

# Supplementary Material

## Data source

Patients with HF were identified through the Swedish HF Registry (SwedeHF). SwedeHF has been previously described(1). Briefly, it is an ongoing voluntary health care quality registry founded in 2000 and implemented on a national basis in 2003. Written consent is not required, but patients are informed of registration and allowed to opt-out. A majority of Swedish hospitals (~60 out of 75 hospitals) and to a minor extent also primary care centers enroll patients without financial compensation, and collect approximately 80 variables, i.e. data on demographics, comorbidities, clinical parameters, biomarkers, treatments and organizational aspects, from adult in-patient wards and out-patient clinics ([www.swedehf.se](http://www.swedehf.se)). The inclusion criterion was clinician-judged HF until April 2017 and after that defined as a diagnosis of HF according to the following ICD-10 codes: I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0 and I13.2. Reported coverage of SwedeHF in 2019 was 30.4% of prevalent HF population in Sweden.

Linkage to Statistics Sweden provided socioeconomic data. The National Patient Registry provided data on additional comorbidities and hospital accesses outcomes. The Cause of Death Registry provided date and cause of death. More details on selection criteria and variable definitions are available at <https://kiheartfailure.github.io/shfdb3/>. Linkage between the registries was allowed by the personal identification number, which all residents in Sweden have.

Establishment of the HF registry and this analysis with linking of the registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki.

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**Supplementary Table 1. Guideline recommended drugs and doses for heart failure with reduced ejection fraction.**

<b>RASI</b>	<b>Target dose</b>	<b>Target dose percentage</b>
<b>Captopril</b>		
	150 mg daily	≥100%
	75 – <150 mg	≥50 - 99%
	<75 mg	<50%
<b>Enalapril</b>		
	20 mg daily	≥100%
	10 - <20 mg	≥50 - 99%
	<10 mg	<50%
<b>Lisinopril</b>		
	35 mg daily	≥100%
	17.5 - <35 mg	≥50 - 99%
	<17.5 mg	<50%
<b>Ramipril</b>		
	10 mg daily	≥100%
	5 - <10 mg	≥50 - 99%
	<5 mg	<50%
<b>Trandolapril</b>		
	4 mg daily	≥100%
	2 - <4 mg	≥50 - 99%
	< 2 mg	<50%
<b>Candesartan</b>		
	32 mg daily	≥100%
	16 - <32 mg	≥50 - 99%
	< 16 mg	<50%
<b>Valsartan</b>		
	320 mg daily	≥100%
	160 - <320 mg	≥50 - 99%
	< 160 mg	<50%
<b>Losartan</b>		
	150 mg daily	≥100%
	75 - <150 mg	≥50 - 99%
	< 75 mg	<50%
<b>ARNI</b>	<b>Target dose</b>	<b>Target dose percentage</b>
<b>Sacubitril/Valsartan</b>		
	194/206 mg daily	≥100%
	97/103 - <194/206 mg	≥50 - 99%
	< 97/103 mg	<50%
<b>Beta-blocker</b>	<b>Target dose</b>	<b>Target dose percentage</b>
<b>Metoprolol</b>		
	200 mg daily	≥100%
	100 – <200 mg	≥50 - 99%
	<100 mg	<50%
<b>Bisoprolol</b>		
	10 mg daily	≥100%
	5 – <10 mg	≥50 - 99%
	<5 mg	<50%
<b>Carvedilol</b>		
	50 mg daily (<85 kg) 100 mg 2x daily (>85 kg)	≥100%
	25 – <50 mg (<85 kg) 50 – <100 mg (>85 kg)	≥50 - 99%
	<25 mg (<85 kg)	<50%

	<50 mg (>85 kg)	
<b>MRA</b>		
<b>Spirolactone</b>		
	50 mg daily	≥100%
	25 - <50 mg	≥50 - 99%
	< 25 mg	<50%
<b>Eplerenone</b>		
	50 mg daily	≥100%
	25 - <50 mg	≥50 - 99%
	< 25 mg	<50%

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**Abbreviations.** ARNI = angiotensin-receptor neprilysin inhibitor; MRA = mineralocorticoid receptor; RASI = renin-angiotensin-system inhibitor

**Supplementary Table 2. Characteristics of the overall study population and divided according to treatments use vs non-use.**

Variable	Total population	RASI/ARNI			Beta-blockers		
		non-use	use	p-value	non-use	use	p-value
n	12421	2002 (16%)	10419 (84%)		1480 (12%)	10941 (88%)	
<b>Demographic/Organizational characteristics</b>							
Sex Male, n (%) <sup>*^</sup>	7921 (64%)	1125 (56%)	6796 (65%)	<0.001	972 (66%)	6949 (64%)	0.100
Age (years), mean (SD)	74 (12)	79 (11)	73 (12)	<0.001	77 (12)	74 (12)	<0.001
Age category, n (%) <sup>*^</sup>				<0.001			<0.001
<70 years	3676 (30%)	301 (15%)	3375 (32%)		301 (20%)	3375 (31%)	
70-79 years	4100 (33%)	526 (26%)	3574 (34%)		431 (29%)	3669 (33%)	
≥80 years	4645 (37%)	1175 (59%)	3470 (33%)		748 (50%)	3897 (36%)	
Outpatient, n (%) <sup>*^</sup>	7987 (64%)	796 (40%)	7191 (69%)	<0.001	805 (54%)	7182 (66%)	<0.001
F-up referral HF nurse clinic, n (%) <sup>*^</sup>	6148 (52.0%)	689 (37%)	5459 (55%)	<0.001	634 (46%)	5514 (53%)	<0.001
F-up referral specialty, n (%) <sup>*^</sup>				<0.001			<0.001
Hospital	7132 (60%)	838 (45%)	6294 (62%)		691 (49%)	6441 (61%)	
Primary care	4493 (37%)	931 (50%)	3562 (35%)		663 (47%)	3830 (36%)	
Other	319 (3%)	88 (5%)	231 (2%)		52 (4%)	267 (2%)	
Year of registration, n (%) <sup>*^</sup>				<0.001			<0.001
< 2009	3207 (26%)	449 (28)	2648 (25%)		440 (30%)	2767 (25%)	
2010-2013	3191 (26%)	568 (28%)	2623 (25%)		417 (28%)	2774 (25%)	
2014-2016	3159 (25%)	532 (27%)	2627 (25%)		341 (23%)	2818 (26%)	
> 2016	2864 (23%)	343 (17%)	2521 (24%)		281 (19%)	2582 (24%)	
<b>Clinical characteristics</b>							
HF duration > 6 months, n (%) <sup>*^</sup>	9404 (77%)	1543 (79%)	7861 (77%)	0.067	1131 (78%)	8273 (77%)	0.220
NYHA class, n (%) <sup>*^</sup>				<0.001			0.070
I-II	5971 (65%)	634 (53%)	5337 (67%)		626 (62%)	5345 (66%)	
III-IV	3164 (35%)	564 (47%)	2600 (33%)		371 (37%)	2793 (34%)	
SBP, mmHg, mean (SD)	128 (20)	128 (21)	128 (20)	0.420	129 (20)	128 (20)	0.007
DBP, mmHg, mean (SD)	73 (12)	72 (12)	73 (12)	0.004	72 (12)	73 (12)	<0.001
MAP>90 mmHg, n (%) <sup>*^</sup>	5982 (49%)	934 (47%)	5048 (50%)	0.098	683 (47%)	5299 (49%)	0.099

<b>HR, bpm, mean (SD)</b>	72 (14)	76 (16)	71 (14)	<0.001	72 (15)	72 (14)	0.580
<b>HR &gt;70 bpm, n (%)<sup>*^</sup></b>	5583 (47%)	1097 (58%)	4486 (45%)	<0.001	669 (49%)	4914 (47%)	0.290
<b>Laboratory measurements</b>							
<b>eGFR (mL/min/1.73 m<sup>2</sup>), n (%)<sup>*^</sup></b>				<0.001			0.100
eGFR <30 mL/min/1.73 m <sup>2</sup>	929 (8%)	449 (23%)	480 (5%)		120 (8%)	809 (8%)	
eGFR 30-59 mL/min/1.73 m <sup>2</sup>	4812 (40%)	922 (47%)	3890 (38%)		608 (42%)	4204 (39%)	
eGFR ≥60 mL/min/1.73 m <sup>2</sup>	6417 (53%)	598 (30%)	5819 (57%)		733 (50%)	5684 (53%)	
<b>NT-proBNP (ng/L), median (IQR)<sup>*^</sup></b>	1650 (654-3820)	3479 (1530-8311)	1460 (584-3306)	<0.001	1782 (667-4536)	1630 (653-3730)	0.077
NT-proBNP > 1650 ng/L, n (%)	3289 (50%)	690 (73%)	2605 (46%)		353 (48%)	2936 (50%)	
NT-proBNP ≤ 1650 ng/L, n (%)	3289 (50%)	251 (27%)	3038 (54%)		385 (52%)	2910 (50%)	
<b>Potassium, n (%)<sup>*^</sup></b>				<0.001			0.240
Hyperkalemia (> 5 mEq/L)	382 (4%)	64 (4%)	318 (4%)				
Normokalemia (3.5-5.0 mEq/L)	9195 (92%)	1325 (89%)	7870 (93%)				
Hypokalemia (<3.5 mEq/L)	370 (4%)	105 (7%)	265 (3%)				
<b>Medical history/comorbidities</b>							
<b>BMI, kg/m<sup>2</sup>, median (IQR)<sup>*^</sup></b>	27 (24-31)	26 (23-30)	27 (24-31)	<0.001	26 (23-30)	27 (24-31)	<0.001
BMI < 22.5, n (%)	1120 (16%)	278 (24%)	842 (15%)		162 (20%)	958 (16%)	
BMI 22.5-30, n (%)	3725 (54%)	610 (52%)	3115 (54%)		452 (55%)	3273 (53%)	
BMI >30, n (%)	2098 (30%)	289 (25%)	1809 (31%)		202 (25%)	1896 (31%)	
<b>Smoking, n (%)<sup>*^</sup></b>				0.004			0.310
Current	940 (10%)	119 (8%)	821 (10%)		95 (9%)	845 (10%)	
Former	4305 (45%)	638 (44%)	3667 (46%)		498 (45%)	3807 (45%)	
Never	4259 (45%)	707 (48%)	3552 (44%)		505 (46%)	3754 (45%)	
<b>Diabetes, n (%)<sup>*^</sup></b>	3642 (29%)	626 (31%)	3016 (29%)	0.037	416 (28%)	3226 (29%)	0.270
<b>AF, n (%)<sup>*^</sup></b>	7746 (62.4%)	1407 (70%)	6339 (61%)	<0.001	919 (62%)	6827 (62%)	0.820
<b>Ischemic heart disease, n (%)<sup>*^</sup></b>	7482 (60%)	1261 (63%)	6221 (60%)	0.006	860 (58%)	6622 (60%)	0.075
<b>Anemia, n (%)<sup>-*^</sup></b>	4349 (37.4%)	994 (51%)	3355 (35%)	<0.001	622 (44%)	3727 (36%)	<0.001
<b>Hypertension, n (%)<sup>*^</sup></b>	8555 (69%)	1418 (71%)	7137 (68%)	0.039	964 (65%)	7591 (69%)	<0.001
<b>Peripheral artery disease, n (%)<sup>*^</sup></b>	1294 (10%)	255 (13%)	1039 (10%)	<0.001	160 (11%)	1134 (10%)	0.600
<b>Revascularization, n (%)<sup>*^</sup></b>	4429 (36%)	619 (31%)	3810 (37%)	<0.001	466 (31%)	3963 (36%)	<0.001

<b>Stroke/TIA, n (%)**^</b>	2176 (17%)	470 (23%)	1706 (16%)	<0.001	286 (19%)	1890 (17%)	0.052
<b>Valve disease, n (%)**^</b>	3906 (32%)	840 (43%)	3066 (30%)	<0.001	523 (36%)	3383 (31%)	<0.001
<b>Malignant cancer &lt;3 years, n (%)**^</b>	1610 (13%)	267 (13%)	2493 (24%)	0.032	238 (16%)	1372 (12%)	<0.001
<b>COPD, n (%)**^</b>	2092 (17%)	426 (21%)	1666 (16%)	<0.001	297 (20%)	1795 (16%)	<0.001
<b>Liver disease, n (%)**^</b>	270 (2%)	70 (3%)	200 (2%)	<0.001	28 (2%)	242 (2%)	0.430
<b>Treatments</b>							
<b>RASI/ARNI, n (%)**^</b>	10419 (84%)	-	-	-	1087 (73%)	9332 (85%)	<0.001
<b>Beta-blockers, n (%)**^</b>	10941 (88%)	1609 (80%)	9332 (90%)	<0.001	-	-	-
<b>MRA, n (%)**^</b>	4501 (36%)	688 (34%)	3813 (37%)	0.057	464 (31%)	4037 (37%)	<0.001
<b>Diuretics, n (%)**^</b>	9643 (78%)	1731 (87%)	7912 (76%)	<0.001	1144 (77%)	8499 (78%)	0.700
<b>Digoxin, n (%)**^</b>	1765 (14%)	295 (15%)	1470 (14%)	0.44	177 (12%)	1588 (14%)	0.008
<b>Antiplatelet therapy, n (%)**^</b>	5062 (41%)	815 (41%)	4247 (41%)	0.99	592 (40%)	4470 (41%)	0.520
<b>Anticoagulant therapy, n (%)**^</b>	6054 (49%)	883 (44%)	5171 (50%)	<0.001	605 (41%)	5449 (50%)	<0.001
<b>Statins, n (%)**^</b>	6284 (51%)	771 (38%)	5513 (53%)	<0.001	551 (37%)	5733 (52%)	<0.001
<b>Nitrates, n (%)**^</b>	2042 (16%)	414 (20%)	1628 (16%)	<0.001	244 (16%)	1798 (16%)	0.960
<b>ICD**^</b>	581 (5%)	59 (3%)	522 (5%)	<0.001	21 (2%)	560 (5%)	<0.001
<b>CRT**^</b>	468 (4%)	40 (2%)	428 (4%)	<0.001	20 (1%)	448 (4%)	<0.001
<b>Socioeconomic characteristics</b>							
<b>Family type Living alone, n (%)**^</b>	5940 (48%)	1103 (55%)	4837 (46%)	<0.001	746 (50%)	5194 (47%)	0.036
<b>Children, n (%)**^</b>	10444 (84%)	1706 (85%)	8738 (84%)	0.13	1246 (84%)	9198 (84%)	0.910
<b>Education, n (%)**^</b>				<0.001			0.160
Compulsory school	5393 (44.3%)	1004 (51%)	4389 (43%)		657 (45%)	4736 (44%)	
Secondary school	4751 (39.1%)	662 (34%)	4089 (40%)		532 (37%)	4219 (39%)	
University	2017 (16.6%)	278 (14%)	1739 (17%)		255 (18%)	1762 (16%)	
<b>Income, n (%)**^</b>				<0.001			0.086
Low	4289 (34%)	792 (40%)	3497 (33%)		517 (35%)	3772 (34%)	
Medium	4763 (38%)	810 (40%)	3953 (38%)		596 (40%)	4167 (38%)	
High	3363 (27%)	400 (20%)	2963 (28%)		367 (25%)	2996 (27%)	

32 **Legend.** AF: Atrial fibrillation; ARNI: Angiotensin receptor neprilysin inhibitor; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRT: Cardiac  
33 resynchronization therapy; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); F-up; follow-up, HF: Heart failure; HR: Heart  
34 rate; ICD: Implantable cardioverter defibrillator; IQR: Interquartile range; MAP: Mean arterial pressure; MRA: Mineralocorticoid receptor antagonist; NT-proBNP; N terminal pro-

35 brain natriuretic peptide, NYHA: New York heart association; RAS-inhibitor: Renin-angiotensin-system inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; TIA:  
36 Transient ischemic attack.  
37 ~ defined as Hb < 130 g/dl in men and 120 g/dl in women  
38 \* = variables included in multiple imputation together with index year, duration of HF, the composite outcome, and beta-blocker use (yes/no);  
39 ^ = variables included to estimate the propensity score together with index year and duration of HF  
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**Supplementary Table 3. Missing data.**

<b>Variable</b>	<b>Missing rate (%)</b>
Sex	0
Age	0
Outpatient	5
F-up referral HF nurse clinic	0
F-up referral speciality	4
Year of registration	0
HF duration > 6 months	2
NYHA class	26
SBP, mmHg	2
DBP, mmHg	2
HR	5
eGFR	2
NT-proBNP	46
Dyskalemia	19
BMI	44
Smoking	23
Diabetes	0
AF	0
Ischemic heart disease	0
Anemia	6
Hypertension	0
Peripheral artery disease	0
Revascularization	0
Stroke/TIA	0
Valve disease	2
Malignant cancer <3 years	0



<b>COPD</b>	<b>0</b>
<b>Liver disease</b>	<b>0</b>
<b>MRA</b>	<b>0</b>
<b>Diuretics</b>	<b>0</b>
<b>Digoxin</b>	<b>0</b>
<b>Antiplatelet therapy</b>	<b>0</b>
<b>Anticoagulant therapy</b>	<b>0</b>
<b>Statins</b>	<b>0</b>
<b>Nitrates</b>	<b>0</b>
<b>ICD</b>	<b>2</b>
<b>CRT</b>	<b>2</b>
<b>Family type Living alone</b>	<b>0</b>
<b>Children</b>	<b>0</b>
<b>Education</b>	<b>2</b>
<b>Income</b>	<b>0</b>

*For abbreviations see Table 1 in the main text.*

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**Supplementary Table 4. Characteristics of the study population matched according to treatments use vs non-use.**

Variable	RAS/ARNI			Beta-blockers		
	non-use	use	absolute standardized difference	non-use	use	absolute standardized difference
n	1915	1915		1468	1468	
<b>Demographic/Organizational characteristics</b>						
Sex Male, n (%)	1081 (56%)	1079 (56%)	0%	960 (65%)	943 (64%)	2%
Age (years), mean (SD)	79 (11)	79 (10)	5%	77 (12)	76 (11)	5%
Age category, n (%)			3%			7%
<70 years	294 (15%)	284 (15%)		301 (20%)	321 (22%)	
70-79 years	515 (27%)	540 (28%)		429 (29%)	458 (31%)	
≥80 years	1106 (58%)	1091 (57%)		738 (50%)	689 (47%)	
Outpatient, n (%)	788 (41%)	795 (42%)	1%	804 (55%)	841 (57%)	5%
F-up referral HF nurse clinic, n (%)	677 (38%)	714 (40%)	3%	633 (46%)	638 (46%)	0%
F-up referral speciality, n (%)			2%			6%
Hospital	815 (46%)	843 (46%)		691 (49%)	707 (50%)	
Primary care	881 (50%)	894 (49%)		656 (47%)	638 (45%)	
Other	80 (5%)	89 (5%)		48 (3%)	64 (4%)	
Year of registration, n (%)			9%			8%
< 2009	538 (28%)	583 (30%)		432 (29%)	406 (28%)	
2010-2013	539 (28%)	494 (26%)		414 (28%)	384 (26%)	
2014-2016	506 (26%)	463 (24%)		340 (23%)	368 (25%)	
> 2016	332 (17%)	375 (20%)		282 (19%)	310 (21%)	
<b>Clinical characteristics</b>						
HF duration > 6 months, n (%)	1476 (78%)	1495 (79%)	2%	1121 (78%)	1126 (78%)	1%
NYHA class, n (%)			1%			2%
I-II	618 (53%)	648 (53%)		621 (63%)	651 (63%)	
III-IV	548 (47%)	584 (47%)		370 (37%)	374 (36%)	
SBP, mmHg, mean (SD)	128 (21)	129 (21)	1%	130 (20)	128 (20)	7%
DBP, mmHg, mean (SD)	72 (12)	72 (12)	1%	72 (12)	72 (11)	4%

<b>MAP&gt;90 mmHg, n (%)</b>	891 (47%)	901 (48%)	1%	677 (47%)	695 (48%)	2%
<b>HR, bpm, mean (SD)</b>	76 (16)	75 (15)	8%	72 (15)	72 (14)	2%
<b>HR &gt;70 bpm, n (%)</b>	1033 (57%)	1033 (57%)	0%	665 (49%)	686 (49%)	0%
<b>Laboratory measurements</b>						
<b>eGFR (mL/min/1.73 m<sup>2</sup>), n (%)</b>			7%			5%
eGFR <30 mL/min/1.73 m <sup>2</sup>	372 (20%)	335 (18%)		119 (8%)	99 (7%)	
eGFR 30-60 mL/min/1.73 m <sup>2</sup>	912 (49%)	907 (48%)		601 (41%)	606 (42%)	
eGFR >60 mL/min/1.73 m <sup>2</sup>	598 (32%)	656 (35%)		729 (50%)	730 (51%)	
<b>NT-proBNP (ng/L), median (IQR)</b>			2%			5%
NT-proBNP > 1650 ng/L, n (%)	251 (28%)	258 (27%)		352 (48%)	376 (50%)	
NT-proBNP ≤ 1650 ng/L, n (%)	652 (72%)	694 (73%)		385 (52%)	372 (50%)	
<b>Potassium, n (%)</b>			6%			4%
Hyperkalemia (> 5 mEq/L)	61 (4%)	54 (4%)		370 (37%)	374 (36%)	
Normokalemia (3.5-5.0 mEq/L)	1274 (89%)	1331 (91%)		1038 (92%)	1054 (91%)	
Hypokalemia (<3.5 mEq/L)	95 (7%)	54 (4%)		37 (3%)	46 (4%)	
<b>Medical history/comorbidities</b>						
<b>BMI, kg/m<sup>2</sup>, median (IQR)</b>			8%			1
BMI < 22.5, n (%)	263 (24%)	229 (20%)		159 (20%)	160 (20%)	
BMI 22.5-30, n (%)	576 (51%)	590 (53%)		446 (55%)	449 (55%)	
BMI >30, n (%)	280 (25%)	302 (27%)		201 (25%)	207 (25%)	
<b>Smoking, n (%)</b>			2%			8%
Current	114 (8%)	119 (8%)		95 (9%)	100 (9%)	
Former	606 (43%)	620 (44%)		491 (45%)	450 (41%)	
Never	680 (49%)	678 (48%)		503 (46%)	551 (50%)	
<b>Diabetes, n (%)</b>	598 (31%)	594 (31%)	1%	410 (28%)	440 (30%)	5%
<b>AF, n (%)</b>	1346 (70%)	1346 (70%)	0%	911 (62%)	905 (62%)	1%
<b>Ischemic heart disease, n (%)</b>	1203 (63%)	1245 (65%)	5%	854 (58%)	885 (60%)	4%
<b>Anemia, n (%)</b> <sup>~</sup>	932 (50%)	911 (49%)	2%	612 (44%)	590 (42%)	3%
<b>Hypertension, n (%)</b>	1353 (71%)	1365 (71%)	0%	959 (65%)	993 (68%)	5%
<b>Peripheral artery disease, n (%)</b>	244 (13%)	251 (13%)	1%	159 (11%)	182 (12%)	5%

<b>Revascularization, n (%)</b>	589 (31%)	662 (34%)	8%	466 (32%)	468 (32%)	0%
<b>Stroke/TIA, n (%)</b>	244 (13%)	251 (13%)	0%	282 (19%)	274 (19%)	1%
<b>Valve disease, n (%)</b>	1353 (71%)	1365 (71%)	1%	515 (36%)	511 (36%)	1%
<b>Malignant cancer &lt;3 years, n (%)</b>	273 (14%)	257 (13%)	2%	233 (16%)	208 (14%)	5%
<b>COPD, n (%)</b>	244 (13%)	251 (13%)	2%	294 (20%)	299 (20%)	1%
<b>Liver disease, n (%)</b>	64 (3%)	69 (4%)	1%	28 (2%)	20 (1%)	4%
<b>Treatments</b>						
<b>RASI/ARNI, n (%)</b>	0 (0%)	1927 (100%)	-	1087 (74%)	1144 (78%)	9%
<b>Beta-blockers, n (%)</b>	1550 (81%)	1552 (81%)	0%	0 (0%)	1468 (100%)	-
<b>MRA, n (%)</b>	663 (35%)	675 (35%)	1%	463 (31%)	466 (32%)	0%
<b>Diuretics, n (%)</b>	1655 (87%)	1656 (87%)	0%	1136 (77%)	1133 (77%)	0%
<b>Digoxin, n (%)</b>	289 (15%)	296 (16%)	1%	177 (12%)	179 (12%)	0%
<b>Antiplatelet therapy, n (%)</b>	778 (41%)	771 (40%)	1%	591 (40%)	608 (41%)	2%
<b>Anticoagulant therapy, n (%)</b>	867 (46%)	895 (47%)	3%	604 (41%)	631 (43%)	4%
<b>Statins, n (%)</b>	754 (39%)	784 (41%)	3%	551 (38%)	604 (41%)	7%
<b>Nitrates, n (%)</b>	396 (21%)	425 (22%)	4%	243 (17%)	263 (18%)	4%
<b>ICD</b>	57 (3%)	54 (3%)	2%	21 (1%)	30 (2%)	4%
<b>CRT</b>	40 (2%)	45 (2%)	1%	20 (1%)	27 (2%)	4%
<b>Socio-economic characteristics</b>						
<b>Family type Living alone, n (%)</b>	1046 (55%)	1011 (53%)	4%	741 (50%)	742 (51%)	0%
<b>Children, n (%)</b>	1629 (85%)	1657 (87%)	4%	1236 (84%)	1243 (85%)	1%
<b>Education, n (%)</b>			1%			5%
Compulsory school	948 (51%)	953 (51%)		649 (45%)	639 (45%)	
Secondary school	642 (35%)	650 (35%)		530 (37%)	562 (39%)	
University	269 (15%)	265 (14%)		253 (18%)	231 (16%)	
<b>Income, n (%)</b>			6%			3%
Low	760 (40%)	813 (43%)		514 (35%)	534 (36%)	
Medium	765 (40%)	744 (39%)		590 (40%)	569 (39%)	
High	390 (20%)	358 (19%)		364 (25%)	364 (25%)	

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AF: Atrial fibrillation; ARNI: Angiotensin receptor neprilysin inhibitor; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRT: Cardiac resynchronization therapy; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); HF: Heart failure; HR: Heart rate; ICD: Implantable cardioverter

48 defibrillator; IQR: Interquartile range; MAP: Mean arterial pressure; MRA: Mineralocorticoid receptor antagonist; NYHA: New York heart association; RAS-inhibitor: Renin-  
49 angiotensin-system inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; TIA: Transient ischemic attack.  
50 ~ defined as Hb < 130 g/dl in men and 120 g/dl in women  
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52 **Supplementary Table 5. Negative control analysis (cancer related hospitalizations).**

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Overall population						Matched population			
RASI/ARNI									
	use n=10419 events/1000 pts-yr (95%CI)	non-use n=2002 events/1000 pts-yr (95%CI)	IRR (95%CI)	Crude HR (95% CI)	PS adjusted HR (95% CI)	use n=10419 events/1000 pt-yr (95%CI)	non-use n=2002 events/1000 pts-yr (95%CI)	IRR (95%CI)	Matched HR (95%CI)
<b>Cancer related hospitali- zation</b>	20 (18-21)	26 (22-32)	0.77 <sup>^</sup> (0.63-0.93)	0.81* (0.67-0.98)	0.93 (0.75-1.13)	21 (18-26)	25 (21-30)	0.84 (0.65-1.09)	0.86 (0.66- 1.11)
Beta-blockers									
	use n=10419 events/1000 pt-yr (95% CI)	non-use n=2002 events/1000 pts-yr (95%CI)	IRR (95%CI)	Crude HR (95%CI)	PS adjusted HR (95% CI)	use n=10419 events/1000 pt- yr (95%CI)	non-use n=2002 events/1000 pts-yr (95%CI)	IRR (95%CI)	Matche d HR (95%CI)
<b>Cancer related hospitali- zation</b>	20 (19-21)	24 (20-29)	0.83 (0.68-1.01)	0.85 (0.69-1.04)	0.96 (0.78-1.18)	22 (18-27)	24 (20-29)	0.91 (0.70-1.19)	0.91 (0.65- 1.26)

76 **Legend.** CI=confidence interval; CV=cardiovascular; HFH=heart failure hospitalization; HR=hazard ratio; IRR=incidence rate ratio; RASI/ARNI=renin angiotensin system  
77 inhibitors/angiotensin receptor neprilyisin inhibitor.

78 \* *p value <0.05*

79 <sup>^</sup> *p value <0.01*

83 **Supplementary Table 6. Characteristics of the overall positive control cohort and divided according to treatments use vs non-use.**

	Total population	RASII/ARNI			Beta-blockers		
Variable		non-use	use	p-value	non-use	use	p-value
n	26143	2691 (10%)	23452 (90%)		2246 (9%)	23897 (11%)	
<b>Demographic/Organizational characteristics</b>							
Sex Male, n (%) <sup>*^</sup>	19083 (73%)	1866 (69%)	17217 (73%)	<0.001	1619 (72%)	17464 (73%)	0.310
Age (years), mean (SD)	73 (12)	79 (10)	72 (12)	<0.001	77 (11)	73 (12)	<0.001
Age category, n (%) <sup>*^</sup>				<0.001			<0.001
<70 years	8802 (34%)	391 (15%)	8411 (36%)		477 (21%)	8325 (35%)	
70-79 years	8922 (34%)	729 (27%)	8193 (35%)		666 (30%)	8256 (34%)	
≥80 years	8419 (32%)	1571 (58%)	6848 (29%)		1103 (49%)	7316 (31%)	
Outpatient, n (%) <sup>*^</sup>	15899 (61%)	919 (34%)	14980 (64%)	<0.001	1141 (51%)	14758 (62%)	<0.001
F-up referral HF nurse clinic, n (%) <sup>*^</sup>	13829 (56%)	911 (37%)	12918 (58%)	<0.001	919 (44%)	12910 (57%)	<0.001
F-up referral specialty, n (%) <sup>*^</sup>				<0.001			<0.001
Hospital	17818 (71%)	1222 (50%)	16596 (73%)		1177 (56%)	16641 (72%)	
Primary care	6505 (26%)	1105 (45%)	5400 (24%)		843 (40%)	5662 (25%)	
Other	689 (3%)	116 (5%)	573 (3%)		81 (4%)	608 (3%)	
Year of registration, n (%) <sup>*^</sup>				<0.001			<0.001
< 2009	8474 (32%)	937 (35)	7537 (32%)		944 (42%)	7530 (31%)	
2010-2013	7257 (28%)	756 (28%)	6501 (28%)		564 (25%)	6693 (28%)	
2014-2016	5668 (22%)	628 (23%)	5040 (21%)		425 (19%)	5243 (22%)	
> 2016	4744 (18%)	370 (14%)	4374 (19%)		313 (14%)	4431 (19%)	
<b>Clinical characteristics</b>							
HF duration > 6 months, n (%) <sup>*^</sup>	19393 (75%)	2117 (80%)	17276 (75%)	<0.001	1743 (79%)	17650 (75%)	<0.001
NYHA class, n (%) <sup>*^</sup>				<0.001			<0.001
I-II	10540 (52%)	578 (35%)	9962 (54%)		725 (46%)	9815 (53%)	
III-IV	9569 (48%)	1085 (65%)	8484 (46%)		856 (54%)	8713 (47%)	
SBP, mmHg, mean (SD)	123 (20)	123 (20)	123 (20)	0.80	124 (21)	123 (20)	0.013
DBP, mmHg, mean (SD)	72 (12)	71 (12)	72 (12)	<0.001	71 (12)	72 (12)	<0.001

<b>MAP&gt;90 mmHg, n (%)**^</b>	10766 (42%)	1042 (40%)	9724 (42%)	0.015	910 (41%)	9856 (42%)	0.480
<b>HR, bpm, mean (SD)</b>	73 (15)	77 (16)	72 (15)	<0.001	74 (15)	73 (15)	<0.001
<b>HR &gt;70 bpm, n (%)**^</b>	12107 (49%)	1517 (60%)	10590 (47%)	<0.001	1131 (54%)	10976 (48%)	<0.001
<b>Laboratory measurements</b>							
<b>eGFR (mL/min/1.73 m<sup>2</sup>), n (%)#**^</b>				<0.001			<0.001
eGFR <30 mL/min/1.73 m <sup>2</sup>	1994 (8%)	731 (27%)	1263 (5%)		221 (10%)	1773 (8%)	
eGFR 30-59 mL/min/1.73 m <sup>2</sup>	10192 (40%)	1301 (49%)	8891 (38%)		970 (44%)	9222 (39%)	
eGFR ≥60 mL/min/1.73 m <sup>2</sup>	13572 (52%)	622 (23%)	12950 (56%)		1028 (46%)	12544 (53%)	
<b>NT-proBNP (ng/L), median (IQR)**^</b>	2623 (1070-6165)	6211 (2690-15881)	2406 (1004-5600)	<0.001	2892 (1158-6797)	2600 (1063-6130)	0.280
NT-proBNP > 2623 ng/L, n (%)	6383 (50%)	851 (76%)	5532 (48%)		502 (53%)	5881 (50%)	
NT-proBNP ≤ 2623 ng/L, n (%)	6383 (50%)	274 (24%)	6109 (52%)		447 (47%)	5936 (50%)	
<b>Potassium, n (%)**^</b>				<0.001			0.068
Hyperkalemia (> 5 mEq/L)	673 (3%)	146 (7%)	527 (3%)		68 (4%)	605 (3%)	
Normokalemia (3.5-5.0 mEq/L)	18538 (93%)	1717 (88%)	16821 (93%)		1427 (92%)	17111 (93%)	
Hypokalemia (<3.5 mEq/L)	821 (4%)	92 (5%)	729 (4%)		61 (4%)	760 (4%)	
<b>Medical history/comorbidities</b>							
<b>BMI, kg/m<sup>2</sup>, median (IQR)**^</b>	26 (23-30)	25 (22-29)	26 (24-30)	<0.001	25 (22-28)	26 (23-30)	<0.001
BMI < 22.5, n (%)	2829 (19%)	427 (28%)	2402 (18%)		320 (27%)	2509 (18%)	
BMI 22.5-30, n (%)	8591 (57%)	810 (53%)	7781 (57%)		660 (55%)	7931 (57%)	
BMI >30, n (%)	3654 (24%)	284 (19%)	3370 (25%)		219 (18%)	3435 (25%)	
<b>Smoking, n (%)**^</b>				0.004			<0.001
Current	2551 (12%)	162 (9%)	2389 (13%)		170 (10%)	2381 (13%)	
Former	9674 (47%)	900 (47%)	8774 (47%)		762 (46%)	8912 (47%)	
Never	8293 (40%)	845 (44%)	7448 (40%)		744 (44%)	7549 (40%)	
<b>Diabetes, n (%)**^</b>	8188 (31%)	888 (33%)	7300 (31%)	0.047	588 (26%)	7600 (32%)	<0.001
<b>AF, n (%)**^</b>	14897 (57%)	1741 (65%)	13156 (56%)	<0.001	1285 (57%)	13612 (57%)	0.820
<b>Ischemic heart disease, n (%)**^</b>	17174 (66%)	1954 (73%)	15220 (65%)	<0.001	1455 (65%)	15719 (66%)	0.340
<b>Anemia, n (%)**^</b>	8738 (35%)	1364 (52%)	7374 (33%)	<0.001	916 (42%)	7822 (34%)	<0.001
<b>Hypertension, n (%)**^</b>	16173 (62%)	1776 (66%)	14397 (61%)	<0.001	1274 (57%)	14899 (62%)	<0.001
<b>Peripheral artery disease, n (%)**^</b>	2787 (11%)	431 (16%)	2356 (10%)	<0.001	268 (12%)	2519 (10%)	0.041



<b>Revascularization, n (%)**^</b>	10753 (41%)	1053 (39%)	9700 (41%)	0.026	805 (36%)	9948 (42%)	<0.001
<b>Stroke/TIA, n (%)**^</b>	4748 (18%)	673 (25%)	4075 (17%)	<0.001	490 (22%)	4258 (18%)	<0.001
<b>Valve disease, n (%)**^</b>	7609 (29%)	1154 (44%)	6455 (28%)	<0.001	805 (37%)	6804 (29%)	<0.001
<b>Malignant cancer &lt;3 years, n (%)**^</b>	1610 (13%)	404 (15%)	2753 (12%)	<0.001	329 (15%)	2828 (12%)	<0.001
<b>COPD, n (%)**^</b>	3792 (14%)	464 (17%)	3328 (14%)	<0.001	395 (18%)	3397 (14%)	<0.001
<b>Liver disease, n (%)**^</b>	627 (2%)	92 (3%)	535 (2%)	<0.001	62 (3%)	565 (2%)	0.240
<b>Treatments</b>							
<b>RASI/ARNI, n (%)**^</b>	23452 (90%)	-	-	-	1764 (79%)	21688 (91%)	<0.001
<b>Beta-blockers, n (%)**^</b>	23897 (91%)	2209 (82%)	21688 (92%)	<0.001	-	-	-
<b>MRA, n (%)**^</b>	11405 (44%)	896 (33%)	10509 (45%)	<0.001	833 (37%)	10572 (44%)	<0.001
<b>Diuretics, n (%)**^</b>	21339 (82%)	2403 (89%)	18936 (81%)	<0.001	1848 (82%)	19491 (82%)	0.420
<b>Digoxin, n (%)**^</b>	4008 (15%)	367 (14%)	3641 (15%)	0.010	313 (14%)	3695 (15%)	0.055
<b>Antiplatelet therapy, n (%)**^</b>	11842 (45%)	1317 (49%)	10525 (45%)	<0.001	1024 (46%)	10818 (45%)	0.077
<b>Anticoagulant therapy, n (%)**^</b>	12377 (47%)	1037 (39%)	11340 (48%)	<0.001	877 (39%)	11500 (48%)	<0.001
<b>Statins, n (%)**^</b>	14065 (54%)	1090 (40%)	12975 (55%)	<0.001	886 (39%)	13179 (55%)	<0.001
<b>Nitrates, n (%)**^</b>	4301 (16%)	647 (24%)	3654 (16%)	<0.001	392 (17%)	3909 (16%)	0.170
<b>ICD**^</b>	2819 (11%)	136 (5%)	2683 (12%)	<0.001	90 (4%)	2729 (12%)	<0.001
<b>CRT**^</b>	2201 (8%)	142 (5%)	2059 (9%)	<0.001	114 (5%)	2087 (9%)	<0.001
<b>Socioeconomic characteristics</b>							
<b>Family type Living alone, n (%)**^</b>	12033 (46%)	1399 (52%)	10634 (45%)	<0.001	1096 (49%)	10937 (46%)	0.006
<b>Children, n (%)**^</b>	21756 (83%)	2258 (84%)	19498 (83%)	0.31	1896 (84%)	19860 (83%)	0.110
<b>Education, n (%)**^</b>				<0.001			<0.001
Compulsory school	11543 (45%)	1409 (54%)	10134 (44%)		1103 (50%)	10440 (45%)	
Secondary school	10040 (39%)	886 (34%)	9154 (40%)		770 (35%)	9270 (40%)	
University	4001 (16%)	328 (12%)	3673 (16%)		325 (15%)	3676 (16%)	
<b>Income, n (%)**^</b>				<0.001			<0.001
Low	8839 (34%)	1019 (38%)	7820 (33%)		806 (36%)	8033 (34%)	
Medium	9870 (38%)	1092 (41%)	8778 (38%)		908 (40%)	8962 (38%)	
High	7394 (28%)	577 (21%)	6817 (29%)		529 (24%)	6865 (29%)	

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AF: Atrial fibrillation; ARNI: Angiotensin receptor neprilysin inhibitor; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRT: Cardiac resynchronization therapy; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); HF: Heart failure; HR: Heart rate; ICD: Implantable cardioverter

86 defibrillator; IQR: Interquartile range; MAP: Mean arterial pressure; MRA: Mineralocorticoid receptor antagonist; NYHA: New York heart association; RAS-inhibitor: Renin-  
87 angiotensin-system inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; TIA: Transient ischemic attack.  
88 ~ defined as Hb < 130 g/dl in men and 120 g/dl in women  
89 \* = variables included in multiple imputation together with index year, duration of HF, the composite outcome, and beta-blocker use (yes/no);  
90 ^ = variables included to estimate the propensity score together with index year and duration of HF  
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**Supplementary Table 7. Characteristics of the positive control cohort matched according to treatments use vs non-use.**

Variable	RAS/ARNI			Beta-blockers		
	non-use	use	absolute standardized difference	non-use	use	absolute standardized difference
n	2630	2630		2244	2244	
<b>Demographic/Organizational characteristics</b>						
Sex Male, n (%)	1822 (69%)	1791 (68%)	2%	960 (65%)	943 (64%)	2%
Age (years), mean (SD)	79 (10)	79 (10)	-	77 (12)	76 (11)	-
Age category, n (%)			3%			7%
<70 years	390 (15%)	415 (16%)		301 (21%)	321 (22%)	
70-79 years	724 (27%)	733 (28%)		429 (29%)	458 (31%)	
≥80 years	1516 (58%)	1482 (56%)		738 (50%)	689 (47%)	
Outpatient, n (%)	917 (35%)	972 (37%)	4%	804 (55%)	841 (57%)	5%
F-up referral HF nurse clinic, n (%)	909 (38%)	972 (40%)	3%	633 (46%)	638 (46%)	0%
F-up referral speciality, n (%)			6%			6%
Hospital	1212 (51%)	1285 (52%)		691 (50%)	707 (50%)	
Primary care	1070 (45%)	1065 (43%)		656 (47%)	638 (45%)	
Other	108 (5%)	141 (6%)		48 (3%)	64 (5%)	
Year of registration, n (%)			9%			7%
< 2009	921 (35%)	958 (36%)		432 (29%)	406 (28%)	
2010-2013	737 (28%)	744 (28%)		414 (28%)	384 (26%)	
2014-2016	609 (23%)	513 (19%)		340 (23%)	368 (25%)	
> 2016	363 (14%)	415 (16%)		282 (19%)	310 (21%)	
<b>Clinical characteristics</b>						
HF duration > 6 months, n (%)	2070 (80%)	2058 (79%)	2%	1121 (78%)	1126 (78%)	1%
NYHA class, n (%)			1%			2%
I-II	577 (35%)	643 (35%)		621 (63%)	651 (63%)	
III-IV	1063 (65%)	1169 (64%)		370 (37%)	374 (37%)	
SBP, mmHg, mean (SD)	123 (20)	124 (20)	-	129 (20)	128 (20)	-
DBP, mmHg, mean (SD)	71 (12)	71 (12)	-	72 (12)	72 (11)	-

<b>MAP&gt;90 mmHg, n (%)</b>	1022 (40%)	1028 (40%)	1%	677 (47%)	695 (48%)	2%
<b>HR, bpm, mean (SD)</b>	77 (16)	75 (15)	-	72 (15)	72 (14)	-
<b>HR &gt;70 bpm, n (%)</b>	1470 (60%)	1431 (58%)	3%	665 (49%)	686 (49%)	0%
<b>Laboratory measurements</b>						
<b>eGFR (mL/min/1.73 m<sup>2</sup>), n (%)</b>			6%			5%
eGFR <30 mL/min/1.73 m <sup>2</sup>	673 (26%)	645 (25%)		119 (8%)	99 (7%)	
eGFR 30-60 mL/min/1.73 m <sup>2</sup>	1298 (50%)	1267 (49%)		601 (42%)	606 (42%)	
eGFR >60 mL/min/1.73 m <sup>2</sup>	622 (24%)	694 (27%)		729 (50%)	730 (51%)	
<b>NT-proBNP (ng/L), median (IQR)</b>	6034 (2627- 15449)	4884 (2260- 11539)	-	1785 (667- 4536)	1638 (686- 4310)	-
NT-proBNP > 2623 ng/L, n (%)	825 (75%)	821 (71%)	9%	294 (40%)	280 (37%)	5%
NT-proBNP ≤ 2623 ng/L, n (%)	273 (25%)	340 (29%)		443 (60%)	468 (63%)	
<b>Potassium, n (%)</b>			5%			4%
Hyperkalemia (> 5 mEq/L)	136 (7%)	118 (6%)		51 (5%)	54 (5%)	
Normokalemia (3.5-5.0 mEq/L)	1676 (88%)	1702 (90%)		1038 (92%)	1054 (91%)	
Hypokalemia (<3.5 mEq/L)	90 (5%)	78 (4%)		37 (3%)	46 (4%)	
<b>Medical history/comorbidities</b>						
<b>BMI, kg/m<sup>2</sup>, median (IQR)</b>	25 (22-29)	25 (22-28)		26 (23-30)	26 (23-30)	1%
BMI < 22.5, n (%)	411 (28%)	388 (28%)	9%	159 (20%)	160 (20%)	
BMI 22.5-30, n (%)	788 (53%)	906 (58%)		446 (55%)	449 (55.0%)	
BMI >30, n (%)	281 (19%)	273 (17%)		201 (25%)	207 (25%)	
<b>Smoking, n (%)</b>			4%			8%
Current	159 (9%)	184 (10%)		95 (9%)	100 (9%)	
Former	885 (47%)	891 (46%)		491 (45%)	450 (41%)	
Never	828 (44%)	866 (44%)		503 (46%)	551 (50.0%)	
<b>Diabetes, n (%)</b>	871 (33%)	905 (34%)	3%	410 (28%)	440 (30%)	4%
<b>AF, n (%)</b>	1698 (65%)	1697 (65%)	0%	911 (62%)	905 (62%)	1%
<b>Ischemic heart disease, n (%)</b>	1910 (73%)	1912 (73%)	0%	854 (58%)	885 (60%)	4%
<b>Anemia, n (%)</b> <sup>~</sup>	1314 (51%)	1268 (50%)	3%	612 (44%)	590 (42%)	3%
<b>Hypertension, n (%)</b>	1732 (66%)	1723 (66%)	1%	959 (65%)	993 (68%)	5%

Peripheral artery disease, n (%)	410 (16%)	422 (16%)	1%	159 (11%)	182 (12%)	5%
Revascularization, n (%)	1028 (39%)	1094 (42%)	5%	466 (32%)	468 (32%)	0%
Stroke/TIA, n (%)	653 (25%)	627 (24%)	2%	282 (19%)	274 (19%)	1%
Valve disease, n (%)	1117 (43%)	1105 (42%)	2%	515 (36%)	511 (36%)	1%
Malignant cancer <3 years, n (%)	397 (15%)	382 (15%)	2%	233 (16%)	208 (14%)	4%
COPD, n (%)	457 (17%)	473 (18%)	2%	294 (20%)	299 (20%)	1%
Liver disease, n (%)	86 (3%)	79 (3%)	2%	28 (2%)	20 (1%)	4%
<b>Treatments</b>						
RASI/ARNI, n (%)	0 (0%)	2630 (100%)	-	1087 (74%)	1144 (78%)	
Beta-blockers, n (%)	2180 (83%)	2198 (84%)	2%	0 (0%)	1468 (100%)	-
MRA, n (%)	888 (34%)	898 (34%)	1%	463 (32%)	466 (32%)	0%
Diuretics, n (%)	2352 (90%)	2362 (90%)	2%	1136 (77%)	1133 (77%)	0%
Digoxin, n (%)	366 (14%)	386 (15%)	2%	177 (12%)	179 (12%)	0%
Antiplatelet therapy, n (%)	1292 (49%)	1300 (49%)	0%	591 (40%)	608 (41%)	2%
Anticoagulant therapy, n (%)	1027 (39%)	1044 (40%)	1%	604 (41%)	631 (43%)	4%
Statins, n (%)	1085 (41%)	1123 (43%)	3%	551 (38%)	604 (41%)	7%
Nitrates, n (%)	630 (24%)	615 (23%)	1%	243 (17%)	263 (18%)	4%
ICD	134 (5%)	141 (5%)	1%	21 (1%)	30 (2%)	5%
CRT	140 (5%)	151 (6%)	2%	20 (1%)	27 (2%)	4%
<b>Socio-economic characteristics</b>						
Family type Living alone, n (%)	1370 (52%)	1364 (52%)	0%	741 (50%)	742 (51%)	0%
Children, n (%)	2211 (84%)	2206 (84%)	1%	1236 (84%)	1243 (85%)	1%
Education, n (%)			2%			5%
Compulsory school	1372 (53%)	1342 (53%)		649 (45%)	639 (45%)	
Secondary school	871 (34%)	885 (34%)		530 (37%)	562 (39%)	
University	321 (13%)	323 (13%)		253 (18%)	231 (16%)	
Income, n (%)			4%			3%
Low	997 (38%)	991 (38%)		514 (35%)	534 (36%)	
Medium	1059 (40%)	1101 (42%)		590 (40%)	569 (39%)	

High	571 (22%)	535 (20%)		364 (25%)	364 (25%)	
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93 AF: Atrial fibrillation; ARNI: Angiotensin receptor neprilysin inhibitor; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRT: Cardiac resynchronization  
94 therapy; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); HF: Heart failure; HR: Heart rate; ICD: Implantable cardioverter  
95 defibrillator; IQR: Interquartile range; MAP: Mean arterial pressure; MRA: Mineralocorticoid receptor antagonist; NYHA: New York heart association; RAS-inhibitor: Renin-  
96 angiotensin-system inhibitor; SBP: Systolic blood pressure; SD: Standard deviation; TIA: Transient ischemic attack.  
97 ~ defined as Hb < 130 g/dl in men and 120 g/dl in women  
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**Supplementary Table 8. Primary and secondary study outcomes in the positive control population (HFREF, n=26143).**

Overall population					Matched population				
RASI/ARNI									
	use n=23452 events/1000 pt-yr (95% CI)	non-use n=2691 events/1000 pts-yr (95%CI)	IRR (95%CI)	HR (95% CI)	PS adjusted HR (95% CI)	use n=2630 events/1000 pt-yr (95%CI)	non-use n=2630 events/1000 pts-yr (95%CI)	IRR (95%CI)	HR (95%CI)
<b>CV mortality/ HFH</b>	223 (219-226)	562 (538-587)	0.40 <sup>^</sup> (0.38-0.42)	0.50 <sup>^</sup> (0.47-0.52)	0.91 <sup>^</sup> (0.85-0.97)	437 (418-456)	552 (528-577)	0.79 <sup>^</sup> (0.74-0.84)	0.82 <sup>^</sup> (0.77-0.87)
<b>All-cause mortality</b>	134 (132-137)	397 (381-314)	0.34 <sup>^</sup> (0.32-0.35)	0.36 <sup>^</sup> (0.34-0.37)	0.72 <sup>^</sup> (0.69-0.76)	279 (267-292)	389 (373-406)	0.72 <sup>^</sup> (0.68-0.76)	0.68 <sup>^</sup> (0.64-0.73)
<b>CV mortality</b>	89 (88-91)	269 (256-283)	0.33 <sup>^</sup> (0.31-0.35)	0.36 <sup>^</sup> (0.34-0.38)	0.75 <sup>^</sup> (0.70-0.79)	193 (183-203)	263 (250-276)	0.73 <sup>^</sup> (0.68-0.79)	0.73 <sup>^</sup> (0.67-0.78)
<b>HFH</b>	179 (176-183)	388 (368-408)	0.46 <sup>^</sup> (0.44-0.49)	0.59 <sup>^</sup> (0.56-0.63)	0.88 <sup>^</sup> (0.82-0.93)	320 (304-337)	384 (365-405)	0.83 <sup>^</sup> (0.77-0.90)	0.88 <sup>^</sup> (0.82-0.95)
Beta-blockers									
	use n=23897 events/1000 pt-yr (95% CI)	non-use n=2246 events/1000 pts-yr (95%CI)	IRR (95%CI)	HR (95%CI)	PS adjusted HR (95% CI)	use n=2244 events/1000 pt-yr (95%CI)	non-use n=2244 events/1000 pts-yr (95%CI)	IRR (95%CI)	HR (95%CI)
<b>CV mortality/ HFH</b>	233 (229-237)	347 (331-365)	0.67 <sup>^</sup> (0.64-0.71)	0.73 <sup>^</sup> (0.69-0.77)	0.87 <sup>^</sup> (0.83-0.92)	273 (260-287)	347 (330-364)	0.79 <sup>^</sup> (0.73-0.84)	0.85 <sup>^</sup> (0.79-0.91)
<b>All-cause mortality</b>	142 (140-145)	236 (225-248)	0.60 <sup>^</sup> (0.57-0.63)	0.62 <sup>^</sup> (0.59-0.65)	0.87 <sup>^</sup> (0.82-0.91)	182 (173-192)	236 (225-247)	0.77 <sup>^</sup> (0.72-0.83)	0.77 <sup>^</sup> (0.72-0.83)
<b>CV mortality</b>	95 (93-96)	163 (154-173)	0.58 <sup>^</sup> (0.55-0.62)	0.60 <sup>^</sup> (0.56-0.63)	0.84 <sup>^</sup> (0.79-0.89)	123 (115-131)	163 (154-173)	0.75 <sup>^</sup> (0.69-0.82)	0.76 <sup>^</sup> (0.70-0.83)
<b>HFH</b>	186 (182-189)	255 (241-270)	0.73 <sup>^</sup> (0.69-0.77)	0.80 <sup>^</sup> (0.75-0.85)	0.88 <sup>^</sup> (0.83-0.94)	206 (195-218)	255 (240-270)	0.81 <sup>^</sup> (0.75-0.88)	0.88 <sup>^</sup> (0.81-0.96)

**Legend.** CI=confidence interval; CV=cardiovascular; HFH=heart failure hospitalization; HR=hazard ratio; IRR=incidence rate ratio; PS=propensity score; RASI/ARNI=renin angiotensin system inhibitors/angiotensin receptor neprilysin inhibitor.

\* p value <0.05

<sup>^</sup> p value <0.01

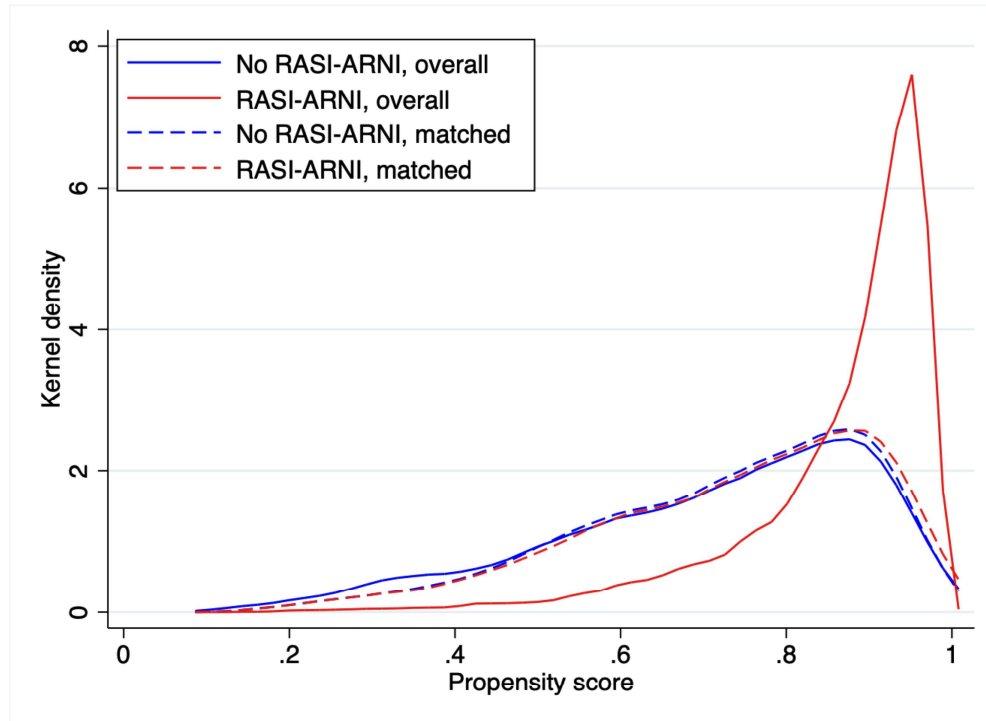
135 **Supplementary Figure 1. Kernel density plot reporting the propensity score distribution in the overall (n = 12421) and**  
136 **matched (n = 1915 for RASI/ARNI, left panel and n = 1468 for beta-blockers, right panel) cohort of patients with HFmrEF of**  
137 **age by treatment arm.**

138 **Legend.** RASI/ARNI=renin angiotensin system inhibitors/angiotensin receptor neprilysin inhibitor

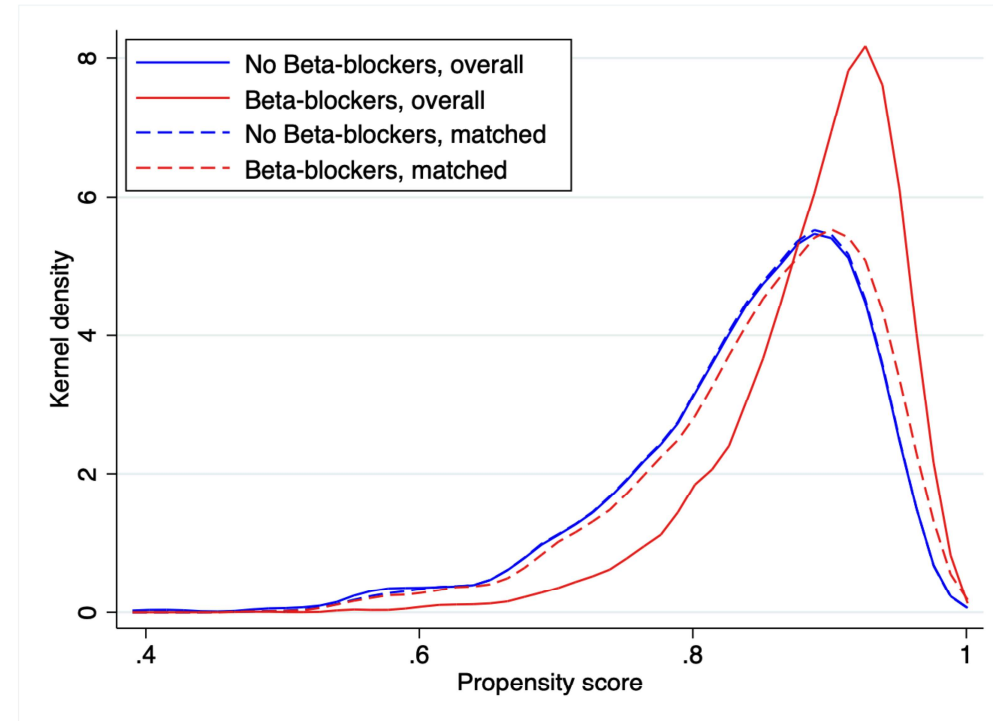
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### RASI/ARNI



### Beta-blockers



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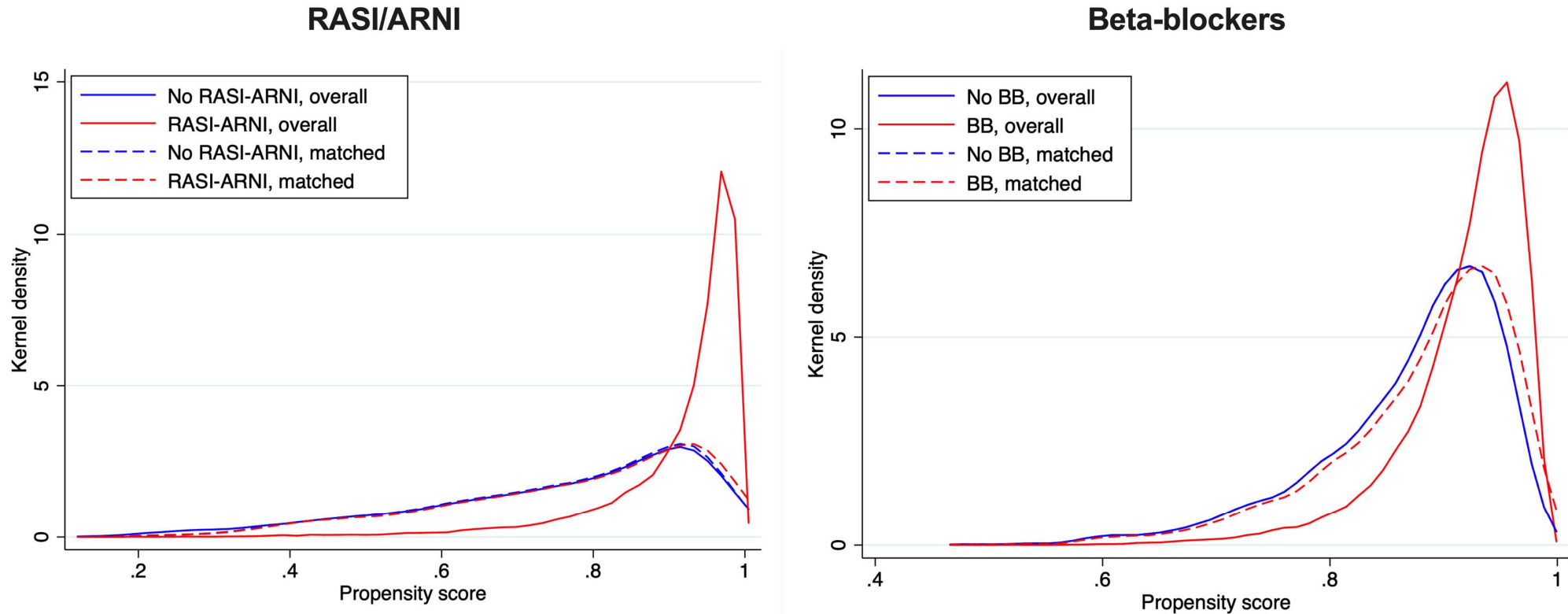
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145 **Supplementary Figure 2. Kernel density plot reporting the propensity score distribution in the overall (n = 26143) and**  
146 **matched (n = 2630 for RASI/ARNI, left panel and n = 2244 for beta-blockers, right panel) positive control cohort of patients**  
147 **with HFrEF by treatment arm.**

148 **Legend.** RASI/ARNI=renin angiotensin system inhibitors/angiotensin receptor neprilysin inhibitor

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153 **References**

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