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Heart failure treatment in patients with and without obesity with an ejection fraction below 50%

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Abstract

Background: The aim of this study was to assess heart failure (HF) treatment in patients with and without obesity in a large contemporary real-world Western European cohort.

Methods: Patients with a left ventricular ejection fraction (LVEF) <50% and available information on body mass index (BMI) were selected from the CHECK-HF registry. The CHECK-HF registry included chronic HF patients in the period between 2013 and 2016 in 34 Dutch outpatient clinics. Patients were divided into BMI categories. Differences in HF medical treatment were analysed, and multivariable logistic regression analysis (dichotomized as BMI <30 kg/m^2 and ≥30 kg/m^2) was performed.

Results: Seven thousand six hundred seventy-one patients were included, 1284 (16.7%) had a BMI ≥30 kg/m^2, and 618 (8.1%) had a BMI ≥35 kg/m^2. Median BMI was 26.4 kg/m^2. Patients with obesity were younger and had a higher rate of comorbidities such as diabetes mellitus, hypertension and obstructive sleep apnoea (OSAS). Prescription rates of guideline-directed medical therapy (GDMT) increased significantly with BMI. The differences were most pronounced for mineralocorticoid receptor antagonists (MRAs) and diuretics. Patients with obesity

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more often received the guideline-recommended target dose. In multivariable logistic regression, obesity was significantly associated with a higher likelihood of receiving ≥100% of the guideline-recommended target dose of beta-blockers (OR 1.34, 95% CI 1.10–1.62), renin–angiotensin system (RAS)-inhibitors (OR 1.34, 95% CI 1.15–1.57) and MRAs (OR 1.40, 95% CI 1.04–1.87).

Conclusions: Guideline-recommended HF drugs are more frequently prescribed and at a higher dose in patients with obesity as compared to HF patients without obesity.

KEYWORDS

guideline adherence, heart failure, obesity, pharmacotherapy

1 | INTRODUCTION

The rising number of people with obesity worldwide is considered to be an important contributor to the increasing incidence of heart failure (HF).[1,2] Individuals with obesity have a double lifetime risk of heart failure, and the risk increases with every unit increase in body mass index (BMI).[3] Furthermore, obesity is associated with comorbidities such as hypertension, atrial fibrillation and diabetes mellitus.[4] As a result, individuals with obesity are rarely naïve to cardioprotective medication at the time of HF diagnosis, which may lead to differences in HF drug treatment and dosage in patients with and without obesity. The difference in HF treatment in patients with obesity has been postulated as a reason for the obesity paradox, the phenomenon that refers to lower mortality in HF patients with mild overweight and obesity compared with their leaner counterparts.[5–7]

Unfortunately, there is a considerable gap of knowledge with regard to HF treatment in patients with obesity and a left ventricular ejection fraction (LVEF) <50%. As obesity and HF often co-exist, a better understanding of HF drug treatment, including doses, in obesity is important to further improve the pharmacological HF management of this high-risk population. Therefore, the aim of this study was to investigate whether differences in HF treatment exist between patients with and without obesity with an LVEF <50% in a large real-world Western European setting.

2 | METHODS

For this study, data was used from the CHECK-HF (Chronisch Hartfalen ESC—richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry. The design and methods of the CHECK-HF registry have been published in detail before.[8] Briefly, a total of 10,910 patients with chronic HF from 34 participating Dutch centres between 2013 and 2016 were included in this cross-sectional observational cohort. All included patients were diagnosed with HF according to the 2012 European Society of Cardiology (ESC) HF guidelines, and almost all were seen at a dedicated outpatient HF clinic (96%).[9] Detailed information on patient characteristics, comorbidities and guideline-recommended HF drug prescriptions and dosages was recorded. An overview of guideline-recommended prescription rates and dosages is provided in Table S1. Comorbidities were noted as recorded in medical history diabetes mellitus, hypertension, hypercholesterolaemia, renal insufficiency (estimated glomerular filtration rate <60 mL/min/1.73 m^2), anaemia (haemoglobin below age-dependent threshold), chronic obstructive pulmonary disease (COPD) or obstructive sleep apnoea (OSAS).[8] The study was conducted according to the Declaration of Helsinki. Ethical approval was provided for anonymously analysing existing patient data by the Ethical Committee of the Maastricht University Medical Centre, the Netherlands, approval number MUMC-METC-18-4-282.

In the CHECK-HF registry, patients were classified based on LVEF or visual assessment of the left ventricle (LV) into HF with an LVEF <50% (n = 8360) or HF with an LVEF ≥50% (n = 2267) and were treated according to the 2012 ESC HF guidelines.[9] For the current analysis, patients with an LVEF ≥50% were excluded as the focus of this study was on guideline-recommended therapy in patients with systolic dysfunction. Furthermore, in 283 patients, the recording of LV function was insufficient to classify these patients into HF type and they were excluded from this analysis as well. Additionally, patients with missing data on BMI (N = 689) were excluded, leaving a total of 7671 patients to be included in this analysis. For a subanalysis according to the later 2016 ESC HF

guidelines, patients with an LVEF <50% were categorized into HF with reduced ejection fraction (HFrEF, LVEF <40%, $n = 5276$) and HF with mid-range ejection fraction (HFmrEF, LVEF 40%–49%, $n = 1462$). Patients without an exactly specified ejection fraction, but in whom reduced LV function was visually assessed, were presented separately as a semiquantitative group ($n = 933$).

For the current analysis, patients were divided into five BMI (body mass index) categories according to the World Health Organization classification: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.99 kg/m^2), overweight (BMI 25–29.99 kg/m^2), obesity class I (BMI 30–34.99 kg/m^2) and obesity class II (BMI 35–39.99 kg/m^2).[10] Prescription rates and prescribed doses of guideline-recommended HF therapy were compared between the BMI groups. Reporting of the study conforms to broad EQUATOR guidelines.[11]

2.1 | Statistical analysis

Continuous data are expressed as mean or median with standard deviation or interquartile range, depending on the distribution of the data. Comparisons were performed using the Student's *t*-test or Kruskal–Wallis test. Categorical data are expressed as counts and percentages and were compared with the Pearson's chi-squared test or the Fisher's exact test as appropriate. A two-sided *p*-value ≤0.05 was considered statistically significant. In order to investigate whether treatment differences between patients with and without obesity were independent of potential confounders, we dichotomized patients into those with a BMI <30 kg/m^2 and BMI ≥30 kg/m^2, and univariable and multivariable logistic regression analyses were used. The results of these regression analyses are expressed as odds ratios (OR) with corresponding 95% confidence intervals (CIs). In the multivariable model, we adjusted for age, gender, New York Heart Association (NYHA) classification, OSAS, atrial fibrillation, diabetes mellitus, renal insufficiency (defined as estimated glomerular filtration rate < 60ml/min/1.73m^2 or a history of renal insufficiency), COPD and QRS duration, as we hypothesized that these variables and comorbidities would be clinically relevant for the association between obesity and treatment, which was also based upon early research.[12–18] Analyses were performed using SPSS Statistical Package version 25.0.

3 | RESULTS

Of the 7671 patients included, 1284 (16.7%) had a BMI ≥30 kg/m^2, and 618 (8.1%) had a BMI ≥35 kg/m^2. The baseline characteristics of the study population overall and in the five groups based on BMI are shown in Table 1. Median age of the study population was 74 years, 35.9% were female, and median LVEF was 30%. Median BMI was 26.4 kg/m^2 and most patients were in NYHA class II (57.5%). Hypertension was diagnosed in 40.3% of the patients and as many as 28.8% of patients suffered from diabetes mellitus. Almost half of the patients had renal insufficiency (47.5%).

Several baseline characteristics differed significantly between the BMI groups. Patients in obesity class I and II were younger and more often severely symptomatic (NYHA class III) compared with patients in lower BMI groups. As for comorbidities, patients in obesity class I and II had higher rates of hypertension, diabetes mellitus and OSAS. Patients in the underweight group were most often female, had lower diastolic and systolic blood pressure and were most often in NYHA class I-II.

3.1 | Pharmacological treatment

The pharmacological HF treatment of patients according to the BMI groups is shown in Figure 1. In short, patients in obesity class I and II significantly more often received renin–angiotensin system (RAS)-inhibitors, mineralocorticoid receptor antagonists (MRAs) and diuretics. Overall, the proportion of patients who were prescribed guideline-recommended drugs appeared to increase with BMI with the exception of beta-blockers. In multivariable logistic regression, obesity (BMI ≥30 kg/m^2) was associated with higher prescription rates of RAS-inhibitors (OR 1.31, 95% CI 1.08–1.59), MRAs (OR 1.16, 95% CI 1.00–1.33), diuretics (OR 1.70, 95% CI 1.36–2.12) and beta-blockers (OR 1.20, 95% CI 1.00–1.44).

Patients with obesity class I and II significantly more frequently received triple therapy (Figure 2). Furthermore, the proportion of patients who received ≥100% of the guideline-recommended target dose for beta-blockers, RAS-inhibitors and MRAs was significantly higher in patients with a BMI ≥35 kg/m^2. In general, patients with a BMI ≥30 kg/m^2 more often received the guideline-recommended target dose compared to those without obesity (Figure 3). Interestingly, patients in the normal BMI group (18.5 kg/m^2 ≤BMI <25 kg/m^2) less frequently received the guideline-recommended dose than the average patient. In multivariable logistic regression, obesity (BMI ≥30 kg/m^2) was significantly associated with a higher likelihood of receiving ≥100% of the guideline-recommended target dose of beta-blockers (OR 1.34, 95% CI 1.10–1.62), RAS-inhibitors (OR 1.34, 95% CI 1.15–1.57) and MRAs (OR 1.40, 95% CI 1.04–1.87) (Table 2).

TABLE 1 Baseline characteristics of the study population.

	Total population (*n* = 7671)	BMI <18.5 (*n* = 123)	BMI ≥18.5 & <25 (*n* = 2668)	BMI ≥25 & <30 (*n* = 2978)	BMI ≥30 & < 35 (*n* = 1284)	BMI ≥35 (*n* = 618)	*p*-Value*
Age, years (*n* = *7664*)	74 (16)	76 (20)	77 (14)	74 (15)	72 (15)	67 (18)	<0.001
Female (*n* = *7638*)	2745 (35.9)	77 (62.6)	1029 (38.8)	909 (30.7)	454 (35.5)	340 (44.8)	<0.001
Weight, kg (*n* = *7671*)	80 (21)	49 (6)	68 (15)	81 (13)	94 (14)	112 (24)	<0.001
Height, cm (*n* = *7671*)	172 (13)	167 (10)	173 (14)	173 (12)	171 (13)	171 (16)	<0.001
BMI, kg/m^2 (*n* = *7671*)	26.4 (6.4)	17.4 (1.4)	22.9 (2.5)	27.1 (2.7)	31.8 (2.2)	37.4 (4.1)	<0.001
Systolic BP, mmHg (*n* = *7631*)	120 (23)	115 (28)	120 (20)	120 (23)	125 (27)	125 (28)	<0.001
Diastolic BP, mmHg (*n* = *7636*)	70 (18)	65 (15)	70 (15)	70 (20)	72 (15)	67 (18)	<0.001
LVEF, % (*n* = 5693)	30 (15)	30 (18)	30 (15)	30 (15)	30 (14)	33 (15)	0.021
Heart rate, bpm (*n* = 7590)	69 (16)	79 (17)	70 (17)	68 (17)	70 (14)	70 (17)	<0.001
QRS ≥130 ms (*n* = *6505*)	2598 (39.9)	31 (30.1)	926 (40.6)	1005 (39.9)	446 (41.1)	190 (36.7)	0.11
eGFR (*n* = *5472*)	57 (34)	51 (39)	54 (33)	58 (33)	58 (33)	60 (38)	0.007
NT-proBNP, pg/ml (*n* = *2793*)	908 (2375)	1059 (10061)	1375 (3419)	747 (1860)	576 (1511)	694 (1796)	<0.001
NYHA class (*n* = *7604*)							
I	1194 (15.7)	21 (17.2)	435 (16.5)	496 (16.8)	184 (14.4)	158 (9.5)	<0.001
II	4376 (57.5)	67 (54.9)	1507 (57.2)	1759 (59.4)	695 (54.5)	348 (56.9)	
III	1900 (25.0)	30 (24.6)	646 (24.5)	648 (21.9)	381 (29.9)	195 (31.9)	
IV	134 (1.7)	4 (3.3)	46 (1.7)	58 (2.0)	15 (1.2)	11 (1.8)	
Cause of HF (*n* = *7449*)							
Ischaemic	3842 (51.6)	52 (43.3)	1305 (50.3)	1575 (54.6)	651 (51.8)	259 (43.5)	<0.001
Nonischaemic	3607 (48.4)	68 (56.7)	1290 (49.7)	1307 (45.4)	606 (48.2)	336 (56.5)	
Comorbidities							
Hypertension (*n* = *6980*)	2814 (40.3)	32 (28.6)	882 (36.5)	1071 (39.7)	552 (46.5)	277 (48.7)	<0.001
Diabetes mellitus (*n* = *6980*)	2009 (28.8)	19 (17)	459 (19)	761 (28.2)	497 (41.9)	273 (48.0)	<0.001
OSAS (*n* = *6980*)	460 (6.6)	1 (0.9)	57 (2.4)	152 (5.6)	139 (11.7)	111 (19.5)	<0.001
COPD (*n* = *6980*)	1289 (18.5)	35 (31.3)	459 (19.0)	463 (17.2)	234 (19.7)	98 (17.2)	0.002
Hypercholesterolemia (*n* = *6980*)	937 (13.4)	10 (8.9)	309 (12.8)	363 (13.5)	167 (14.1)	88 (15.5)	0.26
Atrial fibrillation (*n* = *7599*)	1918 (25.2)	31 (25.6)	696 (26.3)	722 (24.5)	316 (24.9)	458 (25.0)	0.66
Anaemia (*n* = *6980*)	374 (4.9)	5 (4.5)	150 (6.2)	141 (5.2)	49 (4.1)	29 (5.1)	0.12
Kidney insufficiency, (*n* = *6459*)	3645 (47.5)	44 (45.8)	1285 (58.0)	1414 (56.1)	621 (56.7)	250 (52.9)	0.05

Abbreviations: BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSAS, obstructive sleep apnoea syndrome.

*Continuous data were non-normally distributed and were therefore presented as median with interquartile range and compared between the BMI groups with the Kruskal–Wallis test. Categorical data were compared with the Pearson's chi-squared test or the Fisher's exact test as appropriate.

3.2 | Medical therapy in patients with HFrEF and HFmrEF according to the 2016 European Society of Cardiology HF guidelines

Prescription rates of GDMT according to BMI group in patients with HFrEF, HFmrEF and those with a semiquantitative recording of LV function are shown in Figure S1. In the HFrEF group, inferences were similar to the main analysis. In the HFmrEF group, patients with a BMI <18.5 kg/m^2 had higher and patients with BMI ≥18.5 kg/m^2 had lower prescription rates of RAS-inhibitors and MRAs as compared to the main analysis, and differences between BMI groups were therefore less pronounced. In the semiquantitative group, patients with a BMI <18.5 kg/m^2 had strikingly low rates of RAS-inhibitor and MRA use, and differences between groups in beta-blocker and diuretic use were less pronounced and nonsignificant.

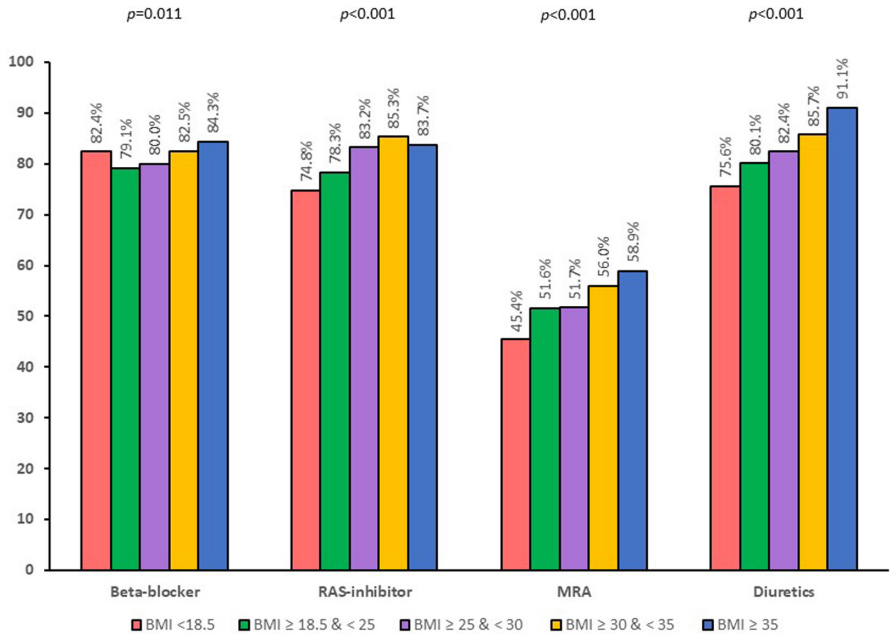

FIGURE 1 Prescription rates of guideline-recommended heart failure drugs according to the BMI group. BMI—body mass index; RAS-inhibitor—renin–angiotensin system; MRA—mineralocorticoid receptor antagonist. Prescription rates were compared with the Pearson's chi-squared test or the Fisher's exact test as appropriate.

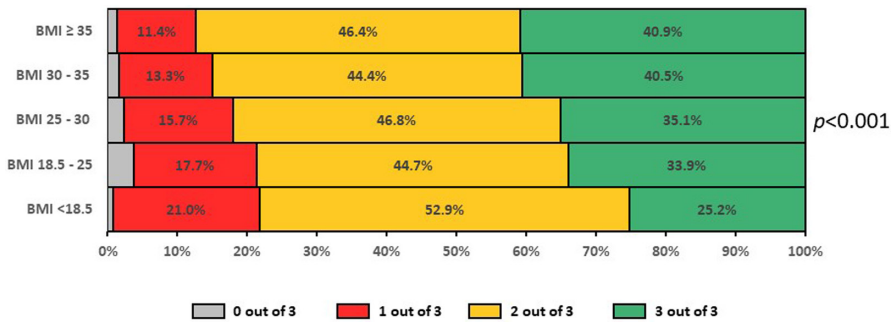

FIGURE 2 Proportion of patients receiving triple therapy across different BMI groups. BMI—body mass index. Prescription rates were compared with the Pearson's chi-squared test or the Fisher's exact test as appropriate.

4 | DISCUSSION

In this large registry of chronic HF patients, guideline-recommended HF drugs were more frequently prescribed in patients with obesity class I and class II as compared to patients without obesity, and patients with obesity more often received triple therapy. Additionally, patients with obesity more often received the guideline-recommended dose of HF drugs. Overall, HF patients with obesity had a higher level of GDMT than HF patients without obesity.

The global prevalence of obesity and HF is increasing which places a large burden on healthcare resources.[19,20] In our cohort, obesity was present in 16.7% of the HFrEF population, highlighting the fact that obesity constitutes an important proportion of the HFrEF population. For this reason, it is important to study the treatment of patients with obesity and HF. Only a few studies have reported prescription rates of HF drugs specifically in patients with obesity, but this was not the primary aim of these studies. In a recent analysis from Marcks et. al in which the investigators aimed to address the obesity paradox in HF, prescription rates of BB and RAS-inhibitors appeared to increase with BMI, but this was not the case for MRAs. Interestingly, the prescription rates were different from our study.[21] Beta-blockers and MRAs were prescribed in 46.5% and 16.4% of the total study population, which is markedly lower than in our study. Prescription rates of ACE-inhibitors/ARB, on the contrary, were comparable to our study. Several characteristics of the study by Marcks et al. need to be discussed in this context. First, the included studies in their meta-analysis were randomized clinical trials and were therefore comprised of selected populations, whereas our study is a reflection of real-world practice. Furthermore, not all studies reported on drug use, and this may have resulted in lower prescription rates. Lastly, there were some differences with regard to patient characteristics: Patients in our study were on average older (74 vs. 64.9 years) and suffered from atrial fibrillation more often (25.2% vs. 15.4%), whereas patients in the study by Marcks et al. were more often in NYHA class III/IV (39.2% vs. 26.7%, respectively). Limited data exist on the prescription of target doses

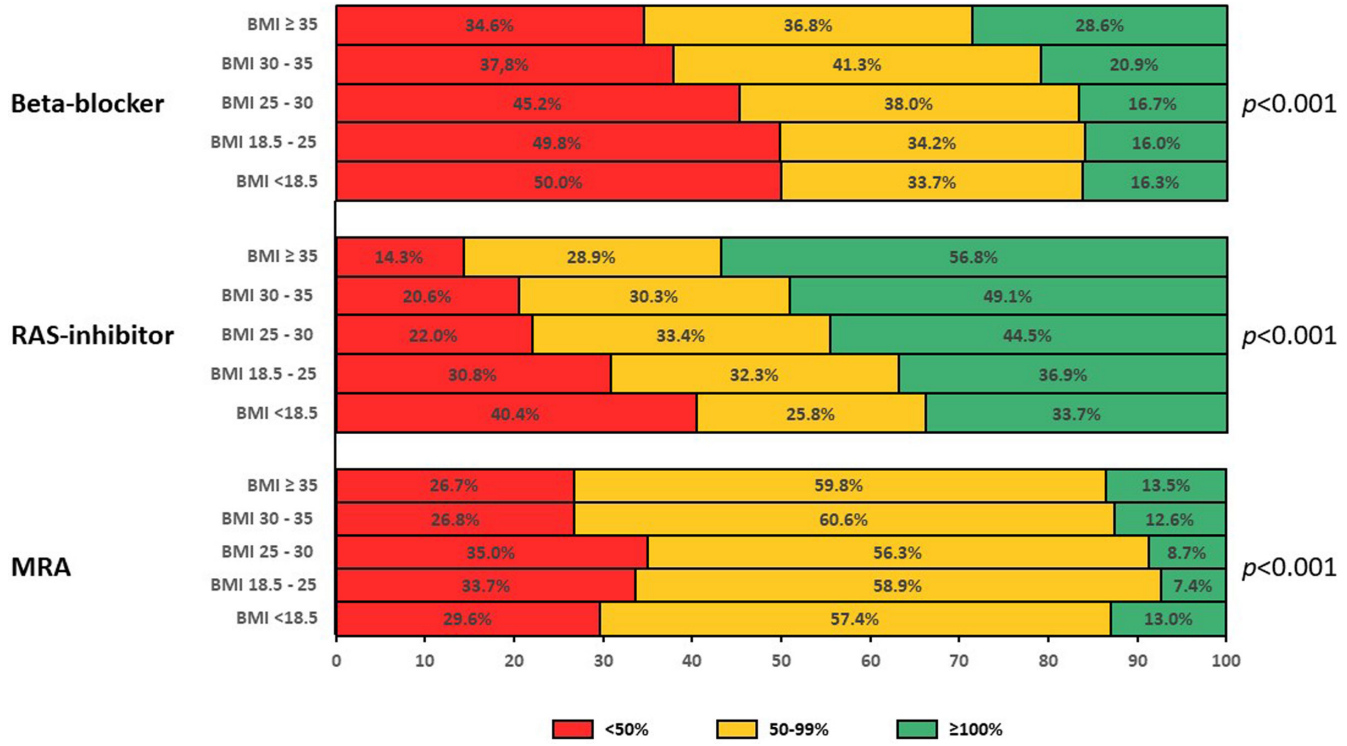

FIGURE 3 Percentage of the guideline-recommended target dose prescribed according to the BMI group. BMI—body mass index; RAS-inhibitor—renin–angiotensin system; MRA—mineralocorticoid receptor antagonist. Prescription rates were compared with the Pearson's chi-squared test or the Fisher's exact test as appropriate.

TABLE 2 Multivariable analysis: the likelihood (displayed as odds ratio) of receiving guideline-recommended therapy for patients with obesity compared to patients without obesity.

	Univariable model		Multivariable model	
Prescription of drug	**OR**	***p*-Value**	**OR**	***p*-Value**
Beta-blocker	1.26	0.001	1.20	0.05
RAS-inhibitor	1.33	<0.001	1.31	0.006
MRA	1.24	<0.001	1.16	0.047
Diuretics	1.61	<0.001	1.70	<0.001
Prescription of guideline-recommended target dose	OR	p-value	OR	*p*-Value
Beta-blocker	1.57	<0.001	1.34	0.003
RAS-inhibitor	1.53	<0.001	1.34	<0.001
MRA	1.65	<0.001	1.40	0.026

Note: The multivariable model included: age, gender, NYHA classification, hypertension, diabetes mellitus, obstructive sleep apnoea syndrome, atrial fibrillation, renal insufficiency (defined as estimated glomerular filtration rate <60/ml/min/1.73 m^2 or a history of renal insufficiency), chronic obstructive pulmonary disease and QRS duration.

Abbreviations: MRA, mineralocorticoid receptor antagonist; OR, odds ratio; RAS, renin–angiotensin system.

in patients with obesity. In the U.S. CHAMP-HF registry, patients who were prescribed target doses of ACE-inhibitor/ARB/ARNI, BB and MRA were more likely to have a BMI ≥30 kg/m^2.[22] In addition, HF patients with obesity were more likely to receive the target dose of beta-blocker in multivariable regression analysis, and obesity was associated with a higher likelihood of receiving treatment with MRA.[23] These findings are in line with our results, but the main strength of our study is that our analysis specifically focussed on treatment differences between BMI groups in a real-world chronic HF population, both with regard to prescription rates and daily dose. We found that patients with obesity significantly more often received ≥100% of the guideline-recommended dose of beta-blockers, RAS-inhibitors and MRAs. In our subanalysis, where HFrEF was defined according to the 2016 ESC guidelines,[24] the inferences of prescription rates were similar to the main analysis; further strengthening our finding that HFrEF patients with obesity more often receive GDMT. Our findings are important, as target doses of ACE-inhibitors, ARBs and beta-blockers have been associated with a significant reduction in all-cause mortality.[22] In addition, we demonstrated that BMI ≥30 kg/m^2 was associated with a higher likelihood to receive target doses, even after adjusting for potential confounders. This is important as accompanying comorbidities such as hypertension and diabetes were more prevalent among those with obesity. The multivariable regression analyses suggest that obesity is independently associated with the prescription of guideline-recommended doses.

Many factors may play a role in the prescription of higher doses of HF drugs in patients with obesity. Due to their higher body weight, patients with obesity often develop hypertension and symptoms such as dyspnoea and oedema at a younger age and are therefore rarely naïve to HF treatment. In our cohort, 16.7% of the patients were in the obesity group, they were on average younger, more often in NYHA class III and more often suffered from comorbidities such as hypertension, diabetes and OSAS. The higher doses of GDMT in patients with obesity may partially be attributed to a higher prevalence of hypertension and the higher average blood pressure. Low blood pressure and orthostatic hypotension are common reasons for suboptimal doses of RAS-inhibitors in clinical practice, especially in older patients.[12,16] Obesity can lead to drug-resistant hypertension and can cause alterations in the RAAS system, which may explain why HF patients with obesity require higher doses of antihypertensive drugs.[25] The higher proportion of patients in NYHA class III-IV among those with obesity may partially explain the higher prescription rates of diuretics.

Our findings are important as they indicate that patients with HF and obesity are better treated in comparison to those without obesity, but that there is still ample room for improvement in medical therapy, also in HF patients without obesity. Data on the role of lifestyle interventions in established HF are scarce.[26] A few studies have shown that bariatric surgery leads to an improvement in LVEF in patients with HF.[27] A recent meta-analysis demonstrated that intentional weight loss leads to favourable cardiac remodelling in patients with obesity, but it remains unclear whether intentional weight loss results in improved clinical outcomes in HF patients with obesity.[28] Drug optimization according to guideline recommendations is therefore as important in HF patients with obesity as in HF patients without obesity.

Numerous studies have demonstrated that obesity is associated with a reduced mortality risk in established HF, a phenomenon known as the obesity paradox.[7] Remarkably, the paradox mainly exists in patients who are mildly overweight or in class I obesity, whereas underweight patients have a worse prognosis.[7] Interestingly, the obesity paradox is less pronounced in severe obesity (BMI ≥35 kg/m^2).[28] There has been debate on whether this paradox is valid or mainly the result of methodological shortcomings.[29] Several mechanisms of action have been postulated to explain the obesity paradox in HF, such as greater metabolic reserve, attenuation of harmful inflammatory processes and the use of more cardioprotective medications at higher doses.[5,30] In the 2014 meta-analysis from the MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) investigators, mortality in HFrEF patients was U-shaped with a nadir at BMI levels 30.0–34.9 kg/m^2, confirming the obesity paradox.[29] Similar findings were found in a recent meta-analysis in which overweight and class I obesity were associated with lower all-cause mortality and underweight with higher mortality all-cause mortality.[28] However, the multivariable models in these studies were not adjusted for medication use, leaving it unclear whether potential differences in medical treatment may have mediated the observed mortality differences between those with and without obesity. Yet, a recent study by Gelini et al. included medication use in the multivariable model and confirmed the presence of the obesity paradox by demonstrating lower mortality in the overweight and class I obesity groups.[31]

In our cohort, we observed that the presence of obesity was associated with a higher likelihood to receive GDMT. As target doses of the guideline-recommended HF drugs have been proven superior to lower doses in terms of survival,[22,32] the obesity paradox may be explained at least in part by the treatment differences that we found to favour those with a BMI of 30.0–34.99 kg/m^2. However, it should be noted that guideline implementation was also better in the more severe obesity group, while the favourable outcomes in mortality are less pronounced in this BMI group. The titration process of HF drugs may also deviate from HF patients without obesity and may require a different approach due to differences in tolerability and side effects. Our results show that there is an important difference in HF treatment between patients with and without obesity. Given the expanding population incidence of obesity and HF, future studies that focus specifically on medication use and outcomes in patients with obesity are required to further optimize treatment in this high-risk population.

4.1 | Strengths and limitations

The CHECK-HF registry is a large-scale real-world registry consisting of chronic heart failure patients in a Western European setting with detailed information on patient characteristics and medication use. It is therefore well suited to study guideline implementation in patients with HF and obesity compared to those without obesity. Unfortunately, due to the cross-sectional design of the study, there are no data on longitudinal patient outcomes. Furthermore, data on sodium glucose transporter 2 (SGLT2) inhibitors and angiotensin-receptor neprilysin inhibitors[33] were unavailable, as they were not yet recommended by the guidelines at the time of this study. Finally, BMI does not take into account body composition, whereas relative fat mass and waist circumference are less influenced by muscle mass and may have a stronger association with outcomes. However, the WHO

still recommends the use of BMI to categorize the severity of obesity, and BMI is still frequently used in daily clinical practice.

5 | CONCLUSION

In this large real-world registry of chronic HF patients with an LVEF <50%, guideline-recommended drugs were more frequently prescribed and at a higher dose in patients with obesity as compared to HF patients without obesity. Better pharmacological treatment of patients with obesity may contribute to the obesity paradox. Additional research is required to further identify therapy trends in HF patients with obesity and to assess reasons for treatment differences between HF patients with and without obesity.

AUTHOR CONTRIBUTIONS

Y.A. and S.R. were involved in the data analysis and manuscript writing; they share the first authorship. S.R., G.C.M.L., P.C.R., P.R.G., M.W.F.G., I.A., L.O., H.P.B., B.M.D and J.J.B. were involved in the manuscript preparation and participated in the critical revision of all drafts of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data in this study were obtained from the CHECK-HF registry where restrictions may apply. Such a dataset may be requested from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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