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ORIGINAL PAPER

Guideline-directed medical therapy in real-world heart failure patients with low blood pressure and renal dysfunction

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Abstract

Background Among patients with heart failure and reduced ejection fraction (HFrEF), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB), β-blockers (BB) and mineralocorticoid receptor antagonist (MRA) are known as guideline-directed medical therapy to improve prognosis. However, low blood pressure (BP) and renal dysfunction are often challenges prevent clinical implementation, so we investigated the association of different combinations of GDMT treatments with all-cause mortality in HFrEF population with low BP and renal dysfunction.

Methods This study initially included 51, 060 HF patients from the Swedish Heart Failure Registry, and finally 1464 HFrEF patients with low BP (systolic BP ≦ 100 mmHg) and renal dysfunction (estimated glomerular filtration rate (eGFR) ≦ 60 ml/min/1.73m^2) were ultimately enrolled. Patients were receiving oral medication for HF at study enrollment, and divided into four groups (group 1–4: ACEI/ARB + BB + MRA, ACEI/ARB + BB, ACEI/ARB + MRA or ACEI/ARB only, and other). The outcome is time to all-cause mortality.

Results Among the study patients, 485 (33.1%), 672 (45.9%), 109 (7.4%) and 198 (13.5%) patients were in group 1–4. Patients in group 1 were younger, had highest hemoglobin, and most with EF < 30%. During a median of 1.33 years follow-up, 937 (64%) patients died. After adjustment for age, gender, LVEF, eGFR, hemoglobin when compared with the group 1, the hazard ratio for all-cause mortality in group 2 was 1.04 (0.89–1.21) ($p = 0.62$), group 3 1.40 (1.09–1.79) ($p = 0.009$), and group 4 1.71 (1.39–2.09) ($p < 0.001$).

Conclusions In real-world HFrEF patients with low BP and renal dysfunction, full medication of guideline-directed medical therapy is associated with improved survival. The benefit was larger close to the index date and decreased with follow-up time.

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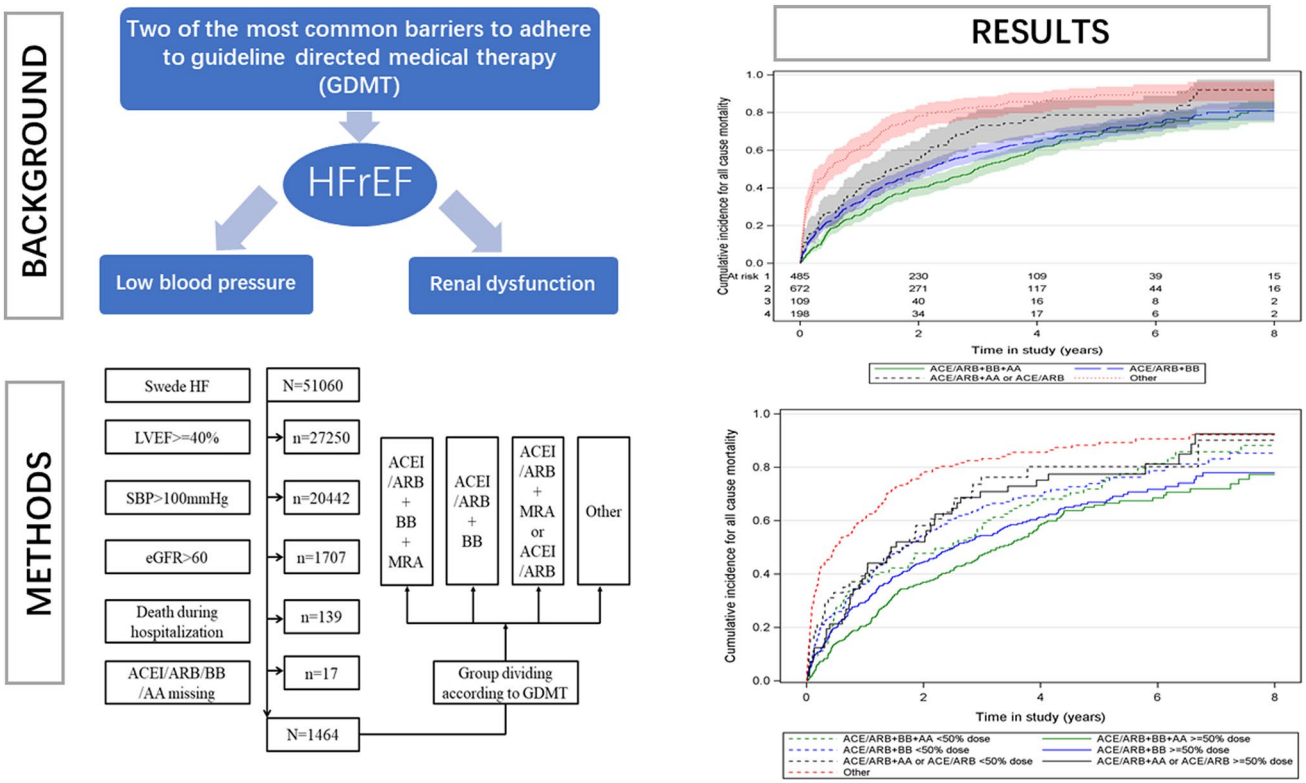
Graphic abstract



Keywords Heart failure · Low blood pressure · Renal dysfunction · Guideline-directed medical therapy · Mortality

Introduction

Heart failure (HF) has a prevalence of approximately 2% in adults in developed countries [1] and mainly affects elderly patients, who may have multiple comorbidities. Two such comorbidities, low systolic blood pressure (SBP) and impaired renal function [2, 3], have been shown to be strong predictors of mortality and can be present in about 50% of patients treated for HF [4]. To improve patient outcome, guideline-directed medical therapy, including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), beta blockers (BB) and Mineralocorticoid receptor antagonist (MRA), is recommended for patients with HF with reduced ejection fraction (HFrEF) [5, 6].

Despite proven benefits and strong guideline recommendations, medication usage and dosing remain suboptimal in routine clinical practice. Two of the most common barriers to adhere to guideline-directed medical therapy are low SBP and renal dysfunction, which often occur simultaneously [7]. Therefore, in this study, we sought to compare whether different combinations of guideline-directed medical therapy treatments upon discharge or at an outpatient visit in patients with HFrEF included in the Swedish Heart Failure Registry (SwedeHF), with coexisting low SBP and renal dysfunction are associated with different risks for all-cause mortality.

Methods

Study design and setting

This study utilized patients from the SweHF, with available data from 11 May 2000 to 31 December 2012, which is described previously [8]. Inclusion criteria are clinician-judged HF. Ejection fraction (EF) is categorized as < 30, 30–39, 40–49, or ≥ 50%. Approximately, 80 variables are recorded at discharge from hospital or at an outpatient visit and entered into a web-based database managed by the Uppsala Clinical Research Center (www.ucr.uu.se/en). Deaths are obtained from the Swedish Population Registry. The protocol, registration form, and annual reports are available at www.swedehf.se. Establishment of the registry and this analysis conform to the Declaration of Helsinki and were approved by a multisite ethics committee. Individual patient

consent is not required, but patients are informed of entry into national registries.

Patient population

The HF patients were receiving oral medication for HF at study enrollment (including diuretics, ACEI, ARB, BB, MRA, antihypertensive, or other cardiovascular medications). Key inclusion criteria included: (1) Patients with HFrEF (defined as EF < 40%); (2) HFrEF patients with renal insufficiency, defined as estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m^2 [corresponding to chronic kidney disease (CKD) 3, 4 and 5] [9]; (3) HFrEF patients with low SBP ≤ 100 mmHg [10]. Patients were excluded if they died during hospitalization or having missing information on the use of ACEI, ARB, BB or MRA.

Group dividing and outcome

Patients treated with guideline-directed medical therapy were divided into 4 groups: group 1: treated with all three: ACEI/ARB + BB + MRA; group 2: treated with ACEI/ARB + BB; group 3: treated with ACEI/ARB + MRA or ACEI/ARB only; group 4: others (the patients were treated dominated by BB and to some extent MRA). Furthermore, groups 1–3 were divided into two subgroups according to the dose levels of ACEI/ARB < 50% or ≥ 50% of target doses [5].

The eGFR was used to assess renal function and calculated by CKD-EPI [7], renal dysfunction was defined as eGFR ≤ 60 ml/min/1.73m^2.

Blood pressure and renal function were measured at the first registration into our registry, and the medical therapy was collected at discharge or at the outpatient visit. The endpoint for this study was time to all-cause mortality during study follow-up.

Co-existing comorbidities at or prior to index date were defined either at the clinical examination in SwedeHF (hypertension, ischemic heart disease, atrial fibrillation/flutter, diabetes, stroke/TIA and anemia) or existing in the patient register between 1 January 1997 and index date (hypertension ICD-10 I10–I15, atrial fibrillation/flutter I48, diabetes E10–E14, stroke/TIA I60–I64 I690–I694 G45, anemia D50–D64).

Statistical analysis

For baseline characteristics, categorical variables are presented as frequencies with percentages and continuous variables as mean with standard deviation (SD) or median and interquartile range (IQR) as applicable. The overall differences in baseline characteristics between the treatment groups were tested using the Kruskal–Wallis rank-sum test for continuous variables, and chi-square test for categorical variables. Crude event rates were estimated as number of events divided by number of follow-up years and were expressed per 100 person years with 95% confidence intervals (CI) estimated applying exact Poisson limits. Event rates with 95% CI adjusted for age and sex were estimated using Poisson regression. Time to all-cause mortality was studied using Cox proportional hazards models, adjusted for age and sex in model 1, and additionally adjusted for known risk factors smoking, NYHA, LVEF, eGFR and hemoglobin in model 2. Missing data for smoking and NYHA, 26% and 21%, respectively, were handled as unknown categories in this model. Hazard ratios (HR) with 95% CI were presented. Proportional hazards assumption was checked adding an interaction term between the treatment group variable and the natural logarithm of follow-up time in the Cox model, which was not found to be satisfied. Therefore, the HRs obtained from the Cox regression were regarded as overall treatment effects for the studied time period, and additionally continuous HRs over time were estimated based on flexible parametric survival models by Royston and Parmar [11], using a developed SAS macro for the method [12], for further evaluation. The variables having missing data in the models were smoking (26% missing) and NYHA (21%). Those patients were handled as an own Unknown category in the adjustments.

We considered a 2-sided p value < 0.05 as significant, and used SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) for all analyses.

Results

Patient disposition

Between 11 May 2000 and 5 June 2013, there were 85, 291 registrations from 68 of 77 hospitals and 102 of 1011 primary care outpatient clinics in Sweden, and they were recorded for 51, 060 unique patients. After exclusion of 27, 250 (53.4%) HF patients with EF ≥ 40%, 20, 422 (40.0%) with SBP > 100 mmHg, 1707 (3.3%) with eGFR > 60% and others with missing data, 1464 HF patients were finally enrolled for this analysis, 1435 (98.0%) from the hospitals and 29/1464 (2.0%) from the primary care clinics. The flow chart of study population is depicted in Fig. 1.

Baseline characteristics

Baseline characteristics of subgroups are presented in Table 1. In general, patients treated with pre-defined 3 combinations in guideline-directed medical therapy (group 1, 2 and 3) were younger, more current smoker, had less atrial fibrillation/flutter, less anemia, less CKD (stage 4/5), and

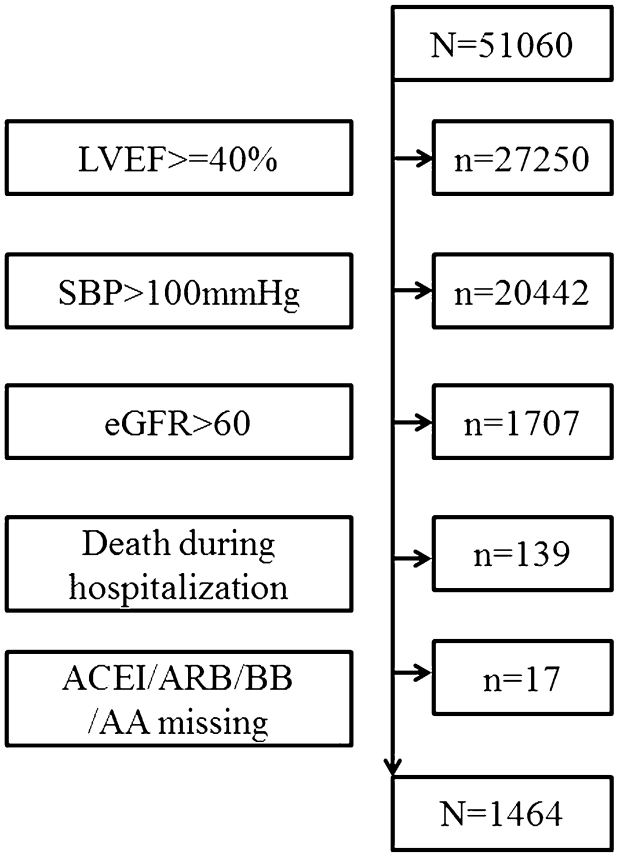


Fig. 1 The flow chart of study populations

more EF < 30% compared with other combinations (group 4) in which 90% were treated with BB, 39% with MRA but no ACEI/ARB. In particular, patients treated with ACEI/ARB + BB + MRA (group 1) were youngest among all groups. Furthermore, when guideline-directed medical therapy use was further stratified by its dose level (Table 2), patients treated with ACEI/ARB + BB + MRA (group 1) and with ≥ 50% dose were the youngest, had less anemia and less CKD (stage 4/5).

Outcomes

Of the 1464 HF patients with low BP and renal dysfunction, 937 (64%) died during a median of 1.33 (IQR 0.41–3.25)-year follow-up. Event rate adjusted for age and sex was highest in group [4 67.3 (95% CI 57.7–78.7) events per 100 person years, 163 (82.3%)] and lowest in group 1 (patients treated with ACEI/ARB + BB + MRA) [26.6 (95% CI 23.7–29.9) events per 100 person years, 286 (59%)], followed by group 2 (ACEI/ARB + BB group) [28.1 (95% CI 25.5–31.0) events per 100 person years, 406 (60.4%)] and group 3 (ACEI/ARB + MRA or ACEI/ARB) [36.3 (95% CI 29.2–45.2) events per 100 person years, 82 (75.2%)] (Table 2, Figs. 2,3).When the dose effect was taken into account, mortality remained lowest in group 1 (patients treated with ACEI + BB + MRA) with ≥ 50% dose [24.1 (95% CI 20.9–27.8) events per 100 person years, 191 (55.8%)] (Table 2).

After adjustments, patients treated with ACEI/ARB + BB + MRA (group 1) still had lowest mortality among all groups, and compared with group 1, group 3 (ACEI/ARB + MRA or ACEI/ARB group) had an 40% higher all-cause mortality [HR 1.40 (95% CI 1.09–1.79), $p = 0.0087$], while group 4 had a 1.71-fold higher mortality [HR 1.71 (95% CI 1.39–2.09), $p < 0.001$] (Table 3, Fig. 2). However, the comparison of risks for all-cause mortality between the groups is illustrated in Fig. 3, when compared with ACE/ARB + BB + MRA group, all the other three groups have higher risk for all-cause mortality, and this risk was shown to be highest close to the index visit and decreased during the follow-up time. Comparing low and high dose within each medication group, even lower mortality was found in patients treated ACEI/ARB + BB + MRA ≥ 50% dose. (Table 4, Fig. 2).

Discussion

To our knowledge, this is the first study that evaluated whether guideline-directed medical therapy affects the outcome in HFrEF patients with low SBP and renal dysfunction. The main findings of this study were that: (1) about one third of patients with HFrEF and with coexisting low SBP and renal dysfunction were treated with all 3 guideline-directed medical therapy drugs (ACEI/ARB + BB + MRA); (2) patients treated with ACEI/ARB + BB + MRA were younger, had highest levels of eGFR and hemoglobin, and more had EF < 30%; (3) HFrEF patients treated with all three guideline-directed medical therapy had lower risk for all-cause mortality, and the outcome was better in those treated with ≥ 50% of the target dose.

The HR is relatively higher and then declined quickly, we also retrieved information about very early deaths, during the first month post-index visit, that is affecting the appearance of the continuous HR curves. The number of patients with early death in the ACE/ARB + BB + AA group was 15 (3.1%), in the ACE/ARB + BB group 41 (6.1%), in the ACE/ARB + AA or ACE/ARB group 12 (11.0%) and in the other group 46 (23.2%). The patients in other medication groups than ACE/ARB + BB + AA are older and higher proportion have had longer HF duration with more severe comorbidity profiles, resulting in higher proportion of very early deaths. Moreover, it is known that it is the early post-discharge period, so called the "vulnerable phase" where the greatest number of adverse outcomes occurs. So this phenomenon may because the patients are not stable at discharge and

Table 1 Demographics and patient characteristics by medication group

Variable	ACE/ ARB + BB + MRA ($n = 485$)	ACE/ARB + BB ($n = 672$)	ACE/ARB + MRA or ACE/ARB ($n = 109$)	Other ($n = 198$)	p value
Patient characteristics					
Age	72.9 (9.7)	76.1 (9.2)	77.4 (9.0)	79.5 (8.9)	< .0001
Gender					
Male	351 (72.4%)	478 (71.1%)	80 (73.4%)	148 (74.7%)	–
Female	134 (27.6%)	194 (28.9%)	29 (26.6%)	50 (25.3%)	0.78
Smoking					
Never	153 (40.1%)	202 (40.8%)	49 (57.6%)	49 (38.3%)	–
Previous	191 (50.0%)	228 (46.1%)	28 (32.9%)	70 (54.7%)	–
Current	38 (9.9%)	65 (13.1%)	8 (9.4%)	9 (7.0%)	0.012
Alcohol					
Never	27 (9.5%)	42 (11.8%)	13 (21.0%)	12 (14.0%)	–
Normal	229 (80.6%)	291 (81.5%)	46 (74.2%)	67 (77.9%)	–
Previous problematic	20 (7.0%)	13 (3.6%)	2 (3.2%)	5 (5.8%)	–
Current problematic	8 (2.8%)	11 (3.1%)	1 (1.6%)	2 (2.3%)	0.28
Medical history					
Hypertension	219 (45.2%)	310 (46.1%)	45 (41.3%)	90 (45.5%)	0.83
Ischemic heart disease	288 (60.6%)	404 (62.3%)	70 (66.7%)	120 (61.9%)	0.71
Atrial fibrillation/flutter	299 (61.6%)	392 (58.3%)	59 (54.1%)	135 (68.2%)	0.040
Diabetes	140 (28.9%)	176 (26.2%)	27 (24.8%)	60 (30.3%)	0.53
Stroke/TIA	91 (18.8%)	117 (17.4%)	24 (22.0%)	32 (16.2%)	0.57
Anemia	69 (14.2%)	104 (15.5%)	24 (22.0%)	45 (22.7%)	0.016
Physical examination and laboratory measurements					
Systolic blood pressure (mmHg)	94.5 (6.5)	95.2 (5.8)	95.2 (5.7)	94.0 (6.7)	0.078
Diastolic blood pressure (mmHg)	61.0 (8.8)	61.1 (7.8)	59.6 (10.9)	60.5 (9.2)	0.87
NYHA					
I	13 (3.2%)	17 (3.2%)	3 (3.4%)	7 (5.4%)	–
II	116 (28.9%)	161 (30.1%)	11 (12.5%)	20 (15.5%)	–
III	235 (58.5%)	298 (55.8%)	67 (76.1%)	69 (53.5%)	–
IV	38 (9.5%)	58 (10.9%)	7 (8.0%)	33 (25.6%)	< .0001
EF category					
< 30	341 (70.3%)	434 (64.6%)	75 (68.8%)	115 (58.1%)	–
30–39	144 (29.7%)	238 (35.4%)	34 (31.2%)	83 (41.9%)	0.015
NT-proBNP	5580 (158; 69, 999)	4612 (134; 46, 994)	5343 (1301; 36, 562)	9000 (780; 66, 564)	0.100
eGFR (CKD-EPI)	43.2 (11.1)	42.1 (11.5)	43.5 (11.1)	34.5 (12.5)	< .0001
CKD stages					
CKD stage 3a (eGFR 45- < 60)	231 (47.6%)	295 (43.9%)	54 (49.5%)	42 (21.2%)	–
CKD stage 3b (eGFR 30- < 45)	187 (38.6%)	263 (39.1%)	38 (34.9%)	82 (41.4%)	–
CKD stage 4 (eGFR 15- < 30)	64 (13.2%)	106 (15.8%)	16 (14.7%)	59 (29.8%)	–
CKD stage 5 (eGFR < 15)	3 (0.6%)	8 (1.2%)	1 (0.9%)	15 (7.6%)	< .0001
Hemoglobin (g/l)	131.9 (17.3)	130.6 (17.3)	126.7 (16.3)	125.2 (16.9)	< .0001
Device therapy					
None/PM	398 (82.7%)	593 (89.6%)	95 (89.6%)	177 (90.3%)	–
ICD without CRT	34 (7.1%)	22 (3.3%)	2 (1.9%)	7 (3.6%)	–
CRT without ICD	21 (4.4%)	33 (5.0%)	4 (3.8%)	7 (3.6%)	–
CRT with ICD	28 (5.8%)	14 (2.1%)	5 (4.7%)	5 (2.6%)	0.0026
Medical therapy at discharge or revisit					
ACEI/ARB	485 (100.0%)	672 (100.0%)	109 (100.0%)	0 (0.0%)	< .0001
Beta blockers	485 (100.0%)	672 (100.0%)	0 (0.0%)	178 (89.9%)	< .0001

Table 1 (continued)

Variable	ACE/ ARB + BB + MRA ($n = 485$)	ACE/ARB + BB ($n = 672$)	ACE/ARB + MRA or ACE/ARB ($n = 109$)	Other ($n = 198$)	p value
Aldosterone antagonists	485 (100.0%)	0 (0.0%)	41 (37.6%)	78 (39.4%)	< .0001
Digitalis	106 (21.9%)	96 (14.3%)	20 (18.3%)	29 (14.6%)	0.0059
Diuretics	458 (94.4%)	621 (92.7%)	102 (93.6%)	185 (93.9%)	0.69
Nitrates	86 (17.8%)	123 (18.4%)	15 (13.9%)	41 (20.7%)	0.52
Statins	252 (52.3%)	322 (47.9%)	52 (47.7%)	70 (35.4%)	0.0010
Platelet inhibitors	204 (42.2%)	358 (53.5%)	52 (48.1%)	109 (55.1%)	0.0007
Oral anticoagulants	265 (54.6%)	301 (44.9%)	49 (45.0%)	68 (34.5%)	< .0001

NYHA New york heart association, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *PM* pacemaker, *ICD* implanted cardiac defibrillation, *CRT* cardiac resynchronization therapy defibrillation, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers

should receive more GDMT and be titrated medication at the suitable time.

Renal dysfunction represents a significant comorbidity of HF, may lead to further deterioration of HF and worsened clinical outcomes [13, 14], and the mortality risk substantially increases when eGFR is < 45 [15–17]. In addition to structural renal abnormalities related to hypertension, diabetes or atherosclerosis, renal dysfunction in HF patients may result from renal hypoperfusion caused by hemodynamic, neurohumoral and inflammatory factors [17]. Several encouraging retrospective analyses had been published demonstrating the safety and efficacy of treatment with renin–angiotensin system (RAS) inhibitors in elderly patients with HFrEF and moderate to severe renal dysfunction [18].

Heart failure and reduced ejection fraction patients, having a low SBP often have signs and/or symptoms of hypoperfusion and a very poor prognosis [19, 20] [21–23]. Studies have found that patients with HF and low SBP were more likely to have had a history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), hypercholesterolemia and less likely a history of hypertension [19, 20], and treatment with RAS and BBs has been shown to result in improved outcomes, independent of the baseline SBP [24, 25]. When low SBP was accompanied with renal dysfunction, the situation seems to get worse, so our study adds to the body of evidence showing that despite low SBP and renal dysfunction, treatment with guideline-directed medical therapy was still associated with an improved outcome. In our study, patients in group 1 with full medications of ACEI/ARB + BB + MRA were clearly more beneficial than those in group 4 in which only ACEI/ARB were not included, suggesting that ACEI/ARB are indispensable, and moreover, when dose level was taken into account, at a dose level ≥ 50% of target dose, full medications of ACEI/ARB + BB + MRA were clearly more beneficial than those in group 3 in which BB were not included or group 4 in which ACEI/ARB were not included, indicating that both BB and ACEI/ARB are very essential drugs when treating patients with HF.

Limitations

Our study should be taken in the context of some limitations. First, the study population was derived from SwedeHF, so the results may not be generalizable to other populations or geographic regions. Second, participation in the registry is voluntary, so while most health care facilities (or hospitals if we limit the study to hospital-based patients) report to the registry, the registry does not capture all care throughout Sweden. In addition, we were limited by the data available in the registry and due to the large scale of this registry, some data were missing. Third, as a part of the nature of a registry study, we are unable to validate diagnosis. Fourth, blood pressure and renal function were assessed at a single time which meant that we could not address the influence on outcomes of changes in renal function related to the treatment given. Fifth, the observational nature of this study, unknown residual unmeasured confounders could have influenced our results. Last, we only have the data on drugs at the enrollment, so we cannot evaluate the changes for medical therapy.

Conclusions

About one third of the HFrEF patients with low SBP and renal dysfunction were treated with all three guideline-directed medical therapy drugs, and these patients are associated with a better outcome than those treated with only ACEI/ARB or BB. The benefit was larger close to the index date and decreased with follow-up time.

Table 2 Demographics and patient characteristics by medication/dose group

Variable	ACE/ ARB + BB + MRA < 50% dose ($n = 143$)	ACE/ ARB + BB + MRA > = 50% dose ($n = 342$)	ACE/ ARB + BB < 50% dose ($n = 271$)	ACE/ ARB + BB > = 50% dose ($n = 401$)	ACE/ ARB + MRA or ACE/ ARB < 50% dose ($n = 52$)	ACE/ ARB + MRA or ACE/ ARB > = 50% dose ($n = 57$)	Other ($n = 198$)	p value
Patient characteristics								
Age	74.1 (10.0)	72.3 (9.6)	76.9 (10.0)	75.5 (8.6)	77.1 (9.0)	77.7 (9.1)	79.5 (8.9)	< .0001
Gender								
Male	104 (72.7%)	247 (72.2%)	200 (73.8%)	278 (69.3%)	35 (67.3%)	45 (78.9%)	148 (74.7%)	–
Female	39 (27.3%)	95 (27.8%)	71 (26.2%)	123 (30.7%)	17 (32.7%)	12 (21.1%)	50 (25.3%)	0.60
Smoking								
Never	50 (46.7%)	103 (37.5%)	75 (37.7%)	127 (42.9%)	24 (61.5%)	25 (54.3%)	49 (38.3%)	–
Previous	48 (44.9%)	143 (52.0%)	96 (48.2%)	132 (44.6%)	12 (30.8%)	16 (34.8%)	70 (54.7%)	–
Current	9 (8.4%)	29 (10.5%)	28 (14.1%)	37 (12.5%)	3 (7.7%)	5 (10.9%)	9 (7.0%)	0.052
Alcohol								
Never	9 (10.8%)	18 (9.0%)	18 (12.7%)	24 (11.2%)	5 (17.9%)	8 (23.5%)	12 (14.0%)	–
Normal	64 (77.1%)	165 (82.1%)	114 (80.3%)	177 (82.3%)	21 (75.0%)	25 (73.5%)	67 (77.9%)	–
Previous problematic	6 (7.2%)	14 (7.0%)	5 (3.5%)	8 (3.7%)	1 (3.6%)	1 (2.9%)	5 (5.8%)	–
Current problematic	4 (4.8%)	4 (2.0%)	5 (3.5%)	6 (2.8%)	1 (3.6%)	0 (0.0%)	2 (2.3%)	0.69
Medical history								
Hypertension	62 (43.4%)	157 (45.9%)	126 (46.5%)	184 (45.9%)	18 (34.6%)	27 (47.4%)	90 (45.5%)	0.81
Ischemic heart disease	81 (57.9%)	207 (61.8%)	152 (57.6%)	252 (65.6%)	32 (64.0%)	38 (69.1%)	120 (61.9%)	0.36
Atrial fibrillation/ flutter	86 (60.1%)	213 (62.3%)	160 (59.0%)	232 (57.9%)	26 (50.0%)	33 (57.9%)	135 (68.2%)	0.16
Diabetes	48 (33.6%)	92 (26.9%)	56 (20.7%)	120 (29.9%)	11 (21.2%)	16 (28.1%)	60 (30.3%)	0.060
Stroke/TIA	27 (18.9%)	64 (18.7%)	43 (15.9%)	74 (18.5%)	9 (17.3%)	15 (26.3%)	32 (16.2%)	0.65
Anemia	32 (22.4%)	37 (10.8%)	44 (16.2%)	60 (15.0%)	11 (21.2%)	13 (22.8%)	45 (22.7%)	0.0024
Physical examination and laboratory measurements								
SBP (mmHg)	94.6 (6.7)	94.4 (6.5)	94.5 (6.1)	95.7 (5.5)	94.8 (6.1)	95.7 (5.3)	94.0 (6.7)	0.043
DBP (mmHg)	61.0 (8.9)	61.0 (8.7)	61.1 (7.6)	61.1 (8.0)	59.2 (10.6)	59.9 (11.2)	60.5 (9.2)	0.99
NYHA								
I	4 (3.4%)	9 (3.2%)	4 (1.9%)	13 (4.1%)	3 (6.7%)	0 (0.0%)	7 (5.4%)	–
II	31 (26.3%)	85 (29.9%)	66 (30.6%)	95 (29.9%)	6 (13.3%)	5 (11.6%)	20 (15.5%)	–
III	69 (58.5%)	166 (58.5%)	124 (57.4%)	174 (54.7%)	32 (71.1%)	35 (81.4%)	69 (53.5%)	–
IV	14 (11.9%)	24 (8.5%)	22 (10.2%)	36 (11.3%)	4 (8.9%)	3 (7.0%)	33 (25.6%)	< .0001
EF category								
< 30	100 (69.9%)	241 (70.5%)	174 (64.2%)	260 (64.8%)	38 (73.1%)	37 (64.9%)	115 (58.1%)	–
30–39	43 (30.1%)	101 (29.5%)	97 (35.8%)	141 (35.2%)	14 (26.9%)	20 (35.1%)	83 (41.9%)	0.078
eGFR (CKD-EPI)	40.4 (11.6)	44.3 (10.7)	40.0 (12.3)	43.5 (10.7)	41.4 (10.6)	45.5 (11.2)	34.5 (12.5)	< .0001
CKD stages								
CKD stage 3a (eGFR 45- < 60)	49 (34.3%)	182 (53.2%)	105 (38.7%)	190 (47.4%)	22 (42.3%)	32 (56.1%)	42 (21.2%)	–
CKD stage 3b (eGFR 30- < 45)	66 (46.2%)	121 (35.4%)	97 (35.8%)	166 (41.4%)	20 (38.5%)	18 (31.6%)	82 (41.4%)	–
CKD stage 4 (eGFR 15- < 30)	27 (18.9%)	37 (10.8%)	63 (23.2%)	43 (10.7%)	10 (19.2%)	6 (10.5%)	59 (29.8%)	–
CKD stage 5 (eGFR < 15)	1 (0.7%)	2 (0.6%)	6 (2.2%)	2 (0.5%)	0 (0.0%)	1 (1.8%)	15 (7.6%)	< .0001
Hemoglobin (g/l)	127.7 (18.8)	133.6 (16.4)	130.6 (17.6)	130.6 (17.1)	126.3 (16.0)	126.9 (16.7)	125.2 (16.9)	< .0001
Device therapy								
None/PM	128 (89.5%)	270 (79.9%)	241 (90.3%)	352 (89.1%)	42 (84.0%)	53 (94.6%)	177 (90.3%)	–
ICD without CRT	4 (2.8%)	30 (8.9%)	10 (3.7%)	12 (3.0%)	1 (2.0%)	1 (1.8%)	7 (3.6%)	–
CRT without ICD	4 (2.8%)	17 (5.0%)	16 (6.0%)	17 (4.3%)	4 (8.0%)	0 (0.0%)	7 (3.6%)	–

Table 2 (continued)

Variable	ACE/ ARB + BB + MRA < 50% dose ($n = 143$)	ACE/ ARB + BB + MRA > = 50% dose ($n = 342$)	ACE/ ARB + BB < 50% dose ($n = 271$)	ACE/ ARB + BB > = 50% dose ($n = 401$)	ACE/ ARB + MRA or ACE/ ARB < 50% dose ($n = 52$)	ACE/ ARB + MRA or ACE/ ARB > = 50% dose ($n = 57$)	Other ($n = 198$)	*p* value
CRT with ICD	7 (4.9%)	21 (6.2%)	0 (0.0%)	14 (3.5%)	3 (6.0%)	2 (3.6%)	5 (2.6%)	0.0002
Medical therapy at discharge								
ACEI/ARB	143 (100.0%)	342 (100.0%)	271 (100.0%)	401 (100.0%)	52 (100.0%)	57 (100.0%)	0 (0.0%)	< .0001
Beta blockers	143 (100.0%)	342 (100.0%)	271 (100.0%)	401 (100.0%)	0 (0.0%)	0 (0.0%)	178 (89.9%)	< .0001
Aldosterone antagonists	143 (100.0%)	342 (100.0%)	0 (0.0%)	0 (0.0%)	17 (32.7%)	24 (42.1%)	78 (39.4%)	< .0001
Digitalis	26 (18.3%)	80 (23.4%)	36 (13.3%)	60 (15.0%)	11 (21.2%)	9 (15.8%)	29 (14.6%)	0.019
Diuretics	135 (94.4%)	323 (94.4%)	249 (91.9%)	372 (93.2%)	49 (94.2%)	53 (93.0%)	185 (93.9%)	0.92
Nitrates	20 (14.1%)	66 (19.4%)	48 (17.7%)	75 (18.8%)	7 (13.7%)	8 (14.0%)	41 (20.7%)	0.64
Statins	67 (46.9%)	185 (54.6%)	107 (39.5%)	215 (53.6%)	25 (48.1%)	27 (47.4%)	70 (35.4%)	< .0001
Platelet inhibitors	68 (47.6%)	136 (40.0%)	144 (53.5%)	214 (53.5%)	27 (51.9%)	25 (44.6%)	109 (55.1%)	0.0029
Oral anticoagulants	65 (45.5%)	200 (58.5%)	105 (38.7%)	196 (49.1%)	22 (42.3%)	27 (47.4%)	68 (34.5%)	< .0001

NYHA New york heart association, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *PM* pacemaker, *ICD* implanted cardiac defibrillation, *CRT* cardiac resynchronization therapy defibrillation, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers

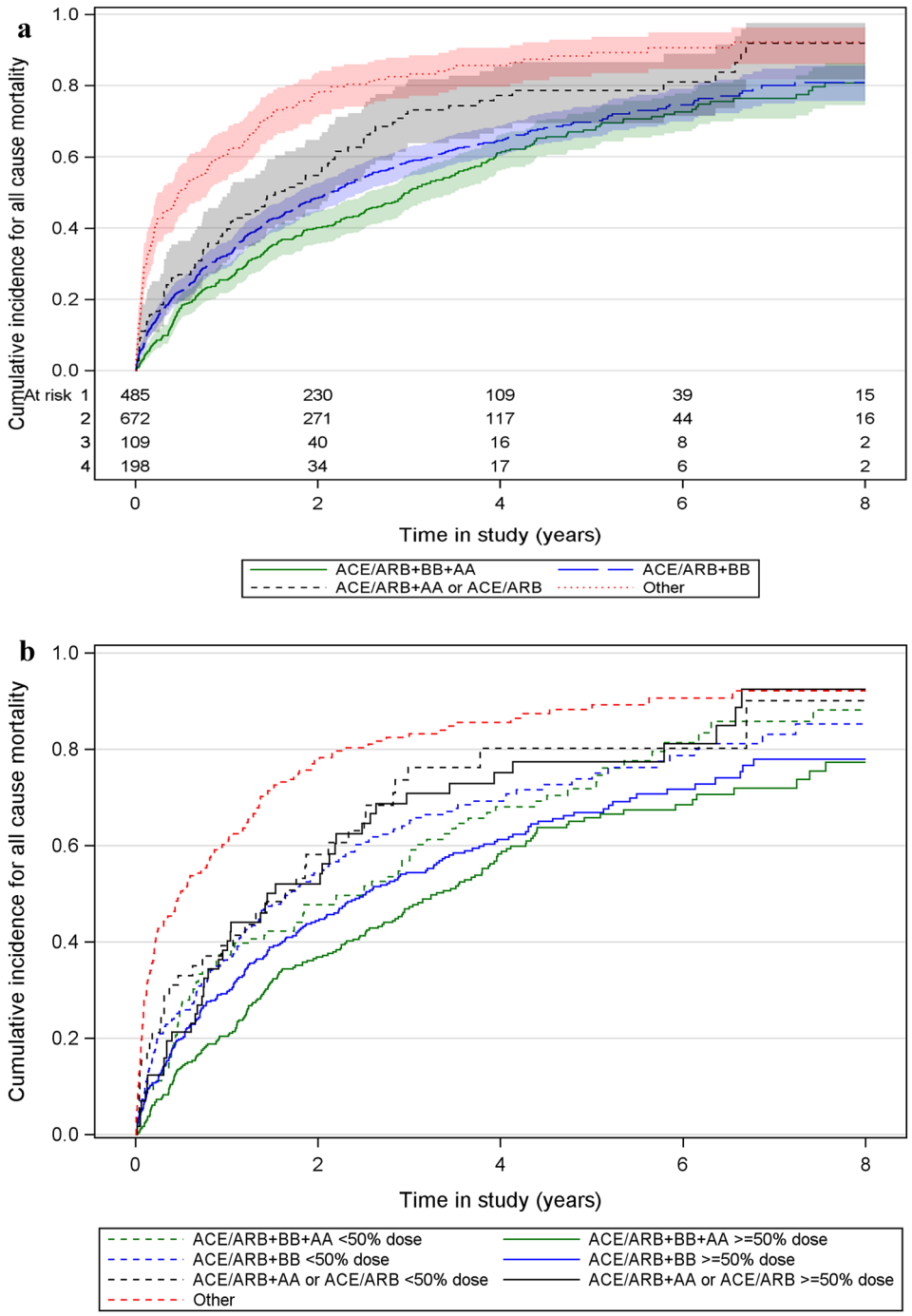


Fig. 2 Cumulative incidence for all-cause mortality by medication group (**A**) and medication/dosage group (**B**)

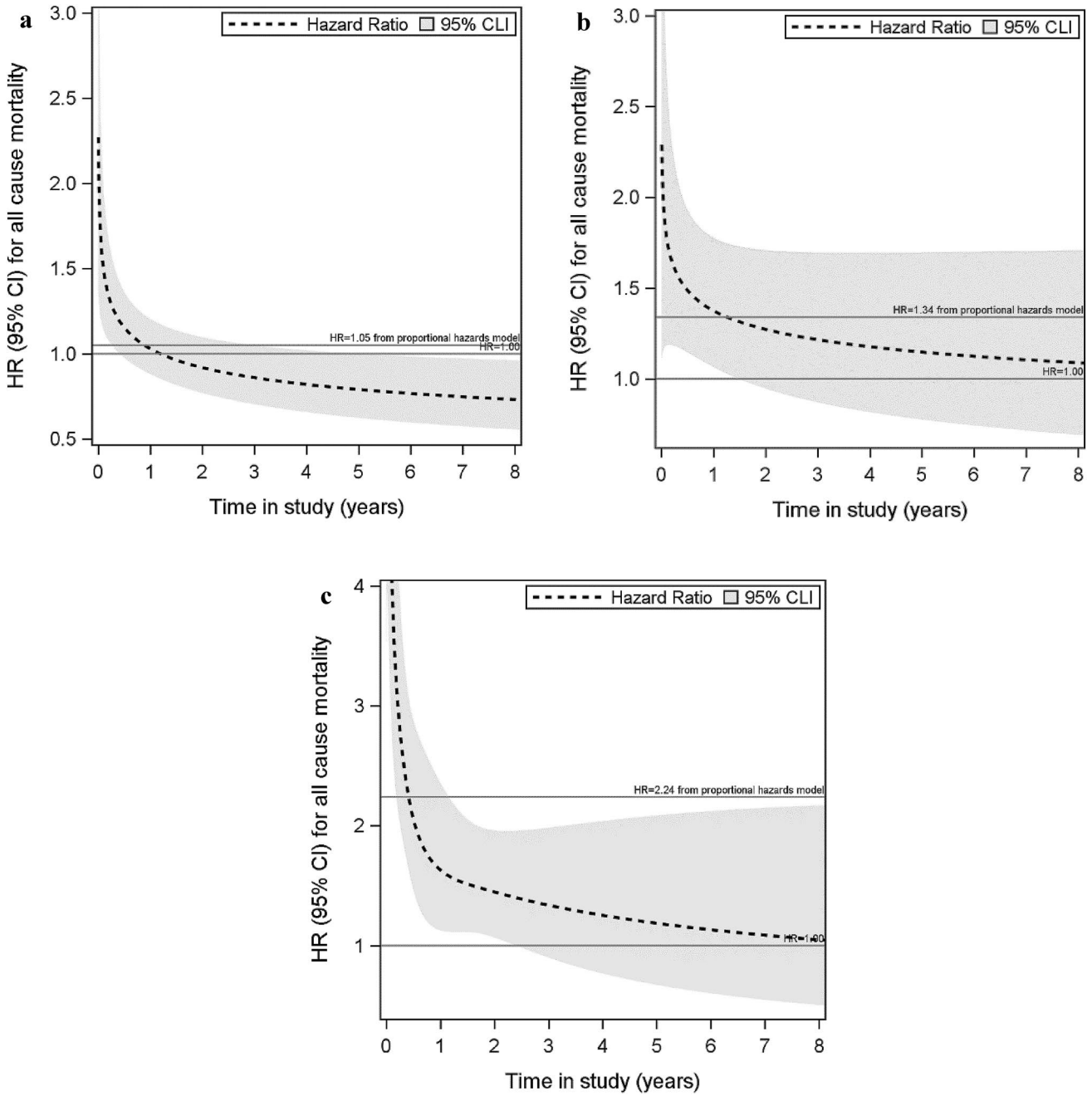


Fig. 3 Flexible parametric models for time to all-cause mortality comparison between treatment groups. (**A**) ACE/ARB + BB vs ACE/ARB + BB + MRA; (**B**) ACE/ARB + MRA or ACE/ARB vs. ACE/ARB + BB + MRA; (**C**) Other vs. ACE/ARB + BB + MRA

Table 3 Number and percent of events, both unadjusted and age- and sex-adjusted event rate (95% CI) by medication/dose group

Medication group	*n* (%) events	Follow-up time (years) Median (IQR)	Unadjusted event rate per 100 person years (95% CI)	Age- and sex-adjusted event rate per 100 person years (95% CI)
ACE/ARB + BB + MRA (group 1)	286 (59.0%)	1.83 (0.64–3.87)	23.8 (21.1–26.7)	26.6 (17.9–39.6)
ACE/ARB + BB (group 2)	406 (60.4%)	1.38 (0.44–3.19)	28.8 (26.1–31.8)	28.1 (20.0–39.4)
ACE/ARB + MRA or ACE/ARB (group 3)	82 (75.2%)	1.20 (0.34–2.63)	39.3 (31.3–48.8)	36.3 (17.2–76.6)
Other	163 (82.3%)	0.45 (0.08–1.43)	70.4 (60.0–82.1)	67.3 (39.6–114.6)
ACE/ARB + BB + MRA (group 1) and < 50% dose	95 (66.4%)	1.23 (0.45–3.19)	31.0 (25.0–37.8)	33.6 (17.0–66.5)
ACE/ARB + BB + MRA (group 1) and > = 50% dose	191 (55.8%)	2.16 (0.78–3.96)	21.4 (18.4–24.6)	24.1 (14.9–39.1)
ACE/ARB + BB (group 2) and < 50% dose	175 (64.6%)	1.19 (0.31–2.80)	34.4 (29.5–39.9)	32.1 (19.3–53.5)
ACE/ARB + BB (group 2) and > = 50% dose	231 (57.6%)	1.56 (0.54–3.43)	25.7 (22.4–29.2)	25.8 (16.6–40.0)
ACE/ARB + MRA or ACE/ARB (group 3) and < 50% dose	37 (71.2%)	1.13 (0.27–2.51)	41.6 (29.3–57.4)	38.3 (12.7–115.0)
ACE/ARB + MRA or ACE/ARB (group 3) and > = 50% dose	45 (78.9%)	1.23 (0.61–2.97)	37.7 (27.5–50.4)	35.0 (13.02–94.8)

Unadjusted 95% CI computed by using exact Poisson limits + Adjusted analyses performed using Poisson regression with log-link function adjusted for age and sex, including log (follow-up time) as offset-parameter, and adjusting for over dispersion

ACEI angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonist

Table 4 Adjusted Cox proportional hazards models for time to all-cause mortality comparison between treatment groups

Comparison	Model 1		Model 2	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
ACE/ARB + BB + *MRA*	1 (ref)		1 (ref)	
ACE/ARB + BB	1.05 (0.90–1.22)	0.54	1.04 (0.89–1.21)	0.62
ACE/ARB + *MRA* or ACE/ARB	1.34 (1.05–1.72)	0.021	1.40 (1.09–1.79)	0.0087
Other	2.24 (1.84–2.72)	< .0001	1.71 (1.39–2.09)	< .0001
ACE/ARB + BB + *MRA* > = 50%	1 (ref)		1 (ref)	
ACE/ARB + BB + *MRA* < 50% dose	1.36 (1.06–1.74)	0.014	1.29 (1.01–1.66)	0.042
ACE/ARB + BB < 50% dose	1.29 (1.05–1.59)	0.017	1.18 (0.96–1.46)	0.12
ACE/ARB + BB > = 50% dose	1.07 (0.88–1.29)	0.51	1.09 (0.90–1.32)	0.39
ACE/ARB + *MRA* or ACE/ARB < 50%	1.53 (1.07–2.17)	0.019	1.53 (1.07–2.19)	0.020
ACE/ARB + *MRA* or ACE/ARB > = 50%	1.43 (1.04–1.99)	0.030	1.50 (1.08–2.09)	0.015
Other	2.47 (1.99–3.05)	< .0001	1.86 (1.49–2.32)	< .0001

ACEI angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *BB* beta blockers, *MRA* mineralocorticoid receptor antagonist

Model 1: Adjusted for age and sex

Model 2: Additionally adjusted for smoking, NYHA, LVEF, eGFR, hemoglobin

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Compliance with ethical standards

Conflicts of interest None.

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