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1 **Association between a hospitalization for heart failure and the initiation/discontinuation of**
2 **guideline-recommended treatments - An analysis from the Swedish heart failure registry**

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25 **Abstract**

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

28

29 *Methods and Results:* Among patients in the Swedish HF registry with an ejection fraction <50%
30 enrolled in 2009-2018, initiation/discontinuation of GDMT was investigated by assessing dispensations
31 of GDMT in those with vs. without a HF hospitalization.

32 Of 14,737 patients, 6,893 (47%) were enrolled when hospitalized for HF. Initiation of GDMT was more
33 likely than discontinuation following a HF hospitalization compared to a control group of patients
34 without a HF hospitalization (odds ratio range 2.1-4.0 vs. 1.4-1.6 for the individual medications,
35 respectively), although the percentage of patients not on GDMT was still high (8.1-44.0%). Key patient
36 characteristics triggering less use of GDMT (i.e., less initiation or more discontinuation) were older age
37 and worse renal function. Following a HF hospitalization, initiation of renin-angiotensin-system-
38 inhibitors/angiotensin-receptor-neprilysin-inhibitors or betablockers was associated with lower and
39 their discontinuation with higher mortality risk, but no association with mortality was observed for
40 initiation/discontinuation of mineralocorticoid-receptor-antagonists.

41

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

47

48 *Keywords:* Heart failure with reduced ejection fraction; Heart failure with mildly reduced ejection
49 fraction; guideline-directed medical treatment; initiation; discontinuation; guidelines; implementation

50

51 **Introduction**

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

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

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

71 The aim of this study was (a) to assess HF treatment initiation/discontinuation in patients with
72 HFmrEF/HFrEF following a HF hospitalization, (b) to identify patient characteristics linked to HF
73 treatment initiation/discontinuation, and (c) to evaluate the associations between HF treatment
74 initiation/discontinuation and mortality.

75

76 **Methods**

77 Study cohort

78 The study population was derived from the Swedish Heart Failure Registry (SwedeHF;
79 www.SwedeHF.se).(11) Detailed information in SwedeHF, including the linkage to Swedish National
80 Registries, is provided in the Supplementary Appendix.

81

82 Patients

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

95

96 Definition of HF treatment initiation and discontinuation

97 RASI/ARNI, betablockers, MRA and loop diuretics were the HF treatments considered in this
98 study. SGLT2i were not considered, as they were not established as a HF treatment in Sweden during
99 the study period.

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

103

104 Statistical analysis

105 As main analysis, reflecting the 2021 ESC HF guidelines recommendations for HFrEF and
106 HFmrEF, HF treatment initiation/discontinuation was analyzed in the overall study cohort (HFrEF and

107 HFmrEF together).(3) Additionally, to reflect previous ESC HF guidelines which did not provide a
108 recommendation for HFmrEF, a secondary analysis was conducted only including patients with
109 HFrEF.(12, 13)

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

113 To determine whether a HF hospitalization was linked with the initiation/discontinuation of HF
114 treatments, for each individual drug separate multivariable logistic regression models were fitted with
115 discontinuation or initiation as the dependent variable and hospitalized vs. out-patients as independent
116 variable. Thus, a patient who had one drug initiated and another discontinued could contribute to both
117 models. Twenty-three variables representing demographics, clinical characteristics, comorbidities, and
118 socioeconomics were considered for adjustments (see *Table 1*). Also, to explore whether renal
119 function was associated with the likelihood of HF treatment initiation/discontinuation following a HF
120 hospitalization, logistic regression models were fitted stratified by, rather than adjusted for, the
121 estimated glomerular filtration rate (eGFR; unadjusted models for eGFR ≥ 60 , 30-59 and < 30
122 ml/min/1.73m² whereas for adjusted models eGFR ≥ 60 and < 60 ml/min/1.73m² were considered due
123 to the limited sample size).

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

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

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

137 cardiovascular death for the outcome cardiovascular death, at emigration from Sweden or at 3 years
138 from the index date.

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

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

144 **Results**

145 Baseline characteristics

146 Between May 11th 2000 and December 31st 2019, there were 156,544 registrations in
147 SwedeHF. After application of the selection criteria, 14,737 patients, 9,374 (64%) with HF_rEF and
148 5,363 (36%) with HF_mrEF, were analyzed. Of these, 6,893 (47%) were patients hospitalized for HF,
149 and 7,844 (53%) were out-patients (*Figure 1*).

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

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

159

160 Treatment initiation and discontinuation in hospitalized vs. out-patients

161 Following a HF hospitalization, initiation of MRA, RASI/ARNI, betablockers or loop diuretics
162 was more frequently observed than discontinuation (*Figure 2*): Initiation vs. discontinuation among
163 patients hospitalized for HF was 41.4% vs. 20.4% for MRA, 64.8% vs. 7.3% for RASI/ARNI, 71.8% vs.
164 4.9% for betablockers, 80.8% vs. 4.3% for loop diuretics, whereas 79.6%, 92.7%, 95.1%, and 95.7%
165 were kept on treatment, respectively. For out-patients, initiation was also more frequent than
166 discontinuation (16.4% vs. 14.5% for MRA, 53.2% vs. 3.6% for RASI/ARNI, 44.1% vs. 3.4% for
167 betablockers, 18.4% vs. 18.6% for loop diuretics, with 85.5%, 96.4%, 96.6%, and 81.4% who were
168 kept on these treatments, respectively), although the frequency of initiation/discontinuation of HF
169 treatments was lower compared to patients with a HF hospitalization.

170 In patients who were not on treatment prior to the index date, initiations of MRA [odds ratio
171 (OR) 3.9, 95% confidence interval (CI) 3.5-4.4], of RASI/ARNI (OR 2.3, 95% CI 1.8-2.8), of
172 betablockers (OR 3.9, 95% CI 3.1-4.8) and of loop diuretics (OR 13.4, 95% CI 11.4-15.7) were more
173 likely in hospitalized vs. out-patients (*Figure 3*). Results were consistent when stratifying by eGFR,

174 although crude initiation rates were lower when renal function was lower (*Supplement Figure 2,*
175 *Supplement Table 1*).

176 In patients who were on treatment prior to the index date, discontinuations of RASI/ARNI (OR
177 1.5, 95% CI 1.2-1.8) and of betablockers (OR 1.4, 95% CI 1.2-1.8) were more likely, whereas
178 discontinuation of loop diuretics (OR 0.3, 95% CI 0.2-0.3) was less likely in hospitalized vs. out-
179 patients, and no significant difference was observed for MRA discontinuation (OR 1.1, 95% CI 0.9-1.3;
180 *Figure 3*). These associations were consistent when stratifying by eGFR, although discontinuation
181 rates of MRA, RASI/ARNI and betablockers increased, and discontinuation rates of loop diuretic
182 decreased when renal function was lower, and discontinuation rates were highest while initiation rates
183 lowest in patients with an eGFR <30 ml/min/1.73m² regardless of whether patients were hospitalized
184 or not (*Supplement Figure 2, Supplement Table 1*). These results were consistent when patients with
185 HFrEF were analyzed separately.

186 When analyzing the impact of recurrent HF hospitalizations, the frequency of MRA and loop
187 diuretic initiation, but also of discontinuation of all the study treatments increased with a higher number
188 of HF hospitalizations (*Supplement Figure 3*).

189

190 *Independent predictors of treatment initiation and discontinuation in patients hospitalized for HF*

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

193 MRA initiation was less likely in older patients or those living alone, in those with a higher
194 blood pressure, lower eGFR, or anemia, but more likely in those with hypokalemia and atrial
195 fibrillation. Initiation of RASI/ARNI was also less likely in older patients, and in those with lower eGFR,
196 with valvular heart disease, with atrial fibrillation, with prior stroke/transient ischemic attack or with
197 anemia, but more likely in male patients. Betablocker initiation was less likely in older patients as well
198 as those with anemia, valvular heart disease, chronic obstructive lung disease and recent cancer, but
199 was not associated with eGFR or blood pressure. Loop diuretic initiation was more likely in older
200 patients, those with a higher heart rate, an eGFR of 30-59 ml/min/1.73m² (but not in those with an
201 eGFR <30 ml/min/1.73m²), a higher NTproBNP and atrial fibrillation, and less likely in those with
202 hyperkalemia.

203 MRA discontinuation was more likely in patients with a lower eGFR, with anemia and in those
204 living alone. RASI/ARNI discontinuation was more likely in patients with lower blood pressure,

205 hypokalemia, lower eGFR and with atrial fibrillation, anemia, and a recent cancer diagnosis, whereas
206 betablocker discontinuation was not associated with any of the tested patient characteristic. Loop
207 diuretic discontinuation was less likely in older patients in those with an eGFR of 30-59 ml/min/1.73m²,
208 but not in those with an eGFR <30 ml/min/1.73m².

209

210 3-year mortality risk associated with treatment initiation/discontinuation following a HF hospitalization

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

214 Initiations of RASI/ARNI and of betablockers were associated with a lower, whereas initiation
215 of loop diuretics with a higher risk of 3-year all-cause and cardiovascular mortality. There was no
216 association between MRA initiation and all-cause/cardiovascular mortality (*Figure 4, Supplement*
217 *Figure 4*). These findings were consistent when patients with HFrEF were analyzed separately, except
218 for the initiation of MRA which was then associated with a lower 3-year all-cause mortality risk (*Figure*
219 *4*).

220 Discontinuations of RASI/ARNI and of betablocker were associated with a higher risk of 3-year
221 all-cause and cardiovascular mortality, whereas discontinuations of MRA and loop diuretics were
222 neither associated with all-cause nor cardiovascular mortality risk (*Figure 4, Supplement Figure 4*).
223 These findings were consistent when considering only patients with HFrEF, except for the
224 discontinuation of loop diuretics which was then associated with a lower 3-year cardiovascular
225 mortality risk (*Figure 4, Supplement Figure 4*).

226

227 **Discussion**

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

234

235 Associations between a HF hospitalization and initiation/discontinuation of HF treatments

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

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

256

257 Factors associated with the initiation/discontinuation of HF treatments following a HF hospitalization

258 A major factor associated with initiation and discontinuation was renal function, as indicated by
259 our results and a recent study from North America.(19) It is particularly concerning that we observed
260 lower use of RASI/ARNI as well as MRA in patients with an eGFR of 30-59 ml/min/1.73m², where
261 there is no contraindication and RASI/ARNI have shown nephroprotective effects.(20, 21) It is
262 however unclear whether low initiation/high discontinuation reflects concerns regarding the relevant
263 medications, or a more general inertia and precaution in frailer patients.

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

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

276

277 Association between initiation/discontinuation of HF treatments and mortality following a HF
278 hospitalization

279 Even after adjustments for potential confounders, initiation of RASI/ARNI and betablocker
280 following a HF hospitalization was associated with lower mortality, whereas discontinuation was
281 associated with higher risk. MRA initiation was only associated with mortality in the HF_rEF population,
282 but not in the overall study population of patients with HF_rEF or HF_mrEF, which likely reflects
283 indication bias (as MRA were recommended as a 2nd line treatment for symptomatic HF_rEF patients
284 despite RASI/betablockers treatment in the 2016 ESC HF guidelines). Overall, the observed
285 association between actual use of HF treatments and lower mortality risk is in line with the vast
286 evidence on the beneficial long-term effects of these treatments in patients with HF.(3, 23, 24)

287 Initiation of loop diuretics was associated with an increase, and their discontinuation with a
288 trend towards a decrease in mortality. As diuretics are more likely to be prescribed in congested

289 patients, this likely reflects the negative prognostic impact of ongoing congestion, rather than any
290 prognostic role of diuretics themselves.

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

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

306

307 Limitations

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

315 Limitations are linked with the observational nature of this analysis, and therefore with
316 potential residual/unmeasured confounding. Discontinuation/initiation was defined over a 6-month
317 period before and after the index event, and thus patients who died within 6-months after the index
318 event were not included, which might have led to underestimate the increase in mortality risk
319 associated with discontinuation and to overestimate the potential reduction in risk associated with

320 initiation of HF treatments. We did not consider up- or down-titration of treatments as this would have
321 added complexity, and opted to use the clearer, but less granular, measure of
322 discontinuation/initiation. Initiation/discontinuation was defined according to the dispensed
323 medications, and not according to the presence of a prescription, so that we cannot discriminate
324 between treatment decisions made at discharge vs. those made during the follow-up. Some patients
325 might however have had a prescription of a HF treatment, but never went to the pharmacy to collect it,
326 so that some missed re-/initiations of HF treatments might be explained by low compliance rather than
327 by clinical factors or inertia. There was a considerable amount missing data for few variables (e.g.,
328 New York Heart Association functional class), and missingness was overall handled by multiple
329 imputation; however we cannot exclude that this might have led to somehow biased results. The
330 limited sample size might have prevented the observation of significant differences for some sub-
331 groups. Finally, our study is based on a national cohort and generalisability to other
332 countries/healthcare systems might be limited.

333 **Conclusion**

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

343

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351

352 **Conflict of interest**

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375

376 **Data availability statement**

377 The data underlying this article will be shared on reasonable request to the corresponding author.

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484

485

486 **Figure legends**

487 *Graphical abstract*



Use of GDMT in patients with vs. without a HF hospitalization	Triggers of less GDMT use in patients with a HF hospitalization	GDMT use and mortality following a HF hospitalization
<p>200-400% Initiation more likely... (use of GDMT in patients previously <u>not</u> on GDMT)</p>	<p> Higher age</p>	<p>~30% Lower mortality risk for RASi/ARNI and betablocker initiation</p>
<p>40-60% ...but so was discontinuation... (use of GDMT in patients previously on GDMT)</p>	<p> Worse renal function</p>	<p>30-50% Higher mortality risk for RASi/ARNI and betablocker discontinuation</p>
<p>8.1-44% ...and a relevant proportion of patients not on GDMT</p>	<p> Lower blood pressure</p>	<p>- No association between MRA use and mortality</p>
<p>Strong call for further implementation of current guidelines recommendation of an earlier re-/initiation of GDMT following a HF hospitalization</p>		

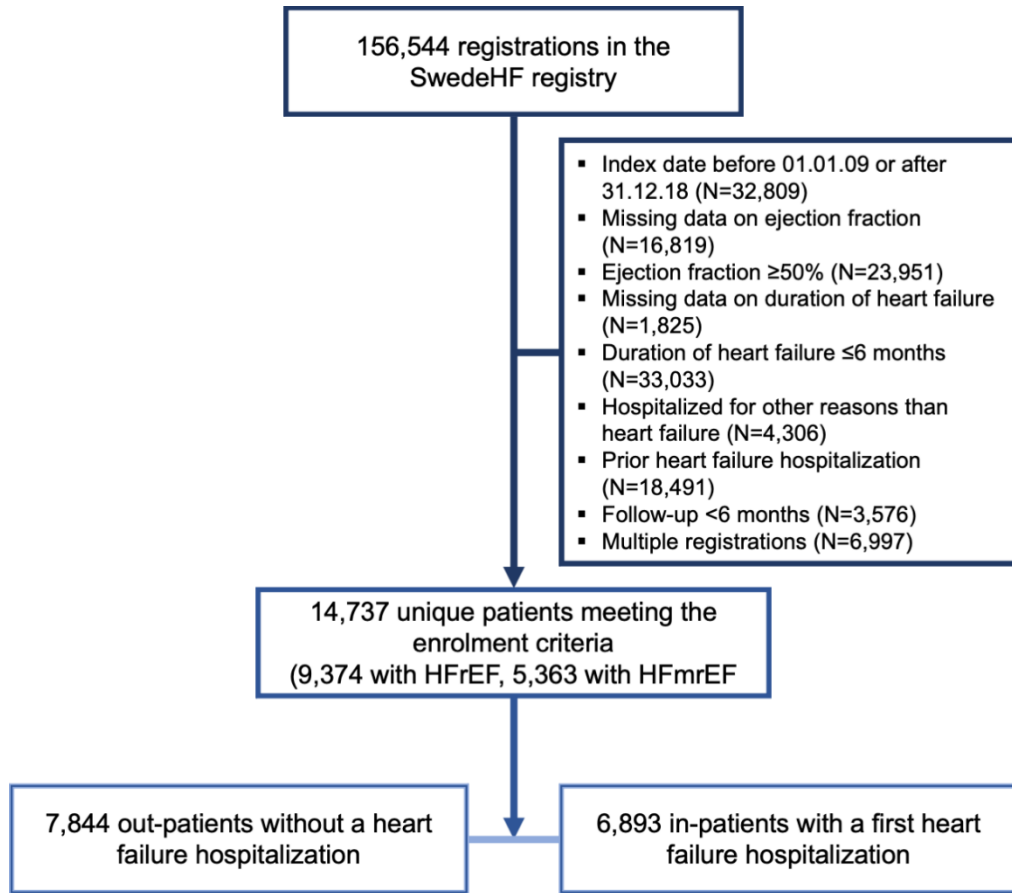
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489 HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mid-ranged ejection fraction; HF: Heart failure;
 490 GDMT: Guideline directed medical therapy; RASi: Renin angiotensin system inhibitors; ARNI: Angiotensin-receptor neprilysin-
 491 inhibitors; MRA: Mineralocorticoid receptor antagonist.

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494 Figure 1. Study flow chart.



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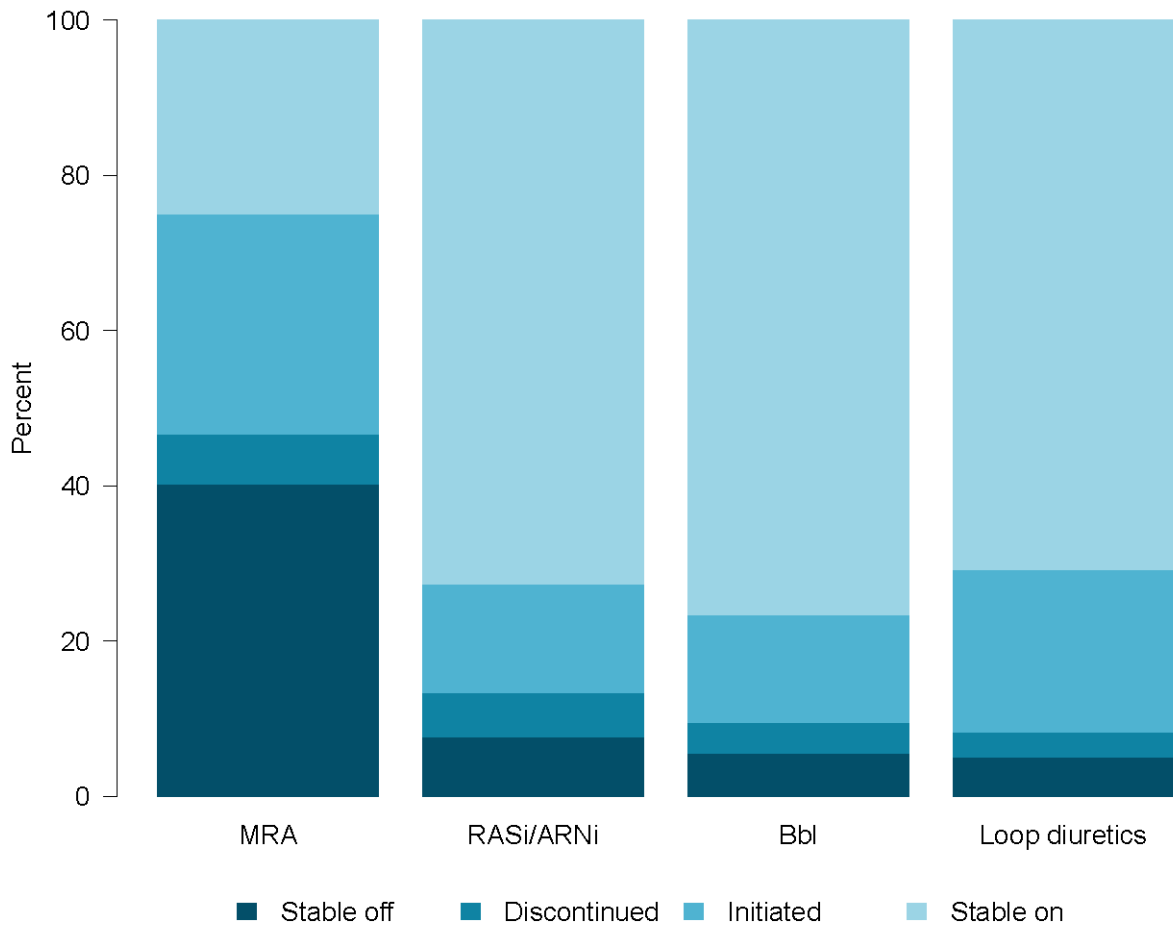
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HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction.

499 *Figure 2. Dispensation of heart failure treatments following a heart failure hospitalization.*



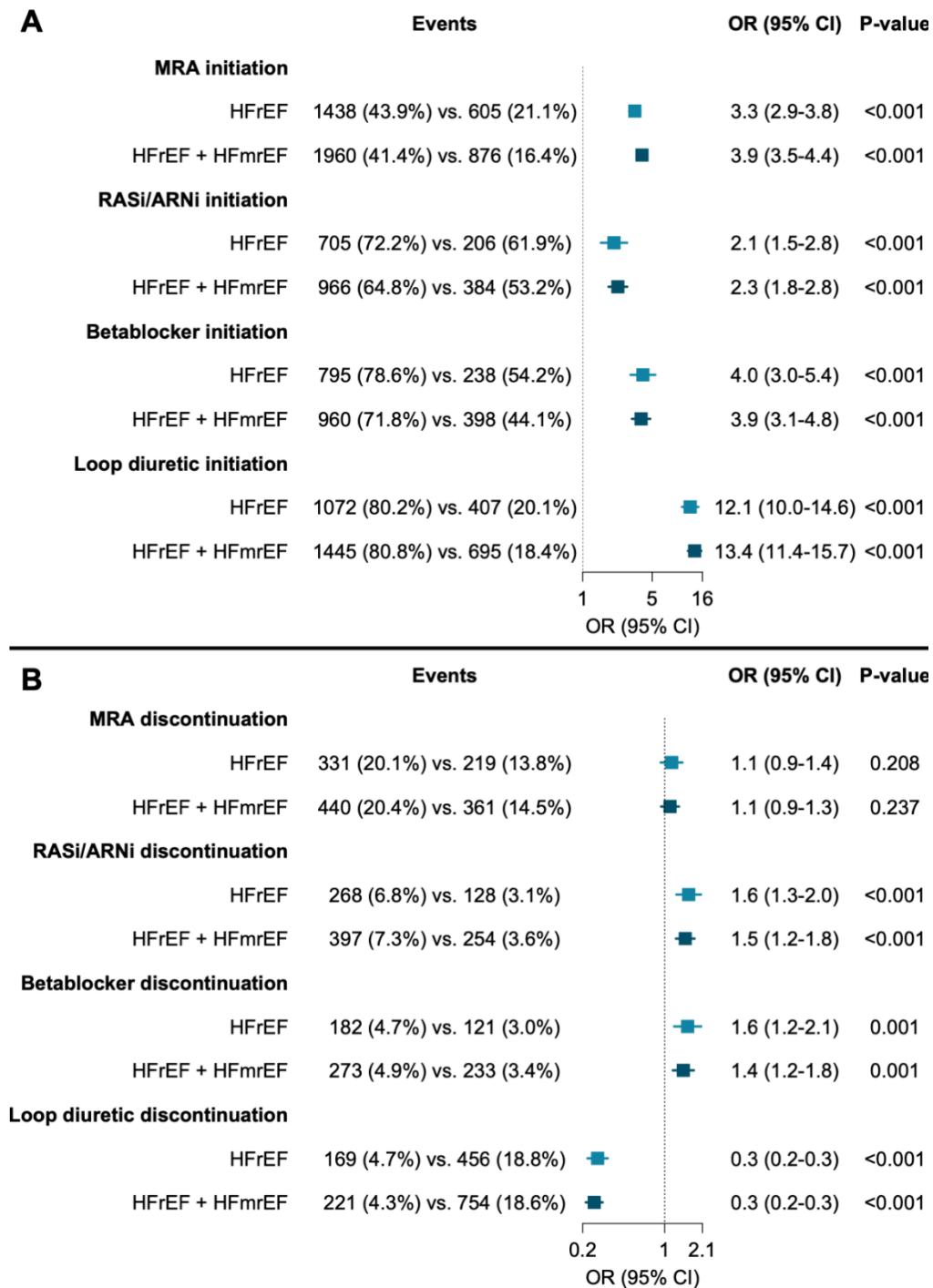
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501 Dispensation of heart failure treatments before and after a heart failure hospitalization were analyzed. No prior treatment was
502 defined as no dispensed prescription within 6 months to 1 day before the index date, and post treatment was defined as 1
503 dispensed prescription from the index date until 6 months thereafter, and vice versa. "Stable off" indicates no dispensed
504 treatment before and after the heart failure hospitalization, "discontinued" indicates dispensed treatment before but not after the
505 heart failure hospitalization, "initiated" indicates no dispensed treatment before but after the heart failure hospitalization and
506 "stable on" indicates dispensed treatment before and after the heart failure hospitalization. MRA: Mineralocorticoid receptor
507 antagonist; RASi: Renin-aldosterone-system inhibitors; ARNI: Angiotensin-receptor neprilysin-inhibitors.

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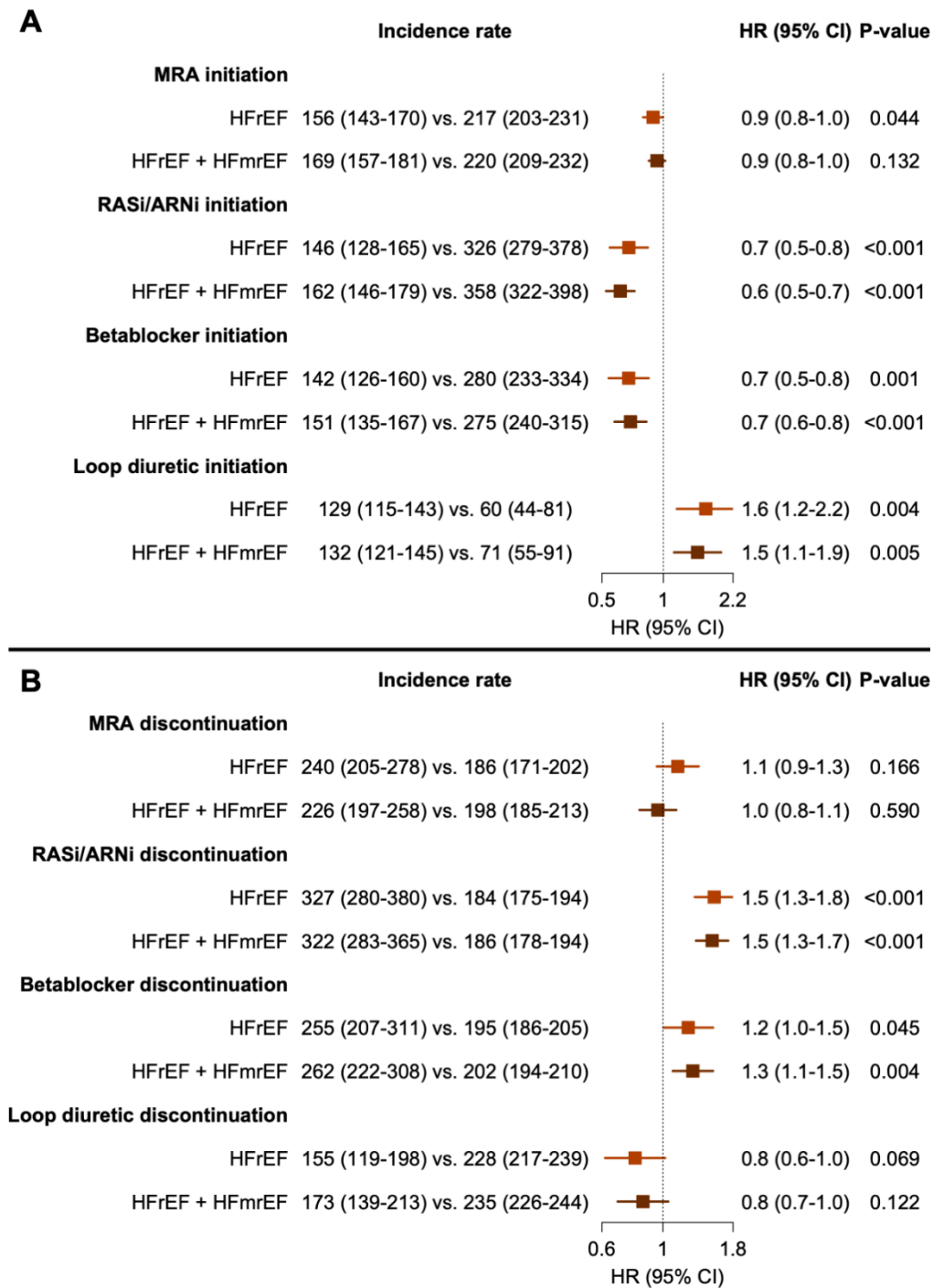
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510 *Figure 3. Likelihood of initiation/discontinuation of heart failure treatments in patients with vs. without a*
 511 *heart failure hospitalization.*



512
 513 Initiation/discontinuation of heart failure treatments is compared between patients with a heart failure hospitalization vs. out-
 514 patients (i.e., patients without a heart failure hospitalization). For initiation of heart failure treatments (A), no prior treatment was
 515 defined as no dispensed prescription within 6 months to 1 day before the index date, and post treatment is defined as 1
 516 dispensed prescription from the index date until 6 months thereafter, and vice versa for discontinuation of heart failure
 517 treatments (B). Crude event rates and adjusted odds ratios are shown, and variables used for adjustment in the underlying
 518 logistic regression model are reported in *Table 1*. An OR >1 indicates a higher, and an OR <1 indicates a lower likelihood of
 519 initiation/discontinuation of heart failure treatments in hospitalized patients. OR: Odds ratio; CI: Confidence interval; MRA:
 520 Mineralocorticoid receptor antagonist; HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mildly
 521 reduced ejection fraction; RASi: Renin-aldosteron-system inhibitors; ARNI: Angiotensin-receptor neprilysin-inhibitors.

522 *Figure 4. Association between initiation/discontinuation of heart failure treatments and 3-year all-cause*
 523 *mortality among patients with a heart failure hospitalization.*



524
 525 Cox regression models were fitted to evaluate the association between initiation/discontinuation vs. no initiation/no
 526 discontinuation (reference) in heart failure treatments and 3-year all-cause mortality among patients with a heart failure
 527 hospitalization. For initiation of heart failure treatments (A), no prior treatment was defined as no dispensed prescription within 6
 528 months to 1 day before the index date, and post treatment was defined as 1 dispensed prescription from the index date until 6
 529 months thereafter, and vice versa for discontinuation of heart failure treatments (B). Crude event rates and adjusted odds ratios
 530 are shown, and variables used for adjustment in the underlying logistic regression model are reported in *Table 1*. HR: Hazard
 531 ratio; CI: Confidence interval; MRA: Mineralocorticoid receptor antagonist; HFrEF: Heart failure with reduced ejection fraction;
 532 HFmrEF: Heart failure with mildly reduced ejection fraction; RASi: Renin-aldosterone-system inhibitors; ARNI: Angiotensin-
 533 receptor neprilysin-inhibitors.

Tables

Table 1. Baseline characteristics of the study cohort.

	Overall study cohort (HFREF + HFmrEF)				HFREF only			
	Missing (%)	Out-patients, not hospitalized (N=7,844)	In-patients with a HF hospitalization (N=6,893)	p	Missing (%)	Out-patients, not hospitalized (N=4,451)	In-patients with a HF hospitalization (N=4,923)	p
Demographics								
Sex (male) [°]	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 [°]	0.0	3742 (47.7)	4161 (60.4)	<0.001	0.0	2060 (46.3)	2781 (56.5)	<0.001
Index year [*]	0.0	2015 [2012, 2017]	2012 [2010, 2015]	<0.001	0.0	2014 [2011, 2017]	2012 [2010, 2015]	<0.001
Clinical variables								
HFmrEF [*]	0.0	3393 (43.3)	1970 (28.6)	<0.001	0	0	0	-
NYHA class [°]	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 [°]	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 [°]	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 [°]	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 [°]	13.9			<0.001	14.5			<0.001
Normokalemia		6763 (95.2)	5082 (91.0)			3838 (94.8)	3624 (91.4)	
Hypokalemia		126 (1.8)	341 (6.1)			74 (1.8)	228 (5.7)	
Hyperkalemia		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 [°]	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, 10496]	<0.001
Above median [°]	43.7	1629 (33.6)	2520 (73.0)	<0.001	44.7	852 (31.0)	1741 (71.3)	<0.001
Comorbidities								
Former/current smoker [°]	22.5	3601 (57.0)	2942 (57.8)	0.404	22.0	2135 (58.7)	2189 (59.6)	0.434
Anemia [°]	5.4	1742 (24.5)	3031 (44.4)	<0.001	4.6	990 (24.3)	2038 (41.8)	<0.001
Diabetes mellitus [°]	0.0	1818 (23.2)	2607 (37.8)	<0.001	0.0	1100 (24.7)	1813 (36.8)	<0.001
Atrial fibrillation/flutter [°]	0.0	4231 (53.9)	4520 (65.6)	<0.001	0.0	2313 (52.0)	3087 (62.7)	<0.001
Ischemic heart disease [°]	0.0	4651 (59.3)	4627 (67.1)	<0.001	0.0	2796 (62.8)	3355 (68.1)	<0.001
Arterial hypertension [°]	0.0	5183 (66.1)	5007 (72.6)	<0.001	0.0	2856 (64.2)	3420 (69.5)	<0.001
Peripheral artery disease [°]	0.0	647 (8.2)	843 (12.2)	<0.001	0.0	396 (8.9)	602 (12.2)	<0.001

Stroke/TIA **	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 *	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 **	0.0	943 (12.0)	884 (12.8)	0.147	0.0	539 (12.1)	606 (12.3)	0.792
COPD **	0.0	857 (10.9)	1226 (17.8)	<0.001	0.0	477 (10.7)	816 (16.6)	<0.001
Severe bleeding *	0.0	1227 (15.6)	1591 (23.1)	<0.001	0.0	683 (15.3)	1045 (21.2)	<0.001
Treatments								
RASI *	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
Betablockers *	0.0	6941 (88.5)	5556 (80.6)	<0.001	0.0	4012 (90.1)	3912 (79.5)	<0.001
MRA *	0.0	2490 (31.7)	2159 (31.3)	0.594	0.0	1583 (35.6)	1648 (33.5)	0.035
Loop diuretic *	0.0	4062 (51.8)	5104 (74.0)	<0.001	0.0	2429 (54.6)	3586 (72.8)	<0.001
CRT/ICD *	2.5	579 (7.7)	973 (14.2)	<0.001	1.7	442 (10.2)	899 (18.4)	<0.001
Digoxin *	0.3	845 (10.8)	1134 (16.5)	<0.001	0.4	470 (10.6)	834 (17.0)	<0.001
Platelet inhibitor *	0.5	3296 (42.2)	3024 (44.1)	0.016	0.5	1981 (44.6)	2238 (45.8)	0.287
Oral anticoagulant *	0.3	3896 (49.8)	3463 (50.5)	0.377	0.3	2168 (48.8)	2432 (49.6)	0.425
Statin *	0.3	4577 (58.5)	3620 (52.7)	<0.001	0.4	2679 (60.4)	2643 (53.9)	<0.001
Nitrate *	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 *	4.6	5533 (72.6)	2944 (45.7)	<0.001	4.6	3193 (73.7)	2313 (50.2)	<0.001
Follow-up referral specialty *	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 **	0.2	3132 (40.0)	3603 (52.4)	<0.001	0.3	1729 (39.0)	2506 (51.0)	<0.001
Children *	0.0	6699 (85.4)	5746 (83.4)	0.001	0.0	3785 (85.0)	4079 (82.9)	0.005
Education **	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 **	0.2	4186 (53.5)	3172 (46.1)	<0.001	0.3	2396 (54.0)	2342 (47.7)	<0.001

Variables marked with a * were used in the multiple imputation, and variables marked with a ° were adjusted for in the logistic/cox regression models. When stratifying patients based on NTproBNP > or ≤ median, the median NTproBNP per EF category (HFrEF or HFmrEF) was considered; and when stratifying patients based on income > or ≤ median, the median income per year of enrolment was considered. HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction; NYHA: New York Heart Association functional class; eGFR: Estimated glomerular filtration rate (calculated by CKD-EPI formula); NTproBNP: N-terminal prohormone of brain natriuretic peptide; TIA: Transient ischemic attack; COPD: Chronic obstructive pulmonary disease; RASI: Renin-aldosterone-system inhibitors; ACEi: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin-receptor neprilysin-inhibitors; MRA: Mineralocorticoid receptor antagonist; CRT: Cardiac resynchronization therapy; ICD: Implantable cardioverter defibrillator.

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

	Initiation/ Discontinuation	MRA	RASI/ARNI	Betablockers	Loop diuretics
		<i>Odds ratio (95% confidence interval), p-value</i>			
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/1.73m 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/1.73m 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

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, betablocker 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 1 dispensed prescriptions from the index date until 6 months thereafter, and vice versa for discontinuation of heart failure treatments. MRA: Mineralocorticoid receptor antagonist; RASI: Renin-aldosterone-system inhibitors; ARNI: Angiotensin-receptor neprilysin-inhibitors; NYHA: New York Heart Association functional class; SBP: Systolic blood pressure; BMI: Body mass index; eGFR: estimated glomerular filtration rate (calculated by CKD-EPI formula); NTproBNP: N-terminal prohormone of brain natriuretic peptide; COPD: Chronic obstructive pulmonary disease; TIA: Transient ischemic attack.

