

Characteristics Associated with Upper-Range Doses of Beta-Blockers and Angiotensin-Renin Inhibitors in Reduced Ejection Fraction

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ABSTRACT **Background:** Heart failure (HF) patients with reduced ejection fraction (HFrEF) are frequently treated with sub-optimal doses of angiotensin converting enzyme-inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and beta blockers (BBs).

Objectives: To determine factors associated with attaining upper-range doses in patients with HFrEF.

Methods: We examined treatment in patients with left ventricular ejection fraction (LVEF) $\leq 40\%$ in a community-based, dedicated heart-failure clinic. Upper-range doses were defined as $\geq 75\%$ of target recommended doses by heart failure society guidelines.

Results: The majority of the 215 patients were men (82%); median age at presentation 73 years (interquartile range [IQR] 65–78) and LVEF of 30% (IQR 25–35%). Following the up-titration program, 41% and 35% of patients achieved upper-range doses of ACE-Is/ARBs and BBs, respectively. Higher body mass index (BMI) was the only parameter found to be associated with achieving upper-range doses of ACE-I/ARBs (odds ratio [OR] 1.13, 95% confidence interval [95%CI] 1.05–1.22, $P = 0.001$). More patients achieved this target as BMI increased, with a sharp decline in the highest obesity category (BMI ≥ 40 m²/kg). Attaining upper-range doses of BBs was associated with pre-existing diabetes mellitus (DM) (OR 2.6, 95%CI 1.34–5.19, $P = 0.005$); women were associated with attaining lower BBs doses (OR 0.34, 95%CI 0.13–0.90, $P = 0.031$).

Conclusions: Achieving upper-range doses of ACE-Is/ARBs and BBs in HFrEF outpatients in a treatment up-titration program were associated with greater BMI and DM, respectively. These findings may serve as benchmarks for up-titration programs.

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KEY WORDS: heart failure, reduced ejection fraction (HFrEF), systolic dysfunction

Studies have clearly demonstrated the efficacy of pharmacological therapies titrated to target doses of angiotensin converting enzyme-inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and beta blockers (BBs) in improving the poor outcomes of heart failure (HF) patients with reduced ejection fraction (HFrEF) [1,2]. Accordingly, this goal is advocated in the relevant European and North-American clinical practice guidelines [3]. Nevertheless, patients are frequently treated with sub-optimal doses [4,5]. In fact, only one-third to one-fourth of patients reach target doses [4,6]. The reasons for this are multifactorial, [4,6], yet in a substantial number of cases the reason remains unknown [5-7]. In an attempt to improve care for HF patients, dedicated HF clinics have been established worldwide [8] and studies that included patients treated in such clinics have shown improvements in the use of evidence-based pharmacological treatment [9,10], possibly because of the use of treatment up-titration protocols in such clinics [7,9].

In our study, we sought to determine the baseline characteristics associated with attaining upper-range recommended doses of angiotensin converting enzyme-inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and beta blockers (BBs) in an up-titration program of patients treated in a community-based, dedicated HF clinic.

PATIENTS AND METHODS

STUDY POPULATION AND DATA COLLECTION

As previously described by Murninkas and colleagues [11], electronic records of all patients 18–85 years old insured by the largest healthcare management organization in Israel (Clalit Health Services) in a designated district were screened (n=115,739 patients). The authors specifically queried for the documented diagnosis of left ventricular ejection fraction (LVEF) $\leq 40\%$ regardless of prior HF hospitalization. Eligible patients were actively invited to attend our community-based dedicated HF clinic, with no additional cost on their behalf. Consenting patients were enrolled into the titration program, supervised by a certified HF specialist.

*The first and second authors contributed equally to this study

Table 1: Baseline characteristic of patients with HFREF treated in a dedicated HF clinic that underwent pharmacological titration.

Variable	Total (n=215)	Patients who subsequently achieve upper-range dose of ACE-Is and ARBs (n=60)	Patients who subsequently achieve upper-range doses of BBs (n=67)
Age (years)	73 (65–78)	71 (62–78)	71 (64–78)
Women (%)	39 (18)	14 (23)	7 (10)
BMI (kg/m ²)	27 (25–30)	30 (26–33)	28 (25–31)
Prior CAD (%)*	161 (75)	43 (72)	46 (69)
Hypertension (%)	151 (72)	42 (70)	44 (66)
Diabetes mellitus (%)	112 (52)	32 (53)	44 (66)
Atrial fibrillation (%)	46 (21)	14 (23)	16 (24)
NYHA class 3 or 4 (%)	118 (55)	(28) 48%	78 (52)
Estimated LVEF (%)	30 (25–35)	35 (25–40)	30 (25–35)
Systolic blood pressure (mmHg)	118 (108–129)	121 (110–130)	119 (110–130)
Heart rate (beats/min)	72 (65–72)	72 (64–78)	72 (64–78)
Estimated GFR** (ml/min)	66 (49–86)	72 (52–84)	70 (49–88)
Sodium (meq/L)	140 (138–142)	141 (138–142)	140 (138–142)
Potassium (meq/L)	4.6 (4.3–4.8)	4.6 (4.2–4.8)	4.7 (4.4–5)
Hemoglobin (g/dl)	13.1 (12–14)	13 (12–14)	13 (12–14)
Prior device implantation (%)***	87 (41)	21 (35)	34 (51)
Prior yearly influenza vaccination (%)	158 (74)	46 (77)	55 (82)
Use of ACE-Is or ARBs (%)	179 (83)	100%	58 (86)
Use of BBs (%)	181 (84)	49 (82)	100%

Data are presented as medians (25th–75th quartiles) or as numbers (percentages), as appropriate

*Significant coronary artery disease in angiography

**Estimated glomerular filtration rate- based on the Cockcroft–Gault formula

***Device implantation included implantation of an implantable cardioverter defibrillator, cardiac resynchronization therapy with or without a defibrillator, or pacemaker

ACE-Is = angiotensin converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, BB = beta-blockers, BMI = body mass index, CAD = coronary artery disease, GFR = glomerular filtration rate, HFREF = heart failure with reduced ejection fraction, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association

Each enrolled patient was examined in our clinic every 2 weeks, as recommended by the European Society of Cardiology guidelines for the initiation and titration of HF medications [3]. The doses of ACE-Is, ARBs, and BBs, were titrated upon each visit aiming to achieve guideline-recommended target doses

or the patient's maximal tolerated doses. The titration process considered different parameters, such as the patient's heart rate, blood pressure, renal function, and electrolyte levels. Medication target doses were defined according to the European Society of Cardiology guidelines [3]. We used $\geq 75\%$ of target recommended dose to define upper-range treatment, as previously defined [12]. To allow us to better define the characteristics associated with achieving upper-range doses, and as drug intolerance and medication maintenance and up-titration were shown to be influenced by drug implementation practice, only patients who attended ≥ 3 visits in the titration program were included in the study. The pre-specified study follow-up was 18 months (1 May 2016–31 October 2017).

Rates of medication usage were based on prescription fill rates, extracted from the unique electronic medical records system of Clalit [11]. LVEF was estimated visually by transthoracic or transesophageal echocardiography.

This study complies with the Declaration of Helsinki. The local institutional review board approved the research protocol.

STATISTICAL METHODS

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) Continuous variables were presented by medians and interquartile range (IQR) and categorical variables were presented as percentage. The Student's *t*-test was used to compare the value of normally distributed continuous variables between study groups. The Wilcoxon test was used for non-normally distributed variables and the Fisher's exact test was used for categorical variables with two categories. Chi-square was used for more than two categories. Univariate and multivariate odds ratios (OR) were evaluated by logistic regression. A 2-sided *P* value < 0.05 was considered as statistical significance.

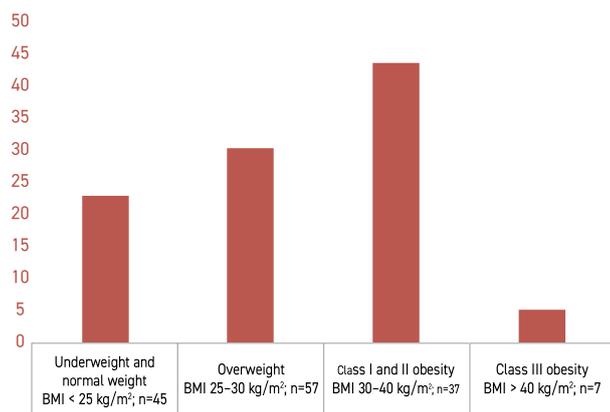
RESULTS

Our current analysis first pertains to the 304 patients who attended our community-based, dedicated HF clinic. Of those attending the clinic, 215 (71%) patients were compliant with ≥ 3 visits in the up-titration program, and they were the focus of our current analysis. Their baseline characteristics are presented in Table 1. The majority of patients in our study group (82%) were male with a median age at presentation of 73 years (25th, 75th IQR of 65–78). At baseline, a substantial number of patients were defined as New York Heart Association (NYHA) 3 or 4 (55%) and presented with a median LVEF of 30% (25th, 75th IQR of 25%–35%). The percentages at baseline for achieving the upper-range doses for both ACE-Is and ARBs, as well as BBs were 6% and 7%, respectively.

Following the up-titration program, upper-range doses ($\geq 75\%$ of recommended target doses [3]) of ACE-Is or ARBs and of BBs were achieved in 41% and 35% of patients, respectively. The baseline characteristics of these subgroups are pre-

Figure 1. Achieving upper-doses of ACE-Is/ARBs categorized by BMI groups

Rates of patients receiving upper-range doses of ACE-Is/ARBs categorized by their BMI (kg/m²) Percentages were calculated from the number of patients receiving ACE-I/ARBs in each BMI sub-group (numbers presented on the X-axis legend)
ACE-Is = angiotensin converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, BMI = body mass index



sented in Table 1. The characteristics associated with ACE-Is or ARBs usage and with achieving upper-range doses in patients with HFrEF treated in a dedicated HF clinic are presented in Table 2. We found that the use of ACE-I and ARBs was associated with increased LVEF level. Moreover, the elevation in body mass index (BMI) was the only parameter associated with achieving upper-range doses of ACE-Is/ARBs in our analysis. To further expand on the correlation between BMI and upper-range doses of ACE-Is/ARBs, we sub-categorized our study population according to the National Institutes of Health (NIH) definitions for obesity [Figure 1] and found an association between BMI as defined by the obesity categories and the achievement of ACE-Is/ARBs at upper-range doses. However, a sharp decline in the rate of patients receiving upper-range doses was noticed in the highest obesity category (BMI ≥ 40 kg/m²).

The characteristics associated with the use of BBs and with achieving upper-range doses in patients with HFrEF treated in a dedicated-HF clinic in an up-titration program are presented in Table 3. In general, patients were more likely to receive BBs if they had previously been implanted with an electronic implantable device. Moreover, achieving upper-range doses of BBs were associated with male sex and diabetes mellitus (DM).

DISCUSSION

This study provides new insights into the pharmacological management of HFrEF patients by exploring the factors that predict achieving guideline-recommended target doses of ACE-Is/ARBs and BBs, a well-established measure for improved outcomes in HFrEF patients [1,2,13]. We found that on an intense up-titration

Table 2: Multivariate analyses of likelihood of patients with HFrEF to receive ACE-Is or ARBs in general and at upper-range doses

Parameter	Use of ACE-Is/ARBs		Use of ACE-Is/ARBs upper-range doses	
	Odds ratio (95% confidence interval)	P value	Odds ratio (95% confidence interval)	P value
Age (years)	1.01 (0.07-1.05)	0.753	0.97 (0.92-1.01)	0.140
Women	1.87 (0.79- 4.43)	0.154	1.26 (0.50-3.18)	0.630
NYHA class 3-4 vs. 1-2	0.68 (0.36-1.27)	0.409	0.67 (0.32-1.44)	0.307
Prior CAD	0.96 (0.45-2.02)	0.904	0.91 (0.36-2.30)	0.843
Hypertension	0.98 (0.49-1.98)	0.963	0.60 (0.25-1.41)	0.240
Diabetes mellitus	0.77 (0.42-1.43)	0.409	0.95 (0.45-2.03)	0.896
Estimated GFR (ml/min)	1.01 (0.99-1.03)	0.242	1.01 (0.99-1.03)	0.429
LVEF (%)	1.07 (1.02-1.12)	0.010	1.04 (0.98-1.11)	0.171
BMI (kg/m ²)	1.02 (0.96-1.08)	0.606	1.13 (1.05-1.22)	0.001
Baseline systolic blood pressure (mmHg)	1.00 (0.98-1.02)	0.932	1.01 (0.99-1.03)	0.283
Baseline potassium level (meq/L)	0.87 (0.46-1.63)	0.654	0.74 (0.31-1.74)	0.490

ACE-Is = angiotensin converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, BMI = body mass index, CAD = coronary artery disease, GFR = glomerular filtration rate, HFrEF = heart failure with reduced ejection fraction, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association

program in a community-based, dedicated HF clinic, higher BMI was independently associated with achieving upper-range doses of ACE-I/ARBs was, whereas DM and male sex were independently associated with upper-range doses of BBs.

We found that achieving upper-range doses of ACE-Is/ARBs was associated with elevated BMI even after adjusting for other co-morbidities such as hypertension and DM. Moreover, we showed an association between higher BMI levels (at the range of BMI < 40 kg/m²) and the achievement of upper-range ACE-I/ARBs dose. These findings correspond with the obesity paradox—a clinical phenomenon in which obese people have a lower risk of mortality within subpopulations. The obesity paradox has been demonstrated repeatedly in HF patients with a consistency of results seen among a wide range of clinical subgroups across age, gender, acuity of symptoms, and the presence or absence of co-morbidities, and across different measures of body fatness, including BMI [14,15]. However, the underlying mechanisms accounting for the obesity paradox remain speculative. A possible mechanism relates to patients’ hemodynamic tolerance of cardio-protective medications. Patients with HF presenting with

Table 3. Multivariate analyses of likelihood of patients with HFrEF to receive BBs in general and at upper-range doses

Parameter	Use of beta-blockers		Use of beta-blockers at upper-range doses	
	Odds ratio (95% confidence interval)	P value	Odds ratio (95% confidence interval)	P value
Age (years)	1.01 (0.95–1.07)	0.766	0.99 (0.95–1.04)	0.722
Women	1.32 (0.42–4.16)	0.636	0.34 (0.13–0.90)	0.031
NYHA class 3–4 vs. 1–2	0.74 (0.26–1.85)	0.520	0.88 (0.46–1.71)	0.707
Prior CAD	0.71 (0.20–1.84)	0.378	0.60 (0.27–1.28)	0.183
Hypertension	1.2 (0.47–3.15)	0.696	0.58 (0.28–1.22)	0.151
Diabetes mellitus	0.89 (0.37–2.13)	0.793	2.6 (1.34–5.19)	0.005
Estimated GFR (ml/min)	1.01 (0.99–1.03)	0.520	1.01 (0.99–1.03)	0.277
Left ventricular ejection fraction (%)	1.05 (0.98–1.13)	0.176	1.00 (0.95–1.06)	0.927
BMI (kg/m ²)	0.98 (0.90–1.06)	0.624	1.03 (0.97–1.10)	0.370
Prior device implantation	4.19 (1.39–12.64)	0.011	1.81 (0.89–3.70)	0.100
Heart rate at baseline (beats/min)	0.98 (0.94–1.02)	0.252	1.00 (0.97–1.03)	0.999

BMI = body mass index, CAD = coronary artery disease, GFR = glomerular filtration rate, HFrEF = heart failure with reduced ejection fraction, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association

higher BMIs typically have concomitant higher arterial blood pressure compared to their leaner counterparts, which allow them to better tolerate renin-angiotensin inhibitors, potentially at higher doses [16,17]. Moreover, obese patients have an attenuated response to the renin-angiotensin-aldosterone system, which may further lead to better HF prognosis [16,17]. Our findings support these speculated mechanisms, demonstrating that patients with higher BMIs are more likely to achieve upper-range doses of angiotensin-renin inhibitors, thus, at least partially, accounting for the obesity paradox in HFrEF patients. In fact, we demonstrated a U-shaped relationship between BMI and the achievement of upper-range ACE-I/ARBs doses, as morbidly obese patients (BMI \geq 40 kg/m²) achieved upper-range doses of ACE-I/ARBs much less frequently. This finding is in concordance with previous studies describing a similar U-shaped curve and excess cardiovascular morbidity and mortality in severely obese patients [16,18].

We found that attaining upper-range doses of BBs was more likely in diabetic patients with HFrEF. Patients with HF and DM have increased basal sympathetic neural outflow, compared to patients with HF without DM [19]; thus, higher doses of BBs may be needed to suppress the excessive sympathetic activation caused by DM [12]. A recent study showed that in a population of patients with LVEF < 32%, patients with DM were

prescribed higher doses of BBs than patients without DM, regardless of a patient's heart rate [12]. Moreover, the impact of increasing BBs dose on survival was greater in patients with DM than in patients without DM [12]. Notably, the interaction between BBs and DM is conflicting and may be dependent on the specific drug in use. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial showed that compared with metoprolol, carvedilol significantly reduced new-onset DM and significantly increased insulin sensitivity [20].

We also found that men were more likely to achieve upper-range doses of BBs. A recent report found no evidence of an interaction between the effect of BBs on survival and sex in any age group [21]. However, there may be sex-specific differences in sympathetic tone in HF patients that may explain our findings [22].

The System Biology Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) European project reported that a lower BMI level was as an independent predictor for achieving lower rates of recommended ACE-inhibitor/ARB doses, among other variables such as female sex and estimated glomerular filtration rate [5]. Predictors for lower BBs doses were higher age, country of inclusion, lower heart rate, diastolic blood pressure, and signs of congestion. Although this research was an important multicenter, multi-national study that was designed to address characteristics and outcomes of patients not reaching target doses, there are several distinct differences between BIOSTAT-CHF and our study. First, the population examined in the BIOSTAT-CHF was heterogeneous and included patients treated in university hospitals and large teaching hospitals. In addition, the majority of patients were initially hospitalized for acute HF [23]. Our study group included ambulatory patients treated in a community-based clinic. Moreover, data on medication doses in our study relied on actual pharmacy refills, while medication data on the BIOSTAT-CHF was most likely self-reported by patient. Furthermore, there was marked variability among countries regarding attainment of target doses, again underscoring the heterogeneity of the patients and practices [5]. Last, following a medication up-titration program, only 22% and 12% of patients achieved the recommended target doses of ACE-Is/ARBs and BBs, respectively. Findings from the Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) showed that implementation of a practice-based performance improvement intervention was associated with the achievement of higher target doses of BBs, but not ACE-Is/ARBs [9]. The investigators described black race, younger age, higher systolic blood pressure, presence of HF clinic, and practice location as predictors for achieving target BBs doses. This study was also limited due to the heterogeneity of the HF population studied and the achievement of low maximal-range doses (30% for BBs and 36% for ACE-Is/ARBs following 24 months of follow-up).

Our study is unique given that it is based on a community, dedicated HF clinic model and included real-life all-comer outpatients with HFrEF. Moreover, as drug intolerance and medication maintenance and up-titration were shown to be influenced

by drug implementation practices [24], only patients who were compliant with a treatment up-titration program were included in this study, thus allowing us to better define the factors associated with achieving target doses.

LIMITATIONS

Our study has several inherent limitations. The data analysis was retrospective, even though the data were captured prospectively. Thus, unmeasured variables may have impacted the results. Second, this study is single-centered, and the results may not apply to other up-titration programs in inpatient or outpatient clinics. Data presented by Shotan et al. [25] showed increased rates for the use of BB and ACE-Is/ARBs in Israeli HFrEF patients compared to HFrEF patients from European countries. Third, we do not have data regarding anthropometric parameters other than BMI, such as waist circumference and waist-to-hip ratio. However, BMI is still the most commonly used anthropometric parameter to assess the degree of adiposity [15]. Fourth, our exclusion criteria make patient selection bias plausible, as patients with good compliance were more likely to adhere to three visits in the clinic. However, our study aim was to explore the factors that contribute to the achievement of upper-range drug doses minimizing patient’s drugs compliance. Fifth, there is a potential inaccuracy of attaining information on medication doses from the electronic drug prescription fill.

CONCLUSIONS

Achieving upper-range doses of ACE-Is/ARBs and BBs in HFrEF outpatients treated in a treatment up-titration program were associated with greater BMI and DM, respectively. Women were less likely to receive upper-range doses of BBs. These findings may serve as benchmarks for community-based, dedicated HF clinics, using up-titration programs of guideline-recommended medications in HFrEF patients.

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