OBSERVATION: BRIEF RESEARCH REPORT

Prescription Bias in the Treatment of Chronic Systolic Heart Failure

Background: Current guidelines recommend specific dosages of β-blockers and renin–angiotensin system inhibitors for patients with heart failure with reduced ejection fraction, because patients who receive this treatment have fewer hospitalizations and live longer (1). However, many eligible patients do not receive the recommended dosage (2); one explanation is that clinicians prescribe lower dosages to avoid side effects. Drugs in the same class have different potencies and thus different recommended dosages. Thus, we wondered whether clinicians prescribe less of the recommended dosage for drugs with higher recommended dosages than those with lower recommended dosages because of an unconscious bias against higher dosages (3, 4).

Objective: Because all these drugs are started at low dosages and then titrated upward toward the recommended dosage, we focused on the dosage at which upward titration stops. Our objective was to determine whether uptitration stops when the dosage is further away from the recommended dosage for drugs with higher than those with lower recommended dosages.

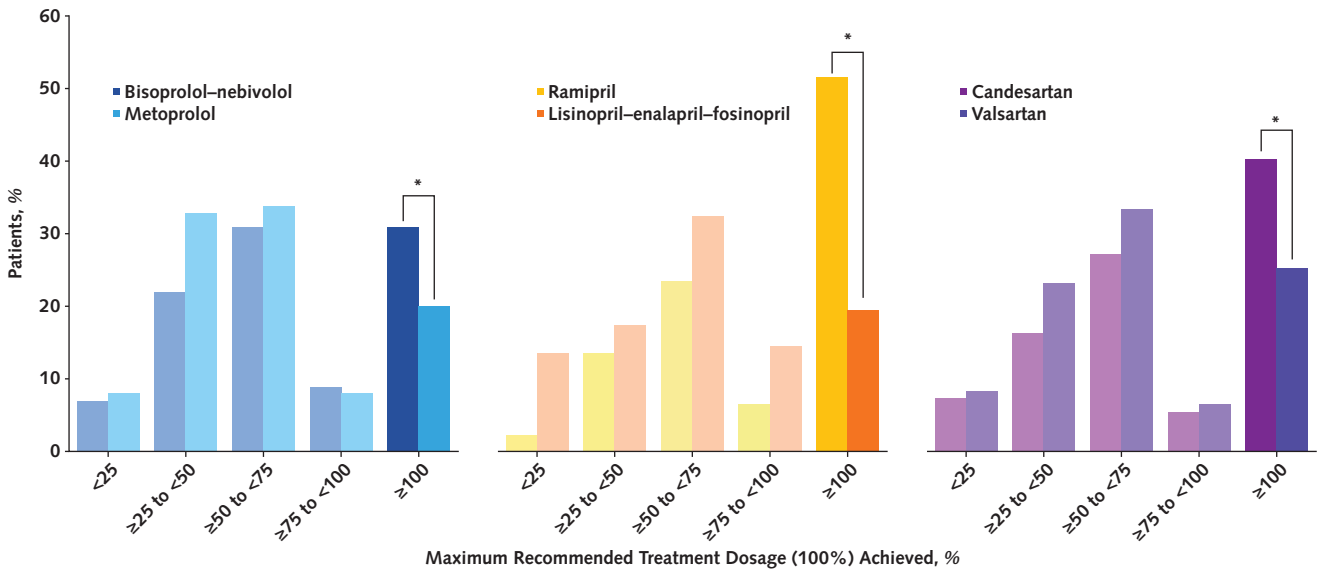
Methods and Findings: We used an existing registry (5) to examine data from 3737 outpatients with heart failure with reduced ejection fraction who were enrolled consecutively

Table. Characteristics of the Total Study Population, According to Type of Therapy*

Characteristic	Total Study Population (*N* = 3737)	β-Blockers			Angiotensin-Converting Enzyme Inhibitors			Angiotensin-Receptor Blockers		
		Bisoprolol-Nebivolol (*n* = 1434)	Metoprolol (*n* = 280)	*P* Value	Ramipril (*n* = 599)	Lisinopril-Enalapril-Fosinopril (*n* = 1138)	*P* Value	Candesartan (*n* = 409)	Valsartan (*n* = 173)	*P* Value
Median age (IQR), *y*	65 (55–74)	65 (55–73)	67 (55–74)	0.29	61 (52–71)	66 (55–73)	<0.001	66 (57–74)	63 (55–73)	0.035
Male sex, *n* (%)	2720 (73)	1017 (71)	204 (73)	0.51	457 (76)	870 (76)	0.94	286 (70)	121 (70)	0.99
Median height (IQR), *cm*	172 (166–178)	172 (166–178)	172 (165–178)	0.90	173 (167–178)	173 (167–178)	0.53	172 (165–178)	171 (165–179)	0.41
Median body weight (IQR), *kg*	80 (69–92)	80 (70–92)	82 (70–95)	0.146	80 (69–94)	81 (70–92)	0.28	80 (70–93)	80 (69–93)	0.88
Median BMI (IQR), kg/m^2	27 (24–30)	27 (24–31)	28 (24–32)	0.050	27 (24–31)	27 (24–30)	0.73	28 (25–31)	27 (24–32)	0.182
Hypertension, *n (%)*	2320 (62)	874 (61)	198 (71)	0.005	360 (60)	740 (65)	0.160	275 (67)	114 (66)	0.90
T2DM, *n (%)*	1047 (28)	392 (27)	87 (31)	0.35	152 (25)	321 (28)	0.57	120 (43)	45 (26)	0.79
Nicotine dependency, *n (%)*				0.55			0.010			0.90
Current smoker	563 (15)	209 (15)	48 (17)	–	112 (19)	168 (15)	–	47 (11)	21 (12)	–
Former smoker	1214 (33)	474 (33)	82 (29)	–	228 (38)	385 (34)	–	128 (31)	57 (33)	–
Nonsmoker	1543 (41)	593 (41)	118 (42)	–	201 (34)	462 (41)	–	189 (46)	74 (43)	–
Unknown	417 (11)	158 (11)	32 (12)	–	58 (10)	123 (11)	–	45 (11)	21 (12)	–
Alcohol dependency, *n (%)*				0.050			0.53			0.098
Current alcohol abuse	73 (2)	23 (2)	8 (3)	–	12 (2)	20 (2)	–	0 (0)	2 (1)	–
Former alcohol abuse	220 (6)	85 (6)	16 (6)	–	42 (7)	85 (7)	–	18 (4)	9 (5)	–
Occasional	1565 (42)	609 (42)	121 (43)	–	252 (42)	524 (46)	–	177 (43)	79 (45)	–
Never	1624 (43)	643 (45)	110 (39)	–	248 (41)	427 (38)	–	194 (47)	70 (40)	–
Unknown	255 (7)	74 (5)	25 (9)	–	45 (8)	82 (7)	–	35 (9)	15 (9)	–
Ischemic cardiomyopathy, *n (%)*	1286 (34)	486 (34)	144 (51)	<0.001	240 (40)	408 (36)	0.153	133 (33)	69 (40)	0.071
Atrial fibrillation, *n (%)*	1216 (33)	484 (34)	102 (36)	0.60	172 (29)	365 (32)	0.28	137 (49)	47 (27)	0.185
Left bundle branch block, *n (%)*	985 (26)	382 (27)	73 (26)	0.90	161 (27)	322 (28)	0.133	113 (28)	48 (28)	0.43
Median heart rate (IQR), *beats/min*	73 (64–84)	72 (63–82)	73 (65–84)	0.26	73 (64–84)	72 (63–82)	0.149	71 (64–83)	71 (64–84)	0.82
Median blood pressure (IQR), *mm Hg*										
Systolic	128 (115–140)	128 (115–140)	130 (120–146)	0.008	127 (114–140)	130 (119–142)	<0.001	128 (115–147)	130 (110–146)	0.90
Diastolic	80 (70–86)	80 (70–85)	80 (73–88)	0.008	80 (70–86)	80 (70–89)	0.101	80 (70–85)	80 (70–85)	0.96
NYHA class, *n (%)*				0.090			0.001			0.69
I	757 (20)	245 (17)	57 (20)	–	136 (23)	200 (18)	–	66 (16)	34 (19)	–
II	1924 (52)	792 (55)	165 (59)	–	300 (50)	652 (57)	–	219 (54)	93 (54)	–
III	1002 (27)	382 (27)	55 (20)	–	150 (25)	278 (24)	–	115 (28)	43 (25)	–
IV	54 (1)	15 (1)	3 (1)	–	13 (2)	8 (1)	–	9 (2)	3 (2)	–
Median eGFR (IQR), $mL/min/1.73\ m^2$	72 (52–97)	73 (53–99)	74 (51–100)	0.92	79 (59–105)	74 (53–100)	0.007	70 (50–91)	68 (53–94)	0.68
Median NT-proBNP (IQR), *ng/L*	1457 (516–3385)	1520 (618–3493)	1290 (589–3000)	0.150	1558 (709–3271)	1350 (516–3025)	0.008	1453 (594–3519)	1660 (502–3489)	0.95
LVEF, *n (%)*				0.103			0.84			0.45
<30%	1252 (34)	492 (34)	79 (28)	–	217 (36)	399 (35)	–	136 (33)	64 (37)	–
30% to 39%	1238 (33)	525 (37)	106 (38)	–	217 (36)	412 (36)	–	152 (37)	55 (32)	–
≥40%	1247 (33)	417 (29)	95 (34)	–	165 (28)	327 (29)	–	121 (30)	54 (31)	–
Dosage achieved, *n (%)*†										
At baseline				0.50			<0.001			0.16
<25%	–	410 (29)	73 (26)	–	158 (26)	376 (33)	–	187 (46)	84 (49)	–
≥25% to <50%	–	363 (25)	85 (30)	–	136 (23)	281 (25)	–	60 (15)	32 (18)	–
≥50% to <75%	–	422 (29)	79 (28)	–	151 (25)	283 (25)	–	83 (20)	38 (22)	–
≥75% to <100%	–	86 (6)	14 (5)	–	41 (7)	84 (7)	–	22 (5)	6 (3)	–
≥100%	–	153 (11)	29 (11)	–	113 (19)	114 (10)	–	57 (14)	13 (8)	–
At 1-y follow-up				0.003			<0.001			0.017
<25%	–	100 (7)	23 (8)	–	20 (3)	161 (14)	–	32 (8)	15 (9)	–
≥25% to <50%	–	316 (22)	83 (30)	–	84 (14)	202 (18)	–	71 (17)	41 (24)	–
≥50% to <75%	–	450 (31)	94 (34)	–	142 (24)	375 (33)	–	113 (28)	60 (34)	–
≥75% to <100%	–	122 (9)	23 (8)	–	40 (7)	169 (15)	–	26 (6)	12 (7)	–
≥100%	–	446 (31)	57 (20)	–	313 (52)	231 (20)	–	167 (41)	45 (26)	–

BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; LVEF = left ventricular ejection fraction; NT-proBNP = *N*-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; T2DM = type 2 diabetes mellitus.
* Continuous data are presented as median and IQR and were compared by using the Kruskal–Wallis test. Discrete data are presented as count and percentage and were analyzed by using a χ^2 test.
† Calculated as percentage of the maximum recommended dosage.

Figure. Categorical distribution of achieved recommended dosages for heart failure therapy after 1-year uptitration visits.



Dosage achieved is calculated as the percentage of the maximum recommended dose (<25%, ≥25% to <50%, ≥50% to <75%, ≥75% to <100%, and ≥100%). Distribution among categories of response differs significantly for all medication groups—patients who received the drug with a higher numerical dosage were less likely to reach the recommended dosage. Overall *P* values were *P* = 0.003 for β-blockers, *P* < 0.001 for angiotensin-converting enzyme inhibitors, and *P* = 0.017 for angiotensin-receptor blockers.
* *P* < 0.001.

between January 2006 and December 2011 and had at least 1 year of follow-up. The drugs with the greatest difference in recommended dosage in each class were bisoprolol or nebivolol, 10 mg/d, versus metoprolol, 200 mg/d, for β-blockers; ramipril, 10 mg/d, versus lisinopril, enalapril, or fosinopril, 40 mg/d, for angiotensin-converting enzyme inhibitors; and candesartan, 32 mg/d, versus valsartan, 320 mg/d, for angiotensin-receptor blockers. For each drug and each patient who received the drug, we calculated the highest achieved dosage as a percentage of the recommended dosage. Uptitration occurred if the baseline dosage was less than 100% of the recommended dosage and the percentage of the patient's recommended dosage at follow-up minus the percentage of recommended dosage at baseline was greater than 0. We used the Wilcoxon signed-rank test to determine the significance of changes in uptitration within each drug class, and we used the χ^2 test to compare distributions of uptitration for each medication pair within the 3 classes. We used logistic regression to determine whether the size of the recommended dosage was related to whether the recommended dosage was achieved (yes or no) after adjustment for blood pressure, heart rate, kidney function, and treating center. We performed analyses using SPSS 24.0 (IBM) and Stata 11 (StataCorp). We considered differences to be statistically significant when 2-sided *P* values were less than 0.050.

Most, but not all, patient characteristics were reasonably balanced at baseline (**Table**). Prescribed dosages increased in all 3 drug classes after 1 year (*P* < 0.001). For all 3 classes, significantly fewer patients received the maximum recommended dosage when it was higher than when it was lower (**Figure**). We confirmed these observations by comparing the probabilities of reaching the maximum dosages that were predicted by the logistic regression model. For β-blockers, the difference in predicted probabilities was 10 (95% CI, 7 to 13 [with values of 0.33 for bisoprolol and nebivolol and 0.23 for metoprolol]). For angiotensin-converting enzyme inhibitors, the difference was 34 (CI, 33 to 36 [with values of 0.56 for ramipril and 0.22 for lisinopril, enalapril, and fosinopril]). For angiotensin-receptor blockers, the difference was 13 (CI, 11 to 15 [with values of 0.41 for candesartan and 0.27 for valsartan]). The results remained virtually unchanged when we examined the subgroup of patients with ischemic heart failure (data not shown).

Discussion: We have shown that for a large number of representative patients with chronic systolic heart failure, the uptitration of drugs stopped when the dosage was further away from the recommended dosage for drugs with higher versus those with lower recommended dosages. Readers should keep in mind that this observational study could establish associations but not causality. In addition, our findings may not generalize to other countries or to other populations.

We believe that the differences we observed are large enough to affect patient outcomes. If additional studies confirm our expectations, we propose that supplementing milligram-based recommendations with guidelines based on relative dosages might attenuate the differences we observed.

We have been unable to identify other studies that have reported this effect, and we propose that the effect be called a "cognitive illusion based on the maximum target dosage."

Henrike Arfsten, MD
Georg Goliasch, MD, PhD
Noemi Pavo, MD, PhD
Medical University of Vienna
Vienna, Austria

Hanno Ulmer, PhD
Medical University of Innsbruck
Innsbruck, Austria

Martin Hülsmann, MD
Medical University of Vienna
Vienna, Austria

Thomas Stefenelli, MD
Donauspital
Vienna, Austria

*on behalf of the Austrian Working Group of Heart Failure**

* Members of the Austrian Working Group of Heart Failure who contributed to this article but did not author it are listed in the **Appendix** (available at Annals.org).

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-0476.

Reproducible Research Statement: *Study protocol, statistical code and data set:* Not available.

This article was published at Annals.org on 1 October 2019.

doi:10.7326/M19-0476

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Appendix: Nonauthor Members of the Austrian Working Group of Heart Failure

The following members of the Austrian Working Group of Heart Failure contributed to this work but did not author it: Guido Strunk, PhD (FH Campus Vienna and Complexity Research, Vienna, Austria); Gerhard Poelzl, MD (Medical University of Innsbruck, Innsbruck, Austria); Christian Ebner, MD (Elisabethinen Hospital Linz, Linz, Austria); Friedrich Fruhwald, MD (Medical University of Graz, Graz, Austria); Claudia Dornaus, MD (Hanusch Hospital, Vienna, Austria); Georg Grimm, MD (Main Hospital Klagenfurt [LKH], Klagenfurt, Austria; Hans Altenberger, MD (Paracelsus Medical University, Salzburg, Austria); Gabriele Jakl, MD (Wilhelminenspital, Vienna, Austria); Johann Auer, MD (Hospital Braunau, Braunau am Inn, Austria); Andreas Winter, MD (Hospital Barmherzigen Schwestern, Linz, Austria); Doris Keroe, MD (private practice, St. Johann, Austria); Hubert Groebner, MD (Hospital St. Johann, St. Joann in Tirol, Austria); and Lalit Kaltenbach (Medical University of Innsbruck, Innsbruck, Austria).