

Supplemental Material

Supplemental Table 1. Latent class analysis class (“cluster”) membership in the HEAAL trial

Latent class assignment	LCA marginal means	Lower95%CI	Upper95%CI
Class 1 (n= 1189)			
Female	0.21	0.18	0.24
Age>70yr	0.13	0.09	0.17
BMI>30Kg/m2	0.18	0.15	0.21
Afib	0.22	0.19	0.25
Ischemic HF	0.53	0.49	0.57
Hypertension	0.18	0.04	0.51
NYHA III/IV	0.22	0.19	0.25
LVEF<35%	0.75	0.72	0.78
eGFR<60ml/min	0.19	0.16	0.24
Class 2 (n= 1405)			
Female	0.30	0.24	0.36
Age>70yr	0.18	0.12	0.27
BMI>30Kg/m2	0.43	0.34	0.53
Afib	0.21	0.18	0.26
Ischemic HF	0.67	0.61	0.71
Hypertension	1.00	0.00	1.00
NYHA III/IV	0.26	0.21	0.32
LVEF<35%	0.58	0.51	0.65
eGFR<60ml/min	0.23	0.17	0.30
Class 3 (n= 1240)			
Female	0.40	0.36	0.44
Age>70yr	0.69	0.59	0.77
BMI>30Kg/m2	0.24	0.20	0.28
Afib	0.40	0.36	0.44
Ischemic HF	0.74	0.70	0.77
Hypertension	0.68	0.62	0.73
NYHA III/IV	0.44	0.40	0.48
LVEF<35%	0.69	0.64	0.73
eGFR<60ml/min	0.67	0.59	0.74

Legend: BMI, body mass index; Afib, atrial fibrillation; HF, heart failure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

Supplemental Table 2. Patients' characteristics by latent class analysis groups in the HEAAL trial

Latent class analysis	Class 1	Class 2	Class 3	p-value
N.	1189	1405	1240	
Age, yr	58.2 ± 11.6	60.6 ± 9.2	74.1 ± 7.3	<0.001
Age >70	123 (10.3%)	132 (9.4%)	1014 (81.8%)	<0.001
Female	247 (20.8%)	365 (26.0%)	531 (42.8%)	<0.001
White race	591 (49.7%)	902 (64.2%)	828 (66.8%)	<0.001
Atrial fibrillation	269 (22.6%)	260 (18.5%)	541 (43.6%)	<0.001
Ischemic heart disease	621 (52.2%)	895 (63.7%)	940 (75.8%)	<0.001
Hypertension	0 (0.0%)	1405 (100.0%)	887 (71.5%)	<0.001
Diabetes mellitus	258 (21.7%)	529 (37.7%)	412 (33.2%)	<0.001
NYHA III/IV	248 (20.9%)	329 (23.4%)	597 (48.1%)	<0.001
LVEF, %	30.2 ± 6.8	32.5 ± 6.5	31.9 ± 6.2	<0.001
LVEF <35	896 (75.4%)	833 (59.3%)	872 (70.3%)	<0.001
SBP, mmHg	117.5 ± 14.7	131.1 ± 17.7	128.6 ± 18.3	<0.001
SBP <110	482 (40.5%)	212 (15.1%)	250 (20.2%)	<0.001
Heart rate, bpm	74.9 ± 15.7	74.3 ± 15.9	74.2 ± 16.2	0.53
Heart rate >75	492 (41.4%)	556 (39.6%)	476 (38.4%)	0.32
BMI, Kg/m ²	27.6 ± 9.7	30.6 ± 10.4	28.1 ± 9.3	<0.001
BMI <25	489 (41.1%)	312 (22.2%)	433 (34.9%)	<0.001
BMI 25-30	485 (40.8%)	505 (35.9%)	550 (44.4%)	
BMI >30	215 (18.1%)	588 (41.9%)	257 (20.7%)	
eGFR, ml/min/1.73m ²	77.5 ± 21.9	74.1 ± 19.3	55.8 ± 19.5	<0.001
eGFR <60	230 (19.3%)	274 (19.5%)	884 (71.3%)	<0.001
Potassium, mmol/L	4.4 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	<0.001
Potassium <4	229 (19.3%)	211 (15.0%)	179 (14.4%)	<0.001
Potassium 4-5	868 (73.0%)	1051 (74.8%)	897 (72.3%)	
Potassium >5	92 (7.7%)	143 (10.2%)	164 (13.2%)	
Hemoglobin, g/dL	14.1 ± 1.4	14.1 ± 1.5	13.4 ± 1.5	<0.001
Anemia	180 (15.1%)	195 (13.9%)	325 (26.2%)	<0.001
Beta-blocker stratum	881 (74.1%)	1096 (78.0%)	781 (63.0%)	<0.001
High-dose losartan allocation	607 (51.1%)	670 (47.7%)	644 (51.9%)	0.068

Legend: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Supplemental Table 3. Treatment effect of high- vs. low dose losartan by latent classes in the HEAAL trial

Outcome	Event rates low-dose	Event rates high-dose	HR (95%CI)	P	Interaction P
CV death or HF hosp.					
Class 1 (n= 1189)	10.9 (9.6-12.3)	7.9 (6.9-9.1)	0.73 (0.61-0.88)	0.001	
Class 2 (n= 1405)	8.4 (7.4-9.5)	7.5 (6.6-8.6)	0.9 (0.75-1.08)	0.25	0.12
Class 3 (n= 1240)	14 (12.4-15.7)	13.2 (11.8-14.8)	0.95 (0.8-1.11)	0.503	
All-cause death or HF hosp.					
Class 1 (n= 1189)	12.4 (11-13.9)	9 (7.9-10.3)	0.74 (0.62-0.88)	0.001	
Class 2 (n= 1405)	9.5 (8.5-10.7)	8.8 (7.8-10)	0.93 (0.78-1.1)	0.386	0.048
Class 3 (n= 1240)	16.6 (14.9-18.5)	16.2 (14.6-18)	0.98 (0.84-1.13)	0.74	
All-cause death or all-cause hosp.					
Class 1 (n= 1189)	20.9 (18.9-23.1)	18.3 (16.5-20.3)	0.89 (0.77-1.02)	0.102	
Class 2 (n= 1405)	19.1 (17.4-20.9)	19.4 (17.6-21.4)	1.02 (0.89-1.16)	0.803	0.32
Class 3 (n= 1240)	31.3 (28.6-34.4)	28.1 (25.7-30.7)	0.9 (0.8-1.03)	0.13	
CV death					
Class 1 (n= 1189)	5.9 (5-6.9)	5 (4.2-5.9)	0.85 (0.68-1.08)	0.186	
Class 2 (n= 1405)	4.2 (3.5-4.9)	3.8 (3.2-4.6)	0.92 (0.72-1.18)	0.509	0.86
Class 3 (n= 1240)	8.4 (7.3-9.6)	7.7 (6.7-8.9)	0.92 (0.76-1.13)	0.44	
All-cause death					
Class 1 (n= 1189)	7.7 (6.7-8.9)	6.6 (5.7-7.6)	0.85 (0.7-1.05)	0.129	
Class 2 (n= 1405)	5.9 (5.2-6.8)	5.4 (4.7-6.3)	0.91 (0.74-1.12)	0.359	0.64
Class 3 (n= 1240)	11.9 (10.5-13.4)	11.5 (10.3-12.9)	0.97 (0.82-1.14)	0.7	

Supplemental Table 4. Treatment effect of high- vs. low dose losartan by individual subgroups in the HEAAL trial

Outcomes by subgroup	HR (95%CI)	Interaction P
Age		
CV death or HF hosp.		
Age ≤70yr (n =2565)	0.86 (0.75-0.97)	0.70
Age >70yr (n =1269)	0.89 (0.75-1.05)	
All-cause death or HF hosp.		
Age ≤70yr (n =2565)	0.87 (0.77-0.98)	0.56
Age >70yr (n =1269)	0.92 (0.79-1.07)	
All-cause death or all-cause hosp.		
Age ≤70yr (n =2565)	0.96 (0.87-1.06)	0.51
Age >70yr (n =1269)	0.91 (0.8-1.03)	
CV death		
Age ≤70yr (n =2565)	0.91 (0.77-1.08)	0.99
Age >70yr (n =1269)	0.91 (0.74-1.12)	
All-cause death		
Age ≤70yr (n =2565)	0.91 (0.79-1.05)	0.70
Age >70yr (n =1269)	0.95 (0.8-1.13)	
eGFR		
CV death or HF hosp.		
eGFR ≥60 ml/min (n =2446)	0.82 (0.72-0.95)	0.31
eGFR <60 ml/min (n =1388)	0.92 (0.79-1.07)	
All-cause death or HF hosp.		
eGFR ≥60 ml/min (n =2446)	0.82 (0.72-0.93)	0.078
eGFR <60 ml/min (n =1388)	0.98 (0.85-1.12)	
All-cause death or all-cause hosp.		
eGFR ≥60 ml/min (n =2446)	0.94 (0.85-1.04)	0.82
eGFR <60 ml/min (n =1388)	0.93 (0.82-1.04)	
CV death		
eGFR ≥60 ml/min (n =2446)	0.89 (0.75-1.06)	0.76
eGFR <60 ml/min (n =1388)	0.93 (0.77-1.12)	
All-cause death		
eGFR ≥60 ml/min (n =2446)	0.86 (0.74-1)	0.2
eGFR <60 ml/min (n =1388)	1 (0.85-1.17)	
NYHA		
CV death or HF hosp.		
NYHA II (n =2660)	0.82 (0.72-0.94)	0.16
NYHA III/IV (n =1174)	0.96 (0.81-1.13)	
All-cause death or HF hosp.		
NYHA II (n =2660)	0.84 (0.74-0.95)	0.074

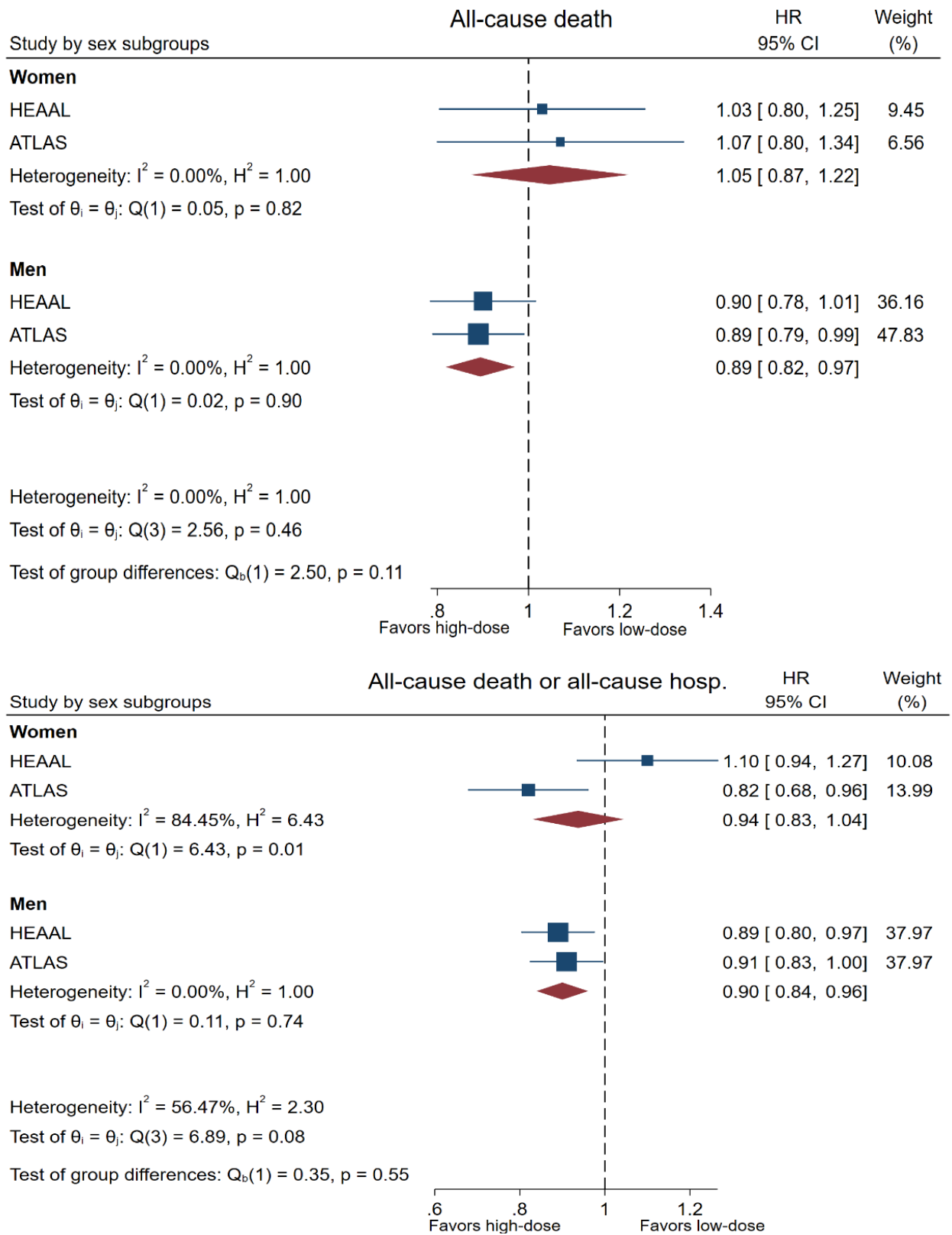
NYHA III/IV (n =1174)	1 (0.86-1.17)	
All-cause death or all-cause hosp.		
NYHA II (n =2660)	0.94 (0.85-1.03)	0.75
NYHA III/IV (n =1174)	0.96 (0.84-1.1)	
CV death		
NYHA II (n =2660)	0.83 (0.7-0.98)	0.049
NYHA III/IV (n =1174)	1.08 (0.88-1.32)	
All-cause death		
NYHA II (n =2660)	0.84 (0.73-0.97)	0.019
NYHA III/IV (n =1174)	1.1 (0.93-1.3)	
BMI		
CV death or HF hosp.		
BMI <30 (n =2774)	0.86 (0.77-0.97)	0.70
BMI ≥30 (n =1060)	0.9 (0.74-1.11)	
All-cause death or HF hosp.		
BMI <30 (n =2774)	0.89 (0.8-1)	0.81
BMI ≥30 (n =1060)	0.92 (0.76-1.11)	
All-cause death or all-cause hosp.		
BMI <30 (n =2774)	0.95 (0.87-1.04)	0.93
BMI ≥30 (n =1060)	0.95 (0.81-1.1)	
CV death		
BMI <30 (n =2774)	0.89 (0.77-1.04)	0.45
BMI ≥30 (n =1060)	1 (0.77-1.3)	
All-cause death		
BMI <30 (n =2774)	0.92 (0.81-1.04)	0.58
BMI ≥30 (n =1060)	0.99 (0.79-1.24)	
Afib		
CV death or HF hosp.		
No Afib (n =2764)	0.84 (0.74-0.95)	0.30
Afib (n =1070)	0.94 (0.79-1.13)	
All-cause death or HF hosp.		
No Afib (n =2764)	0.88 (0.78-0.98)	0.46
Afib (n =1070)	0.94 (0.8-1.11)	
All-cause death or all-cause hosp.		
No Afib (n =2764)	0.96 (0.87-1.06)	0.64
Afib (n =1070)	0.92 (0.8-1.06)	
CV death		
No Afib (n =2764)	0.87 (0.74-1.02)	0.23
Afib (n =1070)	1.03 (0.82-1.29)	
All-cause death		
No Afib (n =2764)	0.89 (0.78-1.01)	0.19

Afib (n =1070)	1.04 (0.86-1.26)	
Ischemic HF		
CV death or HF hosp.		
Non ischemic (n =1378)	0.86 (0.72-1.02)	0.78
Ischemic HF (n =2456)	0.88 (0.78-1)	
All-cause death or HF hosp.		
Non ischemic (n =1378)	0.92 (0.78-1.08)	0.73
Ischemic HF (n =2456)	0.89 (0.79-1)	
All-cause death or all-cause hosp.		
Non ischemic (n =1378)	0.96 (0.84-1.1)	0.83
Ischemic HF (n =2456)	0.94 (0.86-1.04)	
CV death		
Non ischemic (n =1378)	0.89 (0.7-1.12)	0.72
Ischemic HF (n =2456)	0.93 (0.8-1.09)	
All-cause death		
Non ischemic (n =1378)	1 (0.83-1.22)	0.39
Ischemic HF (n =2456)	0.9 (0.79-1.03)	
HTN		
CV death or HF hosp.		
No HTN (n =1542)	0.78 (0.66-0.91)	0.065
HTN (n =2292)	0.95 (0.83-1.08)	
All-cause death or HF hosp.		
No HTN (n =1542)	0.78 (0.67-0.9)	0.013
HTN (n =2292)	0.99 (0.88-1.12)	
All-cause death or all-cause hosp.		
No HTN (n =1542)	0.9 (0.79-1.02)	0.26
HTN (n =2292)	0.99 (0.89-1.09)	
CV death		
No HTN (n =1542)	0.88 (0.73-1.08)	0.65
HTN (n =2292)	0.94 (0.79-1.12)	
All-cause death		
No HTN (n =1542)	0.86 (0.73-1.01)	0.2
HTN (n =2292)	0.99 (0.86-1.14)	
LVEF		
CV death or HF hosp.		
LVEF \geq 35% (n =1233)	0.92 (0.74-1.14)	0.56
LVEF $<$ 35% (n =2601)	0.85 (0.76-0.96)	
All-cause death or HF hosp.		
LVEF \geq 35% (n =1233)	0.95 (0.79-1.16)	0.43
LVEF $<$ 35% (n =2601)	0.87 (0.78-0.97)	
All-cause death or all-cause hosp.		

LVEF \geq 35% (n =1233)	1.05 (0.91-1.21)	0.1
LVEF<35% (n =2601)	0.91 (0.83-0.99)	
CV death		
LVEF \geq 35% (n =1233)	0.97 (0.74-1.28)	0.6
LVEF<35% (n =2601)	0.9 (0.77-1.04)	
All-cause death		
LVEF \geq 35% (n =1233)	0.98 (0.78-1.22)	0.6
LVEF<35% (n =2601)	0.91 (0.81-1.04)	

Legend: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HTN, hypertension; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Supplemental Figure 1. Treatment effect in women and men enrolled in HEAAL and ATLAS trials



Caption: Upper panel - all-cause death: no heterogeneity observed within women and men in the HEAAL and ATLAS trials, but the heterogeneity P-value for the test between women and men was =0.11, suggesting at least some difference in the

treatment response between sexes. Lower panel – all-cause death or all-cause hospitalisation: heterogeneity found within women whereby women responded to high-dose lisinopril in the ATLAS trial but not to high-dose losartan in the HEAAL trial; the global heterogeneity P-value for the test between women and men was =0.55, suggesting lack of heterogeneity between sexes for this outcome.