ESC European Society of Cardiology

European Journal of Heart Failure (2023) **25**, 1132–1144
doi:10.1002/ejhf.2928

RESEARCH ARTICLE

Association between a hospitalization for heart failure and the initiation/discontinuation of guideline-recommended treatments: An analysis from the Swedish Heart Failure Registry

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Received 22 December 2022; revised 25 April 2023; accepted 7 June 2023; online publish-ahead-of-print 27 June 2023

Aims To investigate whether a heart failure (HF) hospitalization is associated with initiation/discontinuation of guideline-directed medical HF therapy (GDMT) and consequent outcomes.

Methods and results Among patients in the Swedish HF registry with an ejection fraction <50% enrolled in 2009–2018, initiation/discontinuation of GDMT was investigated by assessing dispensations of GDMT in those with versus without a HF hospitalization. Of 14 737 patients, 6893 (47%) were enrolled when hospitalized for HF. Initiation of GDMT was more likely than discontinuation following a HF hospitalization compared to a control group of patients without a HF hospitalization (odds ratio range 2.1–4.0 vs. 1.4–1.6 for the individual medications), although the proportion of patients not on GDMT was still high (8.1–44.0%). Key patient characteristics triggering less use of GDMT (i.e. less initiation or more discontinuation) were older age and worse renal function. Following a HF hospitalization, initiation of renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitors or beta-blockers was associated with lower and their discontinuation with higher mortality risk, but no association with mortality was observed for initiation/discontinuation of mineralocorticoid receptor antagonists.

Conclusions Following a HF hospitalization, initiation of GDMT was more likely than discontinuation, although still limited. Perceived or actual low tolerance were barriers to GDMT implementation. Early re-/initiation of GDMT was associated with better survival. Our findings represent a call for further implementing the current guideline recommendation for an early re-/initiation of GDMT following a HF hospitalization.

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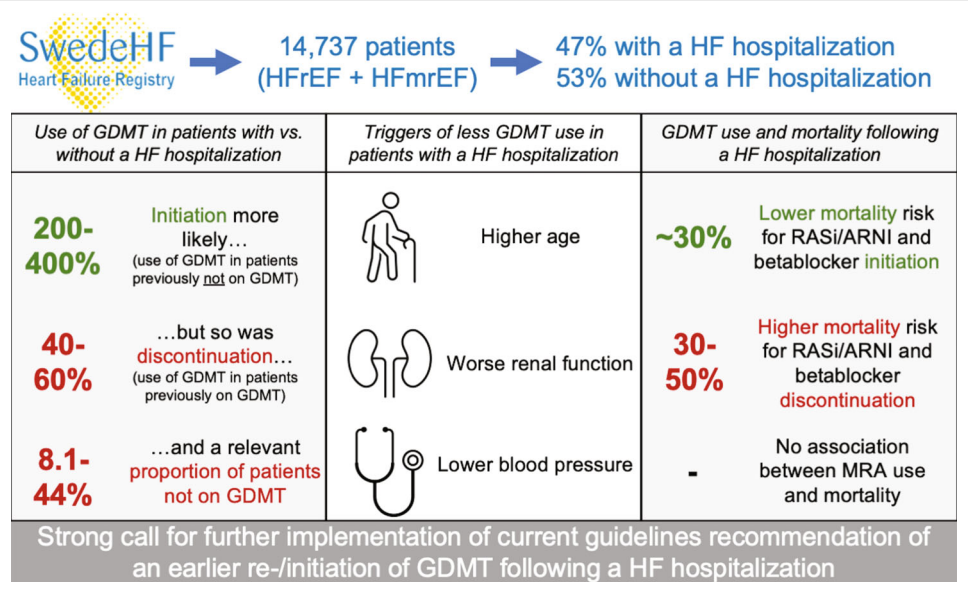
Graphical Abstract



Heart failure hospitalization and initiation/discontinuation of guideline-directed medical therapy: The Swedish Heart Failure Registry. ARNI, angiotensin receptor–neprilysin inhibitor; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor. [Correction added on 26 July 2023, after first online publication: Graphical Abstract caption has been added in this version.]

Keywords Heart failure with reduced ejection fraction • Heart failure with mildly reduced ejection fraction • Guideline-directed medical therapy • Initiation • Discontinuation • Guidelines • Implementation

Introduction

Due to a prevalence of ~2–3% in the Western population and a high morbidity/mortality, heart failure (HF) represents a global pandemic.[1]

Several HF treatments, primarily beta.blockers, renin–angiotensin system inhibitors (RASI), angiotensin receptor–neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i), have been shown to reduce morbidity/mortality in HF with reduced ejection fraction (HFrEF), and there are post-hoc analyses from randomized trials showing consistent results in HF with mildly reduced ejection fraction (HFmrEF).[2] Thus, the 2021 European Society of Cardiology (ESC) HF guidelines recommend these treatments in HFrEF (class I recommendation), and in HFmrEF (class IIB recommendation, except for SGLT2i).[3] Available evidence supports fast initiation of multiple agents.[4,5] However, registries demonstrate persistent underuse/underdosing in clinical practice.[6–8]

Worsening HF often leads to hospitalization and reflects clinical deterioration, therefore representing a vulnerable phase with need and opportunity for treatment optimization. However, a hospitalization may entail tolerance issues, e.g. hypotension, worsening renal function.[9] These factors might trigger treatment discontinuation/down-titration or missed re-initiation, although the 2021 ESC HF guidelines recommend re-initiation/optimization of HF treatments before discharge and early follow-up visit to start/up-titrate therapies (class I recommendation, level of evidence C).[3] Unfortunately, the use of HF treatments in the real world before but also after a worsening HF event seems to be low, which might impact outcomes.[10]

The aim of this study was (i) to assess HF treatment initiation/discontinuation in patients with HFmrEF/HFrEF following a HF hospitalization, (ii) to identify patient characteristics linked to HF treatment initiation/discontinuation, and (iii) to evaluate the associations between HF treatment initiation/discontinuation and mortality.

Methods

Study cohort

The study population was derived from the Swedish Heart Failure Registry (SwedeHF; www.SwedeHF.se).[11] Detailed information in

SwedeHF, including the linkage to Swedish national registries, is provided in online supplementary *Appendix S1*.

Patients

Inclusion criteria were: (1) registration in SwedeHF after 1 January 2009 to enrol patients being treated in accordance with the 2008/2016 ESC HF guidelines[12,13]; (2) ejection fraction <50% (e.g. HFmrEF and HFrEF), as guidelines currently provide treatment recommendations only for these HF phenotypes; (3) HF duration of >6 months to account for the time required to optimize HF therapy; and (4) follow-up of ≥6 months to allow sufficient time for assessment of whether prescribed treatments were also dispensed by the pharmacy. Patients with a history of HF hospitalizations before their SwedeHF registration were excluded to avoid the enrolment of patients at different disease stages. Therefore, only patients with a first HF hospitalization and those who had never been hospitalized, i.e. outpatients (the control population) were included. If a patient had multiple eligible registrations in SwedeHF, only the first one was considered. Patient characteristics were collected at the index date, which was the day of hospital discharge for patients with a HF hospitalization and the day of the outpatient clinic visit for the control population (online supplementary *Figure S1*).

Definition of heart failure treatment initiation and discontinuation

Renin–angiotensin system inhibitors/ARNI, beta-blockers, MRA and loop diuretics were the HF treatments considered in this study. SGLT2i were not considered, as they were not established as a HF treatment in Sweden during the study period.

Discontinuation of a study drug was defined as at least one dispensed prescription within 6 months to 1 day prior to the index date and no dispensed prescription from the index date until 6 months thereafter; and vice versa for initiation.

Statistical analysis

As main analysis, reflecting the 2021 ESC HF guideline recommendations for HFrEF and HFmrEF, HF treatment initiation/discontinuation was analysed in the overall study cohort (HFrEF and HFmrEF together).[3] Additionally, to reflect previous ESC HF guidelines which did not provide a recommendation for HFmrEF, a secondary analysis was conducted only including patients with HFrEF.[12,13]

Categorical variables were presented as frequencies (percentages) and tested by chi-square test for comparisons, while continuous variables were reported as medians (interquartile range) and tested by Kruskal–Wallis test for comparisons.

To determine whether a HF hospitalization was linked with the initiation/discontinuation of HF treatments, for each individual drug separate multivariable logistic regression models were fitted with discontinuation or initiation as the dependent variable and hospitalized versus outpatients as independent variable. Thus, a patient who had one drug initiated and another discontinued could contribute to both models. Twenty-three variables representing demographics, clinical characteristics, comorbidities, and socioeconomics were considered for adjustments (*Table 1*). Also, to explore whether renal function was associated with the likelihood of HF treatment initiation/discontinuation following a HF hospitalization, logistic regression models were fitted stratified by, rather than adjusted for, the estimated glomerular filtration rate (eGFR; unadjusted models for eGFR ≥60, 30–59 and <30 ml/min/1.73 m^2 whereas for adjusted models eGFR ≥60 and <60 ml/min/1.73 m^2 were considered due to the limited sample size).

To investigate the association between recurrent HF hospitalizations and HF treatment initiation/discontinuation, the percentage of patients in whom HF treatments were initiated/discontinued was plotted according to the number of HF hospitalizations within 6 months to 3 years following the index event for patients with complete follow-up for the respective period.

To assess patient characteristics independently associated with HF treatment initiation/discontinuation following a HF hospitalization (i.e. only patients with a HF hospitalization were considered for this analysis), separate logistic regression models were fitted with initiation or discontinuation of each individual study drug as the dependent variable and the above-mentioned 23 variables as the independent variables (*Table 1*).

To evaluate the association between HF treatment initiation/discontinuation and the risk of 3-year all-cause and cardiovascular mortality (again considering only patients with a HF hospitalization), multivariable Cox proportional hazard regressions were fitted. Adjustments were performed for the variables highlighted in *Table 1*. Censoring was performed on 31 December 2019, at time of non-cardiovascular death for the outcome cardiovascular death, at emigration from Sweden or at 3 years from the index date.

In all the multivariable models, missing data for covariates were handled by multiple imputation with 10 imputed datasets generated using the R package *mice*.[14] Variables included in the model are highlighted in *Table 1*.

The level of significance was set to 5% two-sided, and all analyses were performed using R version 4.0.2.

Results

Baseline characteristics

Between 11 May 2000 and 31 December 2019, there were 156 544 registrations in SwedeHF. After application of the selection criteria, 14 737 patients, 9374 (64%) with HFrEF and 5363 (36%) with HFmrEF, were analysed. Of these, 6893 (47%) were patients hospitalized for HF, and 7844 (53%) were outpatients (*Figure 1*).

In the overall cohort, hospitalized patients versus outpatients were older, less frequently male, had more advanced HF, worse renal function and higher comorbidity burden (*Table 1*). Prior treatment with RASI/ARNI and beta-blockers, but not with MRA, was less frequent in hospitalized patients, but use of loop diuretics and devices was higher. Additionally, HF dedicated follow-up care was less frequent in hospitalized patients; they were also more likely living alone, had a lower education and lower income.

When only analysing patients with HFrEF, most of these findings were consistent, except for prior MRA use which was significantly less in hospitalized patients, and there was no significant difference regarding sex distribution (*Table 1*).

Treatment initiation and discontinuation in hospitalized versus outpatients

Following a HF hospitalization, initiation of MRA, RASI/ARNI, beta-blockers or loop diuretics was more frequently observed

Table 1 Baseline characteristics of the study cohort

	Overall study cohort (HFrEF + HFmrEF)				HFrEF only			
	Missing (%)	Outpatients, not hospitalized (*n* = 7844)	Inpatients with a HF hospitalization (*n* = 6893)	*p*-value	Missing (%)	Outpatients, not hospitalized (*n* = 4451)	Inpatients with a HF hospitalization (*n* = 4923)	*p*-value
Demographics								
Male sex[a,b]	0.0	5560 (70.9)	4747 (68.9)	0.008	0.0	3308 (74.3)	3583 (72.8)	0.096
Age (years)	0.0	74.0 [66–80]	78 [69–84]	<0.001	0.0	73 [66–80]	77 [68–83]	<0.001
≥75 years[a,b]	0.0	3742 (47.7)	4161 (60.4)	<0.001	0.0	2060 (46.3)	2781 (56.5)	<0.001
Index year[a]	0.0	2015 [2012–2017]	2012 [2010–2015]	<0.001	0.0	2014 [2011–2017]	2012 [2010–2015]	<0.001
Clinical variables								
HFmrEF[a]	0.0	3393 (43.3)	1970 (28.6)	<0.001	0	0	0	-
NYHA class[a,b]	28.3			<0.001	28.1			<0.001
I		948 (14.0)	158 (4.2)			434 (11.1)	100 (3.5)	
II		3829 (56.4)	1405 (37.2)			2116 (54.3)	969 (34.1)	
III–IV		2016 (29.7)	2213 (58.6)			1349 (34.6)	1771 (62.4)	
Systolic blood pressure (mmHg)	1.8	129.0 [115.0–140.0]	120.0 [110.0–137.0]	<0.001	1.5	125.0 [113.0–140.0]	120.0 [110.0–133.0]	<0.001
>100 mmHg[a,b]	1.8	7033 (92.2)	5915 (86.5)	<0.001	1.5	3935 (90.5)	4123 (84.4)	<0.001
Heart rate (bpm)	2.7	69.0 [60.0–78.0]	73.0 [65.0–84.0]	<0.001	2.3	69.0 [60.0–78.0]	73.0 [65.0–84.0]	<0.001
>70 bpm[a,b]	2.7	3223 (42.7)	3784 (55.7)	<0.001	2.3	1855 (43.0)	2730 (56.4)	<0.001
Body mass index (kg/m^2)	29.6	27.2 [24.2–30.6]	26.6 [23.4–30.5]	<0.001	29.0	27.0 [24.0–30.2]	26.4 [23.2–30.2]	<0.001
≥30 kg/m^2 [a,b]	29.6	1505 (29.2)	1487 (28.5)	0.413	29.0	788 (26.9)	998 (26.7)	0.883
Potassium (mmol/L)	13.9	4.3 [4.0–4.5]	4.1 [3.8–4.4]	<0.001	14.5	4.3 [4.0–4.5]	4.1 [3.8–4.4]	<0.001
Potassium, categorized[a,b]	13.9			<0.001	14.5			<0.001
Normokalaemia		6763 (95.2)	5082 (91.0)			3838 (94.8)	3624 (91.4)	
Hypokalaemia		126 (1.8)	341 (6.1)			74 (1.8)	228 (5.7)	
Hyperkalaemia		215 (3.0)	160 (2.9)			135 (3.3)	115 (2.9)	
eGFR (ml/min/1.73 m^2)	1.9	70.7 [54.3–87.5]	56.5 [41.7–75.2]	<0.001	1.4	70.7 [54.6–88.2]	57.7 [42.5–76.1]	<0.001
eGFR, categorized[a,b]	1.9			<0.001	1.4			<0.001
≥60		5058 (66.6)	3065 (44.7)			2894 (66.7)	2271 (46.3)	
30–59		2332 (30.7)	3190 (46.5)			1320 (30.4)	2234 (45.6)	
<30		208 (2.7)	608 (8.9)			123 (2.8)	398 (8.1)	
NT-proBNP (pg/ml)	43.7	1340 [577–2740]	4609 [2123–9540]	<0.001	44.7	1558 [693–3236]	5071 [2340–10 496]	<0.001
Above median[a,b]	43.7	1629 (33.6)	2520 (73.0)	<0.001	44.7	852 (31.0)	1741 (71.3)	<0.001
Comorbidities								
Former/current smoker[a,b]	22.5	3601 (57.0)	2942 (57.8)	0.404	22.0	2135 (58.7)	2189 (59.6)	0.434
Anaemia[a,b]	5.4	1742 (24.5)	3031 (44.4)	<0.001	4.6	990 (24.3)	2038 (41.8)	<0.001
Diabetes mellitus[a,b]	0.0	1818 (23.2)	2607 (37.8)	<0.001	0.0	1100 (24.7)	1813 (36.8)	<0.001
Atrial fibrillation/flutter[a,b]	0.0	4231 (53.9)	4520 (65.6)	<0.001	0.0	2313 (52.0)	3087 (62.7)	<0.001
Ischaemic heart disease[a,b]	0.0	4651 (59.3)	4627 (67.1)	<0.001	0.0	2796 (62.8)	3355 (68.1)	<0.001
Arterial hypertension[a,b]	0.0	5183 (66.1)	5007 (72.6)	<0.001	0.0	2856 (64.2)	3420 (69.5)	<0.001
Peripheral artery disease[a,b]	0.0	647 (8.2)	843 (12.2)	<0.001	0.0	396 (8.9)	602 (12.2)	<0.001
Stroke/TIA[a,b]	0.0	1229 (15.7)	1448 (21.0)	<0.001	0.0	703 (15.8)	992 (20.2)	<0.001
Valvular heart disease	0.0	1825 (23.3)	2400 (34.8)	<0.001	0.0	1000 (22.5)	1646 (33.4)	<0.001
Liver disease[a]	0.0	109 (1.4)	206 (3.0)	<0.001	0.0	58 (1.3)	167 (3.4)	<0.001
Cancer in past 3 years[a,b]	0.0	943 (12.0)	884 (12.8)	0.147	0.0	539 (12.1)	606 (12.3)	0.792
COPD[a,b]	0.0	857 (10.9)	1226 (17.8)	<0.001	0.0	477 (10.7)	816 (16.6)	<0.001
Severe bleeding[a]	0.0	1227 (15.6)	1591 (23.1)	<0.001	0.0	683 (15.3)	1045 (21.2)	<0.001
Treatments								
RASI[a]	0.0	7122 (90.8)	5403 (78.4)	<0.001	0.0	4118 (92.5)	3946 (80.2)	<0.001
ACEi	0.0	4658 (59.4)	3574 (51.8)	<0.001	0.0	2707 (60.8)	2637 (53.6)	<0.001
ARB	0.0	2875 (36.7)	2150 (31.2)	<0.001	0.0	1669 (37.5)	1559 (31.7)	<0.001
ARNI	0.0	156 (2.0)	27 (0.4)	<0.001	0.0	138 (3.1)	27 (0.5)	<0.001
Beta-blockers[a]	0.0	6941 (88.5)	5556 (80.6)	<0.001	0.0	4012 (90.1)	3912 (79.5)	<0.001
MRA[a]	0.0	2490 (31.7)	2159 (31.3)	0.594	0.0	1583 (35.6)	1648 (33.5)	0.035
Loop diuretic[a]	0.0	4062 (51.8)	5104 (74.0)	<0.001	0.0	2429 (54.6)	3586 (72.8)	<0.001
CRT/ICD[a]	2.5	579 (7.7)	973 (14.2)	<0.001	1.7	442 (10.2)	899 (18.4)	<0.001
Digoxin[a]	0.3	845 (10.8)	1134 (16.5)	<0.001	0.4	470 (10.6)	834 (17.0)	<0.001
Platelet inhibitor[a]	0.5	3296 (42.2)	3024 (44.1)	0.016	0.5	1981 (44.6)	2238 (45.8)	0.287
Oral anticoagulant[a]	0.3	3896 (49.8)	3463 (50.5)	0.377	0.3	2168 (48.8)	2432 (49.6)	0.425
Statin[a]	0.3	4577 (58.5)	3620 (52.7)	<0.001	0.4	2679 (60.4)	2643 (53.9)	<0.001
Nitrate[a]	0.4	830 (10.6)	1344 (19.6)	<0.001	0.5	489 (11.0)	909 (18.6)	<0.001
Follow-up referral to nurse-led HF clinic[a]	4.6	5533 (72.6)	2944 (45.7)	<0.001	4.6	3193 (73.7)	2313 (50.2)	<0.001

Table 1 (Continued)

	Overall study cohort (HFrEF + HFmrEF)				HFrEF only			
	Missing (%)	Outpatients, not hospitalized (*n* = 7844)	Inpatients with a HF hospitalization (*n* = 6893)	*p*-value	Missing (%)	Outpatients, not hospitalized (*n* = 4451)	Inpatients with a HF hospitalization (*n* = 4923)	*p*-value
Follow-up referral specialty[a]	3.3			<0.001	3.2			<0.001
Specialty care		5149 (66.8)	3996 (61.0)			3308 (75.6)	3110 (66.3)	
Primary care		2474 (32.1)	2351 (35.9)			1030 (23.5)	1448 (30.8)	
Other		88 (1.1)	200 (3.1)			40 (0.9)	136 (2.9)	
Socioeconomics								
Living alone[a,b]	0.2	3132 (40.0)	3603 (52.4)	<0.001	0.3	1729 (39.0)	2506 (51.0)	<0.001
Children[a]	0.0	6699 (85.4)	5746 (83.4)	0.001	0.0	3785 (85.0)	4079 (82.9)	0.005
Education[a,b]	2.1			<0.001	2.2			<0.001
Compulsory school		3119 (40.4)	3115 (46.5)			1804 (41.3)	2161 (45.0)	
Secondary school		3189 (41.3)	2555 (38.1)			1787 (40.9)	1901 (39.6)	
University		1416 (18.3)	1029 (15.4)			780 (17.8)	735 (15.3)	
Disposable income above median[a,b]	0.2	4186 (53.5)	3172 (46.1)	<0.001	0.3	2396 (54.0)	2342 (47.7)	<0.001

Values are given as n (%), or median [interquartile range].

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula); HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASI, renin–angiotensin system inhibitor; TIA, transient ischaemic attack.

[a]Variables used in the multiple imputation;

[b]variables adjusted for in the logistic/Cox regression models. When stratifying patients based on NT-proBNP > or ≤ median, the median NT-proBNP per ejection fraction category (HFrEF or HFmrEF) was considered; and when stratifying patients based on income > or ≤ median, the median income per year of enrolment was considered.

than discontinuation (*Figure 2*): initiation versus discontinuation among patients hospitalized for HF was 41.4% versus 20.4% for MRA, 64.8% versus 7.3% for RASI/ARNI, 71.8% versus 4.9% for beta-blockers, 80.8% versus 4.3% for loop diuretics, whereas 79.6%, 92.7%, 95.1%, and 95.7% were kept on treatment, respectively. For outpatients, initiation was also more frequent than discontinuation (16.4% vs. 14.5% for MRA, 53.2% vs. 3.6% for RASI/ARNI, 44.1% vs. 3.4% for beta-blockers, 18.4% vs. 18.6% for loop diuretics, with 85.5%, 96.4%, 96.6%, and 81.4% who were kept on these treatments, respectively), although the frequency of initiation/discontinuation of HF treatments was lower compared to patients with a HF hospitalization.

In patients who were not on treatment prior to the index date, initiations of MRA (odds ratio [OR] 3.9, 95% confidence interval [CI] 3.5–4.4), of RASI/ARNI (OR 2.3, 95% CI 1.8–2.8), of beta-blockers (OR 3.9, 95% CI 3.1–4.8) and of loop diuretics (OR 13.4, 95% CI 11.4–15.7) were more likely in hospitalized versus outpatients (*Figure 3*). Results were consistent when stratifying by eGFR, although crude initiation rates were lower when renal function was lower (online supplementary *Figure S2*, *Table S1*).

In patients who were on treatment prior to the index date, discontinuations of RASI/ARNI (OR 1.5, 95% CI 1.2–1.8) and of beta-blockers (OR 1.4, 95% CI 1.2–1.8) were more likely, whereas discontinuation of loop diuretics (OR 0.3, 95% CI 0.2–0.3) was less likely in hospitalized versus outpatients, and no significant difference was observed for MRA discontinuation (OR 1.1, 95% CI 0.9–1.3; *Figure 3*). These associations were consistent when stratifying by eGFR, although discontinuation rates of MRA, RASI/ARNI and beta-blockers increased, and discontinuation rates of loop diuretics decreased when renal function was lower, and discontinuation rates were highest while initiation rates lowest in patients with an eGFR <30 ml/min/1.73 m^2 regardless of whether patients were hospitalized or not (online supplementary *Figure S2*, *Table S1*). These results were consistent when patients with HFrEF were analysed separately.

When analysing the impact of recurrent HF hospitalizations, the frequency of MRA and loop diuretic initiation, but also of discontinuation of all the study treatments increased with a higher number of HF hospitalizations (online supplementary *Figure S3*).

Independent predictors of treatment initiation and discontinuation in patients hospitalized for heart failure

Several factors were independently associated with initiation/discontinuation of HF treatments in patients hospitalized for HF (*Table 2*).

Initiation of MRA was less likely in older patients or those living alone, in those with a higher blood pressure, lower eGFR, or anaemia, but more likely in those with hypokalaemia and atrial fibrillation. Initiation of RASI/ARNI was also less likely in older patients, and in those with lower eGFR, valvular heart disease, atrial fibrillation, prior stroke/transient ischaemic attack or anaemia, but more likely in male patients. Beta-blocker initiation was less likely in older patients as well as those with anaemia, valvular heart disease, chronic obstructive pulmonary disease and recent cancer, but was not associated with eGFR or blood pressure. Loop diuretic initiation was more likely in older patients, those with higher heart rate, an eGFR of 30–59 ml/min/1.73 m^2 (but not in those with an eGFR <30 ml/min/1.73 m^2), higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) and atrial fibrillation, and less likely in those with hyperkalaemia.

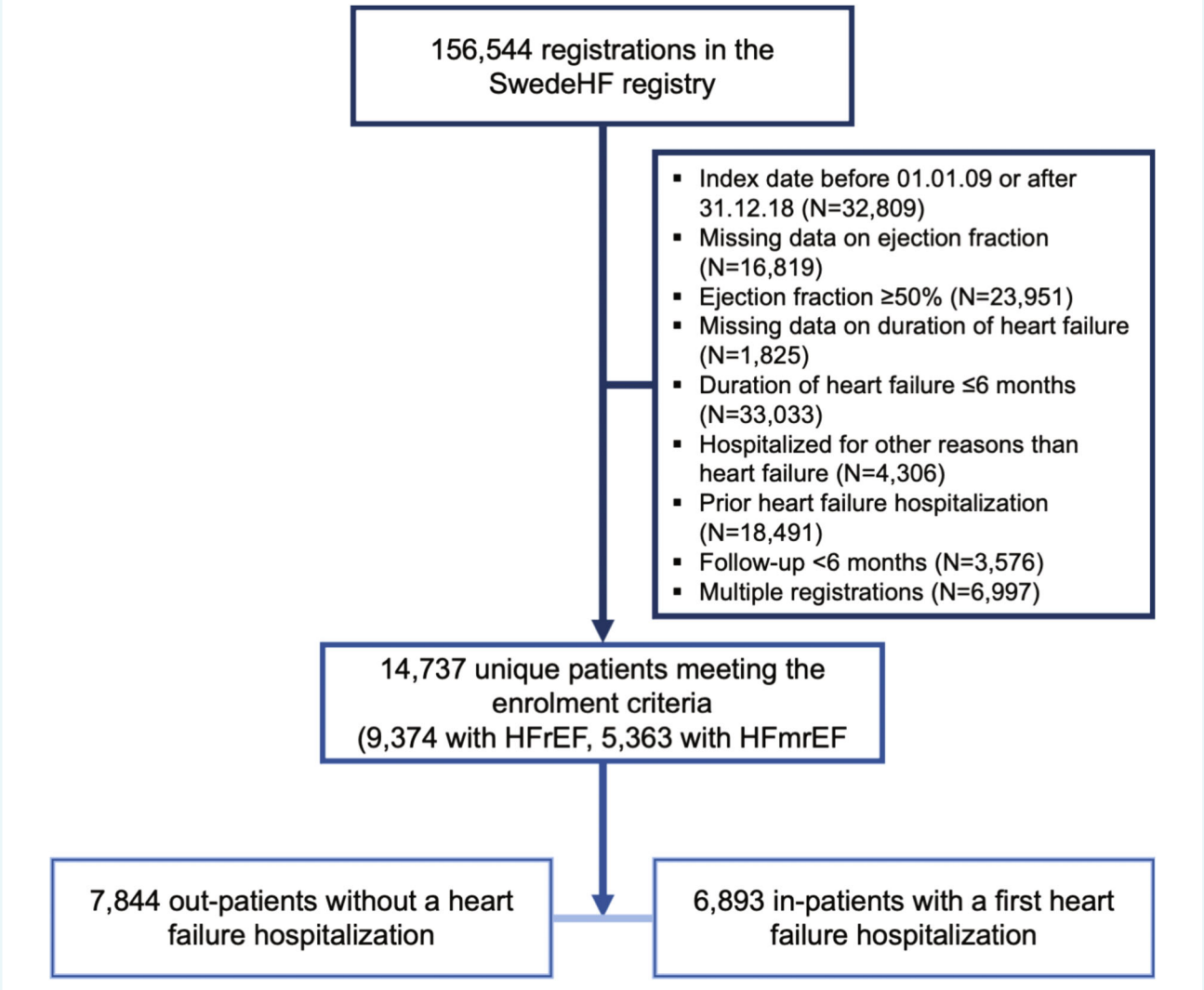


Figure 1 Study flow-chart. HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Discontinuation of MRA was more likely in patients with a lower eGFR, with anaemia and in those living alone. RASI/ARNI discontinuation was more likely in patients with lower blood pressure, hypokalaemia, lower eGFR and with atrial fibrillation, anaemia, and a recent cancer diagnosis, whereas beta-blocker discontinuation was not associated with any of the tested patient characteristic. Loop diuretic discontinuation was less likely in older patients in those with an eGFR of 30–59 ml/min/1.73 m^2, but not in those with an eGFR <30 ml/min/1.73 m^2.

Three-year mortality risk associated with treatment initiation/discontinuation following a heart failure hospitalization

Among patients hospitalized for HF, during a median follow-up time after the index HF hospitalization of 2.8 (minimum 0.5, maximum 3.0) years, event rates for all-cause and cardiovascular death were 200 (95% CI 193–207) and 134 (95% CI 128–140) per 1000 patient-years, respectively.

Initiations of RASI/ARNI and of beta-blockers were associated with a lower, whereas initiation of loop diuretics with a higher risk of 3-year all-cause and cardiovascular mortality. There was no association between MRA initiation and all-cause/cardiovascular mortality (*Figure 4*, online supplementary *Figure S4*). These findings were consistent when patients with HFrEF were analysed separately, except for the initiation of MRA which was then associated with a lower 3-year all-cause mortality risk (*Figure 4*).

Discontinuations of RASI/ARNI and of beta-blocker were associated with a higher risk of 3-year all-cause and cardiovascular mortality, whereas discontinuations of MRA and loop diuretics were neither associated with all-cause nor cardiovascular mortality risk (*Figure 4*, online supplementary *Figure S4*). These findings were consistent when considering only patients with HFrEF, except for the discontinuation of loop diuretics which was then associated with a

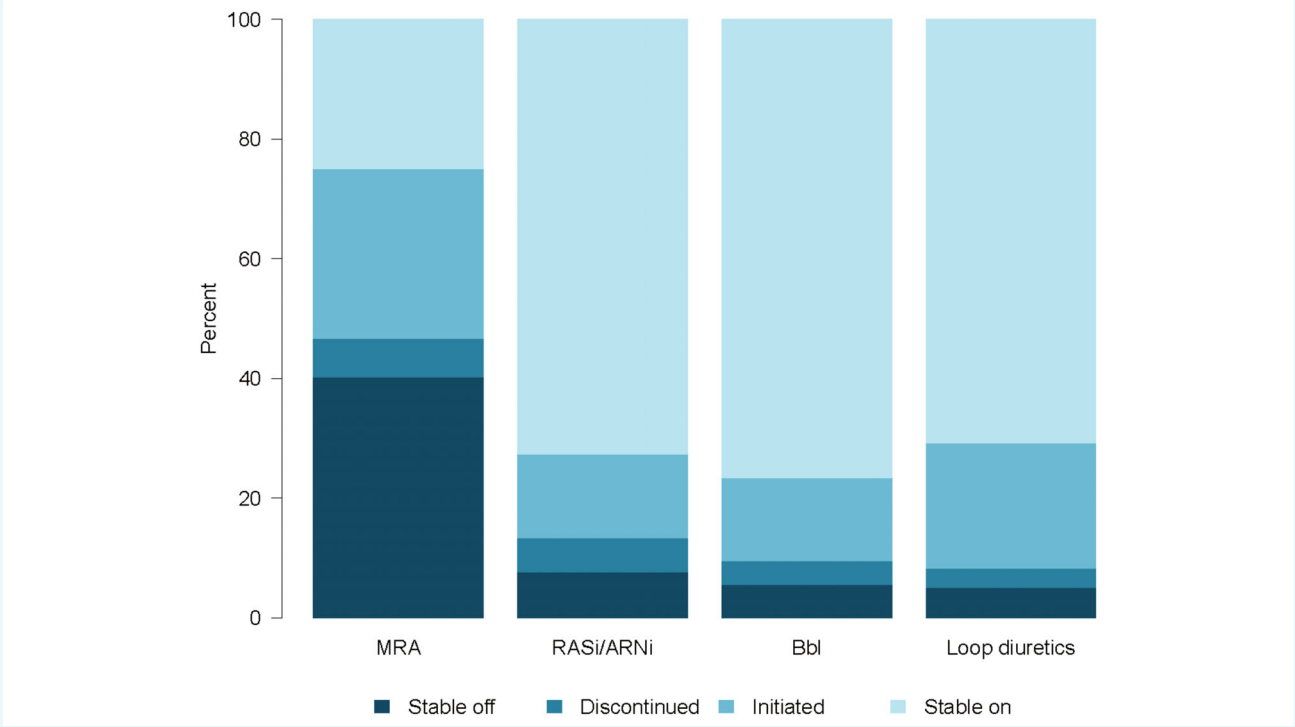


Figure 2 Dispensation of heart failure treatments following a heart failure hospitalization. Dispensation of heart failure treatments before and after a heart failure hospitalization were analysed. No prior treatment was defined as no dispensed prescription within 6 months to 1 day before the index date, and post treatment was defined as one dispensed prescription from the index date until 6 months thereafter, and vice versa. 'Stable off' indicates no dispensed treatment before and after the heart failure hospitalization, 'discontinued' indicates dispensed treatment before but not after the heart failure hospitalization, 'initiated' indicates no dispensed treatment before but after the heart failure hospitalization, and 'stable on' indicates dispensed treatment before and after the heart failure hospitalization. ARNi, angiotensin receptor–neprilysin inhibitor; Bbl, beta-blocker; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor.

lower 3-year cardiovascular mortality risk (*Figure 4*, online supplementary *Figure S4*).

Discussion

Among patients with HFrEF/HFmrEF, a HF hospitalization was associated with more initiation of HF treatments than with their discontinuation, although many patients remained on non-optimal HF therapy. Major barriers to optimization were higher age and worse renal function (*Graphical Abstract*). As initiation of HF treatments was associated with a lower and discontinuation with a higher mortality, our results highlight the importance of early re-/initiation of guideline-recommended HF treatments following a HF hospitalization.

Associations between a heart failure hospitalization and initiation/discontinuation of heart failure treatments

In this analysis, which assessed dispensations instead of prescriptions (e.g. actual vs. intended use of treatments), HF treatments were overall more frequently initiated than discontinued following a HF hospitalization. This may be counter to common perceptions. However, when using an outpatient cohort as comparator, a HF hospitalization was not only associated with HF treatment initiation, but also with considerable discontinuation, although the magnitude of the association was greater for initiation. This highlights that although treatment initiation is more likely, in a non-negligible proportion of patients (i.e. 8.1–44%), HF treatments are not re-/initiated in the early post-discharge period, despite our analysis was conducted within a universal health care system where HF treatments are accessible regardless of the socioeconomic status.[15] Indeed our analysis considered a 6-month time frame for actual dispensation to define treatment initiation/discontinuation which allowed us also to consider potential changes in therapies occurring after the hospitalization, e.g. during an early follow-up.[3] Overall, our findings are consistent with those from the CHAMP-HF registry, where a HF hospitalization was also associated with initiation as well as discontinuation of HF treatments in patients with HFrEF.[16,17] A HF hospitalization can therefore be considered both an opportunity for and a barrier to the implementation of guideline-recommended HF care. Unfortunately, if observed over a longer time, the positive trend toward initiation seems to level off.[7,18] This might even be

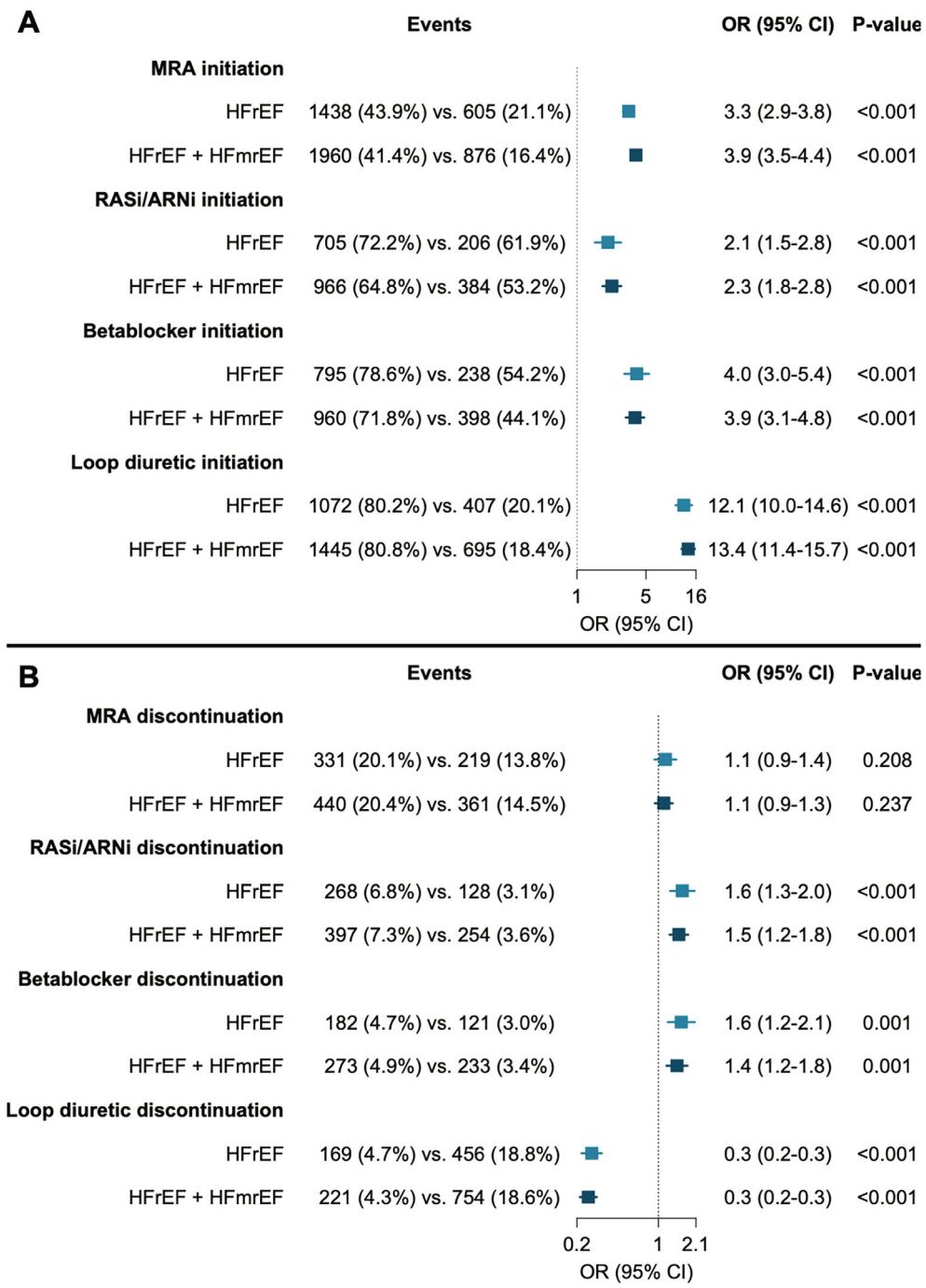


Figure 3 Likelihood of initiation/discontinuation of heart failure treatments in patients with versus without a heart failure hospitalization. Initiation/discontinuation of heart failure treatments is compared between patients with a heart failure hospitalization versus outpatients (i.e. patients without a heart failure hospitalization). For initiation of heart failure treatments (*A*), no prior treatment was defined as no dispensed prescription within 6 months to 1 day before the index date, and post treatment is defined as one dispensed prescription from the index date until 6 months thereafter, and vice versa for discontinuation of heart failure treatments (*B*). Crude event rates and adjusted odds ratios (OR) are shown, and variables used for adjustment in the underlying logistic regression model are reported in *Table 1*. An OR >1 indicates a higher, and an OR <1 indicates a lower likelihood of initiation/discontinuation of heart failure treatments in hospitalized patients. ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor.

Table 2 Predictors of initiation and of discontinuation of heart failure treatments following a heart failure hospitalization

		Odds ratio (95% confidence interval), p-value			
	Initiation/ discontinuation	**MRA**	**RASI/ARNI**	**Betablockers**	**Loop diuretics**
Male vs. female sex	Initiation	0.9 (0.8–1.1), 0.311	1.3 (1.0–1.7), 0.049	1.2 (0.9–1.7), 0.187	0.9 (0.7–1.2), 0.531
	Discontinuation	0.9 (0.7–1.2), 0.673	1.0 (0.7–1.2), 0.702	1.2 (0.9–1.6), 0.269	1.1 (0.8–1.5), 0.732
Age ≥ vs. < 75 years	Initiation	0.6 (0.6–0.7), <0.001	0.5 (0.4–0.7), <0.001	0.5 (0.3–0.6), <0.001	1.5 (1.1–2.0), 0.005
	Discontinuation	0.9 (0.7–1.1), 0.239	1.1 (0.9–1.4), 0.386	1.3 (1.0–1.7), 0.091	0.7 (0.5–1.0), 0.034
NYHA II vs. I	Initiation	1.1 (0.8–1.7), 0.490	1.3 (0.7–2.6), 0.444	1.5 (0.7–3.4), 0.345	1.3 (0.8–2.1), 0.260
	Discontinuation	1.0 (0.5–1.9), 0.929	0.8 (0.4–1.6), 0.593	0.8 (0.4–1.6), 0.561	1.3 (0.5–3.4), 0.531
NYHA III/IV vs. I	Initiation	1.3 (0.9–1.9), 0.239	1.2 (0.6–2.3), 0.547	1.3 (0.6–2.9), 0.560	1.5 (0.9–2.6), 0.155
	Discontinuation	1.1 (0.5–2.4), 0.760	0.9 (0.5–1.8), 0.788	0.8 (0.4–1.6), 0.560	1.2 (0.5–2.9), 0.716
SBP > vs. ≤100 mmHg	Initiation	0.7 (0.6–0.9), 0.002	1.1 (0.8–1.7), 0.502	1.3 (0.9–1.9), 0.132	1.2 (0.8–1.7), 0.444
	Discontinuation	1.0 (0.8–1.3), 0.936	0.7 (0.5–0.9), 0.009	0.8 (0.6–1.1), 0.201	1.0 (0.7–1.4), 0.859
Heart rate > vs. ≤70 bpm	Initiation	1.0 (0.9–1.2), 0.496	1.0 (0.8–1.3), 0.715	1.3 (1.0–1.6), 0.077	1.6 (1.2–2.1), <0.001
	Discontinuation	0.9 (0.7–1.1), 0.261	1.1 (0.9–1.4), 0.395	0.8 (0.6–1.0), 0.059	0.9 (0.7–1.2), 0.646
BMI ≥ vs. <30 kg/m^2	Initiation	1.1 (0.9–1.3), 0.366	1.0 (0.7–1.3), 0.866	1.0 (0.7–1.4), 0.989	1.1 (0.8–1.6), 0.593
	Discontinuation	0.8 (0.6–1.1), 0.131	0.9 (0.7–1.2), 0.552	1.2 (0.9–1.6), 0.273	0.8 (0.6–1.2), 0.331
Hypo- vs. normokalemia	Initiation	1.4 (1.1–1.8), 0.009	0.7 (0.4–1.2), 0.247	0.9 (0.5–1.6), 0.756	1.4 (0.6–3.1), 0.392
	Discontinuation	1.1 (0.6–1.8), 0.801	1.7 (1.1–2.6), 0.021	1.3 (0.8–2.2), 0.298	0.8 (0.4–1.5), 0.415
Hyper- vs. normokalemia	Initiation	0.6 (0.4–1.1), 0.079	1.4 (0.6–3.3), 0.462	0.9 (0.3–2.7), 0.854	0.3 (0.2–0.7), 0.003
	Discontinuation	1.4 (0.8–2.7), 0.269	1.1 (0.6–2.0), 0.692	0.7 (0.3–1.8), 0.457	1.5 (0.7–3.1), 0.255
eGFR 30–59 vs. ≥60 mL/min/1.73 m^2	Initiation	0.6 (0.5–0.7), <0.001	0.4 (0.3–0.6), <0.001	1.0 (0.7–1.3), 0.905	1.8 (1.3–2.5), <0.001
	Discontinuation	1.9 (1.5–2.4), <0.001	1.5 (1.2–2.0), 0.001	0.8 (0.6–1.1), 0.129	0.7 (0.5–1.0), 0.025
eGFR <30 vs. ≥60 mL/min/1.73 m^2	Initiation	0.2 (0.2–0.3), <0.001	0.1 (0.1–0.2), <0.001	1.0 (0.6–1.7), 0.985	1.4 (0.7–2.8), 0.411
	Discontinuation	3.0 (2.0–4.7), <0.001	3.8 (2.7–5.3), <0.001	1.2 (0.8–1.9), 0.314	0.9 (0.5–1.5), 0.600
NTproBNP > vs. ≤ median	Initiation	1.1 (1.0–1.3), 0.174	1.1 (0.7–1.6), 0.700	1.0 (0.7–1.4), 0.928	1.9 (1.4–2.6), <0.001
	Discontinuation	1.2 (0.9–1.6), 0.281	1.0 (0.7–1.3), 0.777	1.1 (0.7–1.6), 0.715	0.8 (0.6–1.2), 0.324
Ischemic heart disease yes vs. no	Initiation	1.0 (0.8–1.1), 0.568	0.8 (0.6–1.0), 0.111	1.0 (0.7–1.2), 0.754	1.3 (1.0–1.7), 0.063
	Discontinuation	0.9 (0.7–1.2), 0.599	0.9 (0.7–1.1), 0.228	1.1 (0.8–1.5), 0.418	1.0 (0.7–1.3), 0.794
Smoking former/current vs. no	Initiation	1.0 (0.9–1.3), 0.619	1.0 (0.7–1.4), 0.958	1.2 (0.9–1.6), 0.196	1.2 (0.9–1.6), 0.320
	Discontinuation	1.0 (0.7–1.3), 0.806	1.0 (0.8–1.3), 0.976	0.8 (0.6–1.1), 0.146	0.9 (0.7–1.3), 0.666
Atrial fibrillation yes vs. no	Initiation	1.2 (1.1–1.4), 0.002	0.7 (0.5–0.9), 0.006	1.0 (0.8–1.3), 0.947	1.6 (1.3–2.1), <0.001
	Discontinuation	1.1 (0.8–1.4), 0.640	1.3 (1.0–1.7), 0.031	1.1 (0.8–1.5), 0.470	0.8 (0.6–1.0), 0.062
Anemia yes vs. no	Initiation	0.8 (0.7–0.9), 0.001	0.7 (0.6–1.0), 0.023	0.7 (0.5–0.9), 0.006	1.0 (0.7–1.3), 0.868
	Discontinuation	1.4 (1.1–1.7), 0.003	1.4 (1.2–1.8), 0.001	0.9 (0.7–1.2), 0.495	0.8 (0.6–1.0), 0.085
Diabetes yes vs. no	Initiation	1.1 (0.9–1.2), 0.365	0.9 (0.7–1.1), 0.274	0.9 (0.7–1.2), 0.648	1.2 (0.9–1.6), 0.224
	Discontinuation	0.9 (0.7–1.2), 0.630	0.9 (0.7–1.1), 0.245	1.2 (0.9–1.6), 0.129	0.8 (0.6–1.1), 0.185
Hypertension yes vs. no	Initiation	1.1 (1.0–1.3), 0.188	1.0 (0.8–1.3), 0.981	1.1 (0.8–1.4), 0.648	1.2 (0.9–1.5), 0.326
	Discontinuation	1.0 (0.8–1.3), 0.916	0.9 (0.7–1.1), 0.323	0.9 (0.7–1.2), 0.427	0.8 (0.6–1.1), 0.109
Valvular heart disease yes vs. no	Initiation	1.1 (0.9–1.3), 0.234	0.5 (0.4–0.7), <0.001	0.7 (0.5–0.9), 0.013	1.2 (0.9–1.6), 0.299
	Discontinuation	0.9 (0.7–1.1), 0.349	1.2 (0.9–1.5), 0.153	1.1 (0.9–1.5), 0.370	1.1 (0.8–1.4), 0.713
Peripheral artery disease yes vs. no	Initiation	1.0 (0.8–1.2), 0.645	0.8 (0.6–1.2), 0.282	0.8 (0.6–1.2), 0.330	0.7 (0.5–1.1), 0.107
	Discontinuation	1.0 (0.7–1.4), 0.879	1.2 (0.9–1.6), 0.234	1.2 (0.9–1.7), 0.283	0.8 (0.5–1.3), 0.411
COPD yes vs. no	Initiation	1.0 (0.8–1.2), 0.923	0.9 (0.6–1.2), 0.365	0.7 (0.5–0.9), 0.016	0.8 (0.6–1.2), 0.281
	Discontinuation	1.0 (0.8–1.4), 0.821	1.0 (0.7–1.3), 0.809	1.1 (0.8–1.6), 0.426	1.1 (0.8–1.6), 0.450
Recent cancer diagnosis yes vs. no	Initiation	0.9 (0.8–1.1), 0.529	0.8 (0.6–1.2), 0.271	0.7 (0.5–0.9), 0.023	0.9 (0.6–1.4), 0.747
	Discontinuation	1.0 (0.7–1.3), 0.774	1.5 (1.2–2.0), 0.002	1.3 (0.9–1.8), 0.163	1.3 (0.9–1.9), 0.156
Stroke/TIA yes vs. no	Initiation	0.9 (0.8–1.1), 0.447	0.7 (0.5–1.0), 0.023	0.8 (0.6–1.1), 0.169	0.7 (0.5–1.0), 0.062
	Discontinuation	1.2 (0.9–1.6), 0.153	0.8 (0.6–1.1), 0.143	1.0 (0.7–1.3), 0.865	1.0 (0.7–1.4), 0.916
Living alone vs. cohabitating	Initiation	0.9 (0.8–1.0), 0.039	0.9 (0.7–1.1), 0.315	1.0 (0.7–1.2), 0.754	1.1 (0.8–1.4), 0.601
	Discontinuation	1.3 (1.0–1.6), 0.043	1.1 (0.8–1.3), 0.632	0.9 (0.7–1.1), 0.279	0.9 (0.7–1.2), 0.508
Secondary vs. compulsory school	Initiation	1.0 (0.9–1.2), 0.756	1.2 (0.9–1.6), 0.206	1.2 (0.9–1.6), 0.162	0.9 (0.7–1.2), 0.563
	Discontinuation	0.9 (0.7–1.2), 0.473	0.9 (0.7–1.2), 0.478	1.1 (0.9–1.5), 0.337	1.2 (0.9–1.7), 0.240
University vs. compulsory school	Initiation	1.1 (0.9–1.3), 0.550	1.2 (0.8–1.8), 0.310	1.2 (0.8–1.8), 0.433	0.8 (0.6–1.2), 0.384
	Discontinuation	1.0 (0.7–1.4), 0.938	0.9 (0.6–1.2), 0.419	0.9 (0.6–1.4), 0.743	1.3 (0.9–2.0), 0.146
Income > vs. ≤ median	Initiation	1.1 (1.0–1.3), 0.103	0.9 (0.7–1.1), 0.220	1.0 (0.7–1.3), 0.726	0.9 (0.7–1.1), 0.331
	Discontinuation	1.0 (0.8–1.2), 0.806	1.1 (0.9–1.4), 0.355	1.1 (0.8–1.4), 0.544	1.3 (0.9–1.7), 0.129

ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula); MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASI, renin–angiotensin system inhibitor; SBP, systolic blood pressure; TIA, transient ischaemic attack.

To evaluate predictors of initiation/discontinuation of heart failure treatments among patients with a heart failure hospitalization, logistic regression models were fitted with either MRA, RASI/ARNI, beta-blocker or loop diuretic initiation/discontinuation as the dependent variable and all variables shown in the table as independent variables. For initiation of heart failure treatments, no prior treatment was defined as no dispensed prescriptions within 6 months to 1 day before the index date, and post treatment was defined as one dispensed prescriptions from the index date until 6 months thereafter, and vice versa for discontinuation of heart failure treatments. Statistically significant associations are marked in dark green for predictors of initiation, and in dark orange for predictors of discontinuation.

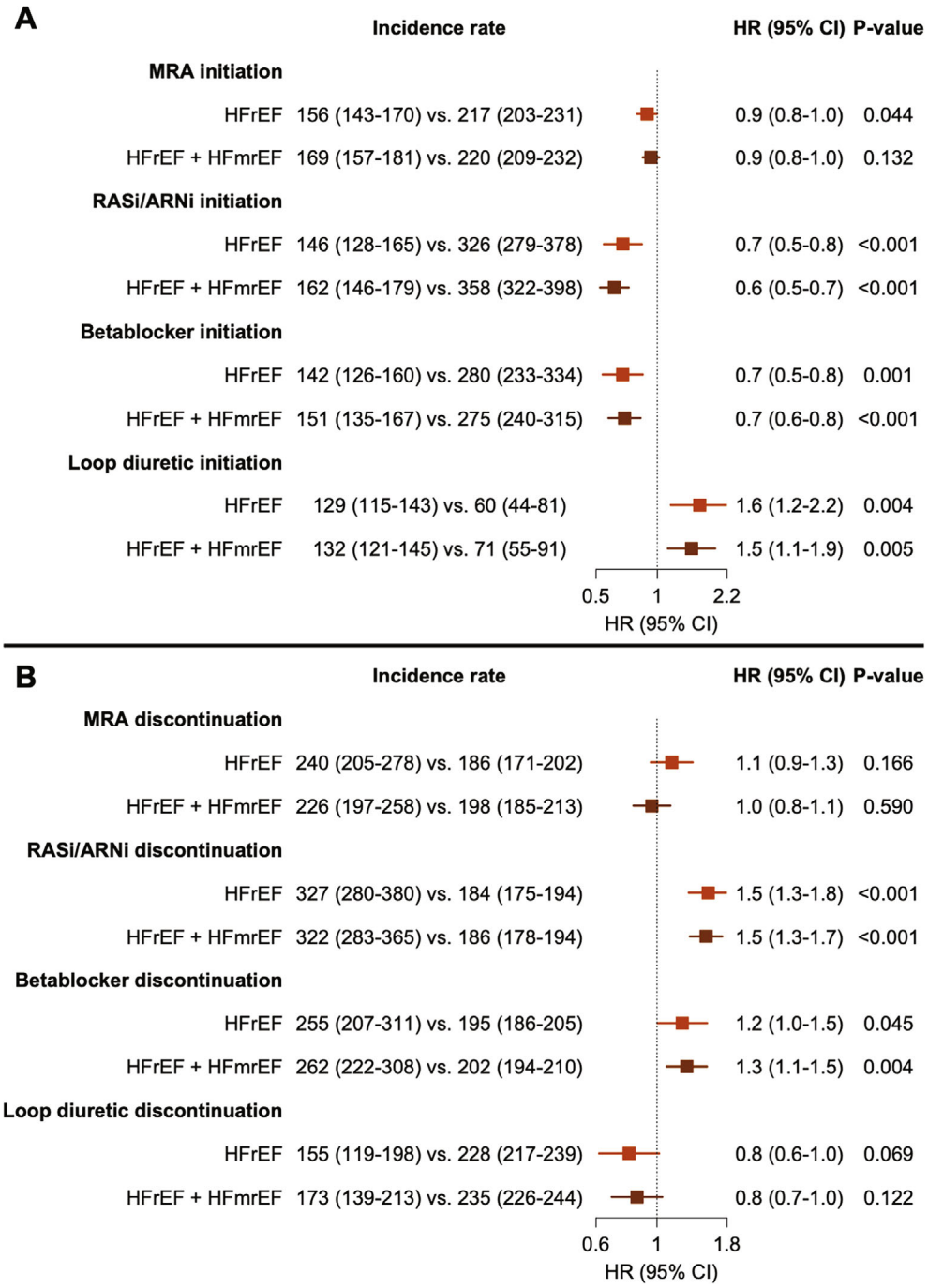


Figure 4 Association between initiation/discontinuation of heart failure treatments and 3-year all-cause mortality among patients with a heart failure hospitalization. Cox regression models were fitted to evaluate the association between initiation/discontinuation versus no initiation/no discontinuation (reference) in heart failure treatments and 3-year all-cause mortality among patients with a heart failure hospitalization. For initiation of heart failure treatments (*A*), no prior treatment was defined as no dispensed prescription within 6 months to 1 day before the index date, and post treatment was defined as one dispensed prescription from the index date until 6 months thereafter, and vice versa for discontinuation of heart failure treatments (*B*). Crude event rates and adjusted hazard ratios (HR) are shown, and variables used for adjustment in the underlying logistic regression model are reported in *Table 1*. ARNi, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor.

more accentuated in patients with recurrent HF hospitalizations, as observed in this study.

Our results, reflecting HF care up to 2018, indicate that the task of managing the later phases of a HF decompensation might not be fully addressed during the hospital stay or the post-discharge period.

Factors associated with initiation/discontinuation of heart failure treatments following a heart failure hospitalization

A major factor associated with initiation and discontinuation was renal function, as indicated by our results and a recent study from North America.[19] It is particularly concerning that we observed lower use of RASI/ARNI as well as MRA in patients with an eGFR of 30–59 ml/min/1.73 m^2, where there is no contraindication and RASI/ARNI have shown nephroprotective effects.[20,21] It is however unclear whether low initiation/high discontinuation reflects concerns regarding the relevant medications, or a more general inertia and precaution in frailer patients.

We also observed less initiation of all HF treatments in older patients. Actual tolerability issues are unlikely to explain this, as the analyses were adjusted for factors such as blood pressure, renal function and comorbidities, which might explain low tolerability. Therefore, unjustified inertia together with precaution, and the limited evidence supporting the use of HF treatments in older patients, might explain this finding.[22] We also observed symptom relief with diuretics prioritized over life-prolonging medications in older patients, which might reflect a carry-on use of diuretics potentially even without residual congestion.[22]

Several comorbidities were also linked to lower use of HF treatments. Some could have been considered as causative for the decompensation, and therefore physicians might have opted to address these comorbidities first and postpone re-/initiation of HF treatments (e.g. surgery for valvular heart disease). Others, e.g. a recent cancer diagnosis, however, might have been perceived as so severe, that specific HF treatments were stopped on purpose to deescalate therapy.

Association between initiation/discontinuation of heart failure treatments and mortality following a heart failure hospitalization

Even after adjustments for potential confounders, initiation of RASI/ARNI and beta-blocker following a HF hospitalization was associated with lower mortality, whereas discontinuation was associated with higher risk. MRA initiation was only associated with mortality in the HFrEF population, but not in the overall study population of patients with HFrEF or HFmrEF, which likely reflects indication bias (as MRA were recommended as a second-line treatment for symptomatic HFrEF patients despite RASI/beta-blockers treatment in the 2016 ESC HF guidelines). Overall, the observed association between actual use of HF treatments and lower mortality risk is in line with the vast evidence on the beneficial long-term effects of these treatments in patients with HF.[3,23,24]

Initiation of loop diuretics was associated with an increase, and their discontinuation with a trend towards a decrease in mortality. As diuretics are more likely to be prescribed in congested patients, this likely reflects the negative prognostic impact of ongoing congestion, rather than any prognostic role of diuretics themselves.

Not optimizing HF care during a HF hospitalization was associated with a higher mortality risk in this study. This might be partly explained by an active discontinuation of HF treatments in patients who were sicker, less tolerant to these treatments, or those selected for palliative care. However, as we adjusted our analysis for several confounders representing disease severity and comorbidity burden, a more likely explanation is that HF treatments were discontinued during the index hospitalization, and never re-/initiated during the follow-up, thus excluding patients from the proven benefits of these HF treatments. This supports the approach of a rapid initiation of HF treatments before discharge, together with an early follow-up in dedicated HF care facilities.[3,9,25]

Finally, our findings have implications for understanding the role of a HF hospitalization in affecting subsequent outcomes. Worsening HF reflects a vulnerable phase; however, several interventions known to reduce mortality may not similarly reduce HF hospitalization.[26] This suggests that HF hospitalization may not be 'bad' and instead offers an opportunity for optimization. Recurrent rather than time to first HF hospitalization is increasingly used as an endpoint in HF trials to increase power, but if control groups in trials are hospitalized and as a result get optimized HF treatment, then this event may reduce, instead of increase, the risk for subsequent events.

Limitations

Strengths of this study include the use of a large, well-characterized and contemporary HF cohort with extensive data on important patient characteristics, which allowed to perform extensive adjustments. Importantly, we assessed the dispensation of HF treatments, as compared to prescriptions, and could therefore analyse the actual use and not only the intended use of these. Another strength of our analysis is we used data from a universal health care system, where HF treatments are widely available irrespective of socioeconomic status, so that accessibility of care is unlikely to impact the results.

Limitations are linked with the observational nature of this analysis, and therefore with potential residual/unmeasured confounding. Discontinuation/initiation was defined over a 6-month period before and after the index event, and thus patients who died within 6 months after the index event were not included, which might have led to underestimate the increase in mortality risk associated with discontinuation and to overestimate the potential reduction in risk associated with initiation of HF treatments. We did not consider up- or down-titration of treatments as this would have added complexity, and opted to use the clearer, but less granular, measure of discontinuation/initiation. Initiation/discontinuation was defined according to the dispensed medications, and not according to the

presence of a prescription, so that we cannot discriminate between treatment decisions made at discharge versus those made during the follow-up. Some patients might however have had a prescription of a HF treatment, but never went to the pharmacy to collect it, so that some missed re-/initiations of HF treatments might be explained by low compliance rather than by clinical factors or inertia. There was a considerable amount of missing data for few variables (e.g. New York Heart Association functional class), and missingness was overall handled by multiple imputation; however we cannot exclude that this might have led to somehow biased results. The limited sample size might have prevented the observation of significant differences for some sub-groups. Finally, our study is based on a national cohort and generalizability to other countries/health care systems might be limited.

Conclusion

Our data show that a HF hospitalization is a likely trigger for the initiation of HF treatments, and that the early re-/initiation of these treatments is associated with a lower mortality risk, which supports the current 2021 ESC HF guideline recommendations. However, we also observed that still a relevant proportion of patients were not initiated or were even discontinued for guideline-recommended HF treatments after a HF hospitalization, which was associated with higher mortality risk. Overall, our findings highlight the need of implementing guideline-recommendations in this clinical setting, and that major efforts should focus on older patients and those with worse renal function, as these subpopulations were more likely to be discontinued from or not initiated with guideline-recommended HF treatments.

Supplementary Information

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

Acknowledgements

We thank all staff members at care units in Sweden as well as all included patients for their contribution to the SwedeHF registry.

Funding

This study received support through a grant from the Swedish Heart and Lung Foundation (project number 20220680) to Dr. Savarese. The grant source had no role in the design or analysis, nor in the interpretation of findings, manuscript preparation, or decision to submit the results.

Conflict of interest: B.S. reports speaker fees from AstraZeneca, Abbott and Abiomed, not related to the current work. L.H.L. reports grants from AstraZeneca, Vifor, Boston Scientific, Boehringer Ingelheim, Novartis, MSD; consulting from Vifor, AstraZeneca, Bayer, Pharmacosmos, MSD, MedScape, Sanofi, Lexicon, Myokardia, Boehringer Ingelheim, Servier, Edwards Life Sciences, Alleviant; speaker's honoraria from Abbott, OrionPharma, MedScape, Radcliffe, AstraZeneca, Novartis, Boehringer Ingelheim, Bayer; patents from AnaCardio. Also funding by the Karolinska Institutet, the Swedish Research Council (grant 523−2014-2336), the Swedish Heart Lung Foundation (grants 20 150 557, 20 190 310), and the Stockholm County Council (grants 20 170 112, 20 190 525). U.D. reports grants from Pfizer, Boehringer Ingelheim, AstraZeneca, Vifor Pharma, Boston Scientific and Roche Diagnostics and honoraria/consultancies from Amgen and AstraZeneca, all outside the submitted work. M.M. reports fees from Actelion, Amgen, AstraZeneca, Livanova, Servier, Vifor Pharma and WindTree Therapeutics as member of clinical trial committees or advisory boards and from Abbott Vascular, Bayer, Boehringer Ingelheim and Edwards Therapeutics for speeches at sponsored meetings in the last 3 years. G.S. reports grants and personal fees from AstraZeneca, Cytokinetics, Novartis, Pharmacosmos, Vifor, grants and non-financial support from Boehringer Ingelheim, personal fees from Roche, Servier, Medtronic, grants from Bayer, Boston Scientific, Merck, funding through the Horizon 2022 programme, outside the submitted work. All other authors have nothing to disclose.

References

1. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev*. 2017;**3**:7−11. https://doi.org/10.15420/cfr.2016:25:2
2. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. *Nat Rev Cardiol*. 2022;**19**:100−116. https://doi.org/10.1038/s41569-021-00605-5
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4−131. https://doi.org/10.1002/ejhf.2333
4. D'Amario D, Rodolico D, Rosano GMC, Dahlstrom U, Crea F, Lund LH, *et al.* Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: Data from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2022;**24**:871−884. https://doi.org/10.1002/ejhf.2477
5. Shen L, Jhund PS, Docherty KF, Vaduganathan M, Petrie MC, Desai AS, *et al.* Accelerated and personalized therapy for heart failure with reduced ejection fraction. *Eur Heart J*. 2022;**43**:2573−2587. https://doi.org/10.1093/eurheartj/ehac210
6. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, *et al.* Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: A comparative analysis of three randomised controlled trials. *Lancet*. 2020;**396**:121−128. https://doi.org/10.1016/S0140-6736(20)30748-0
7. Savarese G, Bodegard J, Norhammar A, Sartipy P, Thuresson M, Cowie MR, *et al.* Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: A multinational observational study (US, UK and Sweden). *Eur J Heart Fail*. 2021;**23**:1499−1511. https://doi.org/10.1002/ejhf.2271
8. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlstrom U, *et al.* Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: An analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2018;**20**:1326−1334. https://doi.org/10.1002/ejhf.1182
9. Lindberg F, Lund LH, Benson L, Schrage B, Edner M, Dahlstrom U, *et al.* Patient profile and outcomes associated with follow-up in specialty vs. primary care in heart failure. *ESC Heart Fail*. 2022;**9**:822−833. https://doi.org/10.1002/ehf2.13848
10. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, *et al.* Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;**73**:935−944. https://doi.org/10.1016/j.jacc.2018.11.049
11. Savarese G, Vasko P, Jonsson A, Edner M, Dahlstrom U, Lund LH. The Swedish Heart Failure Registry: A living, ongoing quality assurance and research in heart failure. *Ups J Med Sci*. 2019;**124**:65−69. https://doi.org/10.1080/03009734.2018.1490831
12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al.*; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;**37**:2129−2200. https://doi.org/10.1093/eurheartj/ehw128
13. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, *et al.*; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in

collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;**29**:2388–2442. https://doi.org/10.1093/eurheartj/ehn309
14. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *J Stat Softw*. 2011;**45**:1–67. https://doi.org/10.18637/jss.v045.i03
15. Schrage B, Lund LH, Benson L, Stolfo D, Ohlsson A, Westerling R, *et al.* Lower socioeconomic status predicts higher mortality and morbidity in patients with heart failure. *Heart*. 2021;**107**:229–236. https://doi.org/10.1136/heartjnl-2020-317216
16. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, *et al.* Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;**73**:2365–2383. https://doi.org/10.1016/j.jacc.2019.02.015
17. Srivastava PK, DeVore AD, Hellkamp AS, Thomas L, Albert NM, Butler J, *et al.* Heart failure hospitalization and guideline-directed prescribing patterns among heart failure with reduced ejection fraction patients. *JACC Heart Fail*. 2021;**9**:28–38. https://doi.org/10.1016/j.jchf.2020.08.017
18. Butler J, Yang M, Sawhney B, Chakladar S, Yang L, Djatche LM. Treatment patterns and clinical outcomes among patients <65 years with a worsening heart failure event. *Eur J Heart Fail*. 2021;**23**:1334–1342. https://doi.org/10.1002/ejhf.2252
19. Greene SJ, Ezekowitz JA, Anstrom KJ, Demyanenko V, Givertz MM, Pina IL, *et al.* Medical therapy during hospitalization for heart failure with reduced ejection fraction: The VICTORIA registry. *J Card Fail*. 2022;**28**:1063–1077. https://doi.org/10.1016/j.cardfail.2022.02.011
20. Lambers Heerspink HJ, de Borst MH, Bakker SJ, Navis GJ. Improving the efficacy of RAAS blockade in patients with chronic kidney disease. *Nat Rev Nephrol*. 2013;**9**:112–121. https://doi.org/10.1038/nrneph.2012.281
21. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, *et al.* Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail*. 2018;**6**:489–498. https://doi.org/10.1016/j.jchf.2018.02.004
22. Stolfo D, Lund LH, Becher PM, Orsini N, Thorvaldsen T, Benson L, *et al.* Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata. *Eur J Heart Fail*. 2022;**24**:1047–1062. https://doi.org/10.1002/ejhf.2483
23. Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD, *et al.* Initiation, continuation, or withdrawal of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and outcomes in patients hospitalized with heart failure with reduced ejection fraction. *J Am Heart Assoc*. 2017;**6**:e004675. https://doi.org/10.1161/JAHA.116.004675
24. Butler J, Young JB, Abraham WT, Bourge RC, Adams KF Jr, Clare R, *et al.* Beta-blocker use and outcomes among hospitalized heart failure patients. *J Am Coll Cardiol*. 2006;**47**:2462–2469. https://doi.org/10.1016/j.jacc.2006.03.030
25. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure-optimizing therapy with the need for speed. *JAMA Cardiol*. 2021;**6**:743–744. https://doi.org/10.1001/jamacardio.2021.0496
26. Savarese G, Lund LH, Dahlstrom U, Stromberg A. Nurse-led heart failure clinics are associated with reduced mortality but not heart failure hospitalization. *J Am Heart Assoc*. 2019;**8**:e011737. https://doi.org/10.1161/JAHA.118.011737