

Figure S1: Association of Heart Failure (HF) treatment dose and systolic blood pressure categories with the primary endpoint of cardiovascular death/First HF hospitalization adjusting on NT-proBNP

**NT-proBNP adjusted association of SBP categories
with cardiovascular death or heart failure hospitalization
according to HF medication dose**

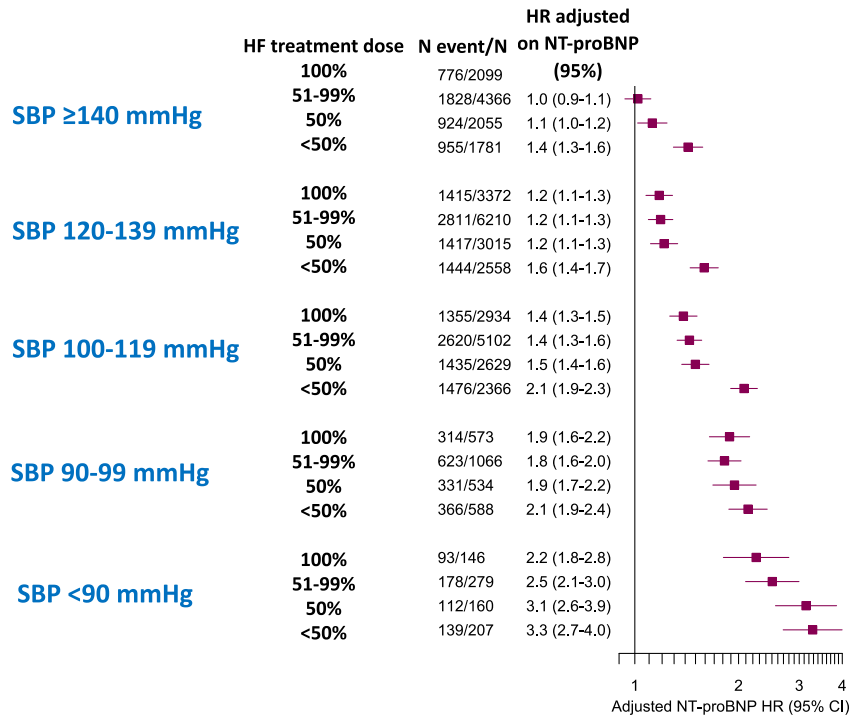


Figure S2: Association of Heart Failure (HF) treatment dose and systolic blood pressure categories with the primary endpoint of cardiovascular death/First HF hospitalization in men and in women.

**Association of SBP categories
with cardiovascular death or heart failure hospitalization
according to HF medication dose**

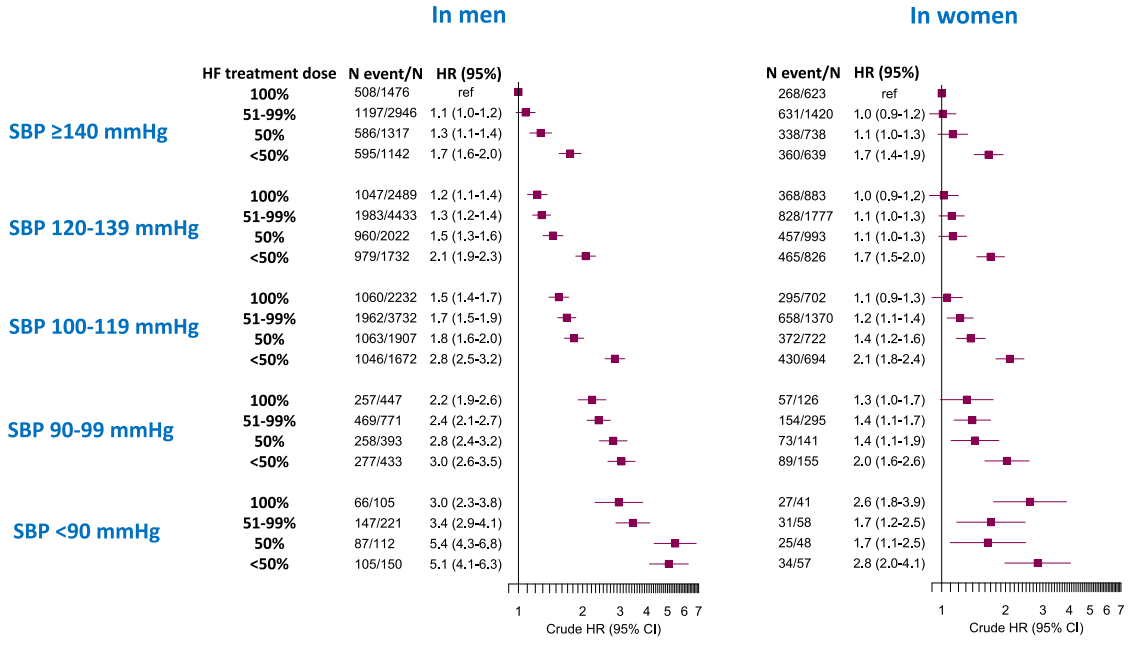
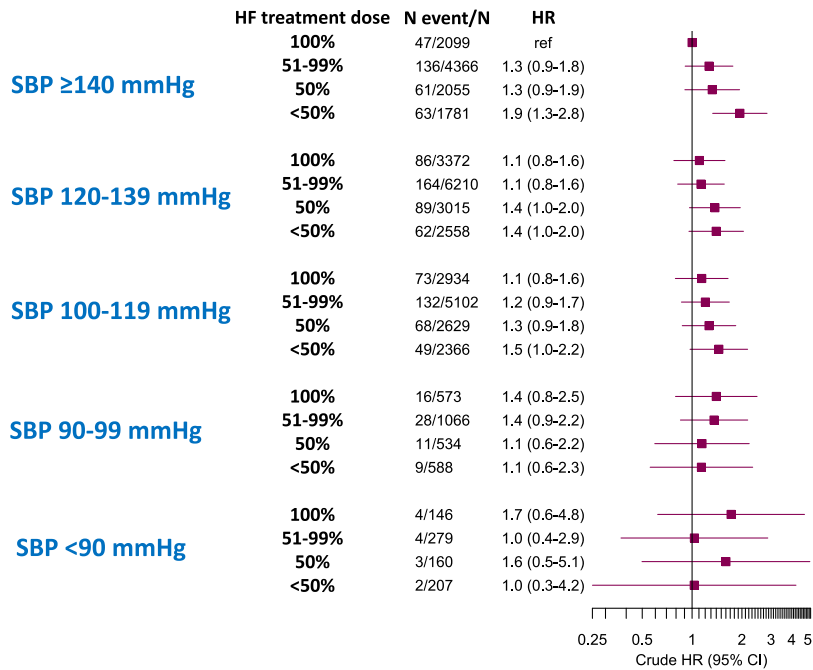


Figure S3: Association of Heart Failure (HF) treatment dose and systolic blood pressure categories with the risk of syncope during follow-up

**Association of SBP categories
with the risk of syncope
according to HF medication dose**



Supplementary Table 1 Treatment characteristics according to supremum medication dose

Variables	Overall	<50%	50%	51-99%	100%
n	42040	7500	8393	17023	9124
ACE-I/Substance, n(%)					
Captopril	195 (0.7)	27 (1.0)	41 (0.8)	88 (0.8)	39 (0.6)
Cilazapril	30 (0.1)	2 (0.1)	8 (0.2)	11 (0.1)	9 (0.1)
Enalapril	12451 (47.3)	945 (36.7)	2424 (45.7)	5729 (49.0)	3353 (49.4)
Fosinopril	28 (0.1)	4 (0.2)	7 (0.1)	13 (0.1)	4 (0.1)
Kinapril	15 (0.1)	2 (0.1)	5 (0.1)	5 (0.0)	3 (0.0)
Lisinopril	197 (0.7)	21 (0.8)	30 (0.6)	88 (0.8)	58 (0.9)
Perindopril	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ramipril	13424 (51.0)	1573 (61.1)	2784 (52.5)	5750 (49.2)	3317 (48.9)
Trandolapril	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
ARB/Substance, n(%)					
Candesartan	7155 (64.0)	902 (57.9)	1547 (60.2)	3015 (64.1)	1691 (72.3)
Eprosartan	2 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Irbesartan	229 (2.0)	29 (1.9)	66 (2.6)	102 (2.2)	32 (1.4)
Losartan	3416 (30.6)	575 (36.9)	885 (34.5)	1410 (30.0)	546 (23.3)
Telmisartan	10 (0.1)	0 (0.0)	2 (0.1)	5 (0.1)	3 (0.1)
Valsartan	359 (3.2)	52 (3.3)	68 (2.6)	171 (3.6)	68 (2.9)
ACE-I/ARB (dose max), median (IQR)	0.7 [0.2, 1.0]	0.1 [0.0, 0.2]	0.5 [0.2, 1.0]	1.0 [0.5, 1.0]	1.0 [1.0, 1.8]
ACE-I/ARB (dose max), n(%)					
No	4528 (10.8)	3367 (44.9)	526 (6.3)	635 (3.7)	0 (0.0)
<50%	8484 (20.2)	2989 (39.9)	2981 (35.5)	2514 (14.8)	0 (0.0)
≥50%	29028 (69.0)	1144 (15.3)	4886 (58.2)	13874 (81.5)	9124 (100.0)
Beta-blocker/Substance, n(%)					
Bisoprolol	16616 (43.1)	1977 (40.6)	3091 (38.1)	7236 (44.0)	4312 (47.3)
Carvedilol	1753 (4.5)	182 (3.7)	330 (4.1)	757 (4.6)	484 (5.3)
Metoprolol	20193 (52.4)	2712 (55.7)	4702 (57.9)	8451 (51.4)	4328 (47.4)
Beta-blocker (dose max), median (IQR)	0.5 [0.2, 1.0]	0.2 [0.0, 0.2]	0.2 [0.2, 0.5]	0.5 [0.4, 1.0]	1.0 [0.5, 1.0]
Beta-blocker (dose max), n(%)					
No	3478 (8.3)	2629 (35.1)	270 (3.2)	579 (3.4)	0 (0.0)
<50%	12739 (30.3)	3522 (47.0)	5412 (64.5)	3805 (22.4)	0 (0.0)
≥50%	25823 (61.4)	1349 (18.0)	2711 (32.3)	12639 (74.2)	9124 (100.0)
MRA (dose max), n(%)	16632 (39.6)	269 (3.6)	796 (9.5)	6443 (37.8)	9124 (100.0)
MRA (dose max), median (IQR)*†	0.0 [0.0, 0.5]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.5]	0.5 [0.5, 0.5]
MRA (dose max), n(%)*†					
No	10253 (54.7)	3028 (97.6)	3237 (91.3)	3988 (54.8)	0 (0.0)
<100%	7420 (39.6)	54 (1.7)	277 (7.8)	2973 (40.8)	4116 (85.3)
≥100%	1080 (5.8)	20 (0.6)	33 (0.9)	317 (4.4)	710 (14.7)
Supremum treatment (dose), n(%)†					
<50%	3379 (18.0)	3102 (100.0)	277 (7.8)	0 (0.0)	0 (0.0)
50%	4252 (22.7)	0 (0.0)	3270 (92.2)	982 (13.5)	0 (0.0)
51-99%	10412 (55.5)	0 (0.0)	0 (0.0)	6296 (86.5)	4116 (85.3)
100%	710 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	710 (14.7)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralcorticoid receptor antagonist; IQR, interquartile range.

* MRA dose is only available from 2014 and is therefore not included in the calculation of the supremum dose variable.

† Data only from 2014

Supplementary Table 2 Interaction between treatment (ACE-I/ARB, beta-blockers, and mineralcorticoid antagonists) and systolic blood pressure (SBP) with regards to rates of cardiovascular deaths and hospitalization for syncope

Legend: HR, Hazard ratio; MRA, mineralcorticoid antagonist; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralcorticoid receptor antagonist; RAS, Renin Angiotensin System.

Cardiovascular death or heart failure hospitalization							
	Subgroup	Crude HR for 1 mmHg increase in SBP (95% CI)	P-value	Interaction P-value	Adjusted HR for 1 mmHg increase in SBP (95% CI)	P-value	Interaction P-value
Interaction of SBP with RAS inhibitors dose	No RASi	0.89 (0.87-0.90)	<0.001	0.001	0.90 (0.89-0.92)	<0.001	0.016
	RASi dose <50%	0.92 (0.91-0.94)	<0.001		0.92 (0.91-0.94)	<0.001	
	RASi dose ≥50%	0.92 (0.91-0.92)	<0.001		0.93 (0.92-0.94)	<0.001	
Interaction of SBP with BB dose	No BB	0.87 (0.85-0.89)	<0.001	<0.001	0.90 (0.88-0.92)	<0.001	0.016
	BB dose <50%	0.91 (0.90-0.92)	<0.001		0.92 (0.91-0.94)	<0.001	
	BB dose ≥50%	0.91 (0.90-0.92)	<0.001		0.93 (0.92-0.94)	<0.001	
Interaction of SBP with MRA dose	No MRA	0.91 (0.91-0.92)	<0.001	0.002	0.93 (0.92-0.94)	<0.001	0.010
	MRA	0.89 (0.88-0.90)	<0.001		0.91 (0.90-0.92)	<0.001	
CV death							
	Subgroup	Crude HR for 10 mmHg increase in SBP (95% CI)	P-value	Interaction P-value	Adjusted HR for 10 mmHg increase in SBP (95% CI)	P-value	Interaction P-value
Interaction of SBP with RAS inhibitors dose	No RASi	0.88 (0.86-0.90)	<0.001	<0.001	0.88 (0.86-0.90)	<0.001	<0.001
	RASi dose <50%	0.92 (0.90-0.94)	<0.001		0.89 (0.87-0.91)	<0.001	
	RASi dose ≥50%	0.93 (0.92-0.94)	<0.001		0.94 (0.92-0.95)	<0.001	
Interaction of SBP with BB dose	No BB	0.85 (0.83-0.87)	<0.001	<0.001	0.88 (0.85-0.90)	<0.001	0.001
	BB dose <50%	0.91 (0.90-0.93)	<0.001		0.91 (0.89-0.92)	<0.001	
	BB dose ≥50%	0.92 (0.91-0.93)	<0.001		0.93 (0.91-0.94)	<0.001	
Interaction of SBP with MRA dose	No MRA	0.91 (0.90-0.92)	<0.001	0.176	0.92 (0.91-0.93)	<0.001	0.101
	MRA	0.90 (0.88-0.91)	<0.001		0.90 (0.89-0.92)	<0.001	
Syncope							
	Subgroup	Crude HR for 10 mmHg increase in SBP (95% CI)	P-value	Interaction P-value	Adjusted HR for 10 mmHg increase in SBP (95% CI)	P-value	Interaction P-value
Interaction of SBP with RAS inhibitors dose	No RASi	1.15 (1.05-1.26)	0.003	0.008	1.15 (1.05-1.27)	0.003	0.009
	RASi dose <50%	1.02 (0.96-1.09)	0.484		1.02 (0.95-1.09)	0.564	
	RASi dose ≥50%	0.99 (0.95-1.02)	0.419		0.99 (0.95-1.02)	0.543	
Interaction of SBP with BB dose	No BB	1.06 (0.96-1.18)	0.223	0.399	1.07 (0.97-1.19)	0.165	0.414
	BB dose <50%	1.02 (0.96-1.07)	0.566		1.02 (0.96-1.07)	0.560	
	BB dose ≥50%	0.99 (0.95-1.03)	0.684		1.00 (0.96-1.04)	0.982	
Interaction of SBP with MRA dose	No MRA	1.02 (0.98-1.06)	0.308	0.154	1.02 (0.98-1.06)	0.245	0.205
	MRA	0.97 (0.93-1.02)	0.306		0.98 (0.93-1.04)	0.498	

Supplementary Table 3 Baseline characteristics by change in systolic blood pressure (SBP) and treatment

Variables	Stable SBP	Decrease SBP/ Increase treatment	Decrease SBP/ Stable treatment	Decrease SBP/ Decreasing	P-value
n	9005	1369	2554	833	
Male sex, n (%)	6681 (74.2)	1011 (73.8)	1878 (73.5)	612 (73.5)	0.896
Age (years), median (IQR)	74.0 [65.0, 81.0]	74.0 [66.0, 80.0]	75.0 [67.0, 82.0]	78.0 [70.0, 83.0]	<0.001
Outpatient setting, n(%)	6267 (69.6)	978 (71.4)	1828 (71.6)	414 (49.7)	<0.001
Follow-up, HF unit, n (%)	4557 (53.2)	746 (56.6)	1267 (52.1)	366 (47.0)	<0.001
Body mass index, kg/m ² , median	26.2 [23.2, 29.7]	26.0 [23.2, 29.3]	26.2 [23.1, 30.0]	25.2 [22.4, 28.7]	0.001
Left ventricular ejection fraction	4736 (52.6)	714 (52.2)	1281 (50.2)	470 (56.4)	0.013
Current smoker, n (%)	988 (12.8)	141 (12.3)	302 (13.8)	72 (10.3)	0.109
Duration of Heart Failure >6 months,	6394 (71.6)	970 (71.6)	1806 (71.4)	707 (85.4)	<0.001
Clinical examination					
NYHA class, n (%)					<0.001
I	755 (10.0)	133 (11.5)	185 (8.6)	26 (4.0)	
II	3346 (44.5)	495 (42.7)	990 (45.9)	175 (27.1)	
III	3046 (40.5)	490 (42.3)	890 (41.2)	365 (56.6)	
IV	376 (5.0)	41 (3.5)	94 (4.4)	79 (12.2)	
Systolic blood pressure, mmHg,	123.0 [110.0, 140.0]	110.0 [100.0, 125.0]	110.0 [100.0, 122.0]	105.0 [95.0, 120.0]	<0.001
Systolic blood pressure, n (%)					<0.001
<90 mmHg	121 (1.3)	66 (4.8)	123 (4.8)	72 (8.6)	
90-99 mmHg	470 (5.2)	162 (11.8)	341 (13.4)	168 (20.2)	
100-119 mmHg	2661 (29.6)	591 (43.2)	1085 (42.5)	354 (42.5)	
120-139 mmHg	3499 (38.9)	413 (30.2)	760 (29.8)	198 (23.8)	
≥140 mmHg	2254 (25.0)	137 (10.0)	245 (9.6)	41 (4.9)	
Diastolic blood pressure, mmHg,	70.0 [65.0, 80.0]	70.0 [60.0, 75.0]	70.0 [60.0, 75.0]	65.0 [60.0, 70.0]	<0.001
Mean arterial pressure, mmHg,	90.0 [81.7, 98.0]	83.3 [75.0, 90.0]	83.3 [75.0, 90.0]	79.3 [71.7, 86.7]	<0.001
Heart rate, b.p.m, median (IQR)	70.0 [62.0, 80.0]	70.0 [62.0, 80.0]	70.0 [62.0, 80.0]	72.0 [64.0, 83.0]	<0.001
Laboratory results					
Haemoglobin, g/L, median (IQR)	133.0 [121.0, 145.0]	134.0 [122.0, 145.0]	132.0 [121.0, 144.0]	127.0 [114.0, 139.0]	<0.001
Potassium, mEq/L, median (IQR)	4.3 [4.0, 4.6]	4.3 [4.0, 4.6]	4.3 [4.0, 4.6]	4.2 [3.9, 4.6]	0.016
eGFR, mL/min, median (IQR)	58.4 [41.5, 78.0]	58.4 [43.6, 76.9]	55.4 [39.7, 73.2]	42.3 [31.2, 59.3]	<0.001
NT-proBNP, pg/mL, median	2453.0 [982.0, 5735.0]	2456.0 [1062.2, 6001.0]	2548.0 [940.0, 6220.0]	5184.5 [2150.0,	<0.001
Treatments					
Diuretic, n (%)	7346 (81.8)	1076 (78.8)	2128 (83.5)	726 (87.5)	<0.001
ACE-I, n (%)	5340 (59.3)	796 (58.1)	1584 (62.0)	291 (34.9)	<0.001
ARB, n (%)	2684 (29.8)	518 (37.8)	742 (29.1)	259 (31.1)	<0.001
ACE-I or ARB, n (%)	8024 (89.1)	1314 (96.0)	2326 (91.1)	550 (66.0)	<0.001
MRA, n (%)	3955 (43.9)	877 (64.1)	1122 (43.9)	178 (21.4)	<0.001
Beta-blocker, n (%)	8392 (93.2)	1320 (96.4)	2386 (93.4)	705 (84.6)	<0.001
Digoxin, n (%)	1418 (15.8)	193 (14.1)	392 (15.4)	114 (13.7)	0.203
Platelet inhibitor, n (%)	3857 (42.9)	580 (42.4)	1156 (45.3)	365 (43.9)	0.159
Anticoagulant, n (%)	4423 (49.2)	663 (48.4)	1203 (47.2)	400 (48.2)	0.368
Statin, n (%)	4754 (52.8)	723 (52.8)	1419 (55.6)	417 (50.1)	0.020
Nitrate, n (%)	1289 (14.3)	194 (14.2)	409 (16.0)	155 (18.7)	0.002
CRT/ICD, n (%)	1691 (18.9)	223 (16.4)	414 (16.4)	154 (18.6)	0.009
Medical history					
Hypertension, n (%)	5401 (60.0)	833 (60.8)	1644 (64.4)	566 (67.9)	<0.001
Diabetes, n (%)	2775 (30.8)	384 (28.0)	787 (30.8)	330 (39.6)	<0.001
Ischemic heart disease, n (%)	5594 (62.1)	802 (58.6)	1648 (64.5)	592 (71.1)	<0.001
Previous MI, n (%)	4343 (48.2)	609 (44.5)	1248 (48.9)	488 (58.6)	<0.001
Peripheral artery disease, n (%)	880 (9.8)	139 (10.2)	290 (11.4)	131 (15.7)	<0.001
Atrial fibrillation, n (%)	5135 (57.0)	770 (56.2)	1464 (57.3)	556 (66.7)	<0.001
COPD, n (%)	312 (14.6)	209 (15.3)	406 (15.9)	171 (20.5)	<0.001

Categorical variables are presented with n (%) and continuous variables with median [q1-q3]

HF, heart failure; NYHA, New York heart association; NT-proBNP, N-terminal pro B-type natriuretic peptide; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor inhibitor; MRA, mineralcorticoid antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; b.p.m., beats per minute.