1	SUPPLEMENTAL APPENDIX
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3	Association between a hospitalization for heart failure and the initiation/discontinuation of
4	guideline-recommended treatments - An analysis from the Swedish heart failure registry
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6	Schrage B et al.
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8 SwedeHF Study cohort

9 SwedeHF is an ongoing nationwide registry prospectively enrolling in- and out-patients since 10 May 11th 2000. Until April 2017, clinician-judged HF was the only enrollment criterion. Thereafter, 11 patients were enrolled when a HF diagnosis according to the International Statistical Classification of 12 Diseases, Tenth Revision (ICD-10) codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, 13 I13.2 was recorded. Beyond the ~80 variables which are recorded at index date (day of hospital 14 discharge for in-patients and of an out-patient visit for out-patients) in SwedeHF, further data were 15 obtained by linkage with other nationwide registries through the Swedish Personal Identification 16 Number, i.e., to the National Patient Register which provided additional comorbidities and data on 17 hospitalizations, to Statistics Sweden which collects socioeconomic data, to the National Prescribed 18 Drug Register which provided data on the dispensed treatments, and to the Cause of Death Register 19 which reports date and cause of death. Further information on this study, e.g., the definition of 20 comorbidities via ICD-10 codes, is provided at https://kiheartfailure.github.io/shfdb3/.

This study, including the linkage of SwedeHF to other nationwide registries, was approved by the Swedish Ethical Review Authority and was designed and conducted in agreement with the Declaration of Helsinki. Individual patient consent is not requested, but patients are informed about enrollment and can opt out. 25 Supplement Table 1. Association between a heart failure hospitalization and initiation/discontinuation

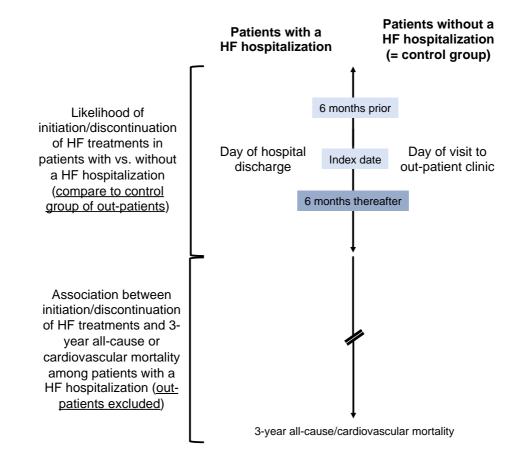
	-05	R ≥60	-050	30-59	-05	२ <30
		≺ ≥60 /1.73m²		30-59 /1.73m ²		
	1111/11111	Initiatior	· · ·		ml/min/1.73m ²	
MRA initiation	1	milialio			[
Event rate in out- vs. inpatients	634	1082	208	794		
Event fate in out- vs. inpatients	(18.1%)	(52.2%)	(13.6%)	(36.6%)	12 (7.5%)	80 (16.9%)
Crude OR (95% CI), p-value		.6), <0.001	3.7 (3.1-4.		· · · /	1.8), 0.004
RASi/ARNi initiation				, 101001	2.0 (
Event rate in out- vs. inpatients	243	524	117	375		
	(61.7%)	(80.5%)	(45.0%)	(58.9%)	10 (21.3%)	64 (32.2%)
Crude OR (95% CI), p-value	2.6 (1.9-3	.4), <0.001	1.7 (1.3-2.			8.7), 0.147
Betablocker initiation	Ì		```	,.	,	
Event rate in out- vs. inpatients	287	539		361		
	(47.2%)	(75.5%)	92 (36.1%)	(68.0%)	6 (46.2%)	59 (66.3%)
Crude OR (95% CI), p-value	3.4 (2.7-4	.4), <0.001	3.8 (2.7-5.	1), <0.001	2.3 (0.7-7	'.4), 0.166
Loop diuretic initiation						
Event rate in out- vs. inpatients	467	814	194	562		
	(16.0%)	(76.1%)	(27.4%)	(88.5%)	13 (43.3%)	65 (85.5%)
Crude OR (95% CI), p-value	16.7 (14.1-1	9.8), <0.001	20.4 (15.2-2	7.3), <0.001	7.7 (2.9-20	0.3), <0.001
		Discontinua	tion			
MRA discontinuation						
Event rate in out- vs. inpatients	176	139	156	252		
	(11.3%)	(14.0%)	(19.4%)	(24.8%)	18 (38.3%)	49 (36.0%)
Crude OR (95% CI), p-value	1.3 (1.0-1	.6), 0.045	1.4 (1.1-1	.7), 0.006	0.9 (0.5-1	.8), 0.781
RASi/ARNi discontinuation		1		n		
Event rate in out- vs. inpatients	125 (2.7%)	117 (4.8%)	91 (4.4%)	204 (8.0%)	31 (19.3%)	73 (17.8%)
Crude OR (95% CI), p-value	1.8 (1.4-2	.4), <0.001	1.9 (1.5-2.	4), <0.001	0.9 (0.6-1	.5), 0.696
Betablocker discontinuation						
Event rate in out- vs. inpatients	147 (3.3%)	120 (5.1%)	71 (3.4%)	118 (4.4%)	8 (4.1%)	34 (6.6%)
Crude OR (95% CI), p-value	1.6 (1.2-2	.0), <0.001	1.3 (1.0-1	.8), 0.076	1.6 (0.7-3	8.6), 0.219
Loop diuretic discontinuation		1		r		T
Event rate in out- vs. inpatients	492		221			
	(23.0%)	113 (5.7%)	(13.6%)	86 (3.4%)	13 (7.3%)	20 (3.8%)
Crude OR (95% CI), p-value	0.2 (0.2-0	.2), <0.001	0.2 (0.2-0.	3), <0.001	0.5 (0.2-1	.0), 0.056

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28 Initiation/discontinuation of heart failure treatments is compared between patients with a heart failure hospitalization vs. out-29 patients (i.e., patients without a heart failure hospitalization), stratified by eGFR. For initiation of heart failure treatments, no prior 30 treatment was defined as no dispensed prescription within 8 months to 1 day before the index date, and post treatment was 31 defined as 2 dispensed prescriptions from the index date until 8 months thereafter, and vice versa for discontinuation of heart 32 failure treatments. Crude event rates and crude odds ratios are shown. eGFR: Estimated glomerular filtration rate; OR: Odds 33 ratio; CI: Confidence interval; MRA: Mineralocorticoid receptor antagonist; HFrEF: Heart failure with reduced ejection fraction; 34 HFmrEF: Heart failure with mildly reduced ejection fraction; RASi: Renin-aldosteron-system inhibitors; ARNi: Angiotensin-35 receptor neprilysin-inhibitors.

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Supplement Figure 1. Outline of the study design.

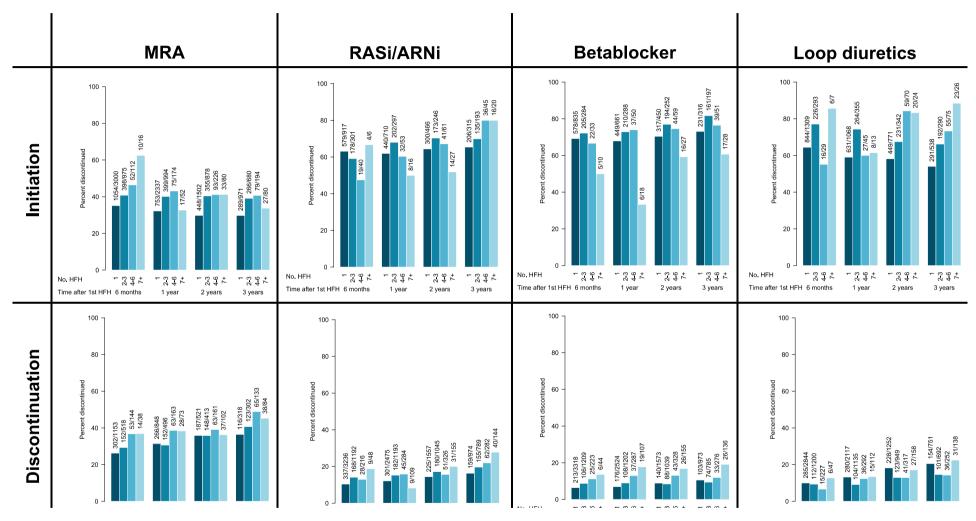


HF: Heart failure.

Supplement Figure 2. Likelihood of initiation/discontinuation of heart failure treatments in patients with vs. without a heart failure hospitalization, stratified by renal function in two strata.

Α		Events		OR (95% CI)	P-value
	MRA initiation				
	eGFR ≥60	1082 (52.2%) vs. 634 (18.1%)		4.4 (3.8-5.0)	<0.001
	eGFR <60	874 (33.1%) vs. 220 (13.0%)	-	3.1 (2.6-3.7)	<0.001
	RASi/ARNi initiation				
	eGFR ≥60	524 (80.5%) vs. 243 (61.7%)		3.0 (2.1-4.1)	<0.001
	eGFR <60	439 (52.5%) vs. 127 (41.4%)	-	1.7 (1.3-2.3)	<0.001
	Betablocker initiation				
	eGFR ≥60	539 (75.5%) vs. 287 (47.2%)	-	4.0 (3.0-5.4)	<0.001
	eGFR <60	420 (67.7%) vs. 98 (36.6%)	-8-	4.0 (2.8-5.7)	<0.001
	Loop diuretic initiation				
	eGFR ≥60	814 (76.1%) vs. 467 (16.0%)	-	12.6 (10.5-15.2) <0.001
	eGFR <60	627 (88.2%) vs. 207 (28.1%)	-	15.8 (11.7-21.4) <0.001
			1 7 2	2	
			OR (95% CI)		
В		Events		OR (95% CI)	P-value
В	MRA discontinuation	Events		OR (95% CI)	P-value
В	MRA discontinuation eGFR ≥60	Events 139 (14.0%) vs. 176 (11.3%)	-	OR (95% CI) 1.1 (0.8-1.4)	P-value 0.711
В				. ,	
_	eGFR ≥60	139 (14.0%) vs. 176 (11.3%)	-#-	1.1 (0.8-1.4)	0.711
_	eGFR ≥60 eGFR <60	139 (14.0%) vs. 176 (11.3%)	*	1.1 (0.8-1.4)	0.711
_	eGFR ≥60 eGFR <60 ASi/ARNi discontinuation	139 (14.0%) vs. 176 (11.3%) 301 (26.1%) vs. 174 (20.4%)	*	1.1 (0.8-1.4) 1.2 (0.9-1.5)	0.711 0.174
R	eGFR ≥60 eGFR <60 ASi/ARNi discontinuation eGFR ≥60	139 (14.0%) vs. 176 (11.3%) 301 (26.1%) vs. 174 (20.4%) 117 (4.8%) vs. 125 (2.7%)	*	1.1 (0.8-1.4) 1.2 (0.9-1.5) 1.6 (1.2-2.1)	0.711 0.174 0.001
R	eGFR ≥60 eGFR <60 ASi/ARNi discontinuation eGFR ≥60 eGFR <60	139 (14.0%) vs. 176 (11.3%) 301 (26.1%) vs. 174 (20.4%) 117 (4.8%) vs. 125 (2.7%)	*	1.1 (0.8-1.4) 1.2 (0.9-1.5) 1.6 (1.2-2.1)	0.711 0.174 0.001
R	eGFR ≥60 eGFR <60 ASi/ARNi discontinuation eGFR ≥60 eGFR <60 ablocker discontinuation	139 (14.0%) vs. 176 (11.3%) 301 (26.1%) vs. 174 (20.4%) 117 (4.8%) vs. 125 (2.7%) 277 (9.4%) vs. 122 (5.5%)	*	1.1 (0.8-1.4) 1.2 (0.9-1.5) 1.6 (1.2-2.1) 1.5 (1.2-1.9)	0.711 0.174 0.001 0.001
R	eGFR ≥60 eGFR <60 ASi/ARNi discontinuation eGFR ≥60 eGFR <60 ablocker discontinuation eGFR ≥60	139 (14.0%) vs. 176 (11.3%) 301 (26.1%) vs. 174 (20.4%) 117 (4.8%) vs. 125 (2.7%) 277 (9.4%) vs. 122 (5.5%) 120 (5.1%) vs. 147 (3.3%)	*	1.1 (0.8-1.4) 1.2 (0.9-1.5) 1.6 (1.2-2.1) 1.5 (1.2-1.9) 1.6 (1.2-2.1)	0.711 0.174 0.001 0.001 0.001
R	eGFR ≥60 eGFR <60 ASi/ARNi discontinuation eGFR ≥60 eGFR <60 ablocker discontinuation eGFR ≥60 eGFR <60	139 (14.0%) vs. 176 (11.3%) 301 (26.1%) vs. 174 (20.4%) 117 (4.8%) vs. 125 (2.7%) 277 (9.4%) vs. 122 (5.5%) 120 (5.1%) vs. 147 (3.3%)		1.1 (0.8-1.4) 1.2 (0.9-1.5) 1.6 (1.2-2.1) 1.5 (1.2-1.9) 1.6 (1.2-2.1)	0.711 0.174 0.001 0.001 0.001
R	eGFR ≥60 eGFR <60 ASi/ARNi discontinuation eGFR ≥60 eGFR <60 eGFR ≥60 eGFR ≥60 eGFR <60	139 (14.0%) vs. 176 (11.3%) 301 (26.1%) vs. 174 (20.4%) 117 (4.8%) vs. 125 (2.7%) 277 (9.4%) vs. 122 (5.5%) 120 (5.1%) vs. 147 (3.3%) 152 (4.8%) vs. 79 (3.5%)		1.1 (0.8-1.4) 1.2 (0.9-1.5) 1.6 (1.2-2.1) 1.5 (1.2-1.9) 1.6 (1.2-2.1) 1.3 (1.0-1.8)	0.711 0.174 0.001 0.001 0.001 0.070
R	eGFR ≥60 eGFR <60 ASi/ARNi discontinuation eGFR ≥60 eGFR <60 eGFR ≥60 eGFR <60 o diuretic discontinuation eGFR ≥60	139 (14.0%) vs. 176 (11.3%) 301 (26.1%) vs. 174 (20.4%) 117 (4.8%) vs. 125 (2.7%) 277 (9.4%) vs. 122 (5.5%) 120 (5.1%) vs. 147 (3.3%) 152 (4.8%) vs. 79 (3.5%) 113 (5.7%) vs. 492 (23.0%) 106 (3.4%) vs. 234 (13.0%)		1.1 (0.8-1.4) 1.2 (0.9-1.5) 1.6 (1.2-2.1) 1.5 (1.2-1.9) 1.6 (1.2-2.1) 1.3 (1.0-1.8) 0.2 (0.2-0.3) 0.3 (0.2-0.4)	0.711 0.174 0.001 0.001 0.001 0.070 <0.001

Initiation/discontinuation of heart failure treatments is compared between patients with a heart failure hospitalization vs. outpatients (i.e., patients without a heart failure hospitalization), stratified by eGFR in two strata. 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 1 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 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. eGFR: Estimated glomerular filtration rate; OR: Odds ratio; CI: Confidence interval; MRA: Mineralocorticoid receptor antagonist; HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction; RASi: Renin-aldosteronsystem inhibitors; ARNi: Angiotensin-receptor neprilysin-inhibitors.



Supplement Figure 3. Initiation/discontinuation of heart failure treatments in relation to recurrent heart failure hospitalizations over time.

Initiation/discontinuation of heart failure treatments in patients after an heart failure hospitalization (x-axis) is displayed in relation to the number of heart failure hospitalizations within a given time period (y-axis). MRA: Mineralocorticoid receptor antagonist; RASi: Renin-aldosteron-system inhibitors; ARNi: Angiotensin-receptor neprilysin-inhibitors; HHF: Heart failure hospitalization

Supplement Figure 4. Association between initiation/discontinuation of heart failure treatments and 3year cardiovascular mortality following a heart failure hospitalization.

Α	Incidence rate	HR (95% CI) P-value
MRA initiation		
HFrEF	106 (96-118) vs. 147 (135-159)	
HFrEF + HFmrEF	110 (101-120) vs. 145 (135-154)	• 0.9 (0.8-1.0) 0.158
RASi/ARNi initiation		
HFrEF	100 (86-117) vs. 198 (162-239)	0.8 (0.6-1.0) 0.040
HFrEF + HFmrEF	108 (95-122) vs. 223 (195-254)	■ 0.7 (0.5-0.8) <0.001
Betablocker initiation		
HFrEF	87 (74-101) vs. 200 (160-246) 🛛 🗕	► 0.6 (0.4-0.7) <0.001
HFrEF + HFmrEF	92 (80-105) vs. 194 (165-228) 🚽	■ 0.6 (0.5-0.7) <0.001
Loop diuretic initiation		
HFrEF	86 (76-98) vs. 35 (23-52)	
HFrEF + HFmrEF	88 (79-99) vs. 38 (27-53)	—— 1.7 (1.2-2.5) 0.003
	0.4	1 2.7
	н	R (95% CI)
В	Incidence rate	HR (95% CI) P-value
B MRA discontinuation	Incidence rate	HR (95% CI) P-value
MRA discontinuation	Incidence rate 170 (141-203) vs. 132 (119-145)	HR (95% CI) P-value
MRA discontinuation HFrEF		
MRA discontinuation HFrEF	170 (141-203) vs. 132 (119-145)	— 1.1 (0.9-1.4) 0.306
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation	170 (141-203) vs. 132 (119-145)	— 1.1 (0.9-1.4) 0.306
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation HFrEF	170 (141-203) vs. 132 (119-145) 160 (135-187) vs. 138 (126-150)	 ■ 1.1 (0.9-1.4) 0.306 ■ 1.0 (0.8-1.2) 0.706
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation HFrEF	170 (141-203) vs. 132 (119-145) 160 (135-187) vs. 138 (126-150) 219 (180-263) vs. 129 (121-137)	 1.1 (0.9-1.4) 0.306 1.0 (0.8-1.2) 0.706 1.5 (1.2-1.8) <0.001
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation HFrEF HFrEF + HFmrEF Betablocker discontinuation	170 (141-203) vs. 132 (119-145) 160 (135-187) vs. 138 (126-150) 219 (180-263) vs. 129 (121-137)	 1.1 (0.9-1.4) 0.306 1.0 (0.8-1.2) 0.706 1.5 (1.2-1.8) <0.001
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation HFrEF HFrEF + HFmrEF Betablocker discontinuation HFrEF	170 (141-203) vs. 132 (119-145) 160 (135-187) vs. 138 (126-150) 219 (180-263) vs. 129 (121-137) 216 (184-251) vs. 126 (119-132)	 1.1 (0.9-1.4) 0.306 1.0 (0.8-1.2) 0.706 1.5 (1.2-1.8) <0.001 1.5 (1.3-1.8) <0.001
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation HFrEF HFrEF + HFmrEF Betablocker discontinuation HFrEF	170 (141-203) vs. 132 (119-145) 160 (135-187) vs. 138 (126-150) 219 (180-263) vs. 129 (121-137) 216 (184-251) vs. 126 (119-132) 187 (147-236) vs. 136 (128-144)	 1.1 (0.9-1.4) 0.306 1.0 (0.8-1.2) 0.706 1.5 (1.2-1.8) <0.001 1.5 (1.3-1.8) <0.001 1.3 (1.0-1.7) 0.021
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation HFrEF HFrEF + HFmrEF Betablocker discontinuation HFrEF HFrEF + HFmrEF	170 (141-203) vs. 132 (119-145) 160 (135-187) vs. 138 (126-150) 219 (180-263) vs. 129 (121-137) 216 (184-251) vs. 126 (119-132) 187 (147-236) vs. 136 (128-144)	 1.1 (0.9-1.4) 0.306 1.0 (0.8-1.2) 0.706 1.5 (1.2-1.8) <0.001 1.5 (1.3-1.8) <0.001 1.3 (1.0-1.7) 0.021
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation HFrEF HFrEF + HFmrEF Betablocker discontinuation HFrEF HFrEF + HFmrEF Loop diuretic discontinuation HFrEF	170 (141-203) vs. 132 (119-145) 160 (135-187) vs. 138 (126-150) 219 (180-263) vs. 129 (121-137) 216 (184-251) vs. 126 (119-132) 187 (147-236) vs. 136 (128-144) 171 (138-208) vs. 136 (130-143)	 1.1 (0.9-1.4) 0.306 1.0 (0.8-1.2) 0.706 1.5 (1.2-1.8) <0.001 1.5 (1.3-1.8) <0.001 1.3 (1.0-1.7) 0.021 1.3 (1.0-1.5) 0.035
MRA discontinuation HFrEF HFrEF + HFmrEF RASi/ARNi discontinuation HFrEF HFrEF + HFmrEF Betablocker discontinuation HFrEF HFrEF + HFmrEF Loop diuretic discontinuation HFrEF	170 (141-203) vs. 132 (119-145) 160 (135-187) vs. 138 (126-150) 219 (180-263) vs. 129 (121-137) 216 (184-251) vs. 126 (119-132) 187 (147-236) vs. 136 (128-144) 171 (138-208) vs. 136 (130-143) 90 (63-124) vs. 159 (150-168)	 1.1 (0.9-1.4) 0.306 1.0 (0.8-1.2) 0.706 1.5 (1.2-1.8) <0.001 1.5 (1.3-1.8) <0.001 1.3 (1.0-1.7) 0.021 1.3 (1.0-1.5) 0.035 0.6 (0.5-0.9) 0.010

Cox regression models were fitted to evaluate the association between initiation/discontinuation vs. no initiation/no discontinuation (reference) in heart failure treatments and 3-year cardiovascular 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 1 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 are shown; and variables used for adjustment in the underlying Cox regression model are reported in *Table 1*. HR: Hazard ratio; CI: Confidence interval; MRA: Mineralocorticoid receptor antagonist; HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction; RASi: Renin-aldosterone-system inhibitors; ARNi: Angiotensin-receptor neprilysin-inhibitors.