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RESEARCH ARTICLE

Use of and association between heart failure pharmacological treatments and outcomes in obese versus non-obese patients with heart failure with reduced ejection fraction: data from the Swedish Heart Failure Registry

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Aims To investigate the use of guideline-directed medical therapies (GDMT) and associated outcomes in obese (body mass index ≥30 kg/m^2) versus non-obese patients with heart failure (HF) with reduced ejection fraction (HFrEF).

Methods and results Patients with HFrEF from the Swedish HF Registry were included. Of 16 116 patients, 24% were obese. In obese versus non-obese patients, use of treatments was 91% versus 86% for renin–angiotensin system inhibitors (RASi)/angiotensin receptor–neprilysin inhibitors (ARNi), 94% versus 91% for beta-blockers, 53% versus 43% for mineralocorticoid receptor antagonists. Obesity was shown to be independently associated with more likely use of each treatment, triple combination therapy, and the achievement of target dose by multivariable logistic regressions. Multivariable Cox regressions showed use of RASi/ARNi and beta-blockers being independently associated with lower risk of all-cause/cardiovascular death regardless of obesity, although, when considering competing risks, a lower risk of cardiovascular death with RASi/ARNi in obese versus non-obese patients was observed. RASi/ARNi were associated with lower risk of HF hospitalization in obese but not in non-obese patients, whereas beta-blockers were not associated with the risk of HF hospitalization regardless of obesity. At the competing risk analysis, RASi/ARNi use was associated with higher risk of HF hospitalization regardless of obesity.

Conclusion Obese patients were more likely to receive optimal treatments after adjustment for factors affecting tolerability, suggesting that perceived beyond actual tolerance issues limit GDMT implementation. RASi/ARNi and beta-blockers were associated with lower mortality regardless of obesity, with a greater association between RASi/ARNi and lower cardiovascular death in obese versus non-obese patients when considering competing risk.

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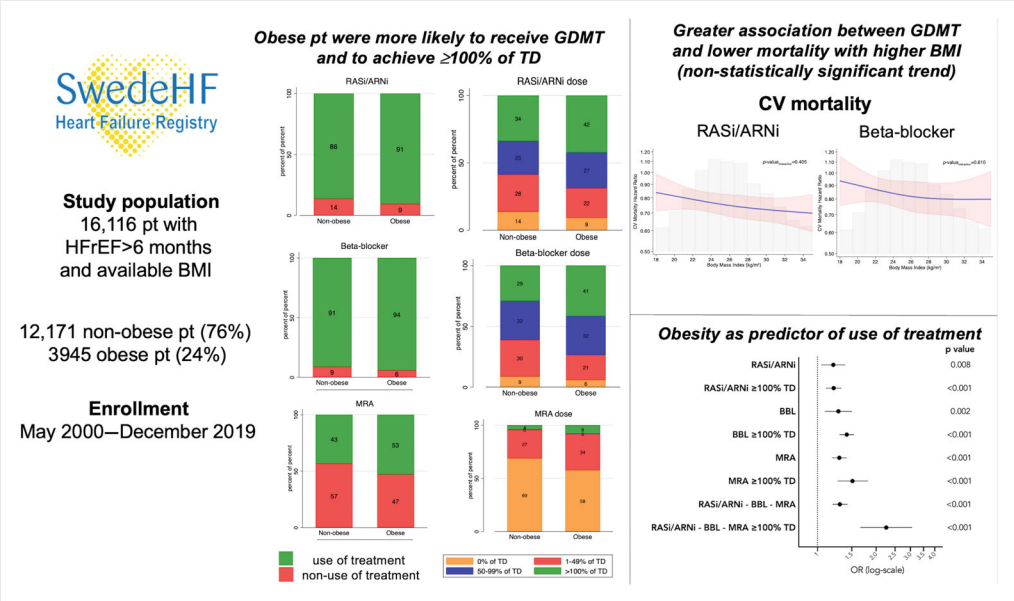
Graphical Abstract



In this analysis from the SwedeHF, obese patients with HFrEF are more likely treated with GDMT and obesity is independently associated with better treatments. ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CV, cardiovascular; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; TD, target dose.

Keywords Heart failure • Obesity • Body mass index • Treatments • Target dose • Swedish Heart Failure Registry

Introduction

Obesity and heart failure (HF) often coexist and have both reached pandemic dimensions over the last decades, representing a major and growing public health problem.[1] Despite the prevalence of obesity in HF with reduced ejection fraction (HFrEF) being estimated ~40%,[2] obese patients are underrepresented in landmark randomized controlled trials (RCT) in HFrEF, where body mass index (BMI) has been generally ~28 kg/m^2 [3,4] or not even reported.[5,6]

Obesity status has been rarely considered in subgroup analyses of HFrEF trials, and several aspects related to the pharmacological management of HFrEF according to BMI are currently unexplored. A better prognosis in obese patients with HFrEF might be explained by (i) the greater tolerance and therefore the achievement of use of a higher number and higher dosages of guideline-directed medical therapies (GDMT); (ii) a potential different association between GDMT use and outcomes in obese versus non-obese patients.[7]

Registry-based studies on large HF cohorts might contribute to fill the knowledge gaps and foster the optimization of GDMT use by targeting specific patients' profiles, and among these the obese/non-obese phenotype.[8] Therefore, in a large nationwide HF registry we aimed to assess (i) the associations between obesity and use of and dosing of GDMT; and (ii) the associations between GDMT use, dosing and outcomes, in patients with HFrEF with and without obesity.

Methods

Study protocol and setting

Data from the Swedish HF Registry (SwedeHF) linked with the National Patient Registry, the Cause of Death Registry and Statistics Sweden were analysed. Data sources are described in detail in online supplementary *Appendix S1*.

Study population and treatments

We included patients with HFrEF (left ventricular ejection fraction [LVEF] <40%) and HF duration >6 months registered in SwedeHF between 10 May 2000 and 31 December 2019. For the main analysis patients without missing data for BMI were considered. As a sensitivity analysis we imputed height which had higher proportion of missing value compared with weight, in order to minimize the amount of missing data for BMI.

Patients treated with renin–angiotensin system inhibitors (RASi), that is angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), or beta-blockers not recommended for

HFrEF according to the 2021 European Society of Cardiology (ESC) guidelines on HF, or those treated with a combination of ACEi and/or ARB and/or angiotensin receptor–neprilysin inhibitors (ARNi) (since these combinations are not recommended) were excluded (online supplementary *Table S1*).[9] For patients with more than one registration in SwedeHF, the last one was selected as more representative of contemporary care. We selected patients >6 months after the diagnosis of HF to allow time for treatment optimization. A flow chart illustrating cohort selection is reported in online supplementary *Figure S1*. We did not investigate the association between use/dose of mineralocorticoid receptor antagonists (MRA) and outcomes since the previous 2016 ESC guidelines on HF recommended their use in HFrEF patients who remain symptomatic despite the use of ACEi/ARB and beta-blocker,[10] which leads to selection bias toward a sicker cohort of patients receiving this treatment and confounding by indication in a registry-based setting.[11] We did not consider sodium–glucose cotransporter 2 inhibitors (SGLT2i) since they were introduced in clinical practice with a specific indication for HFrEF after the data collection. More information on the linkage between registries, initial selection criteria and the definition of variables used in this study are available at https://kiheartfailure.github.io/shfdb3/construction and in online supplementary *Table S2*.

Outcomes and definitions

The primary outcome was 5-year all-cause mortality. Secondary outcomes were 5-year cardiovascular death and 5-year first HF hospitalization, considered separately. Dosage achievement was reported as percentage of the target dose (TD), and categorized into three groups: <50%, 50–99% and ≥100% of TD. TD were defined according to the 2021 ESC guidelines on HF[9] and reported in online supplementary *Table S1*. We defined triple therapy as the simultaneous use of RASi/ARNi, beta-blocker and MRA. Obesity was defined according to the definition of the World Health Organization (www.who.int), that is a BMI ≥30 kg/m^2.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR) and compared in obese versus non-obese patients by the Mann–Whitney test. Categorical variables were reported as counts and proportions (%) and compared by χ^2 test. Multivariable logistic regression models were performed to investigate whether there was an independent association between obesity and the use/non-use and TD achievement of the individual HFrEF pharmacological treatments and use of triple therapy.

Survival functions were visualized by cumulative incidence curves. Multivariable Cox regression models were used to assess (i) the association between HFrEF treatment use/non-use and all-cause mortality, cardiovascular mortality and HF hospitalization; and (ii) the association between percentage of TD achievement and all-cause mortality, cardiovascular mortality and HF hospitalization. For the analysis on TD achievement, patients with missing data for RASi/ARNi and beta-blockers dosages were excluded. An additional outcome analysis was performed using the Fine and Gray competing risk model to estimate proportional sub-hazard ratios (HRs) assuming non-cardiovascular mortality as competing risk for cardiovascular mortality and all-cause mortality as competing risk for HF hospitalization.

Further sensitivity analyses were performed in two different datasets: (i) imputing height in order to reduce missing data for BMI; and (ii) excluding underweight patient (i.e. BMI <18.5 kg/m^2, according to the definition of the World Health Organization; www.who.int).

In order to investigate how the association between treatments and outcomes varied according to continuous BMI values, we performed multivariable Cox regression models including BMI modelled as restricted cubic splines with three knots in the main analysis as well as in the analysis with height imputed.

In all multivariable models, missing data were handled by chained equation multiple imputation (10 datasets generated). In online supplementary *Table S3*, the percentage of missing data for each variable is reported. Variables included in all the multivariable models and in the multiple imputation model – in the main as in the sensitivity analyses – are labelled with 'a' in *Table 1*. The same method was applied to impute height in the sensitivity analysis.

A two-sided p-value of <0.05 was considered statistically significant for all analyses. Statistical analyses were performed using Stata version 17 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics

Baseline characteristics of the overall study population and stratified by obesity are summarized in *Table 1*. Overall, 16 116 patients from SwedeHF met the selection criteria. Of them, 3945 (24%) patients were obese. Approximately 73% of the obese and non-obese populations were male. Compared with non-obese, obese patients were younger (71 [63–78] vs. 77 [69–83] years), more likely referred to nurse-led HF clinic (63% vs. 55%), had higher blood pressure (mean arterial pressure ≥90 mmHg in 50% vs. 42%) and more likely reported a diagnosis of hypertension (61% vs. 51%) and of diabetes mellitus (46% vs. 26%). Socioeconomics variables did not differ significantly between groups. The prevalence of coronary artery disease and atrial fibrillation/flutter was similar across the groups (65% vs. 67% and 59% vs. 61% in obese vs. non-obese patients, respectively). A normal kidney function, defined as an estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2, was observed more frequently in obese patients (52% vs. 47%) who were also less frequently diagnosed with anaemia (30% vs. 40%), stroke/transient ischaemic attack (16% vs. 20%) and cancer (9% vs. 14%) compared with non-obese patients. Obese patients were also more likely treated with statins (63% vs. 52%) and loop diuretics (86% vs. 82%).

Treatments (*Graphical Abstract*)

RASi/ARNi

In the overall population, 87% of patients received RASi/ARNi. Of them, 36% received ≥100% of TD. In obese versus non-obese patients, 91% versus 86% were treated with RASi/ARNi ($p < 0.001$), 42% versus 34% achieved ≥100% of TD ($p < 0.001$).

Data on sacubitril/valsartan were available since 2016 (33% of the overall population). In obese versus non-obese patients, 21% versus 16% were treated with ARNi ($p < 0.001$), and 46% versus 35% achieved ≥100% of TD ($p < 0.001$).

Beta-blocker

Ninety-two percent of the study cohort received a beta-blocker, 32% achieved ≥100% of TD; 94% versus 91% of patients with

Table 1 Baseline characteristics of the study population and the subgroups

	Overall population (n = 16 116)	Non-obese patients (n = 12 171)	Obese patients (n = 3945)	p-value
Demographics/organizational				
Male sex[a], *n* (%)	11 892 (74)	9010 (74)	2882 (73)	0.230
Age[a] (years), median (IQR)	76 (68–82)	77 (69–83)	71 (63–78)	<0.001
Caregiver at SwedeHF registration[a], *n* (%)				<0.001
Inpatient	6472 (40)	5121 (42)	1351 (34)	
Outpatient	9644 (60)	7050 (58)	2593 (66)	
Follow-up nurse-led HF clinic[a], *n* (%)	8773 (57)	6395 (55)	2378 (63)	<0.001
Follow-up referral speciality[a], *n* (%)				<0.001
Hospital	10 617 (68)	7855 (67)	2762 (72)	
Primary care	4417 (29)	3449 (30)	968 (25)	
Other	479 (3)	368 (3)	111 (3)	
Education[a], *n* (%)				<0.001
Compulsory school	7015 (44)	5326 (47)	1689 (44)	
Secondary school	6259 (40)	4607 (39)	1652 (43)	
University	2527 (16)	2004 (17)	523 (14)	
Living alone[a], *n* (%)	7516 (47)	5625 (46)	1891 (48)	0.065
Income[a], *n* (%)				0.006
Low	5576 (35)	4149 (34)	1427 (36)	
Medium	6225 (39)	4783 (39)	1442 (37)	
High	4290 (27)	3218 (27)	1072 (27)	
Year of registration[a], *n* (%)[b]				<0.001
<2009	3630 (22)	2912 (24)	718 (18)	
2010–2013	3819 (24)	2936 (24)	883 (22)	
2014–2016	2873 (18)	2137 (18)	736 (19)	
>2016	5794 (36)	4186 (34)	1608 (41)	
Clinical parameters				
Systolic BP (mmHg), median (IQR)	120 (109–134)	120 (107–132)	120 (110–135)	<0.001
Diastolic BP (mmHg), median (IQR)	70 (60–80)	70 (60–80)	70 (65–80)	<0.001
MAP[a], *n* (%)				<0.001
<90 mmHg	8992 (56)	7040 (58)	1952 (50)	
≥90 mmHg	6971 (44)	5020 (42)	1951 (50)	
Heart rate (bpm), median (IQR)	71 (63–80)	70 (62–80)	71 (64–81)	0.038
Heart rate[a], *n* (%)				
<70 bpm	6637 (43)	5049 (43)	1588 (41)	0.076
≥70 bpm	8989 (58)	6727 (57)	2262 (59)	
NYHA class[a], *n* (%)				0.080
I–II	6148 (48)	4680 (48)	1468 (47)	
III–IV	6672 (52)	4990 (52)	1682 (53)	
Laboratory values				
K^+[a], *n* (%)				0.097
<3.5 mmol/L	497 (4)	391 (4)	106 (3)	
3.5–5 mmol/L	12 107 (92)	9007 (91)	3100 (92)	
>5 mmol/L	623 (5)	467 (5)	156 (5)	
eGFR category[a,c], *n* (%)				<0.001
<30 ml/min/1.73 m^2	1558 (10)	1230 (10)	328 (9)	
30–59 ml/min/1.73 m^2	6545 (42)	5051 (43)	1494 (39)	
≥60 ml/min/1.73 m^2	7546 (48)	5547 (47)	1998 (52)	
NT-proBNP (pg/ml), median (IQR)	2965 (1167–7074)	3536 (1452–8303)	1672 (709–3870)	<0.001
NT-proBNP[a], *n* (%)				<0.001
<2965 pg/ml	4450 (50)	2935 (44)	1515 (67)	
≥2965 pg/ml	4449 (50)	3703 (56)	746 (33)	

Table 1 (Continued)

	Overall population (*n* = 16 116)	Non-obese patients (*n* = 12 171)	Obese patients (*n* = 3945)	*p*-value
Treatments, *n* (%)				
ACEi	8396 (52)	6439 (53)	1957 (50)	<0.001
ACEi drugs				0.320
Captopril	102 (1)	82 (1)	20 (1)	
Enalapril	3822 (46)	2893 (45)	929 (48)	
Lisinopril	88 (1)	67 (1)	21 (1)	
Ramipril	4381 (52)	3395 (53)	986 (50)	
Trandolapril	3 (<1)	2 (<1)	1 (<1)	
ARB	4775 (30)	3456 (28)	1319 (33)	<0.001
ARB drugs				<0.018
Candesartan	3014 (63)	2154 (62)	860 (65)	
Losartan	1585 (33)	1184 (34)	401 (30)	
Valsartan	176 (4)	118 (3)	58 (4)	
ARNi	906 (17)	603 (16)	303 (21)	<0.001
RASi/ARNi[a]	14 077 (87)	10 498 (86)	3578 (91)	<0.001
RASi/ARNi dosage[a] (% of TD)				<0.001
0%	2039 (13)	1673 (14)	366 (9)	
1–49%	4233 (26)	3368 (28)	865 (22)	
50–99%	4060 (25)	3014 (25)	1046 (27)	
≥100%	5784 (36)	4116 (34)	1668 (42)	
Beta-blocker[a]	14 815 (92)	11 103 (91)	3712 (94)	<0.001
Beta-blocker drugs				0.670
Bisoprolol	6555 (44)	4933 (44)	1622 (44)	
Carvedilol	876 (6)	649 (6)	227 (6)	
Metoprolol	7384 (50)	5521 (50)	1863 (50)	
Beta-blocker dosage[a] (% of TD)				<0.001
0%	1301 (8)	1068 (9)	233 (6)	
1–49%	4487 (28)	3670 (30)	817 (21)	
50–99%	5131 (32)	3873 (32)	1258 (32)	
≥100%	5197 (32)	3560 (29)	1637 (42)	
MRA[a]	7370 (46)	5286 (43)	2084 (53)	<0.001
Diuretic[a]	13 369 (83)	9986 (82)	3383 (86)	<0.001
Digoxin[a]	2472 (15)	1926 (16)	546 (14)	0.003
Antiplatelet[a]	6815 (42)	5212 (43)	1603 (41)	0.014
Anticoagulant[a]	8157 (51)	6052 (50)	2105 (53)	<0.001
Statin[a]	8818 (55)	6352 (52)	2466 (63)	<0.001
Device[a]				<0.001
No/PM	12 674 (80)	9693 (81)	2981 (77)	
CRT-P	781 (5)	615 (5)	166 (4)	
CRT-D	1297 (8)	914 (8)	383 (10)	
ICD	1177 (7)	817 (7)	360 (9)	
History and comorbidities, *n* (%)				
Hypertension[a]	8487 (54)	6116 (51)	2371 (61)	<0.001
Diabetes mellitus[a]	4970 (31)	3144 (26)	1826 (46)	<0.001
Smoking[a]				<0.001
Current	1563 (12)	1212 (12)	351 (11)	
Former	6482 (48)	4721 (46)	1761 (53)	
Never	5524 (41)	4282 (42)	1242 (37)	
CAD[a]	10 763 (67)	8208 (67)	2555 (65)	0.002
Previous coronary revascularization[a]	6119 (39)	4608 (39)	1511 (39)	0.570
History of AF/flutter[a]	9778 (61)	7448 (61)	2330 (59)	0.017

Table 1 (Continued)

	Overall population (n = 16 116)	Non-obese patients (n = 12 171)	Obese patients (n = 3945)	p-value
Valve disease[a]	3941 (25)	3196 (27)	745 (19)	<0.001
Anaemia[a,d]	5739 (38)	4624 (40)	1115 (30)	<0.001
Stroke or TIA[a]	3101 (19)	2479 (20)	622 (16)	<0.001
Liver disease[a]	468 (3)	369 (3)	99 (3)	0.090
COPD[a]	2629 (16)	1937 (16)	692 (18)	0.016
Dementia[a]	298 (2)	254 (2)	44 (1)	<0.001
Cancer, past 3 years[a]	2076 (13)	1710 (14)	366 (9)	<0.001
Musculoskeletal disease, past 3 years[a]	5345 (33)	3956 (33)	1390 (35)	0.002

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; RASi, renin–angiotensin system inhibitor; TD, target dose; TIA, transient ischaemic attack.

[a]Variables included in the multiple imputation models and as covariates in the multivariable models. Values are median (IQR Q1–Q3).

[b]In SwedeHF.

[c]eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration formula.

[d]Anaemia, defined as haemoglobin <120 g/L in females and <130 g/L in males.

versus without obesity were on a beta-blocker (p-value <0.001), and 41% versus 29% achieved ≥100% of TD ($p < 0.001$).

MRA

Forty-six percent of the overall population received MRA, 5% at ≥100% of TD; 53% versus 43% of patients in the obese versus non-obese group were treated with MRA ($p < 0.001$), and of them 8% and 4%, respectively, achieved ≥100% of TD ($p < 0.001$).

Triple therapy

Thirty-nine percent of the study population was treated with a combination of RASi/ARNi, beta-blocker and MRA, 47% with versus 36% without obesity ($p < 0.001$); 3% versus <1% ($p < 0.001$) received simultaneously ≥100% of TD for all three treatments.

Independent associations between obesity and use of guideline-directed medical therapy for heart failure

After adjustments, obesity was independently associated with the use of RASi/ARNi (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.05–1.39, $p = 0.008$), beta-blocker (OR 1.28 [1.09–1.50], $p = 0.002$) and MRA (OR 1.29 [1.19–1.40], $p < 0.001$), separately, as with the achievement of ≥100% TD for each drug (OR 1.21 [1.11–1.32], p <0.001; OR 1.41 [1.30–1.54], $p < 0.001$; OR 1.52 [1.27–1.81], $p < 0.001$; respectively). Obesity was also independently associated with the use of triple therapy (OR 1.30 [1.19–1.42], $p < 0.001$) and with the achievement of the maximum TD of all the treatments (OR 2.25 [1.66–3.05], $p < 0.001$) (*Figure 1*).

Outcomes

During a median follow-up period of 2.21 years (IQR 0–17), 58% of the overall population, that is 47% versus 62% of obese versus non-obese patients, died for any cause. Thirty-nine percent of the study population died for cardiovascular reasons, 30% if obese versus 42% if non-obese; and 44% of the population was hospitalized for HF, with the same rate in obese and non-obese patients.

Association between treatments and outcomes

RASi/ARNi

Use versus non-use of RASi/ARNi was associated with lower crude risk of all-cause mortality, cardiovascular mortality and HF hospitalization in the overall population (*Figure 2A–C*). Consistent with these findings, the adjusted HR (95% CI) for all-cause mortality was 0.77 (0.72–0.82), for cardiovascular mortality 0.76 (0.70–0.82) and for HF hospitalization 0.92 (0.84–1.00). Results were consistent in obese versus non-obese patients for the mortality outcomes (*Figure 2D,E*, with non-significant p for interaction). Conversely, a significant interaction (p for interaction = 0.034) was observed between obesity and use of RASi/ARNi for the association with HF hospitalization (*Figure 2F*), with a significant lower risk of HF hospitalization only in the obese group.

Consistent results for the outcome cardiovascular mortality were obtained in the overall population when non-cardiovascular mortality was considered as competing event (sub-HR [95% CI] 0.81 [0.76–0.88] $p < 0.001$), but the risk associated with the use of RASi/ARNi was lower in obese versus non-obese patients (p for interaction = 0.033) (online supplementary *Figure S2A*). In contrast with the main analysis, the competing risk analysis for HF hospitalization where all-cause mortality was used as competing event showed a higher risk of HF hospitalization with RASi/ARNi in the overall population (sub-HR [95% CI] 1.26 [1.03–1.54]), with no interaction between obesity and RASi/ARNi use (*Figure 2C,D*).

Splines analysis showed no statistically significant interaction of RASi/ARNi use across the BMI spectrum as continuous variable

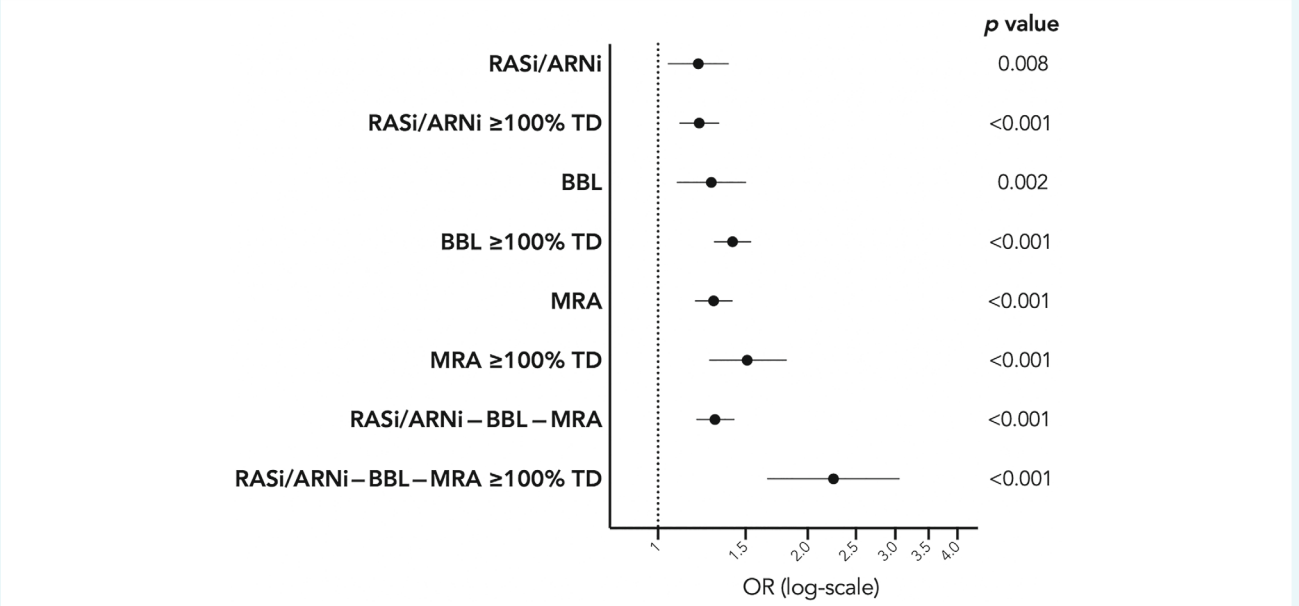


Figure 1 Independent association between obesity and use of heart failure pharmacological treatments. ARNi, angiotensin receptor–neprilysin inhibitor; BBL, beta-blocker; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; OR, odds ratio; TD, target dose. For this specific analysis only patients without missing for MRA dose were considered (26 112/127 456 patients were excluded from the imputed dataset due to missing dose for MRA).

for all the outcomes (*Figure 3A–C*; *p* for interaction = 0.140 for all-cause mortality; = 0.405 for cardiovascular mortality;= 0.230 for HF hospitalization), although an overall non-statistically significant trend toward lower HRs together with higher BMI was observed.

Online supplementary *Figure S3* shows the adjusted HR for outcomes, according to percentage of TD achieved for RASi/ARNi. Higher percentage of TD achievement was similarly associated with better outcomes in obese and non-obese patients (*p* for interaction >0.05 for all the outcomes).

Beta-blockers

Treatment with beta-blocker was associated with significantly lower crude risk of all-cause and cardiovascular mortality in the overall population, but not of HF hospitalization (*Figure 4A–C*). After extensive adjustment, the adjusted HR (95% CI) for the association between use of beta-blocker and all-cause mortality was 0.87 (0.81–0.95), for cardiovascular mortality 0.84 (0.76–0.93), while for HF hospitalization 0.93 (0.84–1.02; *p* = 0.127). The observed results were consistent in both obese and non-obese patients, that is no statistically significant interaction between obesity and use of treatment for the association with all the outcomes (*Figure 4D–F*).

Consistent results were confirmed at the competing risk analysis for cardiovascular mortality when non-cardiovascular mortality was considered as competing event (sub-HR [95% CI] 0.86 [0.78–0.94] for overall population, with no significant interaction for obesity) (online supplementary *Figure S2B*), and for the risk of HF hospitalization when all-cause death was considered as competing event to HF hospitalization, both in overall population (sub-HR [95% CI] 1.04 [0.84–1.29]) and regardless obesity (online supplementary *Figure S2B*).

The lack of a formal interaction between BMI and risk of outcomes was confirmed at the spline analysis (*Figure 3D–F*; *p* for interaction = 0.513 for all-cause mortality; = 0.610 for cardiovascular mortality; = 0.416 for HF hospitalization), although an overall non-statistically significant trend toward lower HRs together with higher BMI was observed.

Higher dosages of beta-blocker were associated with lower risk of outcomes in the overall population, with no significant differences in obese versus non-obese patients (online supplementary *Figure S4*).

Sensitivity analyses

The sensitivity analysis with imputed height was performed in a cohort of 22 223 patients, of which 24% was obese (online supplementary *Table S4* for the main characteristics).

Consistently with the main analysis, obesity was independently associated with higher use of GMDT and higher TD achievement (online supplementary *Figure S5*). Moreover, a significant interaction (*p* for interaction = 0.007) between obesity and use of RASi/ARNi was observed for the association with HF hospitalization, with only obese patients showing a significant association between use of RASi/ARNi and lower risk of HF hospitalization (HR [95% CI] 0.79 [0.69–0.90]) (online supplementary *Figure S6F*). Use of beta-blocker was not associated with a lower risk of HF hospitalization in the overall population and in obese/non-obese patients (*p* = 0.070; *p* for interaction = 0.726) (online supplementary *Figure S7C,F*). Full results of the sensitivity analysis with

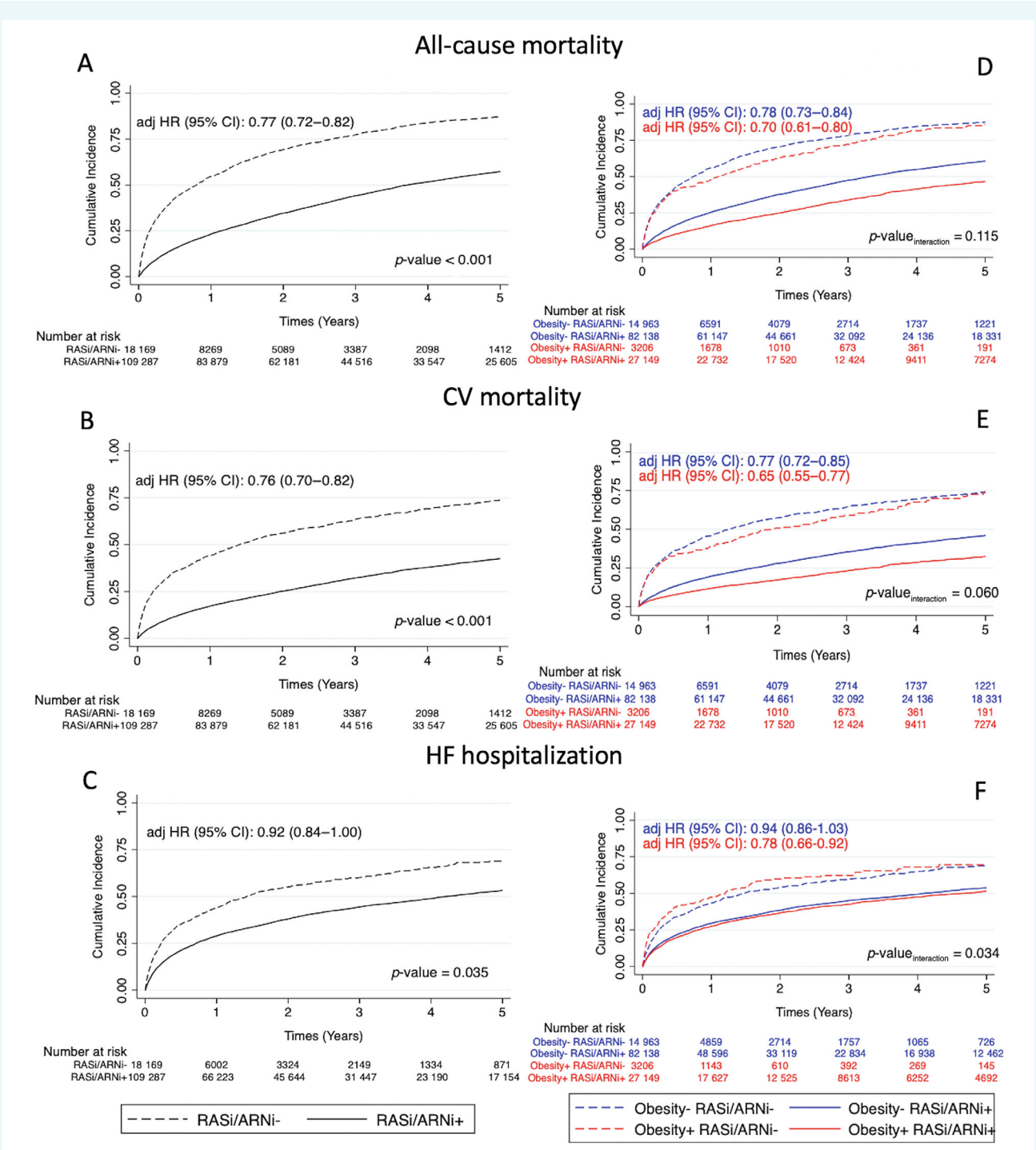


Figure 2 Cumulative incidence curves for all-cause mortality, cardiovascular (CV) mortality and hospitalization for heart failure (HF) in the overall population (*A*–*C*) and in obese/non-obese patients (*D*–*F*) receiving/not receiving renin–angiotensin system inhibitors (RASi)/angiotensin receptor–neprilysin inhibitors (ARNi). Adjusted hazard ratios (adj HR) and *p* for interaction are also reported. CI, confidence interval.

imputed height are reported in online supplementary material (see Results paragraph, supplementary *Table S4* and supplementary *Figures S5–S10*).

In contrast with the main analysis, higher doses of beta-blockers were associated with lower risk of cardiovascular mortality in non-obese but not in obese patients (online supplementary *Figure S10*).

For both the study treatments, the exclusion of underweight patients at the sensitivity analysis did not affect the results observed in the main analyses (online supplementary *Figure S11*).

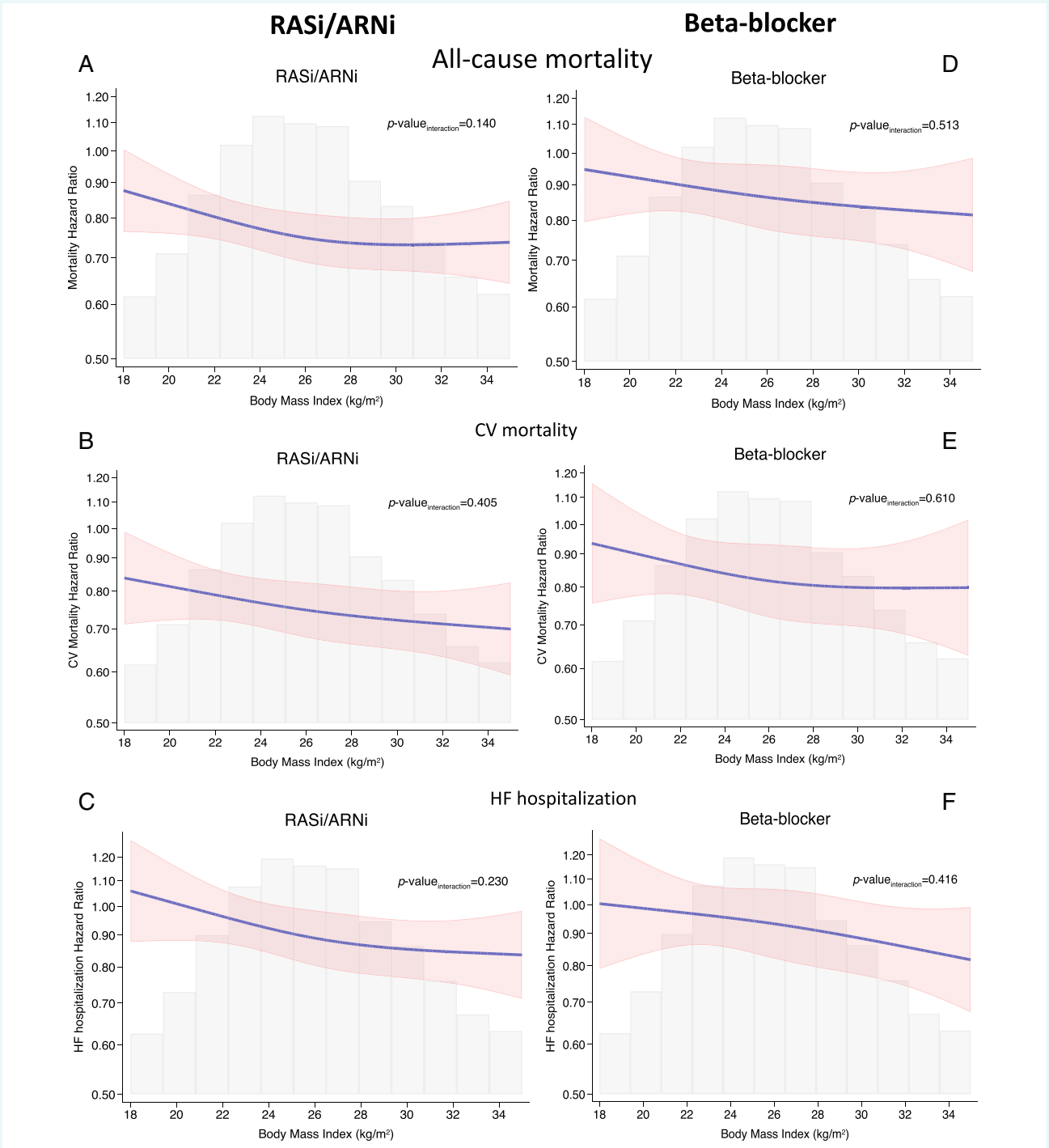


Figure 3 Splines curves for the association between renin–angiotensin system inhibitor (RASi)/angiotensin receptor–neprilysin inhibitor (ARNi) and beta-blocker use and all-cause mortality (*A* and *D*), cardiovascular (CV) mortality (*B* and *E*) and hospitalization for heart failure (HF) (*C* and *F*) according to increasing values of body mass index.

Discussion

To the best of our knowledge, this is the first comprehensive overview of use of HF treatments and association with outcomes in obese versus non-obese patients with HFrEF. The main results of the study are that: (i) compared with non-obese patients, obese patients more likely received GDMT and achieved ≥100% of TD, even after adjustment for several patient characteristics linked with better tolerability (e.g. blood pressure, heart rate, kidney function, potassium levels and multiple comorbidities) and

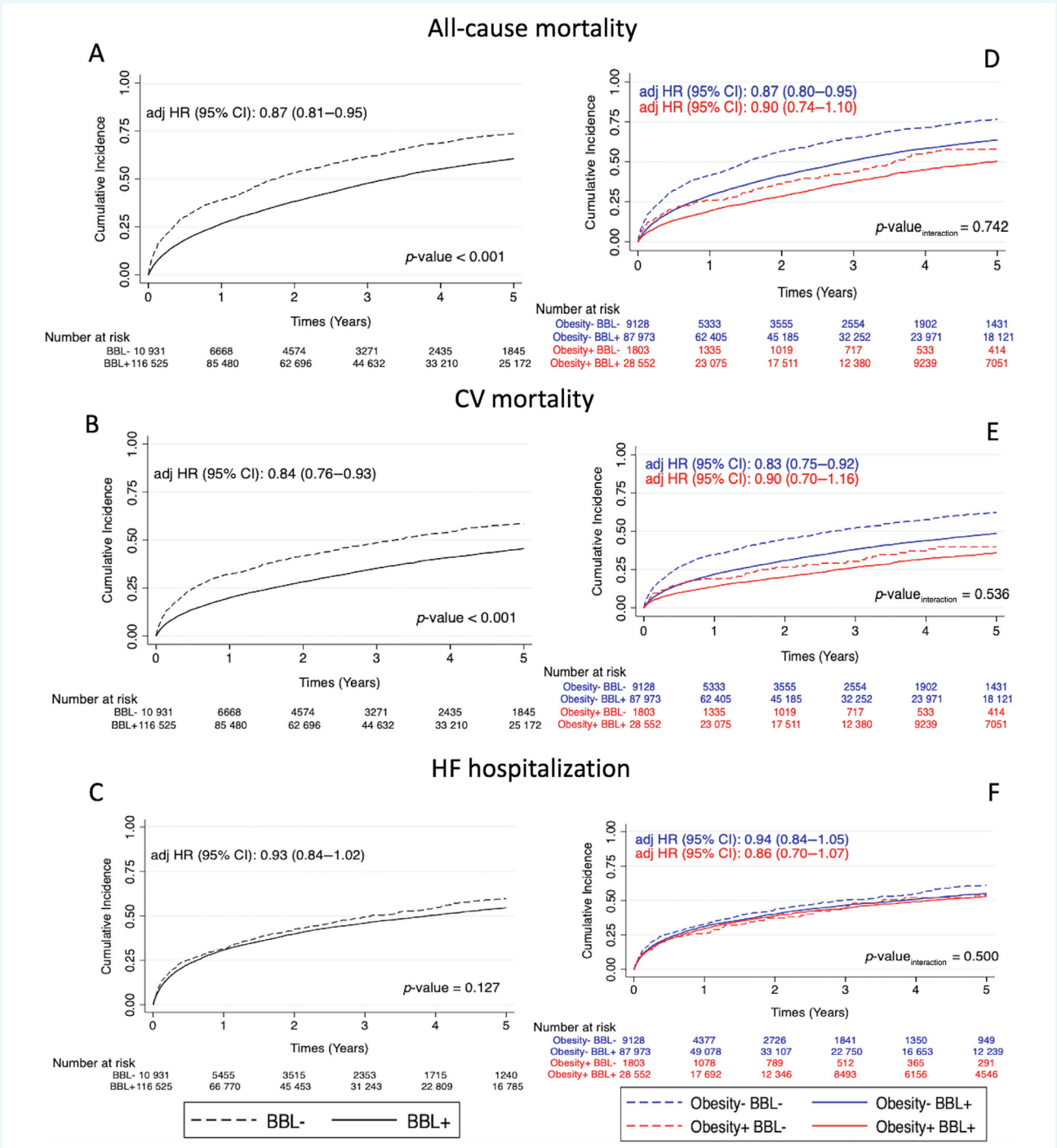


Figure 4 Cumulative incidence curves for all-cause mortality, cardiovascular (CV) mortality and hospitalization for heart failure (HF) in the overall population (*A*–*C*) and in obese/non-obese patients (*D*–*F*) receiving/not receiving beta-blockers. Adjusted hazard ratios (adj HR) and *p* for interaction are also reported. BBL, beta-blocker; CI, confidence interval.

quality of care (follow-up at nurse-led HF clinics and specialty care); (ii) use of GDMT and the achievement of higher dosages of RASi/ARNi and beta-blocker were similarly associated with lower all-cause and cardiovascular mortality in obese and non-obese patients in the main analysis, whereas an overall non-statistically significant trend toward lower HRs together with higher BMI was observed, and at the competing risk analysis the association between RASi/ARNi and lower risk of cardiovascular death was greater in obese versus non-obese patients; (iii) use of RASi/ARNi was associated with a lower risk of HF hospitalization in obese

but not in non-obese patients, whereas when competing risk from all-cause death was considered, it was associated with higher risk in both groups; (iv) use of beta-blocker was not associated with the risk of HF hospitalization regardless of obesity, with consistent results when competing risk from all-cause death was considered.

Differences in HFrEF treatments and patient characteristics according to the obesity status

In our cohort, obese patients were more likely treated with GDMT for HFrEF and with higher dosages. These differences might be at least partially explained by better tolerance to therapies with obesity. Consistently, patients with obesity were more likely to have a history of hypertension and higher blood pressure, which facilitates the initiation and the consequent up-titration of RASi/ARNi, beta-blockers and MRA. Obese patients were also more likely to have diabetes, with use of RASi having been shown to have protective effects on kidney organ damage.[12,13] The prevalence of chronic kidney disease was lower in obese patients, which might also explain higher crude use of RASi/ARNi and MRA with obesity.

Obese patients were also more likely followed up in nurse-led HF clinics, which, as reported in another analysis from SwedeHF, are linked with more optimized use of pharmacological treatments.[14] Higher referral to nurse-led HF clinics in obese patients might be at least partially explained by the younger age and higher comorbidity burden, with younger age having been perceived as a reason *per se* for better treatment by physicians, which might be linked to perceived reduced tolerance and limited evidence from RCT in older populations.[15–17]

An important finding was that obesity *per se* was associated with better and more intensive pharmacological treatment after extensive adjustments for all known and measured confounders, including variables linked with tolerance, that is blood pressure, renal function, heart rate, potassium levels, age, and also follow-up care. This suggests that in a proportion of non-obese patients GDMT might be inappropriately not initiated/up-titrated due to a perceived rather than actual limited tolerance to treatments or due to clinical inertia. Consistent with our results, in the CHAMP-HF study obesity was more prevalent among patients receiving higher doses of medications,[16] although in the BIOSTAT-CHF and the CHECK-HF higher BMI was similarly associated with higher use/doses of GDMT.[18,19] The observed more optimized use of HFrEF treatments in obese patients might contribute to explain the previously reported better prognosis associated with obesity in HF (i.e. obesity paradox).[20,21]

Regarding HF devices, only 9% of obese and 7% of non-obese patients were implanted with a cardioverter-defibrillator for primary prevention of sudden cardiac death. This overall low rate is not surprising and already reported in previous research, partly explained by high perception of complications, higher comorbidity burden and lower perceived effectiveness in selected subgroups (e.g. older patients, non-ischaemic HF aetiology, women).[22]

Association between use of heart failure treatments and outcomes

In our study the association between use of RASi and beta-blockers and lower all-cause/cardiovascular mortality was formally similar in obese versus non-obese patients. However, when considering competing risk, the magnitude of the association between RASi/ARNi use and lower risk of cardiovascular mortality was greater in the obese group. Consistently, although without any statistically significant interaction, splines curves showed lower HRs for the association between treatment use and outcomes together with higher values of BMI. Altogether, these findings might somehow lead to speculate on a potential stronger prognostic role for the analysed HF treatments in overweight/obese patients. No significant association between use of beta-blocker and risk of HF hospitalization was observed in both obese and non-obese patients in the main analysis and also while taking into consideration competing risk from all-cause death. A potential explanation might be related to bias and residual confounding in this observational study, that is better treatment in patients with more severe HF and thus with higher risk of hospitalizations. The higher risk of HF hospitalization associated with the use of RASi/ARNi we have observed at the competing risk analysis, although seeming paradoxical, could instead support this hypothesis. Altogether, our results do not completely exclude a different effectiveness of HF treatments in obese versus non-obese patients, but represent a call for further and more focused research adopting e.g., more precise parameters to assess obesity (measurements of adipose tissue distribution, waist-to-hip ratio, etc.) and more adequate study design, e.g., stratified randomization according to obesity in RCTs.

Although, as previously shown,[23] in our main analysis higher doses of GDMT were associated with better outcomes regardless of BMI which might support the current guidelines where dose adjustment based on BMI is not considered,[9] in the sensitivity analysis considering a larger sample size higher doses of beta-blockers were associated with lower risk of cardiovascular mortality in non-obese but not in obese patients. This finding might further support a potential interest into exploring a more individualized approach for HF drugs based also on BMI, and to better investigate the actual role of BMI on pharmacokinetics/pharmacodynamics, that is volume of distribution and drug clearance.[24,25]

Study limitations

The observational design of our study cannot rule out the presence of unknown/unmeasured confounders and selection bias, and therefore a causal relationship between use of drugs and outcomes cannot be demonstrated in this setting. The exclusion of patients due to missing BMI might have introduced a potential selection bias. However, results were overall confirmed in the sensitivity analysis where height was imputed, which allowed to largely expand the sample size of our cohort. Moreover, we obtained consistent results after the exclusion of underweight patients. Patients were enrolled and outcomes were assessed between 2000 and 2019, and therefore changes in care after 2019, e.g. after the introduction of SGLT2i in HF which have been recently associated with lower

mortality/morbidity across all BMI strata,[26,27] as well as a more optimized use of ARNi in the most recent years, have not been considered in this analysis. However, we considered the year of registration in SwedeHF in all the multivariable models to take into account the changes in practice during the time frame explored by the current analysis. Finally, the higher use of GDMT for HFrEF in SwedeHF compared with other data sources highlights the importance of registries to improve quality of care, but may limit the generalizability of our findings.[16,23]

Conclusions

Obese patients with HFrEF were more likely treated with GDMT and with higher dosages of medications even after extensive adjustment for factors related to tolerance, which might highlight, at least in a proportion of HFrEF patients, a delayed/no initiation/up-titration of GDMT due to perceived rather than actual tolerance issues and clinical inertia.

Our results showed some signals for better survival associated with use of HF treatments together with increasing BMI, which might be hypothesis-generating for further studies testing a personalized approach to HFrEF based on the obesity status.

Supplementary Information

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

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