ASSOCIATION BETWEEN DOSING AND COMBINATION USE OF MEDICATIONS AND OUTCOMES IN HEART FAILURE WITH REDUCED EJECTION FRACTION: DATA FROM THE SWEDISH HEART FAILURE REGISTRY

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1. Variable definition

Variable	Definition
Duration of heart failure	Time since hospitalization/visit in any DIA position to index date.
Education	University/secondary school degree or attendance of compulsory school (9 years or less), from LISA (Statistics Sweden). Education is not registered for individuals < 25 years old.
Family type	From LISA (Statistics Sweden). Unmarried persons cohabiting without children are classified as Living alone.
Disposable income	Disposable income from LISA (Statistics Sweden) categorized according to tertiles within index year.
Hypertension	Diagnosis in Swede-HF
Diabetes	Diagnosis in Swede-HF
Prior myocardial infarction	Diagnosis in the NPR (ICD-10 codes: 410-4, I20-5)
Coronary revascularization	Diagnosis in Swede-HF
Atrial fibrillation	Diagnosis in SwedeHF (history of atrial fibrillation or ECG showing atrial fibrillation)
Valve disease	Diagnosis in SwedeHF
Anemia	Haemoglobin <120 g/L in females and < 130 g/L in males
History of major bleeding	Diagnosis in the NPR (ICD-10 codes: S064-S066, I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920-K922, H431, N02, R04, R58, T810, D629).
Stroke/TIA	Diagnosis in the NPR (ICD-10 codes: 430-4, 438, I60-4, I690-4, G45)
Peripheral artery disease	Diagnosis in the NPR (ICD-10 codes: I70-3)
Chronic obstructive pulmonary disease	Diagnosis in the NPR (ICD-10 codes: J40-4)
Liver disease	Diagnosis in the NPR (ICD-10 codes: B18, I85, I864, I982, K70, K710, K711, K713-7, K72-4, K760, K762-9)
History of malignancies within 3 years	Diagnosis in the NPR (ICD-10 codes: C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97)
CV death	Diagnosis in the NPR (ICD-10 codes: I, J81, K761, R57, G45)
HF hospitalization	Diagnosis in the NPR (ICD-10 codes: I50, I42-I43, I25.5, K761, G45, J81, I11.0)

Abbreviations: NPR=National Patient Registry; TIA=transient ischemic attack.
Further information can be found at https://kiheartfailure.github.io/shfdb3/construction/dm/

SUPPLEMENTARY TABLE 2. Recommended doses of drugs for heart failure with reduced ejection fraction

	Target dose (mg)
ACEi	
Captopril	50 *t.i.d.*
Enalapril	10–20 *b.i.d.*
Lisinopril	20–35 *o.d.*
Ramipril	5 b.i.d.
Trandolapril	4 *o.d.*
β-blockers	
Bisoprolol	10 *o.d.*
Carvedilol	25 *b.i.d.*[a]
Metoprolol succinate (CR/XL)	200 o.d.
ARBs	
Candesartan	32 *o.d.*
Valsartan	160 *b.i.d.*
Losartan	150 *o.d.*
ARNi	
Sacubitril/valsartan	97/103 *b.i.d.*

[a]A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg. Abbreviations: **b.i.d.** = bis in die (twice daily); **o.d.** = omne in die (once daily); **t.i.d.** = ter in die (three times a day). Table adapted from McDonagh TA, Metra M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**(36):3599-3726.

SUPPLEMENTARY TABLE 3. Baseline characteristics of the overall population

Variables	Number of patients (Total 17,809)	% Missing
Demographics/Organizational/Socioeconomical		
Age (years), median (IQR)*	74 (65, 80)	0
<75	9574 (53.8%)	-
≥75	8235 (46.2%)	-
Sex*	-	0
Female	4504 (25.3%)	-
Male	13305 (74.7%)	-
Year of Registration*	-	0
2000-2005	680 (3.8%)	-
2006-2011	5035 (28.3%)	-
2012-2018	12094 (67.9%)	-
Referral to HF nurse-led clinic*	11025 (64.2%)	3.5
Location of follow-up*	-	2.7
Hospital	13411 (77.4%)	-
Primary care	3665 (21.1%)	-
Other	259 (1.5%)	-
Education*	-	1.6
Compulsory school	7387 (42.2%)	-
Secondary school	7163 (40.9%)	-
University	2969 (16.9%)	-
Family type*	-	0.1
Cohabitating	9922 (55.8%)	-
Living alone	7867 (44.2%)	-
Disposable income*	-	0.1
Low	5987 (33.7%)	-
Medium	6708 (37.7%)	-
High	5094 (28.6%)	-
Clinical		
NYHA Class*	-	10.7
I	1497 (9.4%)	-
II	7309 (46.0%)	-
III	6737 (42.4%)	-
IV	354 (2.2%)	-
Ejection Fraction*	-	0
30-39%	9446 (53.0%)	-
<30%	8363 (47.0%)	-
HF Duration (months)*	-	0
<6	2656 (14.9%)	-
≥6	15153 (85.1%)	-
Heart rate (b.p.m.), median (IQR)*	70 (61, 78)	4.7
Mean arterial pressure (mmHg), median (IQR)*	87 (80, 97)	2.7
BMI (kg/m^2), median (IQR)	26 (23, 30)	48.3
Weight (kg). median (IQR)*	80 (70, 92)	13.0

(continued)

Variables	Number of Patients	% Missing
Laboratory values		
Hemoglobin (g/L), median (IQR)	135 (123, 146)	9.2
NT-proBNP (ng/L), median (IQR)*	2070 (844, 4640)	41.4
Sinus rhythm	1390 (530, 3510)	-
Atrial fibrillation	2710 (1360, 5599)	-
eGFR (mL/min/1.73 m²), median (IQR)*	59 (44, 78)	2.6
≥60	8457 (48.7%)	-
30-59	7557 (43.6%)	-
<30	1335 (7.7%)	-
Potassium (mEq/L), median (IQR)*	4.3 (4, 4.6)	14.8
History and comorbidities		
Hypertension*	8659 (50.0%)	2.7
Diabetes*	4780 (27.0%)	0.5
Smoking*	-	18.3
Current	1719 (11.8%)	-
Former	6948 (47.7%)	-
Never	5884 (40.4%)	-
Prior myocardial infarction*	8438 (47.4%)	0
Coronary revascularization*	6345 (36.5%)	2.4
Atrial fibrillation*	8848 (55.5%)	10.5
Valve disease*	3328 (19.1%)	2.2
Anemia*	5087 (31.5%)	9.2
History of major bleeding*	3240 (18.2%)	0
Stroke/TIA*	3277 (18.4%)	0
Peripheral Artery Disease*	1779 (10.0%)	0
Chronic Obstructive Pulmonary Disease*	2510 (14.1%)	0
Liver Disease*	428 (2.4%)	0
History of malignancies within 3 years*	2513 (14.1%)	0
Treatments		
B-blockers	16593 (93.2%)	0
Bisoprolol	7429 (44.8%)	-
Carvedilol	1023 (6.2%)	-
Metoprolol	8141 (49.1%)	-
ACEi	9639 (54.1%)	0
Captopril	99 (1.0%)	-
Enalapril	4376 (45.4%)	-
Lisinopril	94 (1.0%)	-
Ramipril	5067 (52.6%)	-
Trandolapril	3 (<1%)	-
ARB	5662 (31.8%)	0
Candesartan	3853 (68.1%)	-
Losartan	1630 (28.8%)	-
Valsartan	179 (3.2%)	-
ARNi	1273 (7.1%)	
MRA*	8573 (48.3%)	0.2
Diuretic (loop or thiazide)*	13966 (78.5%)	0.2

(continued)

Variables	Number of Patients	% Missing
Loop diuretic#	10036 (76.3%)	-
Digoxin*	2541 (14.3%)	0.2
Anticoagulants*	9158 (51.5%)	0.1
Antiplatelet agents*	7110 (40.0%)	0.2
Nitrate*	2294 (12.9%)	0.1
Statin*	10000 (56.2%)	0.2
HF Device*	-	1.1
CRT-P	786 (4.5%)	-
CRT-D	1449 (8.2%)	-
ICD	1330 (7.6%)	-

* Variables included in multiple imputation model and multivariable analysis along with category of target dose achieved per ACEi/ARB/ARNi and β-blocker, and primary outcome of CV death or HF hospitalization.

#Data available starting June 1, 2010 on a total of 13147 patients.

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; ARNi = Angiotensin Receptor Neprilysin Inhibitor; BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronization Therapy; CV = Cardiovascular; eGFR = Estimated Glomerular Filtration Rate; EF = Ejection Fraction; HF = Heart Failure; ICD = Implantable Cardioverter-Defibrillator; IQR = Interquartile Range; MAP = Mean Arterial Pressure; MI = Myocardial Infarction; MRA = Mineralocorticoid Receptor Antagonist; NYHA = New York Heart Association; NT-proBNP = N-terminal pro hormone Brain Natriuretic Peptide; PAD = Peripheral Artery Disease; TIA = Transient Ischemic Attack.

SUPPLEMENTARY TABLE 4A. Baseline characteristics of patients categorized according to the percentages of target dos achievement for Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor

Variables N	ACEi/ARB/ARNi				p-value
	No use 1235 (6.9%)	1-49% of TD 3962 (22.2%)	50-99% of TD 4469 (25.1%)	≥ 100% of TD 8143 (45.7%)	
Demographics/Organizational/Socioeconomical					
Age (years), median (IQR)*	79 (72, 84)	76 (69, 82)	74 (67, 81)	71 (63, 78)	<0.001
<75	421 (34.1%)	1683 (42.5%)	2287 (51.2%)	5183 (63.6%)	-
≥75	814 (65.9%)	2279 (57.5%)	2182 (48.8%)	2960 (36.4%)	-
Sex*	-	-	-	-	<0.001
Female	330 (26.7%)	1099 (27.7%)	1169 (26.2%)	1906 (23.4%)	-
Male	905 (73.3%)	2863 (72.3%)	3300 (73.8%)	6237 (76.6%)	-
Year of Registration*	-	-	-	-	<0.001
2000-2005	44 (3.6%)	196 (4.9%)	134 (3.0%)	306 (3.8%)	-
2006-2011	370 (30.0%)	1026 (25.9%)	1106 (24.7%)	2533 (31.1%)	-
2012-2018	821 (66.5%)	2740 (69.2%)	3229 (72.3%)	5304 (65.1%)	-
Referral to HF nurse-led clinic*	705 (61.1%)	2617 (68.5%)	2997 (69.2%)	4706 (59.7%)	<0.001
Location of follow-up*	-	-	-	-	<0.001
Hospital	733 (62.9%)	2915 (75.7%)	3408 (78.1%)	6355 (79.9%)	-
Primary care	405 (34.7%)	869 (22.6%)	903 (20.7%)	1488 (18.7%)	-
Other	28 (2.4%)	67 (1.7%)	55 (1.3%)	109 (1.4%)	-
Education*	-	-	-	-	<0.001
Compulsory school	595 (49.1%)	1725 (44.2%)	1850 (42.2%)	3217 (40.1%)	-
Secondary school	437 (36.1%)	1567 (40.2%)	1770 (40.4%)	3389 (42.2%)	-
University	180 (14.9%)	608 (15.6%)	759 (17.3%)	1422 (17.7%)	-
Family type*	-	-	-	-	<0.001
Cohabitating	620 (50.2%)	2187 (55.2%)	2488 (55.8%)	4627 (56.9%)	-
Living alone	614 (49.8%)	1772 (44.8%)	1972 (44.2%)	3509 (43.1%)	-
Disposable income*	-	-	-	-	<0.001
Low	476 (38.6%)	1402 (35.4%)	1549 (34.7%)	2560 (31.5%)	-
Medium	496 (40.2%)	1620 (40.9%)	1729 (38.8%)	2863 (35.2%)	-
High	262 (21.2%)	937 (23.7%)	1182 (26.5%)	2713 (33.3%)	-

Variables N	No use 1235 (6.9%)	1-49% of TD 3962 (22.2%)	50-99% of TD 4469 (25.1%)	≥ 100% of TD 8143 (45.7%)	
Clinical					
NYHA Class*	-	-	-	-	<0.001
I	48 (4.7%)	194 (5.5%)	253 (6.4%)	1002 (13.6%)	-
II	326 (31.9%)	1338 (38.0%)	1807 (45.4%)	3838 (52.1%)	-
III	574 (56.2%)	1881 (53.4%)	1833 (46.0%)	2449 (33.2%)	-
IV	74 (7.2%)	108 (3.1%)	90 (2.3%)	82 (1.1%)	-
Ejection Fraction*	-	-	-	-	<0.001
30-39%	712 (57.7%)	2025 (51.1%)	2317 (51.8%)	4392 (53.9%)	-
<30%	523 (42.3%)	1937 (48.9%)	2152 (48.2%)	3751 (46.1%)	-
HF Duration (months)*	-	-	-	-	<0.001
<6	104 (8.4%)	412 (10.4%)	600 (13.4%)	1540 (18.9%)	-
≥6	1131 (91.6%)	3550 (89.6%)	3869 (86.6%)	6603 (81.1%)	-
Heart rate (b.p.m.), median (IQR)*	72 (64, 81)	70 (62, 80)	70 (62, 79)	68 (60, 76)	<0.001
MAP (mmHg), median (IQR)*	88 (80, 97)	83 (77, 93)	87 (78, 95)	90 (82, 98)	<0.001
BMI (kg/m^2), median (IQR)	25 (22, 29)	26 (23, 29)	27 (24, 30)	27 (24, 31)	<0.001
Weight (kg). median (IQR)*	75 (65, 87)	77 (68, 89)	80 (70, 92)	82 (71, 95)	<0.001
Laboratory values					
Hemoglobin (g/L), median (IQR)	128 (117, 140)	131 (120, 142)	134 (123, 145)	138 (127, 148)	<0.001
NT-proBNP (ng/L), median (IQR)*	4020 (1694, 9493)	2846 (1287, 6442)	2150 (876, 4610)	1539 (630, 3384)	<0.001
in sinus rhythm, median (IQR)	3177 (1218, 9015)	2085 (815, 5392)	1371 (567, 3638)	1040 (422, 2642)	-
in atrial fibrillation, median (IQR)	4589 (2159, 9565)	3430 (1745, 7328)	2718 (1377, 5290)	2216 (1113, 4152)	-
<2070	201 (29.4%)	956 (39.6%)	1340 (48.6%)	2722 (59.3%)	-
≥2070	482 (70.6%)	1458 (60.4%)	1415 (51.4%)	1867 (40.7%)	-
eGFR (mL/min/1.73 m^2), median (IQR)*	42 (29, 59)	50 (37, 67)	57 (43, 75)	67 (52, 83)	<0.001
≥60	285 (23.8%)	1316 (33.9%)	1961 (45.2%)	4895 (61.7%)	-
30-59	571 (47.7%)	2024 (52.1%)	2099 (48.4%)	2863 (36.1%)	-
<30	341 (28.5%)	542 (14.0%)	277 (6.4%)	175 (2.2%)	-
Potassium (mEq/L), median (IQR)*	4.2 (3.9, 4.5)	4.3 (4, 4.6)	4.3 (4.1, 4.6)	4.3 (4.1, 4.6)	<0.001
History and comorbidities					
Hypertension*	653 (54.9%)	1888 (49.0%)	2182 (50.2%)	3936 (49.6%)	0.004
Diabetes*	382 (31.1%)	1078 (27.3%)	1269 (28.5%)	2051 (25.3%)	<0.001

Variables N	No use 1235 (6.9%)	1-49% of TD 3962 (22.2%)	50-99% of TD 4469 (25.1%)	≥ 100% of TD 8143 (45.7%)	p-value
Smoking*	-	-	-	-	<0.001
Current	88 (9.0%)	314 (9.6%)	424 (11.7%)	893 (13.4%)	-
Former	470 (48.1%)	1557 (47.6%)	1766 (48.7%)	3155 (47.3%)	-
Never	419 (42.9%)	1403 (42.9%)	1440 (39.7%)	2622 (39.3%)	-
Prior myocardial infarction*	689 (55.8%)	2084 (52.6%)	2200 (49.2%)	3465 (42.6%)	<0.001
Coronary revascularization*	450 (38.0%)	1542 (40.1%)	1664 (38.2%)	2689 (33.7%)	<0.001
Atrial fibrillation*	694 (62.9%)	2161 (61.0%)	2293 (57.5%)	3700 (50.7%)	<0.001
Valve disease*	344 (29.1%)	877 (22.7%)	852 (19.5%)	1255 (15.7%)	<0.001
Anemia*	529 (46.0%)	1443 (39.5%)	1328 (33.1%)	1787 (24.3%)	<0.001
History of major bleeding*	370 (30.0%)	921 (23.2%)	843 (18.9%)	1106 (13.6%)	<0.001
Stroke/TIA*	307 (24.9%)	858 (21.7%)	863 (19.3%)	1249 (15.3%)	<0.001
PAD*	180 (14.6%)	476 (12.0%)	477 (10.7%)	646 (7.9%)	<0.001
COPD*	219 (17.7%)	661 (16.7%)	669 (15.0%)	961 (11.8%)	<0.001
Liver Disease*	48 (3.9%)	126 (3.2%)	108 (2.4%)	146 (1.8%)	<0.001
History of malignancies within 3 years*	224 (18.1%)	675 (17.0%)	652 (14.6%)	962 (11.8%)	<0.001
Treatments					
β-blockers	1056 (85.5%)	3566 (90.0%)	4194 (93.8%)	7777 (95.5%)	<0.001
Bisoprolol	466 (44.1%)	1682 (47.2%)	1904 (45.4%)	3377 (43.4%)	-
Carvedilol	66 (6.2%)	246 (6.9%)	268 (6.4%)	443 (5.7%)	-
Metoprolol	524 (49.6%)	1638 (45.9%)	2022 (48.2%)	3957 (50.9%)	-
ACEi	0 (0.0%)	1571 (39.7%)	2326 (52.0%)	5742 (70.5%)	<0.001
Captopril	-	25 (1.6%)	54 (2.3%)	20 (0.3%)	-
Enalapril	-	789 (50.2%)	1033 (44.4%)	2554 (44.5%)	-
Lisinopril	-	12 (0.8%)	33 (1.4%)	49 (0.9%)	-
Ramipril	-	745 (47.4%)	1206 (51.8%)	3116 (54.3%)	-
Trandolapril	-	0 (0.0%)	0 (0.0%)	3 (0.1%)	-
ARB	0 (0.0%)	2117 (53.4%)	1690 (37.8%)	1855 (22.8%)	<0.001
Candesartan	-	1133 (53.5%)	1058 (62.6%)	1662 (89.6%)	-
Losartan	-	925 (43.7%)	567 (33.6%)	138 (7.4%)	-

Variables N	No use 1235 (6.9%)	1-49% of TD 3962 (22.2%)	50-99% of TD 4469 (25.1%)	≥ 100% of TD 8143 (45.7%)	p-value
Valsartan	-	59 (2.8%)	65 (3.8%)	55 (3.0%)	-
ARNi	0 (0.0%)	274 (6.9%)	453 (10.1%)	546 (6.7%)	<0.001
MRA*	450 (36.5%)	1561 (39.5%)	2081 (46.6%)	4481 (55.2%)	<0.001
Diuretic (loop or thiazide)*	1051 (85.2%)	3340 (84.5%)	3577 (80.1%)	5998 (73.8%)	<0.001
Loop diuretic[#]	756 (84.5%)	2434 (82.3%)	2687 (77.4%)	4159 (71.4%)	<0.001
Digoxin*	177 (14.4%)	581 (14.7%)	630 (14.1%)	1153 (14.2%)	0.86
Anticoagulants*	591 (47.9%)	2134 (53.9%)	2382 (53.3%)	4051 (49.8%)	<0.001
Antiplatelet agents*	492 (39.9%)	1542 (39.0%)	1785 (40.0%)	3291 (40.5%)	0.49
Nitrate*	221 (17.9%)	589 (14.9%)	599 (13.4%)	885 (10.9%)	<0.001
Statin*	577 (46.8%)	2129 (53.8%)	2545 (57.1%)	4749 (58.4%)	<0.001
HF Device*	-	-	-	-	<0.001
CRT-P	68 (5.6%)	200 (5.1%)	204 (4.6%)	314 (3.9%)	-
CRT-D	84 (7.0%)	319 (8.2%)	409 (9.3%)	637 (7.9%)	-
ICD	50 (4.1%)	282 (7.2%)	374 (8.5%)	624 (7.7%)	-

* Variables included in multiple imputation model and multivariable analysis along with category of target dose achieved per ACEi/ARB/ARNi and β-blockers, and primary outcome of CV death or HF hospitalization.

[#]Data available starting June 1, 2010 on a total of 13147 patients.

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; ARNi = Angiotensin Receptor Neprilysin Inhibitor; BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronization Therapy; CV = Cardiovascular; eGFR = Estimated Glomerular Filtration Rate; EF = Ejection Fraction; HF = Heart Failure; ICD = Implantable Cardioverter-Defibrillator; IQR = Interquartile Range; MAP = Mean Arterial Pressure; MI = Myocardial Infarction; MRA = Mineralocorticoid Receptor Antagonist; NYHA = New York Heart Association; NT-proBNP = N-terminal pro hormone Brain Natriuretic Peptide; PAD = Peripheral Artery Disease; TIA = Transient Ischemic Attack.

SUPPLEMENTARY TABLE 4B. Baseline characteristics of patients categorized according to the percentages of target dose achievement for β-blocker

Variables	β-blocker				p-value
N	No use 1216 (6.8%)	1-49% of TD 4343 (24.4%)	50-99% of TD 5625 (31.6%)	≥ 100% of TD 6625 (37.2%)	
Demographics/Organizational/Socioeconomical					
Age (years), median (IQR)*	78 (70, 84)	76 (68, 82)	74 (66, 80)	71 (63, 78)	<0.001
<75	474 (39.0%)	1964 (45.2%)	2997 (53.3%)	4139 (62.5%)	-
≥75	742 (61.0%)	2379 (54.8%)	2628 (46.7%)	2486 (37.5%)	-
Sex*	-	-	-	-	<0.001*
Female	316 (26.0%)	1181 (27.2%)	1475 (26.2%)	1532 (23.1%)	-
Male	900 (74.0%)	3162 (72.8%)	4150 (73.8%)	5093 (76.9%)	-
Year of Registration*	-	-	-	-	<0.001
2000-2005	76 (6.2%)	154 (3.5%)	229 (4.1%)	221 (3.3%)	-
2006-2011	449 (36.9%)	1250 (28.8%)	1626 (28.9%)	1710 (25.8%)	-
2012-2018	691 (56.8%)	2939 (67.7%)	3770 (67.0%)	4694 (70.9%)	-
Referral to HF nurse-led clinic*	667 (57.0%)	2754 (65.8%)	3446 (63.5%)	4158 (65.0%)	<0.001
Location of follow-up*	-	-	-	-	<0.001
Hospital	743 (63.1%)	3139 (74.3%)	4214 (77.1%)	5315 (82.2%)	-
Primary care	411 (34.9%)	1010 (23.9%)	1176 (21.5%)	1068 (16.5%)	-
Other	24 (2.0%)	75 (1.8%)	74 (1.4%)	86 (1.3%)	-
Education*	-	-	-	-	<0.001
Compulsory school	553 (46.2%)	1883 (44.2%)	2320 (42.0%)	2631 (40.2%)	-
Secondary school	456 (38.1%)	1692 (39.7%)	2254 (40.8%)	2761 (42.2%)	-
University	188 (15.7%)	683 (16.0%)	951 (17.2%)	1147 (17.5%)	-
Family type*	-	-	-	-	0.006
Cohabitating	642 (52.8%)	2394 (55.1%)	3094 (55.1%)	3792 (57.3%)	-
Living alone	573 (47.2%)	1947 (44.9%)	2522 (44.9%)	2825 (42.7%)	-
Disposable income*	-	-	-	-	<0.001
Low	424 (34.9%)	1588 (36.6%)	1885 (33.6%)	2090 (31.6%)	-
Medium	490 (40.3%)	1649 (38.0%)	2141 (38.1%)	2428 (36.7%)	-
High	301 (24.8%)	1104 (25.4%)	1590 (28.3%)	2099 (31.7%)	-

Variables N	No use 1216 (6.8%)	1-49% of TD 4343 (24.4%)	50-99% of TD 5625 (31.6%)	≥ 100% of TD 6625 (37.2%)	p-value
Clinical					
NYHA Class*	-	-	-	-	<0.001
I	98 (9.5%)	368 (9.6%)	429 (8.5%)	602 (10.1%)	-
II	426 (41.2%)	1719 (44.6%)	2290 (45.6%)	2874 (48.0%)	-
III	479 (46.3%)	1658 (43.0%)	2202 (43.8%)	2398 (40.1%)	-
IV	32 (3.1%)	108 (2.8%)	106 (2.1%)	108 (1.8%)	-
Ejection Fraction*	-	-	-	-	<0.001
30-39%	711 (58.5%)	2305 (53.1%)	3006 (53.4%)	3424 (51.7%)	-
<30%	505 (41.5%)	2038 (46.9%)	2619 (46.6%)	3201 (48.3%)	-
HF Duration (months)*	-	-	-	-	0.010
<6	146 (12.0%)	624 (14.4%)	866 (15.4%)	1020 (15.4%)	-
≥6	1070 (88.0%)	3719 (85.6%)	4759 (84.6%)	5605 (84.6%)	-
Heart rate (b.p.m.), median (IQR)*	70 (61, 80)	68 (60, 76)	69 (60, 77)	70 (63, 80)	<0.001
MAP (mmHg), median (IQR)*	87 (78, 97)	87 (77, 94)	87 (79, 96)	90 (82, 97)	<0.001
BMI (kg/m^2), median (IQR)	25 (22, 29)	25.6 (23, 29)	26 (24, 30)	27 (24, 31)	<0.001
Weight (kg), median (IQR)*	75 (66, 87)	77 (66, 87)	80 (70, 92)	84 (73, 97)	<0.001
Laboratory values					
Hemoglobin (g/L), median (IQR)	132 (120, 143)	132 (121, 143)	134 (123, 145)	137 (125, 148)	<0.001
NT-proBNP (ng/L), median (IQR)*	2085 (840, 4680)	2137 (845, 4910)	2158 (869, 4810)	1940 (820, 4285)	-
in sinus rhythm, median (IQR)	1390 (563, 3375)	1555 (595, 3907)	1437 (558, 3610)	1188 (450, 3186)	-
in atrial fibrillation, median (IQR)	2545 (1167, 5599)	2855 (1499, 6035)	2844 (1450, 5793)	2577 (1314, 5238)	-
<2070	316 (49.5%)	1262 (48.6%)	1588 (48.7%)	2053 (52.1%)	-
≥2070	322 (50.5%)	1336 (51.4%)	1674 (51.3%)	1890 (47.9%)	-
eGFR (mL/min/1.73 m^2), median (IQR)*	57 (43, 74)	57 (42, 75)	59 (44, 77)	61 (45, 80)	<0.001
≥60	523 (44.2%)	1944 (45.7%)	2650 (48.3%)	3340 (51.9%)	-
30-59	571 (48.3%)	1951 (45.9%)	2394 (43.7%)	2641 (41.1%)	-
<30	89 (7.5%)	358 (8.4%)	437 (8.0%)	451 (7.0%)	*(continued)*
Potassium (mEq/L), median (IQR)*	4.3 (4, 4.5)	4.3 (4, 4.6)	4.3 (4, 4.6)	4.3 (4.1, 4.6)	<0.001
History and comorbidities					

Hypertension*	540 (45.8%)	1911 (45.2%)	2717 (49.7%)	3491 (54.0%)	<0.001
Diabetes*	276 (23.0%)	970 (22.4%)	1532 (27.3%)	2002 (30.4%)	<0.001
Smoking*	-	-	-	-	<0.001
Current	82 (8.4%)	361 (10.2%)	579 (12.4%)	697 (13.0%)	-
Former	459 (47.2%)	1644 (46.4%)	2274 (48.8%)	2571 (47.8%)	-
Never	431 (44.3%)	1538 (43.4%)	1805 (38.8%)	2110 (39.2%)	-
Prior myocardial infarction*	556 (45.7%)	2294 (52.8%)	2851 (50.7%)	2737 (41.3%)	<0.001
Coronary revascularization*	386 (33.2%)	1636 (38.7%)	2175 (39.6%)	2148 (33.1%)	<0.001
Atrial fibrillation*	618 (56.2%)	1835 (46.9%)	2713 (53.6%)	3682 (62.8%)	<0.001
Valve disease*	269 (23.0%)	919 (21.7%)	1080 (19.6%)	1060 (16.3%)	<0.001
Anemia*	436 (38.2%)	1409 (35.5%)	1653 (32.2%)	1589 (26.9%)	<0.001
History of major bleeding*	253 (20.8%)	849 (19.5%)	1053 (18.7%)	1085 (16.4%)	<0.001
Stroke/TIA*	258 (21.2%)	836 (19.2%)	1084 (19.3%)	1099 (16.6%)	<0.001
PAD*	153 (12.6%)	462 (10.6%)	584 (10.4%)	580 (8.8%)	<0.001
COPD*	209 (17.2%)	558 (12.8%)	826 (14.7%)	917 (13.8%)	<0.001
Liver Disease*	24 (2.0%)	107 (2.5%)	145 (2.6%)	152 (2.3%)	0.55
History of malignancies within 3 years*	219 (18.0%)	710 (16.3%)	752 (13.4%)	832 (12.6%)	<0.001
Treatments					
β-blockers	0 (0.0%)	4343 (100.0%)	5625 (100.0%)	6625 (100.0%)	<0.001
Bisoprolol	-	1583 (36.4%)	2368 (42.1%)	3478 (52.5%)	-
Carvedilol	-	274 (6.3%)	303 (5.4%)	446 (6.7%)	-
Metoprolol	-	2486 (57.2%)	2954 (52.5%)	2701 (40.8%)	-
ACEi	618 (50.8%)	2379 (54.8%)	3069 (54.6%)	3573 (53.9%)	<0.001
Captopril	15 (2.4%)	22 (0.9%)	34 (1.1%)	28 (0.8%)	-
Enalapril	270 (43.7%)	984 (41.4%)	1388 (45.2%)	1734 (48.5%)	-
Lisinopril	10 (1.6%)	23 (1.0%)	28 (0.9%)	33 (0.9%)	-
Ramipril	323 (52.3%)	1348 (56.7%)	1618 (52.7%)	1778 (49.8%)	-
Trandolapril	0 (0.0%)	2 (0.1%)	1 (<1%)	0 (0.0%)	-
ARB	379 (31.2%)	1349 (31.1%)	1832 (32.6%)	2102 (31.7%)	0.036
Candesartan	236 (62.3%)	932 (69.1%)	1233 (67.3%)	1452 (69.1%)	-
Losartan	122 (32.2%)	379 (28.1%)	546 (29.8%)	583 (27.7%)	-
Valsartan	21 (5.5%)	38 (2.8%)	53 (2.9%)	67 (3.2%)	-

ARNi	40 (3.3%)	212 (4.9%)	338 (6.0%)	683 (10.3%)	<0.001
MRA*	465 (38.4%)	1836 (42.4%)	2634 (47.0%)	3638 (55.0%)	<0.001
Diuretic (loop or thiazide)*	937 (77.3%)	3338 (77.0%)	4469 (79.6%)	5222 (78.9%)	0.009
Loop diuretic#	569 (74.1%)	2337 (73.6%)	3177 (77.4%)	3953 (77.6%)	<0.001
Digoxin*	160 (13.2%)	401 (9.3%)	671 (11.9%)	1309 (19.8%)	<0.001
Anticoagulants*	519 (42.8%)	1884 (43.4%)	2836 (50.5%)	3919 (59.2%)	<0.001
Antiplatelet agents*	495 (40.8%)	2019 (46.6%)	2378 (42.4%)	2218 (33.5%)	<0.001
Nitrate*	161 (13.3%)	539 (12.4%)	771 (13.7%)	823 (12.4%)	0.12
Statin*	517 (42.6%)	2421 (55.8%)	3268 (58.2%)	3794 (57.3%)	<0.001
HF Device*	-	-	-	-	<0.001
CRT-P	39 (3.3%)	143 (3.3%)	257 (4.6%)	347 (5.3%)	-
CRT-D	36 (3.1%)	225 (5.3%)	418 (7.5%)	770 (11.7%)	-
ICD	32 (2.7%)	241 (5.6%)	425 (7.6%)	632 (9.6%)	-

*Variables included in multiple imputation model and multivariable analysis along with category of target dose achieved per ACEi/ARB/ARNi and β-blockers, and primary outcome of and primary outcome of CV death or HF hospitalization.

#Data available starting June 1, 2010 on a total of 13147 patients.

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; ARNi = Angiotensin Receptor Neprilysin Inhibitor; BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; CRT = Cardiac Resynchronization Therapy; CV = Cardiovascular; EF = Ejection Fraction; eGFR = Estimated Glomerular Filtration Rate; HF = Heart Failure; ICD = Implantable Cardioverter-Defibrillator; IQR = Interquartile Range; MAP = Mean Arterial Pressure; MI = Myocardial Infarction; MRA = Mineralocorticoid Receptor Antagonist; NYHA = New York Heart Association; NT-proBNP = N-terminal pro hormone Brain Natriuretic Peptide; PAD = Peripheral Artery Disease; TIA = Transient Ischemic Attack.

SUPPLEMENTARY TABLE 5. Baseline characteristics of patients categorized according to the combinations of Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor – β-blocker and percentages of target dose achieved for class of drug

Variables**	No users of both classes	Only 1 class, <50% of TD	Both classes, <50% of TD	Only 1 class, ≥50%-99% of TD	1 class <50% of TD, 1 class ≥50%-99% of TD	Both classes, ≥50%-99% of TD	Only 1 class, ≥100% of TD	1 class ≥100% of TD, 1 class <50% of TD	1 class ≥100% of TD, 1 class ≥50%-99% of TD	Both classes, ≥100% of TD
N	179 (1.0%)	799 (4.5%)	1367 (7.7%)	661 (3.7%)	2428 (13.6%)	1537 (8.6%)	633 (3.5%)	2344 (13.2%)	3931 (22.1%)	3930 (22.1%)
Demographics/Organizational/Socioeconomical										
Age (years), median (IQR)*	79 (69, 85)	80 (72, 85)	77 (70, 83)	79 (72, 84)	76 (69, 82)	74 (66, 80)	76 (68, 82)	74 (66, 80)	72 (64, 78)	69 (61, 76)
<75	68 (38.0%)	250 (31.3%)	551 (40.3%)	221 (33.4%)	1070 (44.1%)	816 (53.1%)	288 (45.5%)	1225 (52.3%)	2361 (60.1%)	2724 (69.3%)
≥75	111 (62.0%)	549 (68.7%)	816 (59.7%)	440 (66.6%)	1358 (55.9%)	721 (46.9%)	345 (54.5%)	1119 (47.7%)	1570 (39.9%)	1206 (30.7%)
Sex*	-	-	-	-	-	-	-	-	-	-
Female	53 (29.6%)	224 (28.0%)	383 (28.0%)	166 (25.1%)	675 (27.8%)	409 (26.6%)	150 (23.7%)	615 (26.2%)	985 (25.1%)	844 (21.5%)
Male	126 (70.4%)	575 (72.0%)	984 (72.0%)	495 (74.9%)	1753 (72.2%)	1128 (73.4%)	483 (76.3%)	1729 (73.8%)	2946 (74.9%)	3086 (78.5%)
Year of Registration*	-	-	-	-	-	-	-	-	-	-
2000-2005	6 (3.4%)	47 (5.9%)	51 (3.7%)	22 (3.3%)	101 (4.2%)	52 (3.4%)	39 (6.2%)	100 (4.3%)	136 (3.5%)	126 (3.2%)
2006-2011	71 (39.7%)	247 (30.9%)	344 (25.2%)	208 (31.5%)	657 (27.1%)	395 (25.7%)	222 (35.1%)	684 (29.2%)	1077 (27.4%)	1130 (28.8%)
2012-2018	102 (57.0%)	505 (63.2%)	972 (71.1%)	431 (65.2%)	1670 (68.8%)	1090 (70.9%)	372 (58.8%)	1560 (66.6%)	2718 (69.1%)	2674 (68.0%)
Referral to HF nurse-led clinic*	84 (51.5%)	470 (61.5%)	922 (70.1%)	388 (61.3%)	1609 (68.5%)	999 (67.3%)	346 (57.7%)	1448 (63.8%)	2448 (64.3%)	2311 (60.8%)
Location of follow-up*	-	-	-	-	-	-	-	-	-	-
Hospital	100 (60.6%)	455 (58.9%)	1005 (75.9%)	406 (64.0%)	1793 (75.8%)	1166 (77.8%)	415 (68.3%)	1796 (78.4%)	3091 (80.6%)	3184 (82.8%)
Primary care	63 (38.2%)	296 (38.3%)	292 (22.1%)	213 (33.6%)	537 (22.7%)	315 (21.0%)	181 (29.8%)	462 (20.2%)	699 (18.2%)	607 (15.8%)
Other	2 (1.2%)	21 (2.7%)	27 (2.0%)	15 (2.4%)	35 (1.5%)	17 (1.1%)	12 (2.0%)	32 (1.4%)	45 (1.2%)	53 (1.4%)
Education*	-	-	-	-	-	-	-	-	-	-
Compulsory school	90 (51.1%)	376 (48.0%)	607 (45.2%)	293 (45.1%)	1047 (44.0%)	640 (42.6%)	299 (47.9%)	971 (42.1%)	1550 (40.1%)	1514 (39.0%)
Secondary school	59 (33.5%)	287 (36.7%)	531 (39.5%)	253 (38.9%)	954 (40.1%)	612 (40.7%)	235 (37.7%)	956 (41.4%)	1593 (41.2%)	1683 (43.3%)
University	27 (15.3%)	120 (15.3%)	205 (15.3%)	104 (16.0%)	381 (16.0%)	250 (16.6%)	90 (14.4%)	380 (16.5%)	725 (18.7%)	687 (17.7%)
Family type*	-	-	-	-	-	-	-	-	-	-
Cohabitating	69 (38.5%)	400 (50.1%)	749 (54.8%)	374 (56.7%)	1340 (55.2%)	836 (54.5%)	350 (55.3%)	1343 (57.3%)	2196 (56.0%)	2265 (57.7%)
Living alone	110 (61.5%)	398 (49.9%)	617 (45.2%)	286 (43.3%)	1087 (44.8%)	697 (45.5%)	283 (44.7%)	1000 (42.7%)	1727 (44.0%)	1662 (42.3%)

Variables** N	No users of both classes 179 (1.0%)	Only 1 class, <50% of TD 799 (4.5%)	Both classes, <50% of TD 1367 (7.7%)	Only 1 class, ≥50%-99% of TD 661 (3.7%)	1 class <50% of TD, 1 class ≥50%-99% of TD 2428 (13.6%)	Both classes, ≥50%-99% of TD 1537 (8.6%)	Only 1 class, ≥100% of TD 633 (3.5%)	1 class ≥100% of TD, 1 class <50% of TD 2344 (13.2%)	1 class ≥100% of TD, 1 class ≥50%-99% of TD 3931 (22.1%)	Both classes, ≥100% of TD 3930 (22.1%)
Disposable income*	-	-	-	-	-	-	-	-	-	-
Low	67 (37.4%)	305 (38.2%)	509 (37.3%)	245 (37.1%)	856 (35.3%)	551 (35.9%)	216 (34.1%)	811 (34.6%)	1231 (31.4%)	1196 (30.5%)
Medium	63 (35.2%)	326 (40.9%)	546 (40.0%)	273 (41.4%)	956 (39.4%)	595 (38.8%)	261 (41.2%)	895 (38.2%)	1451 (37.0%)	1342 (34.2%)
High	49 (27.4%)	167 (20.9%)	311 (22.8%)	142 (21.5%)	615 (25.3%)	387 (25.2%)	156 (24.6%)	637 (27.2%)	1241 (31.6%)	1389 (35.4%)
Clinical										
NYHA Class*	-	-	-	-	-	-	-	-	-	-
I	13 (9.4%)	33 (4.8%)	82 (6.8%)	33 (5.9%)	140 (6.5%)	86 (6.3%)	54 (10.1%)	225 (10.7%)	337 (9.5%)	494 (13.8%)
II	41 (29.7%)	240 (34.9%)	472 (39.1%)	209 (37.5%)	874 (40.4%)	630 (46.1%)	221 (41.2%)	999 (47.3%)	1754 (49.3%)	1869 (52.3%)
III	76 (55.1%)	373 (54.3%)	613 (50.8%)	289 (51.9%)	1088 (50.3%)	620 (45.4%)	239 (44.5%)	852 (40.4%)	1418 (39.9%)	1169 (32.7%)
IV	8 (5.8%)	41 (6.0%)	39 (3.2%)	26 (4.7%)	63 (2.9%)	30 (2.2%)	23 (4.3%)	34 (1.6%)	47 (1.3%)	43 (1.2%)
Ejection Fraction*	-	-	-	-	-	-	-	-	-	-
30-39%	100 (55.9%)	460 (57.6%)	679 (49.7%)	393 (59.5%)	1246 (51.3%)	781 (50.8%)	370 (58.5%)	1266 (54.0%)	2122 (54.0%)	2029 (51.6%)
<30%	79 (44.1%)	339 (42.4%)	688 (50.3%)	268 (40.5%)	1182 (48.7%)	756 (49.2%)	263 (41.5%)	1078 (46.0%)	1809 (46.0%)	1901 (48.4%)
HF Duration (months)*	-	-	-	-	-	-	-	-	-	-
<6	15 (8.4%)	81 (10.1%)	151 (11.0%)	68 (10.3%)	286 (11.8%)	225 (14.6%)	71 (11.2%)	367 (15.7%)	662 (16.8%)	730 (18.6%)
≥6	164 (91.6%)	718 (89.9%)	1216 (89.0%)	593 (89.7%)	2142 (88.2%)	1312 (85.4%)	562 (88.8%)	1977 (84.3%)	3269 (83.2%)	3200 (81.4%)
Heart rate (b.p.m.), median (IQR)*	75 (68, 85)	72 (64, 80)	70 (62, 80)	70 (62, 80)	70 (62, 78)	70 (62, 78)	71 (62, 80)	68 (60, 76)	70 (60, 78)	70 (62, 79)
MAP (mmHg), median (IQR)*	88 (80, 100)	87 (77, 95)	83 (75, 93)	87 (80, 96)	85 (77, 93)	87 (78, 95)	90 (83, 97)	87 (80, 95)	88 (80, 97)	90 (83, 100)
BMI (kg/m^2), median (IQR)	24 (22, 28)	25 (22, 28)	25 (22, 28)	26 (23, 29)	26 (23, 29)	27 (24, 31)	26 (23, 30)	26 (23, 30)	27 (24, 31)	27 (24, 31)
Weight (kg), median (IQR)*	73 (63, 84)	73 (64, 85)	76 (66, 86)	76 (65, 88)	78 (67, 88)	79 (70, 92)	79 (68, 93)	80 (69, 90)	82 (71, 94)	85 (74, 98)
Laboratory values										
Hemoglobin (g/L), median (IQR)	129 (119, 141)	129 (117, 140)	130 (119, 141)	129 (118, 141)	131 (120, 143)	134 (123, 145)	133 (121, 145)	134 (123, 145)	136 (125, 147)	139 (128, 149)

Variables** N	No users of both classes 179 (1.0%)	Only 1 class, <50% of TD 799 (4.5%)	Both classes, <50% of TD 1367 (7.7%)	Only 1 class, ≥50%-99% of TD 661 (3.7%)	1 class <50% of TD, 1 class ≥50%-99% of TD 2428 (13.6%)	Both classes, ≥50%-99% of TD 1537 (8.6%)	Only 1 class, ≥100% of TD 633 (3.5%)	1 class ≥100% of TD, 1 class <50% of TD 2344 (13.2%)	1 class ≥100% of TD, 1 class ≥50%-99% of TD 3931 (22.1%)	Both classes, ≥100% of TD 3930 (22.1%)
NT-proBNP (ng/L), median (IQR)*	2504 (970, 5872)	3379 (1395, 8320)	2598 (1193, 6065)	3085 (1209, 6848)	2434 (1010, 5554)	2111 (848, 4518)	2507 (878, 7230)	2020 (784, 4479)	1891 (784, 3990)	1532 (660, 3392)
in sinus rhythm, median (IQR)	2540 (970, 5599)	2460 (943, 6542)	2120 (847, 5257)	1867 (776, 5299)	1691 (675, 4271)	1392 (572, 3920)	1528 (593, 4230)	1290 (474, 3200)	1237 (471, 3005)	989 (399, 2560)
in atrial fibrillation, median (IQR)	2757 (1310, 5872)	3508 (1700, 7701)	3358 (1766, 7410)	3703 (1960, 7714)	3221 (1604, 6610)	2670 (1400, 5290)	2923 (1267, 8230)	2925 (1492, 5810)	2510 (1301, 4731)	2145 (1110, 4190)
<2070	43 (47.8%)	155 (35.4%)	351 (40.6%)	139 (37.0%)	661 (44.7%)	450 (49.0%)	137 (41.9%)	700 (51.2%)	1228 (52.9%)	1355 (60.0%)
≥2070	47 (52.2%)	283 (64.6%)	513 (59.4%)	237 (63.0%)	819 (55.3%)	469 (51.0%)	190 (58.1%)	666 (48.8%)	1095 (47.1%)	903 (40.0%)
eGFR (mL/min/1.73 m²), median (IQR)*	53 (38, 71)	45 (33, 63)	52 (38, 70)	48 (33, 65)	53 (40, 71)	56 (44, 75)	55 (39, 73)	59 (42, 77)	64 (48, 80)	68 (52, 85)
≥60	66 (38.8%)	211 (27.1%)	499 (37.2%)	204 (31.7%)	943 (39.7%)	669 (44.9%)	261 (42.4%)	1108 (48.3%)	2126 (55.7%)	2370 (62.1%)
30-59	79 (46.5%)	420 (53.8%)	679 (50.6%)	312 (48.4%)	1206 (50.8%)	720 (48.3%)	252 (40.9%)	991 (43.2%)	1535 (40.2%)	1363 (35.7%)
<30	25 (14.7%)	149 (19.1%)	164 (12.2%)	128 (19.9%)	226 (9.5%)	101 (6.8%)	103 (16.7%)	197 (8.6%)	158 (4.1%)	84 (2.2%)
Potassium (mEq/L), median (IQR)*	4.1 (3.9, 4.3)	4.2 (3.9, 4.5)	4.3 (4, 4.6)	4.3 (4, 4.5)	4.3 (4, 4.6)	4.3 (4, 4.6)	4.3 (4, 4.6)	4.3 (4, 4.6)	4.3 (4.1, 4.6)	4.3 (4.1, 4.6)
History and comorbidities										
Hypertension*	85 (48.6%)	376 (48.9%)	602 (45.0%)	327 (51.3%)	1106 (47.0%)	735 (49.1%)	320 (52.3%)	1113 (48.9%)	1996 (52.2%)	1999 (52.0%)
Diabetes*	47 (26.4%)	212 (26.9%)	310 (22.7%)	182 (27.5%)	647 (26.7%)	436 (28.5%)	170 (27.2%)	569 (24.4%)	1100 (28.1%)	1107 (28.3%)
Smoking*	-	-	-	-	-	-	-	-	-	-
Current	11 (7.9%)	56 (8.9%)	99 (8.8%)	48 (8.9%)	207 (10.4%)	166 (13.2%)	44 (8.8%)	214 (11.1%)	416 (12.9%)	458 (14.4%)
Former	58 (41.7%)	289 (45.7%)	513 (45.5%)	271 (50.3%)	992 (49.7%)	615 (48.8%)	253 (50.6%)	894 (46.2%)	1547 (47.8%)	1516 (47.6%)
Never	70 (50.4%)	287 (45.4%)	515 (45.7%)	220 (40.8%)	796 (39.9%)	478 (38.0%)	203 (40.6%)	828 (42.8%)	1273 (39.3%)	1214 (38.1%)
Prior myocardial infarction*	85 (47.5%)	427 (53.4%)	748 (54.7%)	349 (52.8%)	1320 (54.4%)	796 (51.8%)	299 (47.2%)	1135 (48.4%)	1790 (45.5%)	1489 (37.9%)
Coronary revascularization*	52 (30.8%)	282 (37.2%)	535 (40.1%)	255 (40.0%)	978 (41.3%)	609 (40.7%)	195 (31.8%)	848 (37.1%)	1388 (36.1%)	1203 (31.1%)
Atrial fibrillation*	102 (62.6%)	403 (56.7%)	643 (52.3%)	381 (63.4%)	1188 (54.9%)	746 (54.1%)	324 (57.4%)	1119 (52.9%)	1945 (55.2%)	1997 (57.4%)
Valve disease*	46 (26.9%)	226 (29.5%)	304 (22.7%)	166 (26.0%)	522 (22.1%)	279 (18.6%)	129 (21.3%)	440 (19.1%)	686 (17.8%)	530 (13.6%)
Anemia*	73 (44.2%)	338 (44.8%)	501 (39.9%)	269 (43.8%)	840 (37.7%)	462 (33.5%)	212 (35.9%)	672 (31.5%)	948 (26.7%)	772 (22.1%)

Variables** N	No users of both classes 179 (1.0%)	Only 1 class, <50% of TD 799 (4.5%)	Both classes, <50% of TD 1367 (7.7%)	Only 1 class, ≥50%-99% of TD 661 (3.7%)	1 class <50% of TD, 1 class ≥50%-99% of TD 2428 (13.6%)	Both classes, ≥50%-99% of TD 1537 (8.6%)	Only 1 class, ≥100% of TD 633 (3.5%)	1 class ≥100% of TD, 1 class <50% of TD 2344 (13.2%)	1 class ≥100% of TD, 1 class ≥50%-99% of TD 3931 (22.1%)	Both classes, ≥100% of TD 3930 (22.1%)
History of major bleeding*	40 (22.3%)	238 (29.8%)	315 (23.0%)	170 (25.7%)	510 (21.0%)	303 (19.7%)	135 (21.3%)	392 (16.7%)	610 (15.5%)	527 (13.4%)
Stroke/TIA*	40 (22.3%)	189 (23.7%)	281 (20.6%)	170 (25.7%)	498 (20.5%)	307 (20.0%)	126 (19.9%)	445 (19.0%)	665 (16.9%)	556 (14.1%)
PAD*	28 (15.6%)	132 (16.5%)	157 (11.5%)	84 (12.7%)	292 (12.0%)	167 (10.9%)	61 (9.6%)	200 (8.5%)	351 (8.9%)	307 (7.8%)
COPD*	26 (14.5%)	157 (19.6%)	185 (13.5%)	125 (18.9%)	375 (15.4%)	235 (15.3%)	94 (14.8%)	317 (13.5%)	525 (13.4%)	471 (12.0%)
Liver Disease*	5 (2.8%)	23 (2.9%)	44 (3.2%)	26 (3.9%)	71 (2.9%)	38 (2.5%)	13 (2.1%)	51 (2.2%)	80 (2.0%)	77 (2.0%)
History of malignancies within 3 years*	27 (15.1%)	155 (19.4%)	252 (18.4%)	134 (20.3%)	390 (16.1%)	179 (11.6%)	100 (15.8%)	336 (14.3%)	522 (13.3%)	418 (10.6%)
Treatments										
β-blockers	0 (0.0%)	403 (50.4%)	1367 (100.0%)	386 (58.4%)	2428 (100.0%)	1537 (100.0%)	267 (42.2%)	2344 (100.0%)	3931 (100.0%)	3930 (100.0%)
Bisoprolol	-	148 (36.7%)	554 (40.5%)	174 (45.1%)	1000 (41.2%)	675 (43.9%)	144 (53.9%)	1009 (43.0%)	1748 (44.5%)	1977 (50.3%)
Carvedilol	-	22 (5.5%)	94 (6.9%)	20 (5.2%)	156 (6.4%)	92 (6.0%)	24 (9.0%)	154 (6.6%)	211 (5.4%)	250 (6.4%)
Metoprolol	-	233 (57.8%)	719 (52.6%)	192 (49.7%)	1272 (52.4%)	770 (50.1%)	99 (37.1%)	1181 (50.4%)	1972 (50.2%)	1703 (43.3%)
ACEi	0 (0.0%)	180 (22.5%)	633 (46.3%)	163 (24.7%)	1159 (47.7%)	834 (54.3%)	275 (43.4%)	1345 (57.4%)	2405 (61.2%)	2645 (67.3%)
Captopril	-	6 (3.3%)	6 (0.9%)	7 (4.3%)	24 (2.1%)	16 (1.9%)	2 (0.7%)	5 (0.4%)	25 (1.0%)	8 (0.3%)
Enalapril	-	88 (48.9%)	291 (46.0%)	62 (38.0%)	523 (45.1%)	364 (43.6%)	120 (43.6%)	580 (43.1%)	1108 (46.1%)	1240 (46.9%)
Lisinopril	-	4 (2.2%)	4 (0.6%)	3 (1.8%)	13 (1.1%)	9 (1.1%)	3 (1.1%)	10 (0.7%)	27 (1.1%)	21 (0.8%)
Ramipril	-	82 (45.6%)	332 (52.4%)	91 (55.8%)	599 (51.7%)	445 (53.4%)	150 (54.5%)	748 (55.6%)	1244 (51.7%)	1376 (52.0%)
Trandolapril	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	1 (<1%)	0 (0.0%)
ARB	0 (0.0%)	211 (26.4%)	656 (48.0%)	94 (14.2%)	1114 (45.9%)	575 (37.4%)	74 (11.7%)	829 (35.4%)	1164 (29.6%)	945 (24.0%)
Candesartan	-	109 (51.7%)	379 (57.8%)	62 (66.0%)	649 (58.3%)	378 (65.7%)	65 (87.8%)	549 (66.2%)	824 (70.8%)	838 (88.7%)
Losartan	-	90 (42.7%)	258 (39.3%)	27 (28.7%)	433 (38.9%)	180 (31.3%)	5 (6.8%)	265 (32.0%)	293 (25.2%)	79 (8.4%)
Valsartan	-	12 (5.7%)	19 (2.9%)	5 (5.3%)	32 (2.9%)	17 (3.0%)	4 (5.4%)	15 (1.8%)	47 (4.0%)	28 (3.0%)
ARNi	0 (0.0%)	5 (0.6%)	78 (5.7%)	18 (2.7%)	155 (6.4%)	128 (8.3%)	17 (2.7%)	170 (7.3%)	362 (9.2%)	340 (8.7%)
MRA*	58 (32.6%)	275 (34.6%)	510 (37.4%)	247 (37.4%)	1021 (42.1%)	697 (45.4%)	277 (43.8%)	1081 (46.2%)	2053 (52.4%)	2354 (60.0%)
Diuretic (loop or thiazide)*	134 (75.3%)	672 (84.5%)	1114 (81.6%)	554 (83.8%)	1991 (82.1%)	1234 (80.4%)	494 (78.0%)	1787 (76.5%)	3033 (77.3%)	2953 (75.2%)
Loop diuretic#	84 (73.7%)	459 (82.0%)	825 (78.9%)	384 (82.1%)	1425 (79.2%)	912 (77.6%)	314 (77.1%)	1237 (73.5%)	2231 (75.4%)	2165 (73.8%)
Digoxin*	30 (16.9%)	109 (13.7%)	138 (10.1%)	81 (12.3%)	264 (10.9%)	187 (12.2%)	87 (13.8%)	333 (14.2%)	582 (14.8%)	730 (18.6%)
Anticoagulants*	61 (34.3%)	346 (43.4%)	637 (46.7%)	338 (51.1%)	1221 (50.3%)	768 (50.0%)	304 (48.0%)	1177 (50.2%)	2123 (54.1%)	2183 (55.6%)

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Antiplatelet agents*	67 (37.4%)	346 (43.4%)	605 (44.4%)	269 (40.9%)	1041 (43.0%)	646 (42.1%)	238 (37.7%)	964 (41.2%)	1561 (39.8%)	1373 (35.0%)
Nitrate*	28 (15.7%)	124 (15.5%)	181 (13.3%)	109 (16.5%)	363 (15.0%)	198 (12.9%)	93 (14.7%)	279 (11.9%)	502 (12.8%)	417 (10.6%)
Statin*	51 (28.5%)	349 (43.7%)	733 (53.7%)	328 (49.6%)	1355 (55.9%)	879 (57.3%)	315 (49.8%)	1380 (58.9%)	2372 (60.5%)	2238 (57.0%)
HF Device*	-	-	-	-	-	-	-	-	-	-
CRT-P	7 (4.0%)	26 (3.4%)	55 (4.1%)	30 (4.6%)	109 (4.6%)	76 (5.0%)	37 (6.0%)	98 (4.2%)	170 (4.4%)	178 (4.5%)
CRT-D	7 (4.0%)	32 (4.1%)	90 (6.7%)	33 (5.1%)	162 (6.8%)	135 (8.9%)	41 (6.6%)	170 (7.3%)	362 (9.3%)	417 (10.7%)
ICD	6 (3.5%)	13 (1.7%)	89 (6.6%)	28 (4.3%)	164 (6.8%)	131 (8.6%)	29 (4.7%)	168 (7.2%)	345 (8.9%)	357 (9.1%)

*Variables included in multiple imputation model and multivariable analysis with category of target dose achieved per ACEi/ARB/ARNi and β-blockers, and primary outcome of CV death or HF hospitalization.

**p-value <0.001

#Data available starting June 1, 2010 on a total of 13147 patients.

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor BMI = Body Mass Index, COPD = Chronic Obstructive Pulmonary Disease, CRT = Cardiac Resynchronization Therapy, CV = Cardiovascular, EF = Ejection Fraction, eGFR = Estimated Glomerular Filtration Rate, HF = Heart Failure, ICD = Implantable Cardioverter-Defibrillator, IQR = Interquartile Range; MAP = Mean Arterial Pressure, MI = Myocardial Infarction, MRA = Mineralocorticoid Receptor Antagonist, NYHA = New York Heart Association, NT-proBNP = N-terminal pro hormone Brain Natriuretic Peptide, PAD = Peripheral Artery Disease, TIA = Transient Ischemic Attack, TD = Target dose.

SUPPLEMENTARY TABLE 6A. Outcome analysis for Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor and β-blocker. <mark>Risk estimates calculated using no-use as reference.</mark>

	ACEi/ARB/ARNi				β-blocker			
	CV death or HF hospitalization	All-cause death	CV death	HF hospitalization	CV death or HF hospitalization	All-cause death	CV death	HF hospitalization
No use								
Event Rate (per 100 patient-yrs)	43.8 (40.7-47.1)	33.5 (31.2-36.0)	22.6 (20.7-24.7)	31.7 (29.1-34.5)	28.6 (26.4-30.9)	20.9 (19.2-22.6)	14.1 (12.8-15.6)	21.2 (19.4-23.2)
Unadjusted HR (95% CI)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Adjusted HR (95% CI)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1-49% of TD								
Event Rate (per 100 patient-yrs)	30.6 (29.3-32.0)	20.3 (19.3-21.3)	13.8 (13.0-14.6)	24.4 (23.2-25.6)	24.1 (23.1-25.2)	16.7 (15.9-17.5)	11.0 (10.4-11.7)	18.8 (17.9-19.7)
Unadjusted HR (95% CI)	**0.74 (0.68-0.80)**	**0.61 (0.56-0.66)**	**0.62 (0.55-0.68)**	**0.82 (0.74-0.90)**	**0.86 (0.78-0.94)**	**0.80 (0.73-0.88)**	**0.78 (0.70-0.88)**	**0.90 (0.81-1.00)**
Adjusted HR (95% CI)	**0.83 (0.76-0.91)**	**0.76 (0.70-0.84)**	**0.77 (0.69-0.86)**	**0.89 (0.80-0.98)**	**0.86 (0.79-0.95)**	**0.89 (0.81-0.98)**	**0.85 (0.76-0.96)**	**0.88 (0.79-0.98)**
50-99% of TD								
Event Rate (per 100 patient-yrs)	23.7 (22.6-24.8)	15.0 (14.3-15.8)	9.7 (9.1-10.3)	19.1 (18.2-20.1)	22.0 (21.2-22.9)	13.9 (13.3-14.5)	9.1 (8.6-9.6)	17.6 (16.8-18.4)
Unadjusted HR (95% CI)	**0.59 (0.54-0.64)**	**0.45 (0.41-0.49)**	**0.44 (0.39-0.49)**	**0.66 (0.60-0.73)**	**0.80 (0.73-0.87)**	**0.67 (0.61-0.73)**	**0.65 (0.58-0.72)**	**0.86 (0.78-0.95)**
Adjusted HR (95% CI)	**0.78 (0.71-0.86)**	**0.71 (0.64-0.78)**	**0.69 (0.62-0.78)**	**0.83 (0.75-0.92)**	**0.81 (0.74-0.89)**	**0.78 (0.71-0.86)**	**0.74 (0.66-0.83)**	**0.83 (0.75-0.93)**
≥100% of TD								
Event Rate (per 100 patient-yrs)	15.6 (15.1-16.2)	9.2 (8.8-9.6)	5.9 (5.6-6.2)	12.5 (12.1-13.1)	18.4 (17.7-19.1)	11.0 (10.5-11.5)	7.1 (6.8-7.6)	15.1 (14.4-15.7)
Unadjusted HR (95% CI)	**0.41 (0.38-0.45)**	**0.28 (0.26-0.30)**	**0.27 (0.24-0.30)**	**0.47 (0.43-0.52)**	**0.67 (0.61-0.73)**	**0.53 (0.48-0.58)**	**0.51 (0.46-0.57)**	**0.74 (0.67-0.82)**
Adjusted HR (95% CI)	**0.73 (0.67-0.80)**	**0.64 (0.58-0.70)**	**0.64 (0.57-0.71)**	**0.78 (0.70-0.86)**	**0.74 (0.68-0.82)**	**0.72 (0.65-0.79)**	**0.69 (0.61-0.77)**	**0.76 (0.69-0.85)**

HRs (bold) are statistically significant (p-value <0.05)
Abbreviations: ACEi=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; ARNi=angiotensin receptor neprilysin inhibitor TD=target dose; HR=hazard ratio; CI=confidence interval.

SUPPLEMENTARY TABLE 6B. Outcome analysis for Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor and β-blocker. ==Risk estimates calculated using 100% of TD as reference.==

	ACEi/ARB/ARNi				β-blocker			
	CV death or HF hospitalization	All-cause death	CV death	HF hospitalization	CV death or HF hospitalization	All-cause death	CV death	HF hospitalization
No use								
Event Rate (per 100 patient-yrs)	43.8 (40.7-47.1)	33.5 (31.2-36.0)	22.6 (20.7-24.7)	31.7 (29.1-34.5)	28.6 (26.4-30.9)	20.9 (19.2-22.6)	14.1 (12.8-15.6)	21.2 (19.4-23.2)
Unadjusted HR (95% CI)	**2.41 (2.22-2.61)**	**3.59 (3.30-3.91)**	**3.68 (3.32-4.08)**	**2.12 (1.93-2.33)**	**1.49 (1.37-1.63)**	**1.89 (1.72-2.07)**	**1.96 (1.75-2.19)**	**1.35 (1.22-1.49)**
Adjusted HR (95% CI)	**1.36 (1.24-1.49)**	**1.57 (1.43-1.73)**	**1.57 (1.40-1.76)**	**1.29 (1.16-1.43)**	**1.34 (1.23-1.48)**	**1.39 (1.26-1.54)**	**1.46 (1.29-1.65)**	**1.31 (1.18-1.45)**
1-49% of TD								
Event Rate (per 100 patient-yrs)	30.6 (29.3-32.0)	20.3 (19.3-21.3)	13.8 (13.0-14.6)	24.4 (23.2-25.6)	24.1 (23.1-25.2)	16.7 (15.9-17.5)	11.0 (10.4-11.7)	18.8 (17.9-19.7)
Unadjusted HR (95% CI)	**1.77 (1.68-1.88)**	**2.18 (2.05-2.33)**	**2.27 (2.10-2.46)**	**1.74 (1.63-1.85)**	**1.28 (1.20-1.35)**	**1.51 (1.41-1.61)**	**1.53 (1.42-1.66)**	**1.21 (1.13-1.29)**
Adjusted HR (95% CI)	**1.13 (1.06-1.21)**	**1.20 (1.12-1.29)**	**1.21 (1.11-1.32)**	**1.14 (1.06-1.22)**	**1.16 (1.09-1.24)**	**1.24 (1.15-1.33)**	**1.25 (1.14-1.36)**	**1.15 (1.07-1.23)**
50-99% of TD								
Event Rate (per 100 patient-yrs)	23.7 (22.6-24.8)	15.0 (14.3-15.8)	9.7 (9.1-10.3)	19.1 (18.2-20.1)	22.0 (21.2-22.9)	13.9 (13.3-14.5)	9.1 (8.6-9.6)	17.6 (16.8-18.4)
Unadjusted HR (95% CI)	**1.41 (1.33-1.50)**	**1.62 (1.52-1.73)**	**1.61 (1.48-1.74)**	**1.40 (1.32-1.49)**	**1.19 (1.12-1.26)**	**1.26 (1.18-1.34)**	**1.27 (1.17-1.37)**	**1.16 (1.09-1.23)**
Adjusted HR (95% CI)	**1.06 (1.00-1.13)**	**1.11 (1.04-1.19)**	1.09 (1.00-1.18)	**1.07 (1.00-1.15)**	**1.09 (1.03-1.16)**	**1.09 (1.02-1.16)**	1.08 (1.00-1.17)	**1.09 (1.02-1.16)**
≥100% of TD								
Event Rate (per 100 patient-yrs)	15.6 (15.1-16.2)	9.2 (8.8-9.6)	5.9 (5.6-6.2)	12.5 (12.1-13.1)	18.4 (17.7-19.1)	11.0 (10.5-11.5)	7.1 (6.8-7.6)	15.1 (14.4-15.7)
Unadjusted HR (95% CI)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Adjusted HR (95% CI)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

HRs (bold) are statistically significant (p-value <0.05)
Abbreviations: ACEi=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; ARNi=angiotensin receptor neprilysin inhibitor TD=target dose; HR=hazard ratio; CI=confidence interval.

	ACEi/ARB/ARNi		β-blocker	
	Non-CV death [Ref. No use]	Non-CV death [Ref. ≥100% of TD]	Non-CV death [Ref. No use]	Non-CV death [Ref. ≥100% of TD]
No use				
Event Rate (per 100 patient-yrs)	11.0 (9.7-12.4)		6.7 (5.8-7.7)	
Unadjusted HR (95% CI)	Ref.	**3.43 (2.96-3.96)**	Ref.	**1.75 (1.49-2.06)**
Adjusted HR (95% CI)	Ref.	**1.58 (1.34-1.86)**	Ref.	**1.25 (1.05-1.48)**
1-49% of TD				
Event Rate (per 100 patient-yrs)	6.5 (6.0-7.1)		5.6 (5.2-6.1)	
Unadjusted HR (95% CI)	**0.59 (0.51-0.69)**	**2.02 (1.81-2.26)**	**0.84 (0.71-0.99)**	**1.46 (1.31-1.64)**
Adjusted HR (95% CI)	**0.74 (0.63-0.87)**	**1.17 (1.04-1.32)**	0.97 (0.82-1.14)	**1.20 (1.07-1.36)**
50-99% of TD				
Event Rate (per 100 patient-yrs)	5.4 (4.9-5.8)		4.8 (4.5-5.2)	
Unadjusted HR (95% CI)	**0.48 (0.42-0.56)**	**1.65 (1.48-1.85)**	**0.71 (0.61-0.84)**	**1.25 (1.12-1.39)**
Adjusted HR (95% CI)	**0.74 (0.63-0.86)**	**1.16 (1.04-1.30)**	0.87 (0.74-1.03)	1.09 (0.98-1.22)
≥100% of TD				
Event Rate (per 100 patient-yrs)	3.3 (3.0-3.5)		3.8 (3.6-4.2)	
Unadjusted HR (95% CI)	**0.29 (0.25-0.34)**	Ref.	**0.57 (0.49-0.67)**	Ref.
Adjusted HR (95% CI)	**0.63 (0.54-0.74)**	Ref.	**0.80 (0.68-0.95)**	Ref.

HRs (bold) are statistically significant (p-value <0.05)
Abbreviations: ACEi=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; ARNi=angiotensin receptor neprilysin inhibitor TD=target dose; HR=hazard ratio; CI=confidence interval.

SUPPLEMENTARY TABLE 7A. Outcome analysis for combinations of Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor and β-blockers. ==Risk estimates calculated using no-use as reference==.

	Event Rate (per 100 patient-yrs)	HR (95% CI) Unadjusted	HR (95% CI) Adjusted
Composite outcome of HF hospitalization or cardiovascular death			
No use of both classes	46.3 (38.5-55.7)	Ref.	Ref.
Only 1 class, <50% of TD	36.2 (33.0-39.8)	0.82 (0.66-1.00)	**0.78 (0.63-0.96)**
Both classes, <50% of TD	31.2 (28.9-33.6)	**0.70 (0.58-0.86)**	**0.70 (0.57-0.86)**
Only 1 class, ≥50%-99% of TD	39.1 (35.3-43.3)	0.85 (0.69-1.05)	**0.79 (0.64-0.99)**
1 class <50% of TD, 1 class ≥50%-99% of TD	27.2 (25.7-28.8)	**0.63 (0.52-0.77)**	**0.64 (0.52-0.78)**
Both classes, ≥50%-99% of TD	23.4 (21.7-25.2)	**0.56 (0.46-0.68)**	**0.60 (0.49-0.74)**
Only 1 class, ≥100% of TD	26.2 (23.5-29.2)	**0.63 (0.51-0.78)**	**0.70 (0.56-0.87)**
1 class ≥100% of TD, 1 class <50% of TD	20.7 (19.4-22.0)	**0.50 (0.41-0.61)**	**0.61 (0.49-0.74)**
1 class ≥100% of TD, 1 class ≥50%-99% of TD	18.2 (17.3-19.1)	**0.45 (0.37-0.54)**	**0.57 (0.47-0.69)**
Both classes, ≥100% of TD	14.5 (13.8-15.3)	**0.37 (0.30-0.44)**	**0.52 (0.42-0.63)**
All-cause death			
No use of both classes	28.7 (26.7-34.8)	Ref.	Ref.
Only 1 class, <50% of TD	30.4 (27.7-33.2)	1.05 (0.85-1.30)	0.96 (0.77-1.19)
Both classes, <50% of TD	21.0 (19.4-22.8)	**0.73 (0.59-0.90)**	**0.80 (0.65-1.00)**
Only 1 class, ≥50%-99% of TD	29.1 (26.3-32.3)	1.01 (0.81-1.25)	0.97 (0.77-1.21)
1 class <50% of TD, 1 class ≥50%-99% of TD	18.3 (17.2-19.4)	**0.64 (0.52-0.78)**	**0.71 (0.58-0.88)**
Both classes, ≥50%-99% of TD	14.3 (13.1-15.6)	**0.50 (0.41-0.62)**	**0.62 (0.50-0.77)**
Only 1 class, ≥100% of TD	19.1 (17.0-21.5)	**0.67 (0.54-0.84)**	0.80 (0.63-1.01)
1 class ≥100% of TD, 1 class <50% of TD	12.7 (11.8-13.6)	**0.45 (0.36-0.55)**	**0.63 (0.51-0.78)**
1 class ≥100% of TD, 1 class ≥50%-99% of TD	10.6 (10.0-11.3)	**0.37 (0.31-0.46)**	**0.59 (0.48-0.72)**
Both classes, ≥100% of TD	8.3 (7.8-8.8)	**0.29 (0.24-0.36)**	**0.54 (0.43-0.66)**
Cardiovascular death			
No use of both classes	21.0 (16.7-26.3)	Ref.	Ref.
Only 1 class, <50% of TD	20.1 (18.0-22.5)	0.95 (0.74-1.22)	0.88 (0.68-1.14)
Both classes, <50% of TD	14.6 (13.2-16.1)	**0.69 (0.54-0.89)**	**0.77 (0.60-0.99)**
Only 1 class, ≥50%-99% of TD	19.5 (17.2-22.1)	0.92 (0.71-1.19)	0.89 (0.68-1.16)
1 class <50% of TD, 1 class ≥50%-99% of TD	11.9 (11.0-12.8)	**0.57 (0.45-0.72)**	**0.64 (0.50-0.81)**
Both classes, ≥50%-99% of TD	9.4 (8.4-10.4)	**0.45 (0.35-0.58)**	**0.56 (0.43-0.72)**
Only 1 class, ≥100% of TD	12.7 (11.0-14.7)	**0.61 (0.47-0.80)**	**0.75 (0.56-0.98)**
1 class ≥100% of TD, 1 class <50% of TD	8.5 (7.8-9.2)	**0.41 (0.32-0.52)**	**0.58 (0.46-0.75)**
1 class ≥100% of TD, 1 class ≥50%-99% of TD	6.8 (6.3-7.3)	**0.33 (0.26-0.42)**	**0.53 (0.41-0.68)**
Both classes, ≥100% of TD	5.3 (4.9-5.8)	**0.26 (0.20-0.33**	**0.49 (0.38-0.63)**
HF hospitalization			
No use of both classes	32.4 (26.0-40.4)	Ref.	Ref.
Only 1 class, <50% of TD	25.7 (23.0-28.7)	0.83 (0.65-1.07)	0.78 (0.61-1.00)
Both classes, <50% of TD	24.6 (22.6-26.8)	0.80 (0.63-1.02)	**0.75 (0.59-0.96)**
Only 1 class, ≥50%-99% of TD	29.6 (26.3-33.2)	0.92 (0.72-1.19)	0.84 (0.65-1.09)
1 class <50% of TD, 1 class ≥50%-99% of TD	21.6 (20.2-23.0)	**0.72 (0.58-0.91)**	**0.69 (0.55-0.88)**
Both classes, ≥50%-99% of TD	19.0 (17.5-20.7)	**0.66 (0.52-0.83)**	**0.65 (0.51-0.84)**
Only 1 class, ≥100% of TD	20.0 (17.6-22.7)	**0.70 (0.54-0.90)**	**0.74 (0.57-0.97)**
1 class ≥100% of TD, 1 class <50% of TD	16.8 (15.6-18.0)	**0.59 (0.47-0.75)**	**0.66 (0.52-0.84)**
1 class ≥100% of TD, 1 class ≥50%-99% of TD	14.7 (13.9-15.5)	**0.53 (0.42-0.66)**	**0.62 (0.49-0.78)**
Both classes, ≥100% of TD	11.9 (11.2-12.6)	**0.44 (0.35-0.55)**	**0.56 (0.44-0.71)**

HRs (bold) are statistically significant (p-value <0.05)
Abbreviations: TD=target dose; HR=hazard ratio; HF=heart failure; CI=confidence interval

SUPPLEMENTARY TABLE 7B. Outcome analysis for combinations of Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor and β-blocker. Risk estimates calculated using 100% of TD as reference.

	HR (95% CI) Unadjusted	HR (95% CI) Adjusted
Composite outcome of HF hospitalization or cardiovascular death		
No use of both classes	**2.73 (2.26-3.31)**	**1.93 (1.58-2.36)**
Only 1 class, <50% of TD	**2.23 (2.00-2.48)**	**1.50 (1.33-1.68)**
Both classes, <50% of TD	**1.93 (1.76-2.11)**	**1.35 (1.22-1.49)**
Only 1 class, ≥50%-99% of TD	**2.34 (2.08-2.62)**	**1.53 (1.36-1.73)**
1 class <50% of TD, 1 class ≥50%-99% of TD	**1.73 (1.59-1.87)**	**1.24 (1.14-1.34)**
Both classes, ≥50%-99% of TD	**1.52 (1.39-1.67)**	**1.15 (1.05-1.27)**
Only 1 class, ≥100% of TD	**1.71 (1.52-1.94)**	**1.35 (1.18-1.53)**
1 class ≥100% of TD, 1 class <50% of TD	**1.38 (1.27-1.49)**	**1.17 (1.07-1.27)**
1 class ≥100% of TD, 1 class ≥50%-99% of TD	**1.22 (1.13-1.31)**	**1.10 (1.02-1.18)**
Both classes, ≥100% of TD	Ref.	Ref.
All-cause death		
No use of both classes	**3.43 (2.80-4.19)**	**1.86 (1.51-2.30)**
Only 1 class, <50% of TD	**3.61 (3.23-4.03)**	**1.78 (1.58-2.01)**
Both classes, <50% of TD	**2.50 (2.26-2.77)**	**1.50 (1.35-1.67)**
Only 1 class, ≥50%-99% of TD	**3.45 (3.06-3.90)**	**1.80 (1.59-2.05)**
1 class <50% of TD, 1 class ≥50%-99% of TD	**2.18 (2.00-2.39)**	**1.33 (1.21-1.46)**
Both classes, ≥50%-99% of TD	**1.71 (1.54-1.90)**	**1.15 (1.04-1.29)**
Only 1 class, ≥100% of TD	**2.29 (2.01-2.62)**	**1.48 (1.29-1.70)**
1 class ≥100% of TD, 1 class <50% of TD	**1.53 (1.39-1.68)**	**1.18 (1.07-1.30)**
1 class ≥100% of TD, 1 class ≥50%-99% of TD	**1.28 (1.17-1.40)**	**1.09 (1.00-1.20)**
Both classes, ≥100% of TD	Ref.	Ref.
Cardiovascular death		
No use of both classes	**3.85 (3.03-4.89)**	**2.04 (1.59-2.62)**
Only 1 class, <50% of TD	**3.66 (3.19-4.20)**	**1.80 (1.55-2.09)**
Both classes, <50% of TD	**2.67 (2.36-3.03)**	**1.56 (1.37-1.78)**
Only 1 class, ≥50%-99% of TD	**3.53 (3.04-4.10)**	**1.82 (1.56-2.13)**
1 class <50% of TD, 1 class ≥50%-99% of TD	**2.19 (1.96-2.44)**	**1.30 (1.16-1.46)**
Both classes, ≥50%-99% of TD	**1.74 (1.52-1.98)**	1.14 (1.00-1.31)
Only 1 class, ≥100% of TD	**2.36 (2.01-2.78)**	**1.52 (1.28-1.80)**
1 class ≥100% of TD, 1 class <50% of TD	**1.58 (1.40-1.77)**	**1.19 (1.06-1.35)**
1 class ≥100% of TD, 1 class ≥50%-99% of TD	**1.27 (1.14-1.41)**	1.08 (0.97-1.20)
Both classes, ≥100% of TD	Ref.	Ref.
HF hospitalization		
No use of both classes	**2.29 (1.82-2.87)**	**1.79 (1.41-2.27)**
Only 1 class, <50% of TD	**1.91 (1.68-2.16)**	**1.40 (1.22-1.59)**
Both classes, <50% of TD	**1.84 (1.66-2.03)**	**1.34 (1.21-1.50)**
Only 1 class, ≥50%-99% of TD	**2.12 (1.86-2.41)**	**1.50 (1.31-1.72)**
1 class <50% of TD, 1 class ≥50%-99% of TD	**1.66 (1.52-1.81)**	**1.24 (1.13-1.36)**
Both classes, ≥50%-99% of TD	**1.50 (1.35-1.66)**	**1.17 (1.06-1.30)**
Only 1 class, ≥100% of TD	**1.59 (1.38-1.83)**	**1.33 (1.15-1.54)**
1 class ≥100% of TD, 1 class <50% of TD	**1.36 (1.24-1.49)**	**1.19 (1.08-1.31)**
1 class ≥100% of TD, 1 class ≥50%-99% of TD	**1.21 (1.11-1.31)**	**1.10 (1.01-1.20)**
Both classes, ≥100% of TD	Ref.	Ref.

HRs (bold) are statistically significant (p-value <0.05)
Abbreviations: TD=target dose; HR=hazard ratio; HF=heart failure; CI=confidence interval
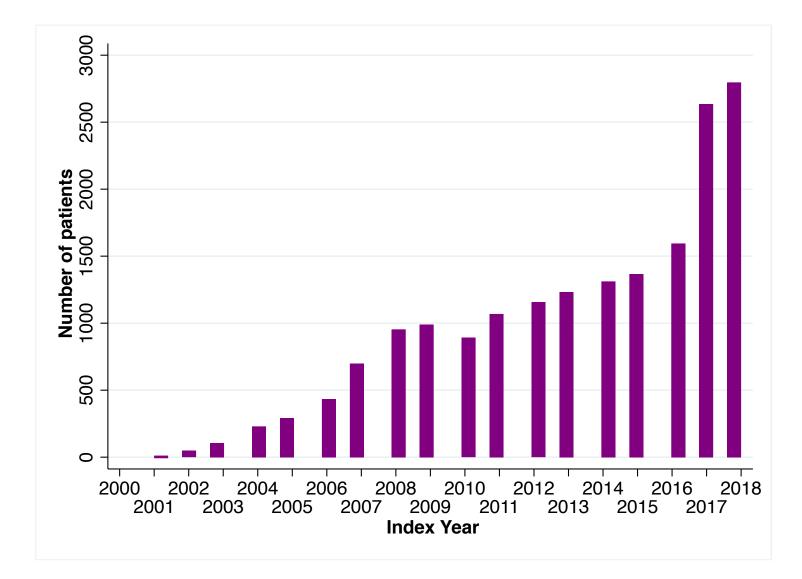
SUPPLEMENTARY TABLE 7C. Sensitivity analysis for non-cardiovascular death with combinations of Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor and β-blocker

	Event Rate (per 100 patient-yrs)	HR (95% CI) Unadjusted	HR (95% CI) Adjusted
Non-CV death (Ref. No use)			
No use of both classes	7.7 (5.3-11.2)	Ref.	Ref.
Only 1 class, <50% of TD	10.3 (8.8-12.0)	1.33 (0.89-1.99)	1.16 (0.77-1.74)
Both classes, <50% of TD	6.4 (5.6-7.4)	0.83 (0.56-1.24)	0.91 (0.61-1.36)
Only 1 class, ≥50%-99% of TD	9.7 (8.1-11.5)	1.26 (0.83-1.90)	1.16 (0.76-1.76)
1 class <50% of TD, 1 class ≥50%-99% of TD	6.4 (5.8-7.1)	0.83 (0.56-1.21)	0.91 (0.62-1.35)
Both classes, ≥50%-99% of TD	4.9 (4.3-5.7)	**0.63 (0.43-0.94)**	0.78 (0.52-1.17)
Only 1 class, ≥100% of TD	6.4 (5.2-7.8)	0.82 (0.54-1.25)	0.93 (0.61-1.43)
1 class ≥100% of TD, 1 class <50% of TD	4.2 (3.8-4.8)	**0.54 (0.37-0.80)**	0.77 (0.52-1.14)
1 class ≥100% of TD, 1 class ≥50%-99% of TD	3.9 (3.5-4.2)	**0.49 (0.34-0.72)**	0.75 (0.51-1.11)
Both classes, ≥100% of TD	3.0 (2.7-3.3)	**0.38 (0.26-0.56)**	**0.66 (0.45-0.98)**
Non-CV death (Ref. Both classes, ≥100% of TD)			
No use of both classes	7.7 (5.3-11.2)	**2.64 (1.79-3.88)**	**1.51 (1.02-2.24)**
Only 1 class, <50% of TD	10.3 (8.8-12.0)	**3.51 (2.90-4.24)**	**1.75 (1.43-2.14)**
Both classes, <50% of TD	6.4 (5.6-7.4)	**2.19 (1.83-2.62)**	**1.37 (1.13-1.65)**
Only 1 class, ≥50%-99% of TD	9.7 (8.1-11.5)	**3.31 (2.69-4.08)**	**1.75 (1.41-2.17)**
1 class <50% of TD, 1 class ≥50%-99% of TD	6.4 (5.8-7.1)	**2.18 (1.87-2.53)**	**1.38 (1.18-1.61)**
Both classes, ≥50%-99% of TD	4.9 (4.3-5.7)	**1.67 (1.40-2.00)**	1.18 (0.99-1.42)
Only 1 class, ≥100% of TD	6.4 (5.2-7.8)	**2.17 (1.73-2.72)**	**1.41 (1.11-1.78)**
1 class ≥100% of TD, 1 class <50% of TD	4.2 (3.8-4.8)	**1.43 (1.22-1.69)**	1.16 (0.98-1.37)
1 class ≥100% of TD, 1 class ≥50%-99% of TD	3.9 (3.5-4.2)	**1.30 (1.13-1.51)**	1.13 (0.98-1.31)
Both classes, ≥100% of TD	3.0 (2.7-3.3)	Ref.	Ref.

HRs (bold) are statistically significant (p-value <0.05)
Abbreviations: TD=target dose; HR=hazard ratio; CV=cardiovascular; CI=confidence

SUPPLEMENTARY FIGURE 2A. Kaplan Meier Curves for the risk of cardiovascular death related to the percentages of target dose achieved per class of drug

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, TD = Target dose, CV=cardiovascular

SUPPLEMENTARY FIGURE 2B. Kaplan Meier Curves for the risk of heart failure hospitalization related to the percentages of target dose achieved per class of drug

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, TD = Target dose, HF=heart failure

SUPPLEMENTARY FIGURE 3A. Independent associations of the percentages of target dose achieved per class of drug with cardiovascular death.

	CV death
	Adjusted HR (95% CI)
ACEi/ARB/ARNi use	
No use	Reference
1-49% of target dose	0.77 (0.69-0.86)
50-99% of target dose	0.69 (0.62-0.77)
≥100% of target dose	0.64 (0.57-0.71)
Beta-blocker use	
No use	Reference
1-49% of target dose	0.85 (0.76-0.96)
50-99% of target dose	0.74 (0.66-0.83)
≥100% of target dose	0.69 (0.61-0.77)

0.50   0.75   1.0   1.1
Lower risk ← → Higher risk

HR for **CV death**
(log scale)

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, HR= hazard ratio, CI = confidence interval, CV=cardiovascular

SUPPLEMENTARY FIGURE 3B. Independent associations of the percentages of target dose achieved per class of drug with heart failure hospitalization.

	HF hospitalization	
		Adjusted HR (95% CI)
ACEi/ARB/ARNi use		
No use		Reference
1-49% of target dose		0.89 (0.80-0.98)
50-99% of target dose		0.83 (0.75-0.92)
≥100% of target dose		0.78 (0.70-0.86)
Beta-blocker use		
No use		Reference
1-49% of target dose		0.88 (0.79-0.98)
50-99% of target dose		0.83 (0.75-0.93)
≥100% of target dose		0.76 (0.69-0.85)

0.50   0.75   1.0   1.1
Lower risk ←——→ Higher risk

HR for **HF hospitalization**
(log scale)

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, HR= hazard ratio, CI = confidence interval, HF=heart failure
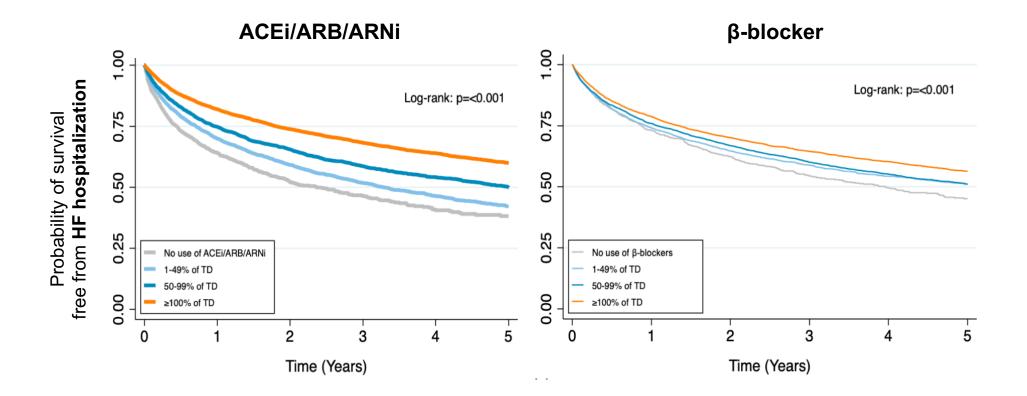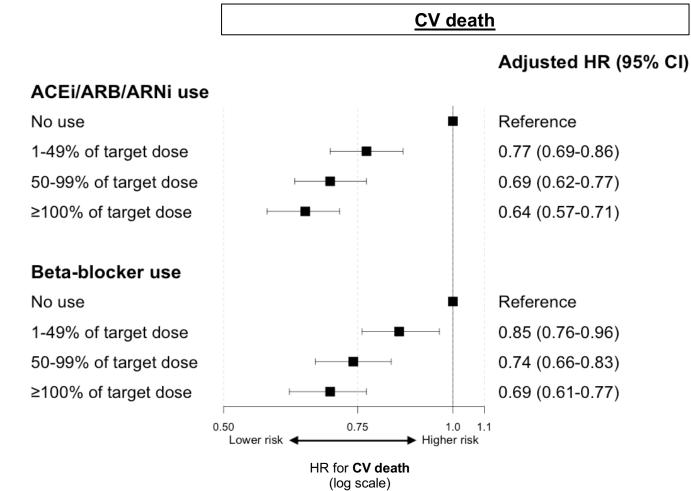
SUPPLEMENTARY FIGURE 4A. Kaplan Meier Curves for the risk of cardiovascular death according to the percentages of target dose achieved and the number of drugs in use
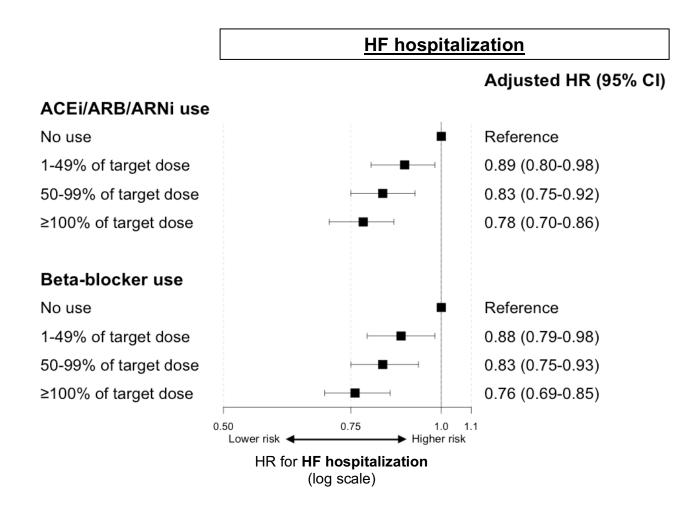

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, TD = Target dose, CV=cardiovascular

[Categories of monotherapy <100% of TD not shown because of very low number of observations, but included in the long-rank test]

SUPPLEMENTARY FIGURE 4B. Kaplan Meier Curves for the risk of heart failure hospitalization according to the percentages of target dose achieved and the number of drugs in use

Combinations of **ACEi/ARB/ARNI + β-blocker**

Log-rank: p=<0.001

Legend:
- No use of both classes
- Both classes, <50% of TD
- 1 class <50% of TD, 1 class ≥50%-99% of TD
- Both classes, ≥50%-99% of TD
- Only 1 class, ≥100% of TD
- 1 class ≥100% of TD, 1 class <50% of TD
- 1 class ≥100% of TD, 1 class ≥50%-99% of TD
- Both classes, ≥100% of TD

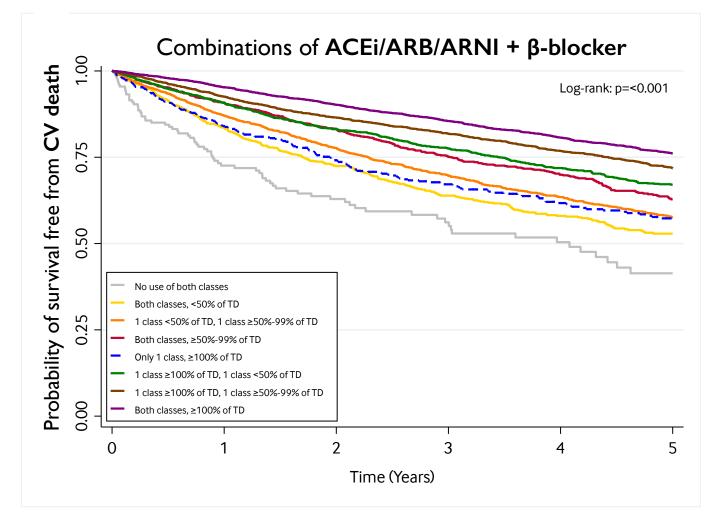ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, TD = Target dose, HF=heart failure

[Categories of monotherapy <100% of TD not shown because of very low number of observations but included in the long-rank test]

SUPPLEMENTARY FIGURE 5A. Independent associations of the different combinations of target dose achievement for Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor and β-blocker with all-cause death.

	All-cause death	**Adjusted HR (95% CI)**
No use of both classes		Reference
Only 1 class, <50% of TD		0.96 (0.77-1.19)
Both classes, <50% of TD		0.80 (0.65-1.00)
Only 1 class, ≥50%-99% of TD		0.97 (0.77-1.21)
1 class <50% of TD, 1 class ≥50%-99% of TD		0.71 (0.58-0.88)
Both classes, ≥50%-99% of TD		0.62 (0.50-0.77)
Only 1 class, ≥100% of TD		0.80 (0.63-1.01)
1 class ≥100% of TD, 1 class <50% of TD		0.63 (0.51-0.78)
1 class ≥100% of TD, 1 class ≥50%-99% of TD		0.59 (0.48-0.72)
Both classes, ≥100% of TD		0.54 (0.43-0.66)

0.30   0.50   0.70   1.0   1.25
Lower risk ⟵   ⟶ Higher risk
HR for **all-cause death**
(log scale)

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, HR= hazard ratio, CI = confidence interval, TD=target dose.
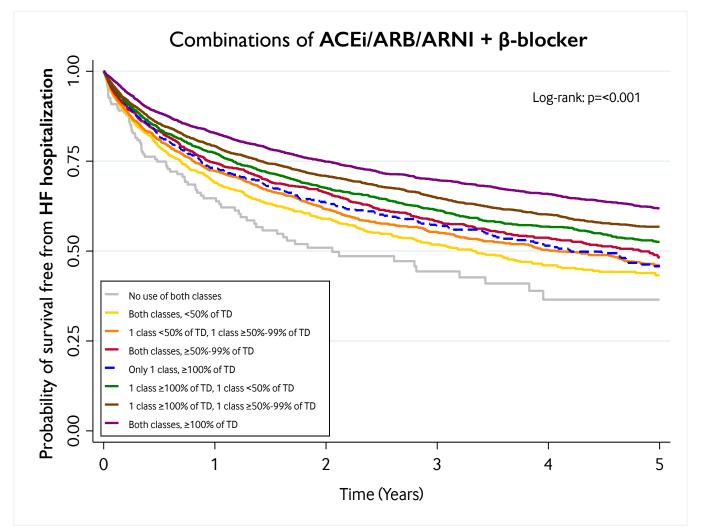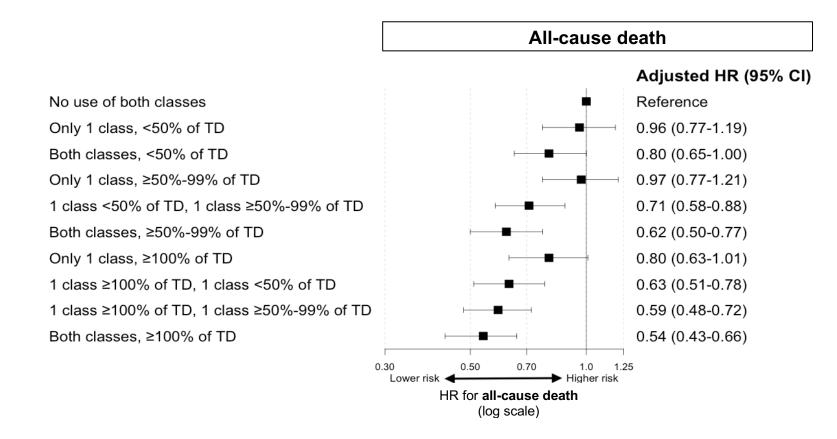
SUPPLEMENTARY FIGURE 5B. Independent associations of the different combinations of target dose achievement for Renin-angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor and β-blocker with cardiovascular death.

	CV death	**Adjusted HR (95% CI)**
No use of both classes		Reference
Only 1 class, <50% of TD		0.88 (0.68-1.14)
Both classes, <50% of TD		0.77 (0.60-0.99)
Only 1 class, ≥50%-99% of TD		0.89 (0.68-1.16)
1 class <50% of TD, 1 class ≥50%-99% of TD		0.64 (0.50-0.81)
Both classes, ≥50%-99% of TD		0.56 (0.43-0.72)
Only 1 class, ≥100% of TD		0.75 (0.56-0.98)
1 class ≥100% of TD, 1 class <50% of TD		0.58 (0.46-0.75)
1 class ≥100% of TD, 1 class ≥50%-99% of TD		0.53 (0.41-0.68)
Both classes, ≥100% of TD		0.49 (0.38-0.63)

0.30   0.50   0.70   1.0   1.25
Lower risk ◄——► Higher risk

HR for **CV death**
(log scale)

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, HR= hazard ratio, CI = confidence interval, TD=target dose, CV=cardiovascular
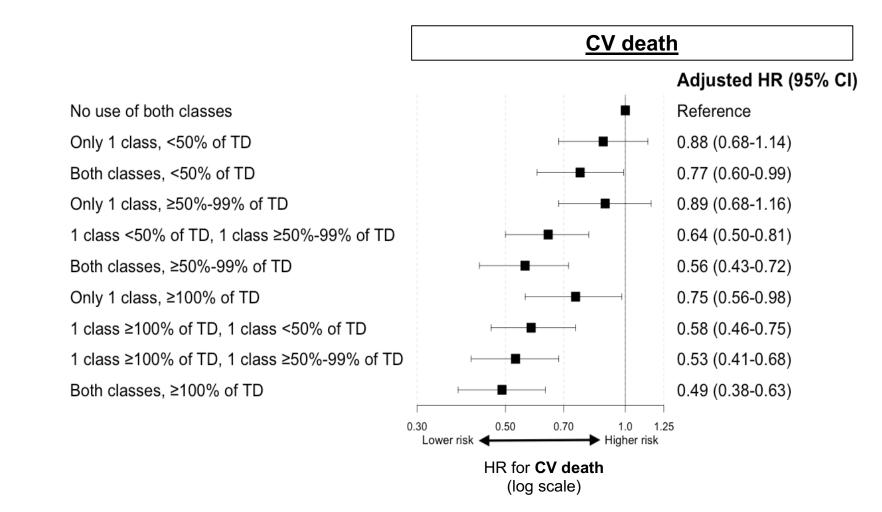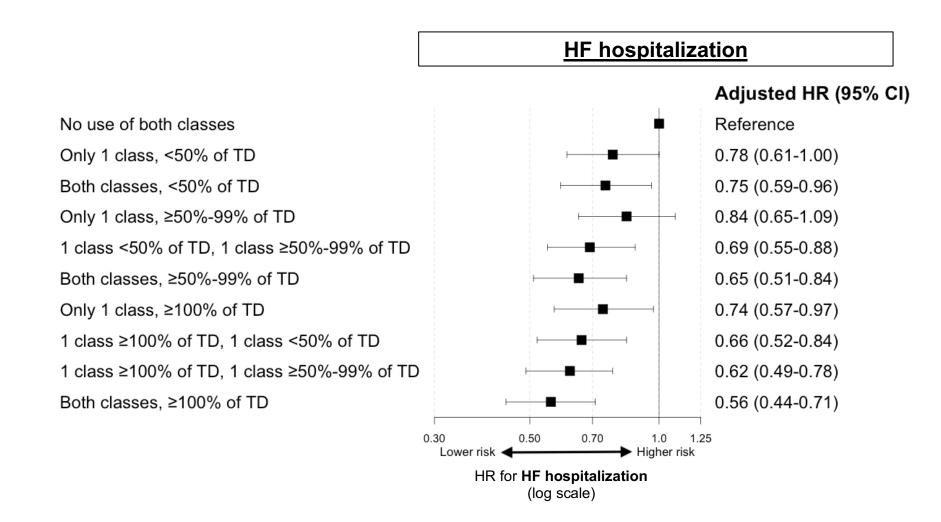
SUPPLEMENTARY FIGURE 5C. Independent associations of the different combinations of target dose achievement for Renin-Angiotensin system inhibitors/Angiotensin receptor neprilysin inhibitor and β-blocker with heart failure hospitalization.

	HF hospitalization	Adjusted HR (95% CI)
No use of both classes		Reference
Only 1 class, <50% of TD		0.78 (0.61-1.00)
Both classes, <50% of TD		0.75 (0.59-0.96)
Only 1 class, ≥50%-99% of TD		0.84 (0.65-1.09)
1 class <50% of TD, 1 class ≥50%-99% of TD		0.69 (0.55-0.88)
Both classes, ≥50%-99% of TD		0.65 (0.51-0.84)
Only 1 class, ≥100% of TD		0.74 (0.57-0.97)
1 class ≥100% of TD, 1 class <50% of TD		0.66 (0.52-0.84)
1 class ≥100% of TD, 1 class ≥50%-99% of TD		0.62 (0.49-0.78)
Both classes, ≥100% of TD		0.56 (0.44-0.71)

0.30   0.50   0.70   1.0   1.25
Lower risk ⟷ Higher risk

HR for **HF hospitalization**
(log scale)

ABBREVIATIONS: ACEi = Angiotensin-Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNi = Angiotensin Receptor Neprilysin Inhibitor, HF= heart failure, HR= hazard ratio, CI = confidence interval, TD=target dose