Dosing of losartan in men vs. women with HFrEF: the HEAAL trial

Short title: Sex-based response to high- vs. low-dose losartan

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Abstract

Background: In heart failure with reduced ejection fraction (HFrEF), guidelines recommend up-titration of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptors blockers (ARBs) to the maximum tolerated dose. However, some studies suggest that women might need lower doses of ACEi/ARBs than men to achieve similar treatment benefit.

Methods: The HEAAL trial compared low vs. high dose of losartan. We reassessed the efficacy and safety of high- vs. low-dose in men vs. women using Cox models and Machine Learning algorithms.

Results: The mean age was 66 years and 30% of the patients were women. Men appeared to have benefited more from high-dose than from low-dose losartan, whereas women appeared to have responded similarly to low and high doses: HR (95%CI) comparing high- vs- low-dose losartan for the composite outcome of all-cause death or all-cause hospitalisation was 0.89 (0.81-0.98) in men and 1.10 (0.95-1.28) in women, interaction P=0.018. Female sex clustered along with older age, ischemic HF, NYHA III/IV, and eGFR<60 ml/min. Patients with these features had a poorer response to high-dose losartan. Subgroup analyses supported no benefit from high-dose losartan in patients with poorer kidney function and severe HF symptoms.

Conclusions: Compared with men, women might need lower doses of losartan to achieve similar treatment benefit. However, beyond sex, other factors (e.g., kidney function, age, and symptoms) may influence the response to high-dose losartan, suggesting that sex-based subgroup findings may be biased by other confounders.

Key-words: sex differences; heart failure; treatment dose; dose-response; machine learning.

Introduction

Heart failure guidelines recommend up-titration of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptors blockers (ARBs), to the maximum tolerated dose, in men and women with heart failure with reduced ejection fraction (HFrEF)[1, 2]. The recommendations rely on trial validated effective doses; however, clinicians may face many challenges in achieving such doses[3, 4]. However, most HFrEF trials used escalating doses, up to a maximum trial defined single doses or maximum tolerated dose. Only the HEAAL (Effects of High-Dose versus Low-Dose Losartan on Clinical Outcomes in Patients with Heart Failure) and ATLAS (Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure) trials compared high versus low treatment doses in well-powered outcome trials, concluding that high-dose losartan and lisinopril are superior to the corresponding low doses[5, 6].

Compared with men, women generally have a smaller body size with higher percentage of body fat. These factors may affect drug metabolism including the duration of action and peak plasma concentrations, which may influence efficacy and safety of certain drugs[7]. If drug metabolism can be influenced by sex, it can also be affected by age, renal function, body mass index, concomitant treatments, and disease severity[8-12]. Compared to men, women with HFrEF are more symptomatic, usually older, more often obese, have poorer kidney function and more co-morbid conditions, and are less frequently treated with guideline-directed therapy[13]. All these factors may influence the response to treatments (including ACEi and ARBs), independently from biological sex.

A study using observational data from two independent cohorts including men and women with HFrEF, suggested that women might need lower doses of ACEi or ARBs than men to obtain similar treatment benefit[14]. Using data from the HEAAL trial, we aim to test whether the response to high vs. low dose losartan differed between men and women, and assess whether other factors such as age, kidney function and clinical presentation (which may differ between men and women) could have influenced the response to high vs. low dose losartan. Additionally, as exploratory analysis, we have also analyzed published data from ATLAS to interpret the effect of high vs. low dose lisinopril in men and women with HFrEF.

Methods

Study design and population

HEAAL was an international, multicentre, double-blind, event-driven trial, comparing the effect of two doses of losartan 150 vs. 50 mg/day among 3846 patients with symptomatic heart failure (New York Heart Association [NYHA] class II to IV), a left ventricular ejection fraction (LVEF) of 40% or less, stable cardiovascular medical therapy for at least 2 weeks, and known intolerance to ACE inhibitors[5]. The primary endpoint was a composite of all-cause death or admission for heart failure. In the present study we have also analysed the composite of cardiovascular death or admission for heart failure, the composite of all-cause death or all-cause hospitalisation, cardiovascular death, and all-cause death, although the trial was underpowered for the study of fatal outcomes in isolation. The median follow-up time was 4.7 (3.5 to 5.5) years. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee or institutional

review board of every site. All patients provided their written informed consent before randomisation. HEAAL is registered with ClinicalTrials.gov, number NCT00090259.

We did not have access to the ATLAS trial database, and, as exploratory analysis, we have used the published results for subgroup analysis (forest plots) depicting the treatment effect of high- vs. low-dose lisinopril in men and women for the outcomes of all-cause death and the composite outcome of all-cause death or all-cause hospitalisation[6]. ATLAS included 3164 patients with NYHA class II to IV and a LVEF of 30% or less. Patients were randomly assigned to receive either low doses (2.5 to 5.0 mg/day) or high doses (32.5 to 35 mg/day) of lisinopril for 39 to 58 months. ATLAS was underpowered to study the effect of high- vs. low-dose lisinopril on all-cause death because the event-rate was lower than expected for this outcome. For this reason and before the blind was broken, the Steering Committee recognized that a composite outcome of time-to-first of hospitalization for any reason or all-cause death would provide power to adequately test the study hypothesis[6]. The trial was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review boards of all participating hospitals. Written informed consent was obtained from all patients.

Statistical analysis

Descriptive statistics and comparison of the characteristics between women and men were performed using categorical and continuous variables with the appropriate tests. Survival analyses were performed by intention-to-treat. We used time-to-event methods (Kaplan-Meier curves and Cox proportional hazards models) to compare the high- vs. low dose losartan groups for the studied outcomes. The heterogeneity of HR estimates for subgroups was tested by including an interaction term between

treatment and subgroup in the Cox model (e.g., treatment-by-sex interaction). Latent class analysis (LCA) is an unsupervised "machine learning" method that allows the grouping of individuals into "classes" with similar characteristics within each "class" and different characteristics between "classes. LCA was performed using maximum-likelihood estimation to identify the most common patterns using 9 variables for a range of 2 to 5 subgroups. The variables were selected based on statistically and clinically significant sex differences found in table 1, and included sex (women vs. men), age (≤70 vs. >70yr), body mass index (BMI ≤30 vs. 30 Kg/m2), ischemic etiology for heart failure (yes vs. no), hypertension (yes vs. no), NYHA (II vs. III or IV), LVEF (<35 vs. ≥35%), atrial fibrillation (yes vs. no), and eGFR (<60 vs. ≥60 ml/min/1.73m2). The optimal number of classes was determined using the first minima of the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) with a condition to the percentage of patients in each class to be at least 20% of the total. Based on these criteria the optimal number of classes was 3. Probabilities of membership in each subgroup for every LCA variable were used to determine the most likely subgroup for each patient.

As exploratory analysis, a fixed-effect meta-analysis with inverse variance weights was conducted using the estimated HR (95%CI) from the HEAAL trial and the sex subgroup estimates (hazard ratios [HR] and 95% confidence intervals [95%CI]) published in the ATLAS trial report[6]. In ATLAS, the treatment effect in men and women was obtained from the published forest plots with an approximation of the estimated HR and corresponding 95%CI for the reported outcomes of all-cause death and all-cause death or all-cause hospitalisation. Statistical heterogeneity of the treatment effect between the HEAAL and ATLAS studies was assessed based on

the p-value derived from Cochran's Q test. The latter was also used to test for treatment-by-sex interactions[15].

Statistical analyses were performed using Stata®, version 16 (Stata Corp, College Station, TX, USA).

Results

Characteristics of the patients by sex

In HEAAL, 30% (n =1143) of the patients were women. Compared with men, women had several different clinical characteristics. Notably, women were older, had more frequent history of hypertension and less frequent history of ischemic heart disease (all P <0.05). Women were more symptomatic, had more frequently a BMI above 30 Kg/m2, and had poorer kidney function including a higher proportion of patients with eGFR below 60 ml/min/1.73m^2 (all P <0.05). *Table 1*. In ATLAS, 21% (n =648) of the patients were women and the mean age was 64 ± 10 years[6].

Event rates and treatment effect of high- vs. low-dose losartan by sex

Men had higher event rates than women for all the studied outcomes. *Table 2*. Men appeared to have benefited more from high-dose (compared with low-dose) losartan, whereas women appeared to have responded similarly to low or high doses. The HR (95%CI) for the primary composite outcome of all-cause death or heart failure hospitalisation was 0.85 (0.76-0.95) in men and 1.03 (0.85-1.24) in women, interaction P =0.089. The HR (95%CI) for the composite outcome of cardiovascular death or heart failure hospitalisation was 0.83 (0.73-0.93) in men and 1.01 (0.82-1.23) in women, interaction P =0.098. The HR (95%CI) for the composite outcome of all-cause death or all-cause hospitalisation was 0.89 (0.81-0.98) in men and 1.10 (0.95-1.28) in women, interaction P =0.018. *Table 2 & Graphical Abstract*.

Safety and discontinuation of high- vs. low-dose losartan by sex

The occurrence of hypotension, hyperkalemia and renal failure was not different between women and men. *Table 3*. Women were more likely than men to discontinue treatment due to adverse events with high-dose losartan: 14/560 (2.5%) women in low dose group and 27/583 (4.6%) women in the high-dose group vs. 44/1353 (3.3%) men in low dose group and 40/1338 (3.0%) men in the high-dose group; interaction P =0.071. Women were more likely than men to discontinue treatment due to any cause if taking high-dose losartan: 82/397 (20.7%) women in low dose group and 99/412 (24.0%) women in the high-dose group vs. 203/851 (23.9%) men in low dose group and 182/874 (20.8%) men in the high-dose group; interaction P =0.072. *Table 3*.

Latent class analysis and additional subgroup analyses

Women clustered together (in class 3) with age >70yr, ischemic HF, NYHA III/IV, atrial fibrillation, and eGFR <60 ml/min/1.73m^2. Hypertension and LVEF <35% were also important components but had more weight in class 2 and 1, respectively. *Figure 1 & Supplemental Table 1*. The comparison of the patients` characteristics across the three classes follows the same pattern described above and are presented in the *Supplemental Table 2*.

The event-rates and the effect of high- vs. low-dose losartan across the three classes in presented in the *Supplemental Table 3*. Patients in class 3 had the highest event rates (worst prognosis) and experienced a similar effect of high and low dose losartan. Patients in class 1 had the lowest event rates (best prognosis) and experienced a similar effect of high and low dose losartan. Patients in class 2 were the only ones that responded to high dose vs. low dose losartan, with patients in class 2 receiving low dose losartan having a similar prognosis to patients assigned to

class 3 and patients in class 2 receiving high dose losartan having a similar prognosis to patients in class 1. For example, the HR (95%CI) for the composite outcome of all-cause death or heart failure hospitalisation was 0.98 (0.84-1.13) in class 3, 0.93 (0.78-1.1) in class 2, and 0.74 (0.62-0.88) in class 1, interaction P =0.048. *Figure 2 (details in the figure legend/caption) & Supplemental Table 3*.

Additional individual subgroup analyses are presented in the *Supplemental Table 4*. In concordance with the latent class analyses, the individual subgroup analyses suggest that patients with poorer kidney function defined by an eGFR below 60 ml/min/1.73m2 and with severe heart failure symptoms defined by a NYHA class III or IV, might have experienced no benefit from high-dose losartan.

Exploratory meta-analysis with individual patient data from HEAAL and published data from ATLAS

In ATLAS, the HR (95%CI) comparing high-dose vs. low-dose lisinopril for all-cause death was 0.89 (0.80-1.00) in men and 1.07 (0.82-1.36) in women. For the composite of all-cause death or all-cause hospitalisation the corresponding HR (95%CI) was 0.91 (0.82-0.99) in men and 0.82 (0.71-0.99) in women. The subgroup interaction P values were not reported in the manuscript[6]. Meta-analysing the treatment effects found in HEAAL with those derived from the forest plots in ATLAS, we found that men might have obtained more benefit from high-dose losartan and lisinopril than women, who seemed to have obtained similar benefit from high- or low dose for the outcome of all-cause death; the dose treatment-by-sex heterogeneity P-value was =0.11. *Supplemental Figure 1 (upper panel)*. For the composite of all-cause death or all-cause hospitalisations, women responded similarly to men with high dose lisinopril in the ATLAS trial. *Supplemental Figure 1 (lower panel)*.

Discussion

The present study shows that men appeared to have benefited more from high-dose (compared with low-dose) losartan, whereas women appeared to have responded similarly to low or high doses. However, the sex differences in losartan dose response are likely not due to sex alone but to concomitant conditions, particularly poorer renal function, older age, and more severe heart failure symptoms among women which may have limited the tolerability to high-dose losartan and caused more frequent drug discontinuation among women. These findings have clinical implications because they suggest that high-dose losartan may benefit men more than women, likely because the tolerability to high-treatment doses may be limited in women, due to comorbid conditions.

In HFrEF populations, high-dose ACEi and ARBs have been shown to provide clinical benefit compared with low-dose. This evidence comes essentially from two well-powered trials: HEAAL and ATLAS. In HEAAL, 3846 HFrEF patients were randomised to either losartan 150 mg/day (high-dose) or losartan 50 mg/day (low-dose). Compared with low-dose, high-dose losartan resulted in a 10% lower rate of the primary composite outcome of all-cause death or heart failure hospitalisation. In ATLAS, 3164 HFrEF patients were randomly assigned to either lisinopril 32.5 to 35 mg/day (high-dose) or 2.5 to 5.0 mg/day (low-dose). Compared with low-dose, high-dose lisinopril resulted in a 15% lower rate of all-cause death or heart failure hospitalisation (to use the same outcome as described for HEAAL) and a 12% reduction in the outcome of all-cause death or all-cause hospitalisation (the outcome for which the trial had adequate power).

Multinational observational studies suggested that the optimal dose of ACEi and ARBs (and β-blockers) may be different between men and women with HFrEF,

with women having the lowest risk of adverse outcomes at lower doses (half the guideline-recommended doses) compared with men, with no further decrease in risk at higher doses[14]. Causality cannot be established from observational studies. It is possible that women tolerated lower doses than men due to reasons other than sex (e.g., lower body weight, poorer renal function, older age). The hypothesis that factors other than sex may play an important role in the dose-response is sound because women with HFrEF are usually older, lighter and with poorer kidney function than men.

Patients with kidney disease have higher risk of developing hyperkalemia and transient elevations in creatinine that may lead clinicians to withhold or permanently stop the treatment[16], which has been associated with poor outcomes[17]. Patients with HFrEF and kidney impairment are also less likely to receive guideline-recommended doses of ACEi and ARBs[18]. Requirement for dose-adaptation, higher risk of adverse events, and decreased efficacy have also been found with other drug classes in patients with kidney disease[12, 19, 20]. In the HEAAL trial, women had poorer renal function which might have contributed for higher rates of drug discontinuation and poorer response to high-dose losartan.

Heart failure symptoms, as evaluated by the NYHA functional class, also could have played an important role in dose-response in the HEAAL trial. Patients with mild symptoms (NYHA II) might have responded better to high-dose losartan than patients with severe symptoms (NYHA III or IV)[5]. These findings are consistent with the published forest plots in ATLAS, where patients in NYHA class II seem to have benefited more from high dose lisinopril than patients in class II or IV[6]. It is possible that patients with severe symptoms benefit from lower doses of treatment, that may be up titrated upon improvement of symptoms.

Other factors such as age, can also influence ACEi/ARBs up-titration and response[18].

The interplay between several characteristics may be better captured in our latent class analysis from the HEAAL trial, where patients included in “class 3” (comprising predominantly elderly women with atrial fibrillation, poor renal function, and severe symptoms) had the poorest prognosis and no increased benefit from high-dose losartan, as compared to lower-dose. The latent class analysis method supports the interplay of multiple factors when it comes to dose response. In HEAAL the response to high dose losartan (vs. low dose) seems to have been driven by hypertensive and obese patients assigned to “class 2”. Whereas patients in “class 1”, who were younger, with mild symptoms and preserved renal function, had the best prognosis overall and did not experience any additional benefit from high dose losartan. Other studies have used similar methods to identify patient “clusters” with difference characteristics, prognosis, and treatment response[21, 22].

Furthermore, in the ATLAS trial, compared with women, men might also have benefited more from high dose lisinopril for all-cause death (with similar between sex response for the composite of all-cause hospitalizations or all-cause death). These findings independently support a greater benefit from high dose losartan and lisinopril in men. It is important to highlight that high dose losartan (and lisinopril) did not have a deleterious impact among women, but the effect of high and low dose was similar in women, whereas in men high dose might have provided greater benefit. This might have been linked to factors other than sex, as above discussed.

Reports from both observational and trial data show that women are often not treated with guideline recommended therapies[13, 23]. Our data show that, beyond sex, a multitude of factors influencing drug response and tolerability play an important

role in dose response; and, in daily clinical judgment, frequently performed under uncertainty in a case-by-case manner.

Limitations

Several limitations should be acknowledged in our study. This was a post-hoc analysis of the HEAAL trial which was underpowered to assess the treatment effect within sex subgroups, and these results should be regarded as “hypothesis generating”. We have performed multiple interaction tests, which might have increased the likelihood of chance findings. Unfortunately, we were unable to access the individual patient data from the ATLAS trial - as checked with the sponsor of the ATLAS study, patient agreements are lacking in some regions and the data are incomplete. Treatment non-adherence and discontinuation is often underreported in trials, and the real discontinuation rates might have been higher than here reported[24]. Finally, our findings apply only to the HEAAL and ATLAS trials with losartan and lisinopril dosing, respectively.

Conclusions

Compared with men, women might need lower doses of losartan to achieve similar treatment benefit. However, beyond sex, other factors (e.g., kidney function, age, and symptoms) may influence the response to high-dose losartan, suggesting that sex-based subgroup findings may be biased by other confounders.

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Table 1. Characteristics of women and men enrolled in the HEAAL trial

Characteristics	Women	Men	p-value
N.	1143	2691	
Age, yr	66.4 ± 11.6	63.3 ± 11.6	<0.001
Age >70	455 (39.8%)	814 (30.2%)	<0.001
White race	678 (59.3%)	1643 (61.1%)	0.31
Atrial fibrillation	291 (25.5%)	779 (28.9%)	0.028
Ischemic heart disease	647 (56.6%)	1809 (67.2%)	<0.001
Hypertension	763 (66.8%)	1529 (56.8%)	<0.001
Diabetes mellitus	367 (32.1%)	832 (30.9%)	0.47
NYHA III/IV	415 (36.3%)	759 (28.2%)	<0.001
LVEF, %	32.0 ± 6.6	31.4 ± 6.5	0.006
LVEF <35	734 (64.2%)	1867 (69.4%)	0.002
SBP, mmHg	129.1 ± 18.7	124.8 ± 17.5	<0.001
SBP <110	241 (21.1%)	703 (26.1%)	<0.001
Heart rate, bpm	75.7 ± 16.2	73.9 ± 15.8	0.002
Heart rate >75	503 (44.0%)	1021 (37.9%)	<0.001
BMI, Kg/m2	29.0 ± 10.7	28.8 ± 9.5	0.52
BMI <25	407 (35.6%)	827 (30.7%)	<0.001
BMI 25-30	384 (33.6%)	1156 (43.0%)	
BMI >30	352 (30.8%)	708 (26.3%)	
eGFR, ml/min/1.73m2	65.4 ± 22.9	70.8 ± 21.8	<0.001
eGFR <60	521 (45.6%)	867 (32.2%)	<0.001
Potassium, mmol/L	4.5 ± 0.5	4.5 ± 0.5	0.39
Potassium <4	184 (16.1%)	435 (16.2%)	0.78
Potassium 4-5	846 (74.0%)	1970 (73.2%)	
Potassium >5	113 (9.9%)	286 (10.6%)	
Hemoglobin, g/dL	13.1 ± 1.4	14.2 ± 1.5	<0.001
Anemia	220 (19.2%)	480 (17.8%)	0.30
Beta-blocker stratum	755 (66.1%)	2003 (74.4%)	<0.001
High-dose losartan	583 (51.0%)	1338 (49.7%)	0.47

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

Table 2. Events, event-rates, and treatment effect in women and men enrolled in the HEAAL trial

Outcomes by sex	Events low dose	Events high dose	Event-rate low dose*	Event-rate high dose*	HR (95%CI)	P-value	Interaction P
CV death or HF hosp.							
Overall (n =3834)	771/1913 (40.3%)	698/1921 (36.3%)	10.7 (10-11.5)	9.3 (8.7-10)	0.88 (0.79-0.97)	0.011	
Women (n =1143)	188/560 (33.6%)	192/583 (32.9%)	8.3 (7.2-9.6)	8.4 (7.3-9.6)	1.01 (0.82-1.23)	-	0.098
Men (n =2691)	583/1353 (43.1%)	506/1338 (37.8%)	11.8 (10.9-12.8)	9.7 (8.9-10.6)	0.83 (0.73-0.93)	-	
All-cause death or HF hosp.							
Overall (n =3834)	889/1913 (46.5%)	828/1921 (43.1%)	12.4 (11.6-13.2)	11.1 (10.3-11.8)	0.90 (0.82-0.99)	0.03	
Women (n =1143)	219/560 (39.1%)	228/583 (39.1%)	9.7 (8.5-11)	9.9 (8.7-11.3)	1.03 (0.85-1.24)	-	0.089
Men (n =2691)	670/1353 (49.5%)	600/1338 (44.8%)	13.6 (12.6-14.7)	11.6 (10.7-12.5)	0.85 (0.76-0.95)	-	
All-cause death or all-cause hosp.							
Overall (n =3834)	1269/1913 (66.3%)	1237/1921 (64.4%)	22.8 (21.6-24.1)	21.6 (20.4-22.8)	0.95 (0.88-1.03)	0.22	
Women (n =1143)	333/560 (59.5%)	363/583 (62.3%)	18.5 (16.6-20.6)	20.6 (18.6-22.8)	1.10 (0.95-1.28)	-	0.018
Men (n =2691)	936/1353 (69.2%)	874/1338 (65.3%)	24.9 (23.4-26.6)	22 (20.6-23.5)	0.89 (0.81-0.98)	-	
CV death							
Overall (n =3834)	478/1913 (25.0%)	448/1921 (23.3%)	5.9 (5.4-6.4)	5.4 (4.9-5.9)	0.92 (0.81-1.05)	0.22	
Women (n =1143)	123/560 (22.0%)	118/583 (20.2%)	4.9 (4.1-5.9)	4.7 (3.9-5.6)	0.95 (0.73-1.22)	-	0.78
Men (n =2691)	335/1353 (26.2%)	330/1338 (24.7%)	6.3 (5.7-7)	5.7 (5.1-6.4)	0.91 (0.78-1.05)	-	
All-cause death							
Overall (n =3834)	665/1913 (34.8%)	635/1921 (33.1%)	8.2 (7.6-8.8)	7.6 (7.1-8.3)	0.94 (0.84-1.05)	0.25	
Women (n =1143)	163/560 (29.1%)	171/583 (29.3%)	6.5 (5.6-7.6)	6.8 (5.8-7.9)	1.03 (0.83-1.28)	-	0.28
Men (n =2691)	502/1353 (37.1%)	464/1338 (34.7%)	8.9 (8.2-9.7)	8 (7.3-8.8)	0.90 (0.79-1.02)	-	

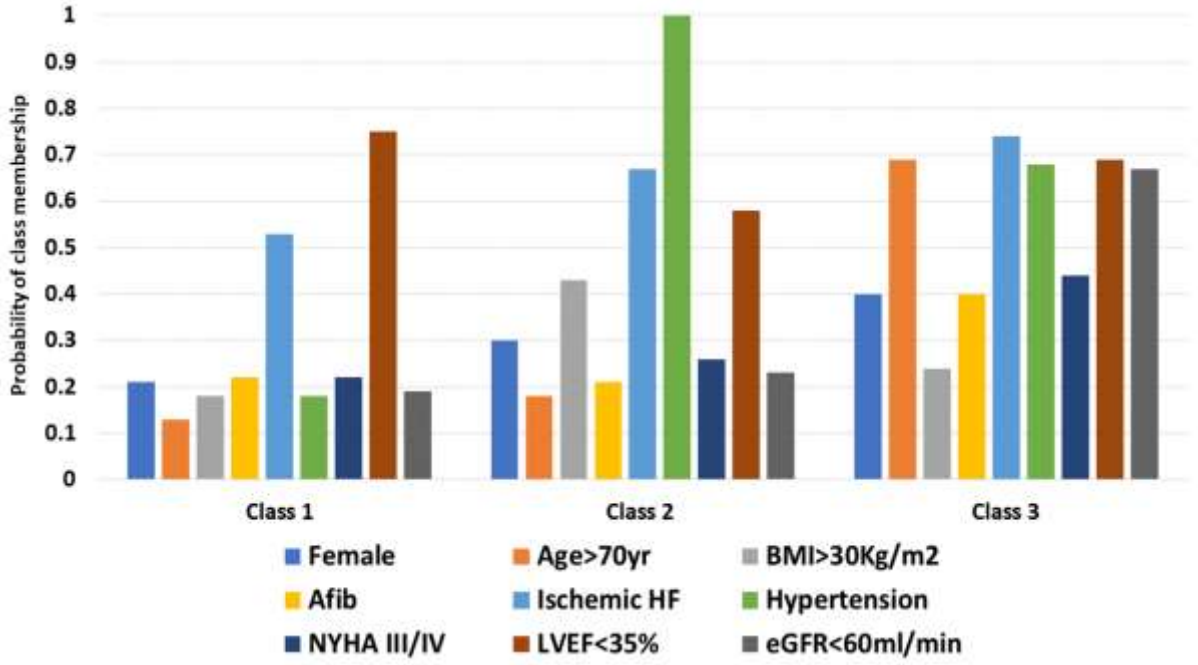
Legend: *Event-rates expressed in 100 person-years;

Table 3. Safety events and percentage of drug compliance in women and men enrolled in the HEAAL trial

Safety event	Events low dose	Events high dose	OR (95%CI)	Interaction P
Hypotension				
Women (n =1143)	39/560 (7.0%)	55/583 (9.4%)	1.39 (0.91-2.13)	0.85
Men (n =2691)	106/1353 (7.8%)	148/1338 (11.1%)	1.46 (1.13-1.9)	
Hyperkalemia				
Women (n =1143)	7/560 (1.3%)	18/583 (3.1%)	2.52 (1.04-6.07)	0.39
Men (n =2691)	15/1353 (1.1%)	23/1338 (1.7%)	1.56 (0.81-3)	
Renal failure				
Women (n =1143)	45/560 (8.0%)	49/583 (8.4%)	1.05 (0.69-1.6)	0.29
Men (n =2691)	101/1353 (7.5%)	134/1338 (10.0%)	1.38 (1.05-1.81)	
Drug discontinuation due to AE				
Women (n =1143)	14/560 (2.5%)	27/583 (4.6%)	1.89 (0.98-3.65)	0.071
Men (n =2691)	44/1353 (3.3%)	40/1338 (3.0%)	0.92 (0.59-1.42)	
Discontinued drug during F-U and was alive at date of last news				
Women (n =1143)	82/397 (20.7%)	99/412 (24.0%)	1.22 (0.87-1.69)	0.072
Men (n =2691)	203/851 (23.9%)	182/874 (20.8%)	0.84 (0.66-1.05)	

Legend: F-U, follow-up. Adverse events (AEs) were reported while patients were taking treatment and for 14 days after the end of treatment. Adverse events were defined by the investigators. Renal failure was defined using the terms from the Medical Dictionary for Regulatory Activities (version 12): renal failure, renal failure acute, renal failure chronic, renal impairment, and pre-renal failure.

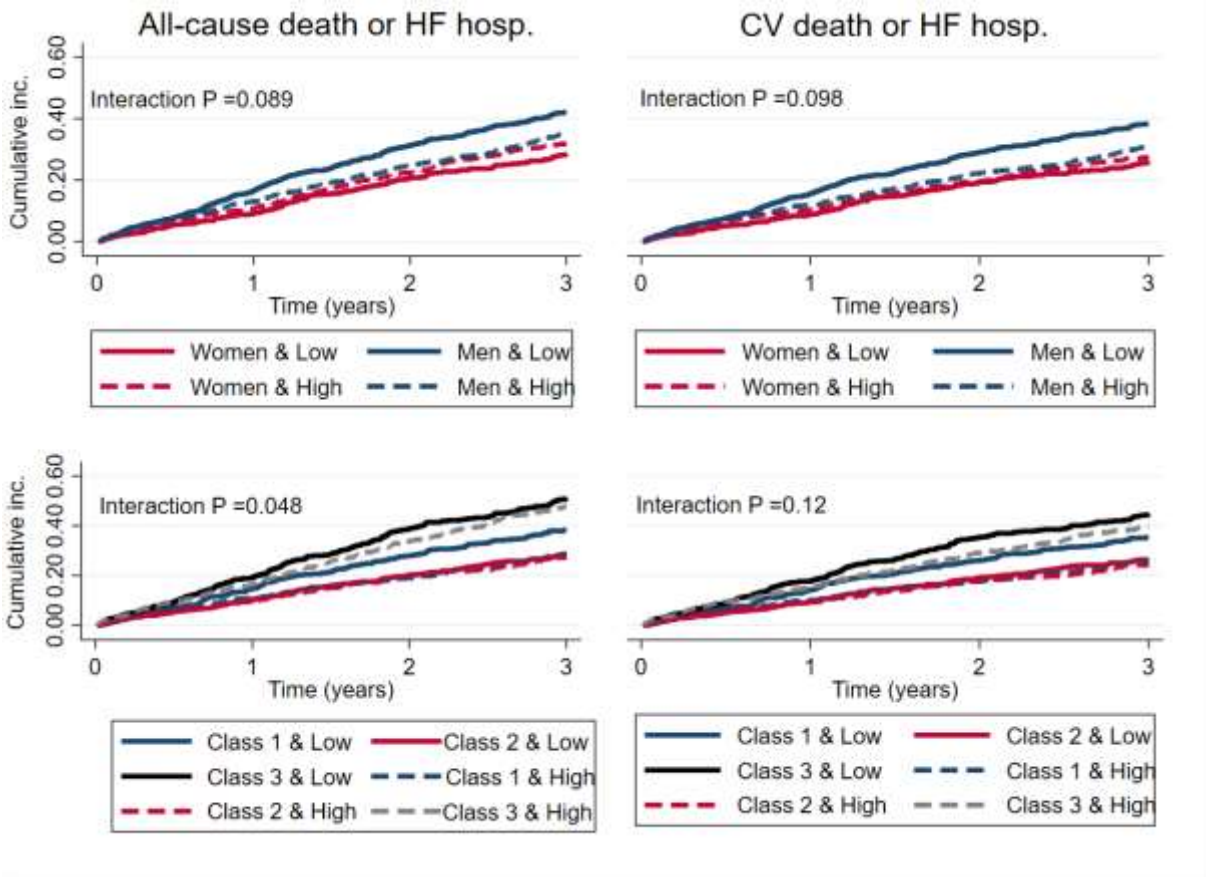
Figure 1. Latent class analysis membership in the HEAAL trial



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

Caption: The figure represents the probability of each individual patient to belong to class 1, 2 or 3. The “class membership probability” (with 0 representing 0% chance of class membership assignment and 1 representing 100% chance of class membership assignment) can been seen in the y-axis, and each class is represented in the x-axis. Women clustered together (in class 3) with age >70yr, ischemic HF, NYHA III/IV, atrial fibrillation, and eGFR <60 ml/min/1.73m^2. Hypertension and LVEF <35% were also important components in class 3 but had more weight in class 2 and 1, respectively.

Figure 2. Treatment effect by sex (upper panel) and latent class analysis “class” membership (lower panel) in the HEAAL trial



Legend: CV, cardiovascular, HF, heart failure; Low, low-dose; High, high-dose.
Caption: Upper-panel – treatment-by-sex interaction: men (blue lines) on high dose (dashed lines) losartan responded better than men on low dose (continuous lines) losartan, whereas women (red lines) responded similarly to low or high dose losartan.
Lower-panel – treatment-by-class (determined with latent class analysis) interaction: “Class 1” (blue lines) had predominance of younger men, with mild symptoms and preserved renal function (see also Figure 1); patients grouped in “class 1” responded favourably to high dose losartan (dashed blue lines) compared with patients grouped in “class 1” and receiving low dose losartan (continuous blue lines).
“Class 2” (red lines) had predominance of hypertensive and obese patients with heart failure of ischemic etiology (see also Figure 1); patients grouped in “class 2” had the best prognosis and the effect of high (dashed red lines) or low (continuous red lines) dose losartan was similar; patients in “class 2” (regardless of the randomly assigned losartan dose) had a favorable prognosis, similar to the prognosis of patients in “class 1” receiving high dose losartan (dashed blue lines overlapped by the red lines).
“Class 3” (black & grey lines) had a patient predominance of elderly women, severely symptomatic, and with poor renal function (see also Figure 1); patients grouped in class 3 had the poorest prognosis and the effect of high (dashed grey lines) or low (continuous black lines) dose losartan was similar.

In resume, the response to high dose losartan was driven by “class 1” patients, while “class 2” had good prognosis and “class 3” poor prognosis regardless of losartan dose.

Graphical abstract. Treatment effect of High- vs. Low-dose Losartan in the HEAAL Trial

Legend: ACM or ACH, all-cause mortality or all-cause hospitalization.

Caption: In HEAAL, men appeared to have benefited more from high-dose (compared with low-dose) losartan, whereas women appeared to have responded similarly to low or high doses.