these findings may inform targeted approaches to optimize outpatient medical therapy. (J Am Coll Cardiol 2018;72:351–66)

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin II receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

GDMT = guideline-directed medical therapy

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

MRA = mineralocorticoid receptor antagonist

For patients with chronic heart failure with reduced ejection fraction (HFrEF), contemporary therapy includes multiple medications proven to decrease mortality and hospitalization rates in large randomized controlled trials (1,2). The robust survival benefits of these medical therapies in clinical trials have been generally shown to apply in routine clinical practice (3). Accordingly, these medications form the cornerstone of contemporary evidence-based HFrEF care and are supported by class I indications in clinical treatment guidelines (1,2). Guidelines also recommend target doses for each medication, as tolerated, based on doses tested in landmark studies (1,2).

SEE PAGE 367

Despite proven benefits and strong guideline recommendations, medication use and dosing in routine clinical practice have traditionally fallen short of levels achieved in clinical trials (4,5). As rates of mortality and morbidity for the general HFrEF population remain high, improving real-world use of proven medications remains a critically important quality improvement initiative (6–8). However, the utilization patterns of chronic HFrEF medical therapies and the barriers to their uptake and dosing in contemporary U.S. outpatient practice are poorly understood. Such information is even more relevant now in light of recent regulatory approval of sacubitril/valsartan and well-described concerns over traditionally slow adoption of novel medical therapies (9,10). Better understanding of current practice patterns, gaps in medication delivery, and barriers to receiving guideline-directed medical therapy (GDMT) are critical to development of targeted initiatives aimed at improving patient outcomes and quality of care. In this context, the CHAMP-HF (Change the Management of Patients with Heart Failure) registry offers the opportunity to study a contemporary U.S. outpatient HFrEF cohort and explore patterns of GDMT use and dosing, the clinical and social patient profiles associated with GDMT use, and the patient-level factors associated with medication use and target dosing.

METHODS

STUDY DESIGN. The design of the CHAMP-HF registry has been published previously (11). Briefly, CHAMP-HF was a prospective, observational, nonrandomized study of adult outpatients with HFrEF. Eligible patients had a diagnosis of chronic HF, a left ventricular ejection fraction (EF) ≤40% according to imaging performed within 12 months of enrollment, and were receiving ≥1 oral medication for HF at study enrollment (including diuretics, angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor blockers [ARB], angiotensin receptor-neprilysin inhibitors [ARNI], beta-blockers, mineralocorticoid receptor antagonists [MRA], antihypertensives, vasoactive/inotropic agents, or other cardiovascular medications). Key exclusion criteria included current or anticipated participation in a clinical trial, currently receiving comfort care or enrolled in hospice, life expectancy <1 year, or history of or plan for heart transplantation, left ventricular assist device, or dialysis. Clinical data were collected at baseline and at specified time intervals during study follow-up, when data were abstracted from the medical record (i.e., no study-specific mandatory follow-up visits) and were recorded in an electronic case report form. Baseline patient data reported by health care providers included patient demographics, HF history, comorbidities, vital signs and laboratory values, EF, and concurrent cardiovascular medication doses. Baseline sociodemographic data were self-reported by patients. The registry was conducted in accordance with Declaration of Helsinki tenets and with institutional review board/ethics committee approval at all sites. All patients provided written informed consent.

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BASELINE MEDICATION DATA. Baseline use and dose of the following HFrEF medication categories were examined within the baseline case report form: ACEI/ARB, ARNI, evidence-based beta-blocker, and MRA. For each medication class, the presence and absence of absolute contraindications were determined based on documentation in the medical record or as ascertained by study investigators. For each patient and each medication, available dose information was reviewed in reference to recommended target doses by clinical practice guidelines (Online Table 1), and patients were divided into 1 of 4 groups according to prescribed dose: patients not receiving medication, patients treated with <50% target dose, patients treated with 50 to <100% target dose, and patients treated with ≥100% target dose (1,2,12).

STATISTICAL ANALYSIS. For each medication class, baseline characteristics of patients without an absolute contraindication were compared across the 4 dose groups. Continuous variables were reported as median (25th percentile, 75th percentile), and categorical variables were recorded as frequencies and percentages.

To assess for independent associations between patient-level characteristics and medical therapy use and dose among eligible patients, logistic regression models were constructed for the probability of being treated; and then among treated patients only, for the probability of receiving a higher dose. For ACEI/ARB and evidence-based beta-blocker analyses, a total of 3 separate regression models were used to assess the probability of: 1) being treated with any dose of medication; 2) being treated with ≥50% target dose; and 3) being treated with ≥100% target dose. For ARNI and MRA analyses, due to lower numbers of treated patients and the distribution of doses, 2 separate regression models were used to assess: 1) being treated with any dose of medication; and 2) being treated with ≥50% target dose for ARNI or treated with ≥100% target dose for MRA. Referent categories were either the "not treated" group or the lowest-dose group, as applicable. To account for clustering of patients within individual study sites, which may be correlated with patient factors and medication doses, hierarchical models were used, including a random effect for site. Model selection was based on backwards elimination, and variables with $p > 0.05$ were removed based on highest p value first. A new model was assessed using the remaining variables. Rates of missing data for most variables were <1% with few exceptions (New York Heart Association [NYHA] functional class 4.4%; systolic blood pressure 5.4%; heart rate 6.7%). Complete case analysis was performed, resulting in slightly different sample sizes for different models. All statistical analyses were performed using SAS version 9.4 software (Cary, North Carolina). Two-tailed p value <0.05 was considered statistically significant.

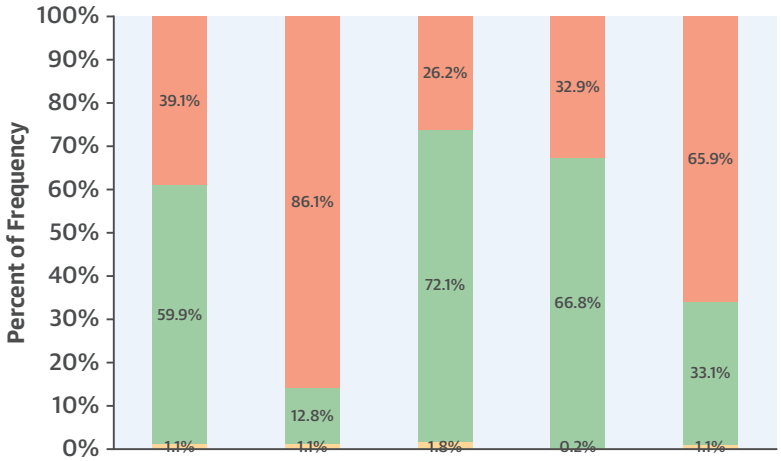
RESULTS

BASELINE MEDICATION USE AND DOSE. The present analysis included 3,518 HFrEF patients with available baseline medication data from 150 U.S. primary care and cardiology practices. Overall, mean age of the study cohort was 66.4 ± 12.6 years, 29.2% were females, 74.9% were white, and mean EF was 29 ± 8%. For each class of medical therapy, proportions of patients: 1) with a contraindication; 2) treated; and 3) without a contraindication but not treated are displayed in the **Central Illustration**. For all therapies, the percentage of patients with a documented absolute contraindication was low, with the highest rate of 1.8% for ACEI/ARB/ARNI. Among eligible patients, 2,536 patients (73.4%), 2,351 patients (67.0%), and 1,163 patients (33.4%) were treated with ACEI/ARB/ARNI, beta-blocker, and MRA, respectively. ACEI/ARB was prescribed to 2,107 eligible patients (60.5%) and ARNI to 452 patients (13.0%). Among patients receiving each medication, <30% of patients were prescribed target doses of ACEI/ARB/ARNI or beta-blocker therapy (**Central Illustration**). In contrast, >75% of patients receiving an MRA were prescribed the target dose. Among patients eligible for all classes of medication, 755 patients (22.1%) were simultaneously prescribed some dose of ACEI/ARB/ARNI, beta-blocker, and MRA therapy, and 37 patients (1.1%) were simultaneously prescribed target doses of all 3 therapies. Medication use and doses among patients enrolled in the first half (December 15, 2015 to August 22, 2016) were similar to those among patients enrolled in the second half (August 23, 2016 to March 6, 2017) (Online Tables 2 and 3). In contrast, with the exception of ACEI/ARB, use of medication was substantially lower among patients enrolled from family medicine or internal medicine practices (n = 485) than among patients enrolled from cardiology outpatient practices (n = 2821) (Online Table 4). Among patients treated with each medication, doses were relatively similar by practice type (Online Table 5).

PATIENT CHARACTERISTICS BY DOSING OF GUIDELINE-DIRECTED MEDICAL THERAPY. Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. Compared to patients receiving <50% target dose, patients not receiving ACEI/ARB therapy tended to be older with similar blood pressure and worse renal function (**Table 1**). Across all dosing groups, NYHA functional class and history of HF hospitalization

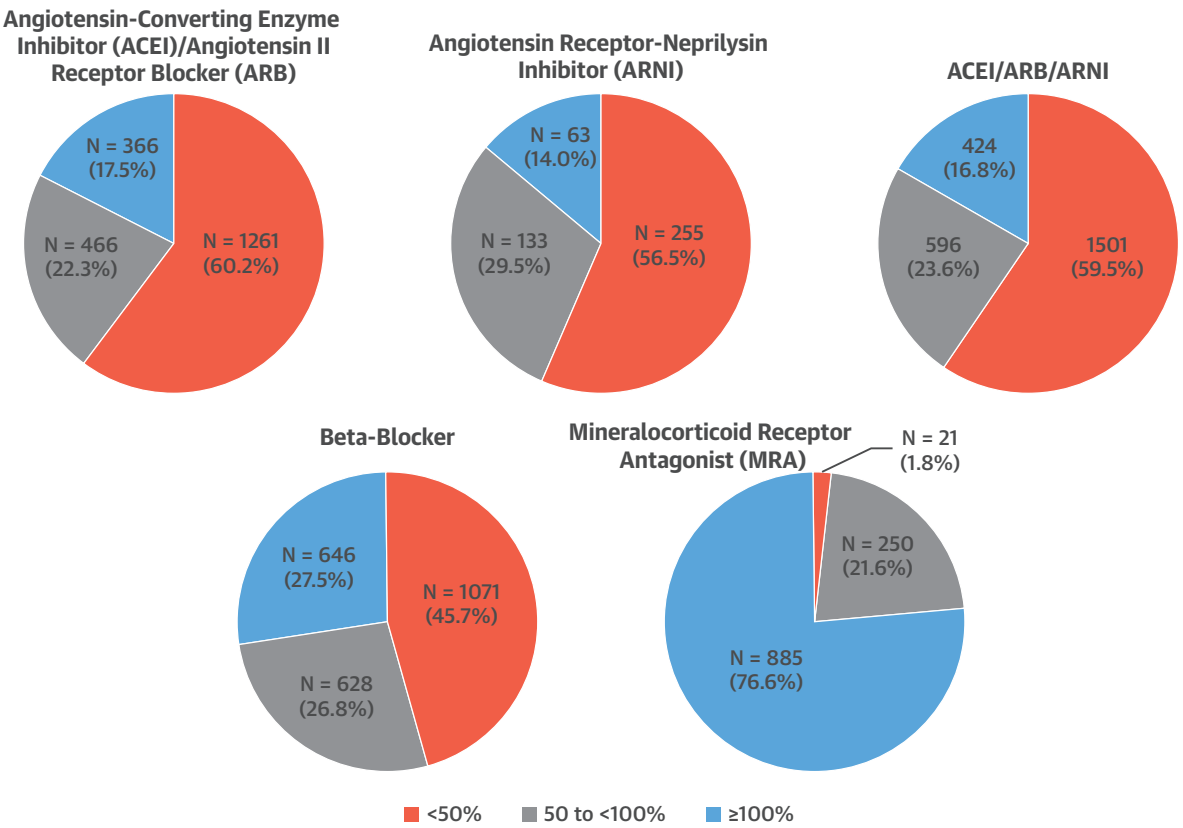
CENTRAL ILLUSTRATION **Use and Dosing of Guideline-Directed Medical Therapy Among Patients With Chronic HFrEF in Contemporary U.S. Outpatient Practice**

A



	ACEI/ARB	ARNI	ACEI/ARB/ ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38

B



Greene, S.J. et al. J Am Coll Cardiol. 2018;72(4):351–66.

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were inversely related to ACEI/ARB dose, with more severe functional class and highest rate of HF hospitalization among patients receiving the lowest doses. Social and economic characteristics were approximately similar by dose group.

Angiotensin receptor neprilysin inhibitor. Patients receiving <50% target ARNI dose tended to have similar renal function but lower blood pressure than those not receiving therapy (Table 2). Among patients receiving ARNI, higher doses correlated with milder NYHA functional class, higher systolic blood pressure, higher rates of blacks and obesity, and lower rates of prior HF hospitalization and coronary artery disease. Patients receiving higher doses of ARNI therapy had greater likelihood of having full-time employment, a graduate or professional degree, and private insurance.

Evidence-based beta-blocker. Compared with patients receiving <50% target dose, patients not receiving beta-blockers tended to be older and were more likely to be female, white, and have a history of asthma or chronic obstructive pulmonary disease (COPD) but less likely to have prior HF hospitalization (Table 3). Among patients receiving beta-blocker therapy, heart rate and NYHA functional class were similar across dose groups, and blood pressure tended to be higher among patients receiving higher doses. Rates of prior HF hospitalization and coronary artery disease declined with increasing dose group. Social and economic characteristics were approximately similar by dose group, with potential exception of lower rates of Medicare insurance, higher rates of medical disability, and lower rates of employment for other reasons among patients receiving target doses.

Mineralocorticoid receptor antagonist. Compared with patients receiving target doses, patients not receiving MRA therapy were more likely to be older, white, male and have worse renal function (Table 4). Patients not prescribed therapy also tended to have milder NYHA functional class, higher systolic blood pressure, and lower rates of prior HF hospitalization. Patient receiving higher doses of MRA had higher rates of managed care or private insurance and lower rates of Medicare, as well as higher rates of medical disability and lower rates of unemployment for other reasons.

FACTORS ASSOCIATED WITH MEDICATION USE AND DOSES. Independent associations among baseline patient characteristics, medication use, and medication dose are displayed in Table 5.

Angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker. Female sex, chronic renal insufficiency, atrial fibrillation, and NYHA functional class III/IV symptoms were strong independent factors associated with not being prescribed an ACEI/ARB (all $p \leq 0.007$). Among those who were treated, factors such as being black, higher levels of systolic blood pressure, and a history of hypertension were associated with target doses (all $p \leq 0.008$), whereas prior HF hospitalization within 12 months, asthma/COPD, and NYHA functional class III/IV status were strongly associated with subtarget doses (all $p \leq 0.011$).

Angiotensin receptor neprilysin inhibitor. For ARNI therapy, multiple clinical factors were independently associated with lower likelihood of treatment, including older age, Hispanic ethnicity, chronic renal insufficiency, and higher EF (all $p \leq 0.009$). Of those treated with an ARNI, higher systolic blood pressure and history of hypertension were associated with ≥50% target dose (all $p \leq 0.037$).

Evidence-based beta-blocker. Increasing age, asthma/COPD, atrial fibrillation, and lower EF were associated with not receiving beta-blocker therapy (all $p \leq 0.016$), whereas a history of chronic renal insufficiency was associated with greater likelihood of beta-blocker treatment ($p = 0.045$). Among patients receiving an evidence-based beta-blocker, black patients and patients with obesity and diabetes mellitus were substantially more likely to receive ≥50% of target or target dose (all $p \leq 0.008$). In contrast, prior HF hospitalization and asthma/COPD were strongly associated with lower likelihood of receiving ≥50% of target (all $p \leq 0.010$) or target dose (all $p \leq 0.030$).

Mineralocorticoid receptor antagonist. Several characteristics were independently associated with not receiving MRA therapy, with the magnitudes of association strongest for Hispanic ethnicity, older age, and chronic renal insufficiency (all $p \leq 0.029$). Of those receiving MRA treatment, female sex and history of hypertension were strongly associated with

CENTRAL ILLUSTRATION Continued

(A) For each medication category, data reflect the proportion of the overall study population with an absolute contraindication, treated with any dose, and without an absolute contraindication but not treated. **(B)** Data show the proportion of eligible patients with available dosage data treated with <50% target dose, 50% to <100% target dose, or ≥100% target dose. The number of patients with contraindications to ACEI, ARB, or ARNI (N = 62) included those with contraindications to ACEI and ARB (N = 37) or ARNI (N = 37) and does not equal the sum of the 2 groups. HFrEF = heart failure with reduced ejection fraction.

TABLE 1 Baseline Patient Characteristics by Dose of ACEI/ARB Therapy

	None (n = 1,374)	<50% Target Dose (n = 1,261)	50% to <100% Target Dose (n = 466)	≥100% Target Dose (n = 366)
Age, yrs	69 (59–76)	67 (58–75)	67 (58–75)	67 (58–74)
Female	428 (31.3)	359 (28.5)	133 (28.5)	90 (24.7)
Race				
White	1,018 (74.5)	984 (78.2)	323 (69.3)	260 (71.2)
Black	237 (17.3)	154 (12.2)	93 (20.0)	84 (23.0)
Other	111 (8.1)	120 (9.5)	50 (10.7)	21 (5.8)
Hispanic ethnicity	203 (14.9)	216 (17.2)	97 (20.8)	67 (18.4)
Ejection fraction, %	30 (23–35)	30 (23–35)	31 (25–36)	32 (25–37)
NYHA functional class				
I	97 (7.1)	140 (11.1)	55 (11.8)	52 (14.2)
II	713 (52.4)	697 (55.4)	257 (55.3)	226 (61.7)
III	455 (33.5)	345 (27.4)	123 (26.5)	65 (17.8)
IV	50 (3.7)	20 (1.6)	8 (1.7)	9 (2.5)
Not available	45 (3.3)	56 (4.5)	22 (4.7)	14 (3.8)
Vital sign and laboratory findings				
Systolic blood pressure, mm Hg	120 (108–130)	120 (109–130)	122 (110–134)	128 (115–140)
Diastolic blood pressure, mm Hg	70 (64–80)	70 (64–80)	74 (67–80)	76 (70–84)
Heart rate, beats/min	72 (66–82)	73 (66–82)	72 (65–81)	72 (64–80)
Obese, BMI ≥30 kg/m^2	547 (40.2)	492 (39.1)	220 (47.3)	168 (45.9)
Hemoglobin, g/dl*	13.0 (11.8–14.3)	13.3 (12.0–14.6)	13.3 (12.2–14.5)	13.4 (12.1–14.5)
Serum sodium, mmol/l†	139 (137–141)	139 (137–141)	140 (138–142)	140 (138–142)
BUN, mg/dl‡	21 (16–30)	19 (15–26)	20 (15–26)	19 (15–26)
eGFR, ml/min per 1.73 m^2§				
<30	74 (8.9)	22 (2.9)	7 (2.5)	10 (4.8)
30–44	159 (19.2)	81 (10.5)	32 (11.4)	27 (12.9)
45–60	188 (22.7)	186 (24.2)	65 (23.1)	44 (21.1)
>60	409 (49.3)	479 (62.4)	177 (63.0)	128 (61.2)
NT-proBNP, pg/ml‖	2,308 (804–5,530)	2,613 (919–5,348)	1,320 (695–2,106)	1,120 (396–2,790)
Hemoglobin A1c, %#	6.6 (5.8–7.7)	6.4 (5.8–7.5)	6.4 (5.9–7.7)	6.4 (6.0–7.5)
Medical history**				
HF hospitalization within past 12 months	566 (41.4)	495 (39.3)	155 (33.3)	94 (25.7)
Coronary artery disease	848 (62.2)	795 (63.0)	284 (61.1)	229 (62.6)
Hypertension	1,112 (81.5)	984 (78.0)	401 (86.2)	341 (93.2)
Hyperlipidemia	1,014 (74.3)	954 (75.7)	352 (75.7)	298 (81.4)
Diabetes mellitus	581 (42.7)	473 (37.6)	196 (42.2)	163 (44.5)
Atrial fibrillation	557 (40.9)	439 (34.8)	137 (29.5)	115 (31.4)
Chronic renal insufficiency	333 (24.5)	208 (16.5)	79 (17.0)	59 (16.1)
Asthma/COPD	422 (31.0)	389 (30.9)	142 (30.5)	86 (23.5)
History of ventricular tachycardia/fibrillation	257 (18.8)	270 (21.4)	71 (15.3)	57 (15.6)
Depression	359 (26.4)	328 (26.1)	105 (22.6)	72 (19.7)
Active cigarette smoking	246 (18.1)	275 (21.8)	100 (21.5)	66 (18.0)
Heart failure device therapy				
Implantable cardioverter-defibrillator	573 (42.1)	551 (43.8)	170 (36.6)	144 (39.3)
Cardiac resynchronization therapy	92 (6.8)	90 (7.1)	25 (5.4)	19 (5.2)

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receiving target dose (all $p \leq 0.021$), whereas atrial fibrillation was strongly associated with lower likelihood of receiving target dose ($p = 0.017$).

PATIENT CHARACTERISTICS BY BASELINE MEDICATION USE. Baseline clinical characteristics by medication use are presented in Online Table 6. Most patients in all medication groups had NYHA functional class II symptoms, and the highest proportion of class III/IV patients were among patients receiving ARNI (37.1%). Rates of prior HF hospitalization were highest among patients receiving MRA (45.7%) and next highest among patients receiving ARNI (42.7%). Across all medication groups, vital signs, laboratory values, and EF were similar. Likewise, the prevalence of comorbidities was high in all groups, with 58.2% to 63.2% of patients having coronary artery disease, 39.2% to 41.7% having diabetes mellitus, and 33.0% to 37.6% having atrial fibrillation. Rates of implantable

TABLE 1 Continued

	None (n = 1,374)	<50% Target Dose (n = 1,261)	50% to <100% Target Dose (n = 466)	≥100% Target Dose (n = 366)
Social and economic characteristics				
Insurance status				
Managed care (HMO, PPO)	206 (15.1)	224 (17.8)	90 (19.3)	50 (13.7)
Private insurance	133 (9.7)	115 (9.1)	41 (8.8)	36 (9.9)
Medicare	817 (59.8)	722 (57.4)	259 (55.6)	214 (58.6)
Medicaid	134 (9.8)	104 (8.3)	45 (9.7)	33 (9.0)
Military health care	26 (1.9)	27 (2.1)	10 (2.1)	9 (2.5)
Uninsured	19 (1.4)	35 (2.8)	5 (1.1)	10 (2.7)
Other	31 (2.3)	31 (2.5)	16 (3.4)	13 (3.6)
Highest level of education				
Less than high school	168 (12.3)	145 (11.5)	65 (13.9)	40 (11.0)
High school/GED	477 (34.9)	417 (33.1)	159 (34.1)	119 (32.6)
Some college	409 (29.9)	400 (31.8)	149 (32.0)	125 (34.2)
4-yr college (baccalaureate)	171 (12.5)	167 (13.3)	49 (10.5)	50 (13.7)
Graduate or other professional degree	141 (10.3)	129 (10.3)	44 (9.4)	31 (8.5)
Total household income				
<$25,000	411 (30.1)	383 (30.4)	155 (33.3)	113 (31.0)
$25,000-$49,999	264 (19.3)	259 (20.6)	86 (18.5)	70 (19.2)
$50,000-$74,999	185 (13.5)	143 (11.4)	49 (10.5)	35 (9.6)
$75,000-$99,999	78 (5.7)	75 (6.0)	27 (5.8)	27 (7.4)
$100,000-$149,999	66 (4.8)	72 (5.7)	26 (5.6)	18 (4.9)
≥$150,000	41 (3.0)	37 (2.9)	9 (1.9)	10 (2.7)
Prefer not to answer	321 (23.5)	289 (23.0)	114 (24.5)	92 (25.2)
Employment status				
Full-time employee (≥35 h/week)	181 (13.3)	173 (13.8)	77 (16.5)	63 (17.3)
Part-time employee (<35 h/week)	94 (6.9)	94 (7.5)	26 (5.6)	33 (9.0)
Disability for medical reasons	342 (25.0)	315 (25.0)	115 (24.7)	95 (26.0)
Not employed for other reasons (e.g., retired, student, unemployed)	749 (54.8)	676 (53.7)	248 (53.2)	174 (47.7)

Values are median (quartile 1 to quartile 3) or n (%). *There were 719, 668, 240, and 179 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. †There were 956, 865, 298, and 227 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. ‡There were 915, 835, 288, and 219 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. §There were 830, 768, 281, and 209 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. ‖There were 131, 138, 42, and 37 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. #There were 237, 230, 105, and 78 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. **Specific conditions defined at the discretion of local investigators in response to the question "Does the patient currently have any of the following diagnoses?"

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; bpm = beats per minute; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; GED = general equivalency diploma; HF = heart failure; HMO = health maintenance organization; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PPO = preferred provider organization.

cardioverter-defibrillator and cardiac resynchronization therapy were 41.3% to 54.9% and 6.4% to 10.0%, respectively.

Descriptive data regarding baseline social and economic characteristics by medication use are displayed in Online Table 7. Regardless of medication group, >50% of patients were insured by Medicare. Patients receiving ARNI therapy had the highest rate of managed care (20.6%) or private insurance coverage (12.6%). Other socioeconomic characteristics differed with ARNI use, for example, ARNI patients had the lowest rates of less than high school education and household income of <$50,000 and highest rates of full-time employment and a household income >$100,000.

DISCUSSION

In this large contemporary U.S. registry of stable outpatients with HFrEF, significant gaps in guideline-directed use and dosing of evidence-based medications remain. Despite <2% of patients having a documented absolute contraindication to any specific therapy, use of each guideline medication fell below 75%. MRA and ARNI therapies were particularly underused, with only 33% and 13% of eligible patients treated, respectively. When GDMT was used, it tended to be used at lower doses with the majority of patients prescribed subtarget doses of ACEI/ARB/ARNI and beta-blocker, and high proportions prescribed <50% of target dose. Only 1% of eligible patients were

TABLE 2 Baseline Patient Characteristics by Dose of ARNI Therapy

	None (n = 3,029)	<50% Target Dose (n = 255)	50% to <100% Target Dose (n = 133)	≥100% Target Dose (n = 63)
Age, yrs	68 (59–76)	65 (55–73)	63 (54–71)	62 (52–68)
Female	873 (28.9)	68 (26.7)	47 (35.6)	26 (41.3)
Race				
White	2,261 (74.9)	194 (76.1)	97 (73.5)	40 (63.5)
Black	475 (15.7)	49 (19.2)	27 (20.5)	19 (30.2)
Other	281 (9.3)	12 (4.7)	8 (6.1)	4 (6.3)
Hispanic ethnicity	557 (18.5)	22 (8.6)	6 (4.5)	3 (4.8)
Ejection fraction, %	30 (23–35)	27 (20–33)	28 (22–32)	29 (23–35)
NYHA functional class				
I	314 (10.4)	20 (7.8)	7 (5.3)	6 (9.5)
II	1,656 (55.0)	131 (51.4)	78 (59.1)	35 (55.6)
III	837 (27.8)	97 (38.0)	41 (31.1)	20 (31.7)
IV	79 (2.6)	5 (2.0)	2 (1.5)	1 (1.6)
Not available	125 (4.2)	2 (0.8)	4 (3.0)	1 (1.6)
Vital signs and laboratory findings				
Systolic blood pressure, mm Hg	120 (110–132)	116 (104–124)	120 (110–130)	120 (110–136)
Diastolic blood pressure, mm Hg	72 (64–80)	70 (62–78)	72 (64–80)	75 (68–82)
Heart rate, beats/min	72 (66–81)	73 (66–82)	70 (64–82)	74 (62–80)
Obese, BMI ≥30 kg/m^2	1217 (40.4)	114 (44.9)	63 (47.7)	38 (60.3)
Hemoglobin, g/dl*	13.3 (11.9–14.5)	13.3 (12.1–14.5)	13.1 (12.1–14.5)	13.5 (12.3–14.3)
Serum sodium, mmol/l†	139 (137–141)	139 (137–141)	140 (138–142)	140 (138–142)
BUN, mg/dl‡	20 (16–27)	20 (15–28)	18 (14–24)	20 (16–25)
eGFR, ml/min per 1.73 m^2§				
<30	109 (6.0)	3 (1.9)	3 (4.3)	0 (0.0)
30–44	260 (14.2)	28 (17.6)	6 (8.6)	7 (16.7)
45–60	419 (23.0)	39 (24.5)	18 (25.7)	9 (21.4)
>60	1037 (56.8)	89 (56.0)	43 (61.4)	26 (61.9)
NT-proBNP, pg/ml‖	1,984 (800–,5210)	1,400 (528–4,299)	1,135 (737–2,622)	2,944 (751–6,289)
Hemoglobin A_{1c}, %#	6.4 (5.8–7.6)	6.6 (6.1–7.8)	6.7 (5.8–7.7)	6.9 (6.6–9.3)
Medical history**				
HF hospitalization within past 12 months	1,118 (37.0)	115 (45.1)	55 (41.4)	23 (36.5)
Coronary artery disease	1,878 (62.2)	172 (67.5)	77 (57.9)	31 (49.2)
Hypertension	2,486 (82.4)	197 (77.3)	109 (82.0)	56 (88.9)
Hyperlipidemia	2,288 (75.8)	196 (76.9)	96 (72.2)	45 (71.4)
Diabetes mellitus	1,234 (40.9)	104 (40.9)	53 (40.2)	29 (46.0)
Atrial fibrillation	1,078 (35.7)	93 (36.5)	52 (39.1)	24 (38.1)
Chronic renal insufficiency	613 (20.3)	42 (16.5)	17 (12.9)	9 (14.3)
Asthma/COPD	929 (30.8)	65 (25.6)	37 (28.0)	17 (27.0)
History of ventricular tachycardia/fibrillation	533 (17.7)	77 (30.2)	26 (19.5)	16 (25.4)
Depression	758 (25.1)	58 (22.8)	33 (25.0)	17 (27.0)
Active cigarette smoking	597 (19.8)	51 (20.1)	27 (20.5)	12 (19.0)
Heart failure device therapy				
Implantable cardioverter-defibrillator	1,195 (39.6)	140 (55.1)	74 (56.1)	32 (50.8)
Cardiac resynchronization therapy	185 (6.1)	29 (11.4)	11 (8.3)	5 (7.9)

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simultaneously treated with target does of ACEI/ARB/ARNI, beta-blocker, and MRA therapy, and <25% of patients simultaneously received any dose of all 3 medications. For each medication class, patient profiles varied with dose of medications prescribed. Notably, with exception of MRA therapy, rates of prior HF hospitalization and NYHA functional class III/VI status were generally inversely related to medication dose, with highest rates among patients receiving the lowest doses. In multivariate analysis, for each medication class, several patient characteristics were independently associated with patients receiving each therapy and the specific dose.

To our knowledge, we present the most comprehensive and contemporary analysis of outpatient HFrEF medical therapy dose in U.S. clinical practice. Although prior HF registry data informed previous quality improvement efforts, recent programs have

TABLE 2 Continued

	None (n = 3,029)	<50% Target Dose (n = 255)	50% to <100% Target Dose (n = 133)	≥100% Target Dose (n = 63)
Social and economic characteristics				
Insurance status				
Managed care (HMO, PPO)	478 (15.8)	59 (23.1)	20 (15.2)	13 (20.6)
Private insurance	265 (8.8)	30 (11.8)	16 (12.1)	11 (17.5)
Medicare	1,794 (59.5)	127 (49.8)	77 (58.3)	29 (46.0)
Medicaid	271 (9.0)	26 (10.2)	13 (9.8)	6 (9.5)
Military health care	66 (2.2)	2 (0.8)	2 (1.5)	1 (1.6)
Uninsured	58 (1.9)	8 (3.1)	2 (1.5)	1 (1.6)
Other	85 (2.8)	3 (1.2)	2 (1.5)	2 (3.2)
Highest level of education				
Less than high school	381 (12.6)	27 (10.6)	7 (5.3)	6 (9.5)
High school/GED	1,032 (34.2)	87 (34.1)	40 (30.3)	19 (30.2)
Some college	938 (31.1)	74 (29.0)	56 (42.4)	18 (28.6)
4-yr college (baccalaureate)	373 (12.4)	38 (14.9)	18 (13.6)	7 (11.1)
Graduate or other professional degree	293 (9.7)	29 (11.4)	11 (8.3)	13 (20.6)
Total household income				
<$25,000	947 (31.4)	70 (27.5)	30 (22.7)	20 (31.7)
$25,000-$49,999	596 (19.8)	41 (16.1)	28 (21.2)	13 (20.6)
$50,000-$74,999	337 (11.2)	38 (14.9)	27 (20.5)	10 (15.9)
$75,000-$99,999	181 (6.0)	20 (8.2)	11 (8.3)	3 (4.8)
$100,000-$149,999	149 (4.9)	21 (8.2)	11 (8.3)	3 (4.8)
≥$150,000	78 (2.6)	7 (2.7)	6 (4.5)	4 (6.3)
Prefer not to answer	729 (24.2)	58 (22.7)	24 (18.2)	9 (14.3)
Employment status				
Full-time employee (≥35 h/week)	400 (13.3)	48 (18.8)	25 (18.9)	16 (25.4)
Part-time employee (<35 h/week)	209 (6.9)	18 (7.1)	16 (12.1)	5 (7.9)
Disability for medical reasons	737 (24.4)	70 (27.5)	42 (31.8)	23 (36.5)
Not employed for other reasons (e.g., retired, student, unemployed)	1,671 (55.4)	119 (46.7)	49 (37.1)	19 (30.2)

Values are median (quartile 1 to quartile 3) or n (%). *There were 1584, 140, 57, and 29 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. †There were 2026, 192, 92, and 46 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. ‡There were 1943, 186, 90, and 46 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. §There were 1825, 159, 70, and 42 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. ‖There were 288, 35, 15, and 10 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. #There were 564, 52, 20, and 13 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. **Specific conditions defined at the discretion of local investigators in response to the question "Does the patient currently have any of the following diagnoses?"

ARNI = angiotensin receptor neprilysin inhibitor; other abbreviations as in Table 1.

focused on patients hospitalized with HF, a notably different population from the stable outpatients recruited in landmark registration trials for GDMT (13,14). In this respect, the current CHAMP-HF data from stable ambulatory HFrEF patients evaluates use of GDMT in a U.S. cohort more representative of the populations from which clinical trial evidence was derived. In addition, the present analysis offers several strengths that provide more granular insight into the pattern of current GDMT use in the United States. First, the registry included pre-specified and detailed dosing information to allow description of target and subtarget doses, as well as associated patient profiles. Importantly, data capture included ARNI therapy, to be consistent with class I recommendations from the recent treatment guideline update (2). Second, recognizing the potential contributions of social factors to the use of HFrEF therapy, CHAMP-HF offers a comprehensive socioeconomic characterization of the patient population. Third, to mitigate potential influences of medical record accuracy and completeness of registry medication data, CHAMP-HF included an electronic case report form with pre-specified capture of medication data, presence of contraindications, and multiple questions regarding tolerability. Fourth, rigorous multivariate modeling inclusive of both clinical and social factors was performed to assess independent patient-level associations with medication use and dose, and hierarchical models were used to account for patient clustering by enrolling study site.

Prior data examining dose of GDMT in U.S. outpatient clinical practice comes largely from the IMPROVE HF (Improve the Use of Evidence-Based

TABLE 3 Baseline Patient Characteristics by Dose of Beta-Blocker Therapy

	None (n = 1,159)	<50% Target Dose (n = 1,071)	50% to <100% Target Dose (n = 628)	≥100% Target Dose (n = 646)
Age, yrs	70 (61–77)	68 (59–76)	67 (58–74)	65 (56–72)
Female	379 (32.9)	305 (28.5)	167 (26.6)	170 (26.4)
Race				
White	911 (79.1)	808 (75.6)	474 (75.5)	420 (65.3)
Black	152 (13.2)	151 (14.1)	109 (17.4)	160 (24.9)
Other	88 (7.6)	110 (10.3)	45 (7.2)	63 (9.8)
Hispanic ethnicity	272 (23.6)	165 (15.4)	74 (11.8)	77 (12.0)
Ejection fraction, %	33 (25–38)	28 (21–35)	30 (23–35)	30 (23–35)
NYHA functional class				
I	85 (7.4)	120 (11.2)	65 (10.4)	76 (11.8)
II	662 (57.9)	575 (53.7)	335 (53.5)	347 (53.8)
III	300 (26.2)	320 (29.9)	190 (30.4)	187 (29.0)
IV	38 (3.3)	22 (2.1)	14 (2.2)	12 (1.9)
Not available	59 (5.2)	33 (3.1)	22 (3.5)	23 (3.6)
Vital sign and laboratory findings				
Systolic blood pressure, mm Hg	120 (110–131)	118 (106–130)	120 (110–130)	121 (110–134)
Diastolic blood pressure, mm Hg	72 (66–80)	70 (63–80)	71 (64–80)	74 (66–80)
Heart rate, beats/min	72 (67–80)	73 (66–83)	72 (64–82)	72 (65–80)
Obese, BMI ≥30 kg/m^2	461 (40.2)	360 (33.6)	273 (43.6)	346 (53.6)
Hemoglobin, g/dl*	13.3 (12.0–14.5)	13.3 (12.0–14.5)	13.1 (11.7–14.4)	13.2 (12.0–14.4)
Serum sodium, mmol/l†	139 (137–141)	139 (137–141)	139 (137–141)	139 (137–141)
BUN, mg/dl‡	20 (15–28)	18 (15–23)	20 (16–27)	20 (15–28)
eGFR, ml/min per 1.73 m^2§				
<30	40 (5.8)	36 (5.5)	21 (5.5)	25 (6.5)
30–44	92 (13.4)	88 (13.4)	66 (17.3)	58 (15.1)
45–60	143 (20.8)	164 (24.9)	83 (21.7)	99 (25.7)
>60	413 (60.0)	371 (56.3)	212 (55.5)	203 (52.7)
NT-proBNP, pg/ml‖	2,309 (1,074–5,620)	2,613 (1,184–5,570)	1,832 (664–5,136)	932 (528–3,059)
Hemoglobin A1c, %#	6.3 (5.8–7.4)	6.3 (5.7–7.5)	6.5 (5.8–7.5)	6.7 (6.0–8.2)
Medical history**				
HF hospitalization within past 12 months	411 (35.7)	481 (44.9)	236 (37.6)	194 (30.0)
Coronary artery disease	697 (60.7)	702 (65.5)	411 (65.4)	370 (57.4)
Hypertension	944 (82.2)	857 (80.0)	524 (83.4)	543 (84.2)
Hyperlipidemia	863 (75.2)	807 (75.4)	485 (77.2)	486 (75.3)
Diabetes mellitus	454 (39.6)	402 (37.6)	264 (42.2)	311 (48.2)
Atrial fibrillation	424 (37.0)	353 (33.0)	256 (40.8)	220 (34.1)
Chronic renal insufficiency	208 (18.2)	216 (20.2)	128 (20.4)	140 (21.7)
Asthma/COPD	400 (34.9)	327 (30.6)	170 (27.2)	157 (24.3)
History of ventricular tachycardia/fibrillation	178 (15.5)	199 (18.6)	140 (22.3)	143 (22.2)
Depression	321 (28.0)	270 (25.2)	132 (21.1)	151 (23.4)
Active cigarette smoking	223 (19.5)	223 (20.8)	141 (22.5)	103 (16.0)
Heart failure device therapy				
Implantable cardioverter-defibrillator	333 (29.1)	458 (42.8)	314 (50.2)	350 (54.3)
Cardiac resynchronization therapy	56 (4.9)	74 (6.9)	53 (8.5)	51 (7.9)

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Heart Failure Therapies in the Outpatient Setting) study (15). Specifically, this large-scale quality improvement initiative found rates of baseline target dosing of ACEI/ARB, beta-blocker, and MRA among eligible patients to be 36.1%, 20.5%, and 74.4%, respectively (16). Despite IMPROVE HF data reflecting HFrEF care approximately a decade ago, contemporary target doses in CHAMP-HF are remarkably similar for beta-blockers (27.5%) and MRA (76.6%) and are considerably lower for ACEI/ARB/ARNI (16.7%). Overall use (i.e., any dose) of GDMT within the 2 cohorts was also similarly low (e.g., baseline use of MRA among eligible patients was 34.5% in IMPROVE HF and 33.4% in CHAMP-HF) (15).

Given that significant gaps in provision of HFrEF medical therapy persist, next steps must focus on why underuse and underdosing continues. Recent prospective investigations strongly suggest that

TABLE 3 Continued

	None (n = 1,159)	<50% Target Dose (n = 1,071)	50% to <100% Target Dose (n = 628)	≥100% Target Dose (n = 646)
Social and economic characteristics				
Insurance status				
Managed care (HMO, PPO)	151 (13.1)	194 (18.1)	110 (17.5)	120 (18.7)
Private insurance	109 (9.5)	98 (9.2)	61 (9.7)	62 (9.6)
Medicare	741 (64.4)	597 (55.8)	352 (56.1)	346 (53.6)
Medicaid	92 (8.0)	104 (9.7)	57 (9.1)	63 (9.8)
Military health care	18 (1.6)	30 (2.8)	13 (2.1)	12 (1.9)
Uninsured	17 (1.5)	17 (1.6)	14 (2.2)	21 (3.3)
Other	23 (2.0)	29 (2.7)	21 (3.3)	19 (3.0)
Highest level of education				
Less than high school	157 (13.6)	136 (12.7)	58 (9.2)	72 (11.2)
High school/GED	405 (35.2)	339 (31.7)	207 (33.0)	239 (37.2)
Some college	343 (29.8)	333 (31.2)	210 (33.4)	204 (31.7)
4-yr college (baccalaureate degree)	135 (11.7)	141 (13.2)	85 (13.5)	78 (12.1)
Graduate or other professional degree	111 (9.6)	120 (11.2)	68 (10.8)	50 (7.8)
Total household income				
<$25,000	389 (33.8)	309 (28.9)	188 (29.9)	188 (29.2)
$25,000-$49,999	209 (18.2)	222 (20.8)	117 (18.6)	137 (21.3)
$50,000-$74,999	142 (12.3)	120 (11.2)	77 (12.3)	76 (11.8)
$75,000-$99,999	70 (6.1)	77 (7.2)	31 (4.9)	35 (5.4)
$100,000-$149,999	57 (5.0)	59 (5.5)	37 (5.9)	32 (5.0)
≥$150,000	25 (2.2)	36 (3.4)	24 (3.8)	11 (1.7)
Prefer not to answer	259 (22.5)	246 (23.0)	154 (24.5)	164 (25.5)
Employment status				
Full-time employee (≥35 h/week)	131 (11.4)	158 (14.8)	106 (16.9)	102 (15.9)
Part-time employee (<35 h/week)	75 (6.5)	84 (7.9)	45 (7.2)	48 (7.5)
Disability for medical reasons	246 (21.4)	255 (23.9)	167 (26.6)	211 (32.8)
Not employed for other reasons (e.g., retired, student, unemployed)	699 (60.7)	572 (53.5)	310 (49.4)	282 (43.9)

Values are median (quartile 1 to quartile 3) or n (%). *There were 624, 573, 317, and 312 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. †There were 773, 751, 423, and 428 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. ‡There were 754, 720, 399, and 412 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. §There were 688, 659, 382, and 385 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. ‖There were 90, 132, 67, and 65 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. #There were 217, 191, 118, and 129 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. **Specific conditions defined at the discretion of local investigators in response to the question "Does the patient currently have any of the following diagnoses?"

Abbreviations are as in Tables 1 and 2.

inadequate rigor of outpatient follow-up may not be the causative factor. For example, the prospective BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) program recruited 2,100 HFrEF patients in Europe, who were either not receiving ACEI/ARB and beta-blocker at baseline or were receiving <50% of target doses (4). Despite the pre-specified intent of the program to encourage medication up-titration, at median follow-up of 21 months, only 22% and 12% of patients achieved target doses of ACEI/ARB and beta-blocker, respectively. Likewise, findings from the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) trial showed that, despite an intensive outpatient follow-up regimen that included a median 12 clinic visits over 12 months and care guided by natriuretic peptide levels, only 15% of patients reached target doses of beta-blockers, and 31% reached target doses of ACEI/ARB (17).

As a complement to these recent prospective experiences, the current study from CHAMP-HF directed attention to the role of patient-level factors in the likelihood of receiving target doses. Although results for specific therapies were varied, lower systolic blood pressure and other unfavorable prognostic factors such as more severe NYHA functional class, older age, chronic renal insufficiency, and recent hospitalization for HF generally favored lower medication use or dose. These findings are compatible with the previously described "risk-treatment paradox," where HF patients with greatest need are less likely to receive appropriate therapy (18). Although these

TABLE 4 Baseline Patient Characteristics by Dose of MRA Therapy

	None (n = 2,317)	<50% Target Dose (n = 21)	50% to <100% Target Dose (n = 250)	≥100% Target Dose (n = 885)
Age, yrs	69 (61–77)	71 (64–76)	65 (56–74)	63 (55–71)
Female	653 (28.3)	7 (33.3)	62 (24.8)	290 (32.8)
Race				
White	1,767 (76.7)	18 (85.7)	197 (78.8)	606 (68.6)
Black	334 (14.5)	2 (9.5)	33 (13.2)	199 (22.5)
Other	204 (8.9)	1 (4.8)	20 (8.0)	79 (8.9)
Hispanic ethnicity	465 (20.2)	0 (0.0)	17 (6.8)	106 (12.0)
Ejection fraction, %	31 (25–37)	32 (29–39)	30 (20–35)	28 (20–33)
NYHA functional class				
I	229 (10.0)	2 (9.5)	27 (10.8)	84 (9.5)
II	1,295 (56.3)	10 (47.6)	138 (55.2)	454 (51.4)
III	624 (27.1)	8 (38.1)	71 (28.4)	290 (32.8)
IV	62 (2.7)	0 (0.0)	4 (1.6)	20 (2.3)
Not available	90 (3.9)	1 (4.8)	10 (4.0)	35 (4.0)
Vital sign and laboratory findings				
Systolic blood pressure, mm Hg	120 (110–132)	121 (102–133)	118 (104–128)	118 (105–129)
Diastolic blood pressure, mm Hg	72 (66–80)	72 (64–79)	70 (62–79)	70 (63–80)
Heart rate, beats/min	72 (65–80)	74 (65–86)	72 (64–82)	74 (67–83)
Obese, BMI ≥30 kg/m^2	896 (38.9)	11 (52.4)	102 (40.8)	416 (47.1)
Hemoglobin, g/dl*	13.2 (11.8–14.4)	13.5 (12.3–14.9)	13.5 (12.3–14.7)	13.3 (12.1–14.5)
Serum sodium, mmol/l†	140 (138–142)	138 (137–141)	139 (137–141)	139 (137–141)
BUN, mg/dl‡	20 (15–28)	21 (17–35)	21 (16–27)	20 (16–26)
eGFR, ml/min per 1.73 m^2§				
<30	83 (6.3)	3 (23.1)	7 (4.0)	22 (3.8)
30–44	208 (15.7)	2 (15.4)	19 (10.8)	66 (11.4)
45–60	297 (22.5)	3 (23.1)	41 (23.3)	142 (24.6)
>60	734 (55.5)	5 (38.5)	109 (61.9)	347 (60.1)
NT-proBNP, pg/ml‖	2,642 (960–6,070)	3,247 (1,246–5,248)	1,400 (591–3,640)	1,608 (638–3,671)
Hemoglobin A1c, %#	6.4 (5.8–7.5)	6.1 (5.8–6.5)	6.4 (5.9–7.6)	6.6 (5.8–7.9)
Medical history**				
HF hospitalization within past 12 months	786 (34.0)	8 (38.1)	104 (41.6)	416 (47.0)
Coronary artery disease	1,484 (64.4)	11 (52.4)	155 (62.0)	507 (57.3)
Hypertension	1,960 (85.0)	17 (81.0)	167 (66.8)	702 (79.3)
Hyperlipidemia	1,794 (77.8)	18 (85.7)	178 (71.2)	630 (71.2)
Diabetes mellitus	966 (42.0)	6 (28.6)	84 (33.6)	362 (41.0)
Atrial fibrillation	830 (36.0)	15 (71.4)	103 (41.2)	303 (34.2)
Chronic renal insufficiency	473 (20.5)	4 (19.0)	39 (15.6)	157 (17.8)
Asthma/COPD	712 (30.9)	6 (28.6)	56 (22.4)	267 (30.2)
History of ventricular tachycardia/fibrillation	382 (16.6)	8 (38.1)	72 (28.8)	192 (21.7)
Depression	602 (26.2)	5 (23.8)	54 (21.6)	207 (23.4)
Active cigarette smoking	453 (19.7)	2 (9.5)	42 (16.8)	187 (21.2)
Heart failure device therapy				
Implantable cardioverter-defibrillator	840 (36.5)	17 (81.0)	136 (54.4)	442 (50.1)
Cardiac resynchronization therapy	128 (5.6)	1 (4.8)	26 (10.4)	75 (8.5)

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observations from CHAMP-HF may be partly intrinsic to greater severity of disease and potential overlapping side effects of many HFrEF medications (e.g., hypotension, worsening renal function), it is conceivable that GDMT underuse and underdosing in higher risk patients may be driven by disproportionate emphasis among providers on potential patient destabilization with medication changes rather than clinical benefits of therapy. Although clinical judgment remains paramount, randomized evidence supports the relative safety of higher doses of GDMT as compared with lower doses. For example, a meta-analysis of ACEI/ARB trials found that, compared to low-dose ACEI/ARB therapy, patients randomized to higher doses experienced improved survival without excess rates of drug discontinuation (19). Similarly, despite enrolling a severely symptomatic HFrEF population, the

TABLE 4 Continued

	None (n = 2,317)	<50% Target Dose (n = 21)	50% to <100% Target Dose (n = 250)	≥100% Target Dose (n = 885)
Social and economic characteristics				
Insurance status				
Managed care (HMO, PPO)	354 (15.4)	1 (4.8)	45 (18.0)	171 (19.3)
Private insurance	197 (8.5)	3 (14.3)	28 (11.2)	100 (11.3)
Medicare	1,418 (61.5)	17 (81.0)	139 (55.6)	438 (49.5)
Medicaid	191 (8.3)	0 (0.0)	22 (8.8)	103 (11.7)
Military health care	49 (2.1)	0 (0.0)	7 (2.8)	17 (1.9)
Uninsured	42 (1.8)	0 (0.0)	6 (250)	21 (2.4)
Other	54 (2.3)	0 (0.0)	3 (1.2)	34 (3.8)
Highest level of education				
Less than high school	305 (13.2)	1 (4.8)	17 (6.8)	95 (10.7)
High school/GED	779 (33.8)	5 (23.8)	73 (29.2)	321 (36.3)
Some college	736 (31.9)	9 (42.9)	77 (30.8)	267 (30.2)
4-yr college (baccalaureate degree)	270 (11.7)	3 (14.3)	48 (19.2)	111 (12.6)
Graduate or other professional degree	215 (9.3)	3 (14.3)	35 (14.0)	90 (10.2)
Total household income				
<$25,000	735 (31.9)	5 (23.8)	52 (20.8)	275 (31.1)
$25,000-$49,999	439 (19.0)	5 (23.8)	47 (18.8)	188 (21.3)
$50,000-$74,999	266 (11.5)	3 (14.3)	32 (12.8)	110 (12.4)
$75,000-$99,999	135 (5.9)	1 (4.8)	20 (8.0)	54 (6.1)
$100,000-$149,999	112 (4.9)	2 (9.5)	24 (9.6)	45 (5.1)
≥$150,000	62 (2.7)	0 (0.0)	8 (3.2)	23 (2.6)
Prefer not to answer	556 (24.1)	5 (23.8)	67 (26.8)	189 (21.4)
Employment status				
Full-time employee (≥35 h/week)	305 (13.2)	0 (0.0)	43 (17.2)	146 (16.5)
Part-time employee (<35 h/week)	152 (6.6)	2 (9.5)	29 (11.6)	60 (6.8)
Disability for medical reasons	486 (21.1)	5 (23.8)	71 (28.4)	312 (35.3)
Not employed for other reasons (e.g., retired, student, unemployed)	1,362 (59.1)	14 (66.7)	107 (42.8)	366 (41.4)

Values are median (quartile 1 to quartile 3) or n (%). *There were 1166, 12, 153, and 474 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. †There were 1479, 14, 199, and 654 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. ‡There were 1424, 15, 193, and 627 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. §There were 1322, 13, 176, and 577 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. ||There were 168, 2, 49, and 124 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. #There were 427, 4, 49, and 165 patients with available data for none, <50% target dose, 50% to <100% target dose, and ≥100% target dose groups, respectively. **Specific conditions defined at the discretion of local investigators in response to the question "Does the patient currently have any of the following diagnoses?"

MRA = mineralocorticoid receptor antagonist; other abbreviations as in Tables 1 to 3.

COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial demonstrated the relative safety and efficacy of carvedilol initiation among >2,200 patients (20).

Numerous studies have explored interventions to improve provision of medical therapy by providers and/or to improve medication adherence among patients (21–23). Although the broad application of most data remain limited by small numbers of study centers, limited numbers of patients, and heterogeneity of interventions, evidence does support the potential impact of some strategies such as quality metric checklists, pharmacist-driven medication programs, and patient education (21–23). Likewise, the recent American College of Cardiology Expert Consensus Document provides recommendations for addressing challenges to appropriate use of HFrEF medical therapy, including clinical, economic, and social barriers (12). Nonetheless, CHAMP-HF highlights the persistently unmet need for generalizable strategies to improve widespread use and dosing of GDMT. Specifically, the current "risk-treatment paradox" findings suggest that patients with the highest clinical risk may particularly benefit from future quality improvement strategies. Moreover, although most patients received care at cardiology practices, larger gaps in GDMT use among patients enrolled at family medicine and internal medicine clinics suggest such practices may have the most to gain from future efforts to improve quality of care. Aside from more conventional approaches, novel interventions grounded in behavioral economics or technological

TABLE 5 Logistic Regression Model Results for Independent Associations Between Patient Characteristics and Medication Doses*

	Treated vs. Not Treated	≥50% Target Dose vs. <50% Target Dose	≥100% Target Dose vs. <100% Target Dose
ACEI/ARB	(n = 3,158)†	(n = 1,938)‡	(n = 1,893)§
Age, per 10-yr increase		0.90 (0.82–0.98), p = 0.014	
Female	0.78 (0.66–0.93), p = 0.005		
Black vs. white		1.87 (1.39–2.51), p < 0.001	1.57 (1.13–2.18), p = 0.008
Other vs. white		0.87 (0.60–1.26), p = 0.457‖	0.58 (0.34–1.00), p = 0.048
Diabetes mellitus		1.23 (1.01–1.51), p = 0.044	
Chronic renal insufficiency	0.62 (0.51–0.75), p < 0.001		
Asthma/COPD			0.66 (0.49–0.88), p = 0.006
Depression		0.74 (0.58–0.93), p = 0.012	
Atrial fibrillation	0.69 (0.58–0.81), p < 0.001		
Hypertension		1.86 (1.39–2.50), p < 0.001	2.62 (1.66–4.14), p < 0.001
HF hospitalization in prior 12 months		0.73 (0.58–0.91), p = 0.005	0.63 (0.47–0.84), p = 0.002
Systolic blood pressure, per 10-mm Hg increase	1.06 (1.01–1.11), p = 0.013	1.22 (1.15–1.30), p < 0.001	1.26 (1.18–1.36), p < 0.001
Heart rate, per 10 beats/min increase		0.89 (0.82–0.96), p = 0.004	
NYHA functional class II vs. I	0.81 (0.61–1.08), p = 0.153‖		0.84 (0.58–1.23), p = 0.374‖
NYHA functional class III/IV vs. I	0.59 (0.43–0.79), p < 0.001		0.57 (0.36–0.88), p = 0.011
Ejection fraction, per 10% absolute increase		1.14 (1.00–1.31), p = 0.049	
ARNI	(n = 3,430)#	(n = 423)**	-
Age, per 10-yr increase	0.82 (0.75–0.90) p < 0.001		
Hispanic ethnicity	0.51 (0.31–0.82), p = 0.006		
Chronic renal insufficiency	0.66 (0.48–0.90), p = 0.009		
Coronary artery disease		0.45 (0.28–0.74), p = 0.002	
Hypertension		1.98 (1.04–3.77), p = 0.037	
History of ventricular tachycardia/fibrillation	1.58 (1.20–2.06), p < 0.001		
Systolic blood pressure, per 10-mm Hg increase		1.17 (1.03–1.33), p = 0.018	
Heart rate, per 10-beats/min increase		0.79 (0.65–0.97), p = 0.026	
Ejection fraction, per 10% absolute increase	0.73 (0.63–0.84), p < 0.001		
Beta-blocker	(n = 3,468)††	(n = 2,163)‡‡	(n = 2,163)‡‡
Age, per 10-yr increase	0.87 (0.81–0.93), p < 0.001	0.83 (0.77–0.90), p < 0.001	0.87 (0.79–0.95), p = 0.003
Black vs. white		1.46 (1.13–1.89), p = 0.004	1.45 (1.10–1.90), p = 0.008
Other race vs. white		0.76 (0.55–1.05), p = 0.091‖	1.15 (0.77–1.71), p = 0.490‖
Hispanic ethnicity			0.66 (0.46–0.96), p = 0.030
Obese, BMI ≥30 kg/m^2		1.58 (1.31–1.92), p < 0.001	1.61 (1.30–1.99), p < 0.001
High school/GED vs. less than high school			1.13 (0.80–1.59), p = 0.501‖
Some college vs. less than high school			0.95 (0.66–1.36), p = 0.771‖
4-yr/graduate/professional degree vs. less than high school			0.75 (0.51–1.10), p = 0.135‖
Diabetes mellitus		1.37 (1.14–1.65), p < 0.001	1.50 (1.22–1.85), p < 0.001
Chronic renal insufficiency	1.24 (1.01–1.52), p = 0.045		
Asthma/COPD	0.81 (0.67–0.96), p = 0.016	0.77 (0.62–0.94), p = 0.010	0.77 (0.60–0.97), p = 0.030
Active cigarette smoking			0.66 (0.50–0.87), p = 0.003
Atrial fibrillation	0.76 (0.64–0.90), p = 0.002	1.53 (1.26–1.87), p < 0.001	
Coronary artery disease			0.78 (0.62–0.98), p = 0.032
HF hospitalization in prior 12 months		0.60 (0.49–0.72), p < 0.001	0.54 (0.43–0.67), p < 0.001
Systolic blood pressure, per 10-mm Hg increase		1.10 (1.05–1.16), p < 0.001	1.10 (1.04–1.16), p < 0.001
Heart rate, per 10-beats/min increase		0.92 (0.85–0.99), p = 0.027	0.91 (0.83–0.99), p = 0.027
Ejection fraction, per absolute 10% increase	0.73 (0.66–0.82), p < 0.001		

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innovation (e.g., mobile applications) may be particularly promising and are being tested (24).

STUDY LIMITATIONS. First, although associations between patient characteristics and medication use reflect rigorous multivariate modeling, the possibility of residual confounding exists, and these observational data cannot definitively determine cause-and-effect relationships. Likewise, this observational study is unable to conclusively discern underlying reasons for such associations. Second, baseline laboratory data are limited, as collection was not specific to the CHAMP-HF registry and was obtained only if recorded in the

TABLE 5 Continued

	Treated vs. Not Treated	≥50% Target Dose vs. <50% Target Dose	≥100% Target Dose vs. <100% Target Dose
MRA	(n = 3,262)§§	-	(n = 1,146)‖‖
Age, per 10-yr increase	0.78 (0.74–0.84), p < 0.001		
Female	1.27 (1.06–1.52), p = 0.008		1.47 (1.06–2.05), p = 0.021
Hispanic ethnicity	0.72 (0.53–0.97), p = 0.029		
Obese, BMI ≥30 kg/m^2	1.26 (1.07–1.50), p = 0.007		
Chronic renal insufficiency	0.78 (0.63–0.96), p = 0.021		
Atrial fibrillation			0.69 (0.51–0.94), p = 0.017
Hypertension			1.86 (1.33–2.59), p < 0.001
History of ventricular tachycardia/fibrillation	1.28 (1.04–1.57), p = 0.018		
HF hospitalization in prior 12 months	1.21 (1.02–1.44), p = 0.032		
Systolic blood pressure, per 10-mm Hg increase	0.91 (0.86–0.95), p < 0.001		
Ejection fraction, per absolute 10% increase	0.72 (0.64–0.80), p < 0.001		0.80 (0.67–0.97), p = 0.020

Values are odds ratio (95% confidence interval), p value. Continuous variables (age, systolic blood pressure, and heart rate) are displayed in terms of per 10-U increase. *Model selection was based on backwards elimination and variables with a p value of >0.05 were removed based on highest p value first, with subsequent assessment completed using the remaining variables. Pre-specified candidate variables included age (per 10 years), systolic blood pressure (per 10 mm Hg), heart rate (10 beats/min), ejection fraction (per absolute 10% change), sex, race (white, black, other), Hispanic ethnicity, obesity, insurance (managed care [HMO, PPO], private insurance [high-deductible health plan/health savings account], Medicare, Medicaid, military healthcare, other/uninsured), level of education (less than high school, high school/GED, some college, 4-year/graduate/professional degree), diabetes mellitus, chronic renal insufficiency, asthma/COPD, depression, cigarette smoking (ever vs. never), atrial fibrillation, coronary artery disease, hypertension, hyperlipidemia, ventricular tachycardia/ventricular fibrillation, cardiac resynchronization therapy, HF hospitalization in 12 months prior to enrollment, NYHA functional classification (I, II, III/IV). †323 were excluded due to missing covariate data. ‡155 were excluded due to missing covariate data; 14 were excluded due to missing dose. §200 were excluded due to missing covariate data, 14 were excluded due to missing dose. ‖All variables carried p value of <0.05 and thus were considered statistically significant. Categorical variables with >2 levels are displayed in the table for completeness, despite some individual levels having p value of >0.05. #51 were excluded due to missing covariate data. **28 were excluded due to missing covariate data, 1 was excluded due to missing dose. ††42 were excluded due to missing covariate data. ‡‡182 were excluded due to missing covariate data, 6 were excluded due to missing dose. §§218 were excluded due to missing covariate data. ‖‖10 were excluded due to missing covariate data, 7 were excluded due to missing dose.

Abbreviations as in Tables 1 to 4.

medical record. Third, although study sites were chosen to include a diverse mix of health care providers and outpatient facilities, data reflect patients from sites who elected to participate in the registry and thus may not be generalizable to all care practices. Fourth, the current analysis defined treatment eligibility by the absence of an absolute contraindication to a given therapy at the discretion of site investigators and did not reflect the potential impact of single or multiple relative contraindications on treatment decisions. Moreover, data regarding the specific nature of contraindications were not collected. Fifth, patients in this voluntary program were predominantly male and white. It is unclear how increased representation of women and racial/ethnic minorities would have influenced results. Sixth, this study did not pre-specify assessment of frailty, and it is possible that a frailty score may correlate with medication use or dose. Last, CHAMP-HF data are based on documentation within the medical record, and, despite aforementioned features designed to lessen any effects of documentation quality and completeness on registry data, inherent limitations remain. Specifically, it is possible that actual treatment rates and doses differed from those recorded and that patients on lower doses were individuals in whom dose titration had been previously attempted but not tolerated. In addition, contraindications might have been present in some instances but not documented.

CONCLUSIONS

In this contemporary registry of outpatients with chronic HFrEF, there remain significant gaps in guideline-directed use and dosing of HFrEF medications. Despite guidelines, educational efforts, and quality improvement initiatives, comparison with prior registry data approximately a decade ago show that outpatient use and dosing of GDMT has generally not improved. Several clinical factors show strong independent associations with baseline use and dose of GDMT, and these findings may inform targeted efforts toward optimal implementation of medical therapy for HFrEF. In the setting of continued high rates of morbidity and mortality in the general HFrEF population, effective strategies to improve use and target dosing of outpatient medical therapy remain urgently needed.

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PERSPECTIVES

COMPETENCY IN PRACTICE-BASED LEARNING: Guideline-directed medical therapies are underused in the care of outpatients who have HFrEF. Most medications are prescribed at doses lower than recommended, particularly among older patients and in those with low systolic blood pressure, severe functional disability, renal insufficiency, and recent hospitalization for HF.

TRANSLATIONAL OUTLOOK: Strategies are needed to improve implementation of guideline-directed therapies at optimum doses for outpatients with HFrEF.

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KEY WORDS dose, medication, reduced ejection fraction, registry

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