# Self-Reported Sodium Intake and Sodium Vulnerability in Heart Failure With Preserved Ejection Fraction

# Self-reported sodium intake and sodium vulnerability in heart failure with preserved ejection fraction

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**ABSTRACT**

**Background:** Questioning patients about sodium intake is a key element of the heart failure (HF) encounter. We sought to determine the pathophysiologic and prognostic meaning of patient's self-reported sodium intake in HF with preserved ejection fraction (HFpEF).

**Methods:** This cohort analysis used data from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial of patients enrolled in the Americas. Tertile of baseline self-reported sodium intake were used in analysis. Cox-regression and linear-mixed models were used to assess the relationship between self-reported sodium intake and outcome and the interaction between self-reported sodium intake and the treatment effect of spironolactone on HF-outcome, blood pressure, dyspnea and edema at follow-up.

**Results:** Self-reported sodium intake of 1748 HFpEF patients included in TOPCAT were divided according to tertiles of sodium intake (47% low, 35% moderate and 18% reported high sodium intake). After covariate adjustment lower self-reported sodium intake associated with higher risk for HF-admission (p=0.009). Patients with a lower sodium intake demonstrated higher E-wave and LV-end diastolic volume and higher estimated plasma volume (p<0.001). Lower sodium intake was associated with a larger treatment effect of spironolactone on HF-admission (HR=0.69, CI=[0.53-0.91] vs highest tertile HR=1.37 CI=[0.79-2.38]), p-interaction=0.030). Additionally, linear-mixed models indicated larger BP-reduction and larger reduction in dyspnea and edema (p-interaction all<0.001) in patients with lower sodium intake receiving spironolactone.

**Conclusion:** Low self-reported sodium in HFpEF is associated with volume status and higher risk of HFH. The more pronounced treatment effect with spironolactone on HF-outcome, blood pressure and volume status potentially suggest low self-reported sodium intake is an indicator of a sodium vulnerable state.

**Keywords:** Spironolactone, outcome, pathophysiology, HFpEF, aldosterone, sodium

## CLINICAL PERSPECTIVES

We investigated the relation between self-reported sodium intake and outcome and treatment response to spironolactone in 1,748 HFpEF patients enrolled in the TOPCAT trial. We observed that 18% of patients admitted to low sodium intake, which was associated with higher risk for HF-admission even after adjustment. Patients with lower sodium intake had higher estimated plasma volume and more signs of echocardiographic congestion and a potential accentuated aldosterone-state that was associated with more benefit from aldosterone inhibition in terms of HF-admissions reduction, more reduction in blood pressures and signs and symptoms of congestion during follow-up.

## INTRODUCTION

Questioning patients about their dietary habits of sodium intake is a part of every heart failure (HF) encounter in clinical practice.[1-3] Such information is used to advise sodium restriction in patients admitting to higher sodium intake, given the historical wide endorsement of sodium restriction by HF guidelines.[1-5] While self-reported sodium intake reflects a degree of adherence to such advice, it might also reflect learned behavior based on a patient's perceived vulnerability to retain sodium. Observational data indicate a wide variability in the degree of sodium intake in HF and it appears that many patients can tolerate chronic high intake of sodium without provoking HF decompensation, while some patients more easily retain sodium with subsequent decompensation despite lower sodium intake. [6;7]

Such vulnerability to an ingested sodium load is well recognized in the hypertension literature and represents the clinical entity of salt sensitive hypertension.[8] This is a condition more often occurring in elderly women, who are at risk for HF with preserved ejection fraction (HFpEF).[8;9] The PATHWAY II trial documented that in patients with drug resistant hypertension, spironolactone reduced blood pressures to a larger extent than beta-blockers or alpha-blockers.[10] Spironolactone incurred the largest treatment effect in patients with a reduced plasma renin activity, which represent a cohort of patients with more volume overload and inappropriate elevated plasma-aldosterone concentrations (forming the basis of salt sensitive hypertension).[10;11] Next to angiotensin II and potassium, other elements increase plasma aldosterone concentration such as adipose-tissue related factors and endothelin which are elevated in HFpEF.[12;13] Herein, we sought to investigate: (1) the variation in self-reported sodium intake in HFpEF, (2) relation between self-reported sodium intake in HFpEF and clinical outcome, (3) relation between self-reported sodium intake and sodium vulnerability in HFpEF and responses to spironolactone.

## METHODS

### Patient cohort and study design

TOPCAT trial data was obtained through the publicly available National Heart, Lung, and Blood Institute BioLINCC data repository. The design and the results of the TOPCAT trial have been previously published.[14;15] Briefly, TOPCAT was a multicenter, international, randomized, double blind, placebo-controlled trial that tested the efficacy and safety of the mineralocorticoid receptor antagonist spironolactone compared with placebo on cardiovascular morbidity and mortality in 3445 subjects. The current *post-hoc* analysis is restricted to patients enrolled in the geographic location of United States of America, Canada, Brazil and Argentina (TOPCAT-Americas), excluding patients enrolled in the geographic area of Russia and Georgia due to marked difference in baseline features and study drug adherence.[16;17] Eligible subjects for enrollment in TOPCAT were at least 50 years old with signs and symptoms of HF and a left ventricular ejection fraction (LVEF) ≥45%. Randomization was stratified by the presence of one of the following inclusion criteria: at least one HF hospitalization within the 12 months before study screening or, if no qualifying HF hospitalization, a BNP (B-type natriuretic peptide) ≥100 pg/mL or NT-proBNP (N-terminal pro-BNP) ≥360 pg/ mL within the 60 days before screening. The study protocol was approved at each participating institutional review board or ethics committee. All study participants provided written informed consent before enrollment.

### Self-reported sodium intake

Self-reported sodium intake was evaluated during the baseline visit pre-randomization using a standardized questioning scale captured in the electronic case record form. Patients were questioned about the degree of addition of sodium during food preparation; adding no sodium = 0, adding a $1/8^{th}$ of a teaspoon= 1, adding a $1/4^{th}$ of a teaspoon= 2, adding a $1/2^{th}$ or more of

a teaspoon= 3. These categories were used to determine the degree of sodium added to; (1) Staple food (e.g. rice, pasta, potatoes, etc), (2) Soup, (3) Meat and (4) Vegetables. Combining the score of 0-3 on these four different food categories generates an overall sodium addition score ranging from 0-12 with 0 indicating least and 12 indication most sodium addition. For analysis (and to account for small numbers in different categories) the overall sodium addition score was categorized into tertiles (low 0-33%, moderate >33-<66% and high >66%). To account for the possibility of an overall low sodium addition score due to patients not preparing their meals themselves, the proportion of meals self-prepared by the patients (excluding commercially prepared meals) was assessed as: (1) all most none, (2) 25%, (3) 50%, (4) 75% and (5) all most all.

**Clinical outcome**

Clinical outcome of interest used to assess the association with self-reported sodium intake included the primary endpoint of TOPCAT (a composite endpoint of cardiovascular mortality, HF hospitalizations and aborted cardiac arrest). Other adjudicated endpoints such stroke and myocardial infarction were also assessed. A previous published risk score (3A3B-score, includes age, anemia, albumin, body mass index, BNP and blood urea nitrogen) validated in the TOPCAT-Americas dataset was used to determine the prognostic association of the different self-reported sodium intake categories in patients classified in the similar risk categories.[18]

**Phenotype assessment of patients in different sodium intake tertiles**

Ancillary investigations including the echocardiography sub-study and laboratory data were used to determine potential differences in patient profiles with differential self-reported sodium intake. We wanted to determine whether low self-reported intake could potentially reflect a

cohort of patients with sodium vulnerability. From the baseline laboratory results, estimated plasma volume was calculated in line with previous reports to determine the degree of plasma volume expansion.[19;20] Briefly estimated plasma (ePV) volume was calculated as ePV = (1 – Hematocrit) x [a + (b x weight in Kg)], with hematocrit being expressed as a fraction and a and b equaling a fixed value varying according to gender (males: a=1530, b=41; females: a=864, b=47.9).[19;20]. Additionally, the Na/K ratio at baseline was calculated as a potential indirect reflection of elevated aldosterone levels.[21] Next to baseline data, longitudinal changes in physical data at follow-up including blood pressure response to spironolactone were investigated to further study the presence of a sodium vulnerable phenotype in HFpEF.[10]

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation or median and interquartile range as appropriate. Categorical variables were presented as frequencies (percentages). Between groups assessment of categorical variables were compared using Pearson's Chi-2 test. Continuous variables were compared using ANOVA or Kruskal-Wallis as appropriate. Linear mixed effects models with repeated measures over time were performed to assess changes in clinical data overtime per baseline sodium tertile and treatment allocation (spironolactone vs. placebo). Baseline sodium tertiles and the interaction of the treatment by time were specified as fixed effects and random effects included geographical of enrollment. Cox regression models were used to assess the relation between baseline sodium tertiles and aforementioned outcomes. Hazard ratios (HR) are presented with their 95% confidence interval (CI). Unadjusted event-rates were visualized as Kaplan-Meier curves. In addition, all outcome analyses were covariate adjusted. Covariates used for adjustment included all covariates with significant differences between sodium tertile at baseline in addition to the percentage of meals not self-prepared to account for low sodium addition score due to eating commercially prepared

food. To determine the impact of self-reported sodium intake on the treatment effect of spironolactone, treatment interaction was assessed for the different endpoints on which sodium tertiles had an independent relation with in multivariable Cox-regression analysis. All analyses were performed using SPSS version 23 or STATA version 12. A p-value of <0.05 was used to indicate statistical significance.

## RESULTS

### Patient population

A total of 1767 patients were enrolled in TOPCAT-Americas, of whom 19 patients (1.07%) were excluded due to an absent or negative sodium addition score. The sodium addition score was not normally distributed (**Supplemental Figure 1**) resulting in an imbalance of the number of study participants per tertile. In total 828 patients fell in the low sodium addition tertile (47%), 602 patients in the moderate sodium addition tertile (36%) and 316 patients in the high sodium addition tertile (18%). Baseline features of the patients are reflected in **Table 1**.

### Association with clinical outcome

**Figure 1** illustrates the Kaplan-Meier curves for the different sodium tertiles and the different outcomes. Patients with the lowest self-reported sodium intake had an increased risk for the primary composite endpoint. This finding was primarily driven by a higher risk for heart failure hospitalizations in patients with low self-reported sodium intake, but not for other endpoint components. **Table 2** shows the results of a cox-proportional hazard models for the primary endpoint and for heart failure hospitalizations (those that were significantly different in **Figure 1** and thus in univariate analysis). After adjustment for difference in baseline characteristics and accounting for the degree of eating commercially prepared food, a low self-reported sodium intake remained independently associated with a higher risk for the primary endpoint and heart

failure hospitalizations. **Figure 2** illustrates the Kaplan-Meier curves for heart failure hospitalization for patients classified in a similar risk category by the A3B3-risk score, illustrating that for patients categorized in the same risk category, self-reported sodium intake confers a similar risk separation. This also indicates that self-reported sodium intakes convey prognostic information beyond the components of the A3B3 risk score.

**Self-reported sodium intake and spironolactone treatment effect**

**Table 3** shows the hazard ratios and confidence intervals for spironolactone use on the primary endpoint and heart failure hospitalizations in the overall population and in the different subgroups according to self-reported sodium intake. In line with previous reports, spironolactone reduced the risk for the primary endpoint and heart failure hospitalizations in the post-hoc generated TOPCAT-Americas. For heart failure hospitalization there was a grade (dose-response) relation between the treatment effect of spironolactone and self-reported sodium intake, with patients in the lowest self-reported sodium intake tertile incurring the largest treatment effect (HR=0.69, 95% CI= [0.53-0.91]) versus no treatment effect in patients with high self-reported sodium intake (HR=1.37, 95% CI= [0.79-2.38]). As indicated by the p-value of interaction this relation between treatment effect of spironolactone and self-reported sodium intake was statistically significant (p=0.030). For the primary endpoint a similar graded treatment effect attenuation was seen towards the higher self-reported sodium intake categories, however the p-value for interaction was not significant (p=0.162)

**Patient profiling according to self-reported sodium tertiles**

The mean values (and numbers of patients with such measurements) of patients undergoing baseline echocardiography are reported in **Supplemental Table 1**. Patients with the lowest self-reported sodium intake had a higher left ventricular end-diastolic volume and a higher E-wave

velocity, other key echocardiographic variables did not differ between. Patients with the lowest self-reported sodium intake had the highest estimated plasma volume, but the highest Na/K ratio and baseline chloride – all indirectly reflecting a potential higher aldosterone state (**Supplemental Figure 2**). Collectively this suggest that sodium restriction is not at the basis of the potentially observed hyper-aldosterone effect, as if it would occur through renin activation this would be expected to occur with a lower plasma volume or chloride level (both stimulating the macula densa). In addition, patients in different sodium tertiles groups had different systolic blood pressures with patients in a low sodium tertile having a lower blood pressure (**Figure 3**). Additionally, spironolactone resulted in a lower blood pressure at follow-up. However, as illustrated by the green areas (reflecting the chronic treatment effect) and the p-value for interaction ($p<0.001$), patients with the lowest self-reported sodium intake had a larger sustained drop in systolic blood pressure over time (larger green area). Similarly, the proportion of patients reporting dyspnea or manifesting lower extremity edema at physical examination at follow-up was lower in patients allocated to spironolactone ($p=0.039$, respectively $p<0.001$), with larger treatment effects again observed in patients in the lower reported sodium intake tertiles (p-interaction =0.004 respectively <0.001).

## DISCUSSION

Guidelines on the management of heart failure recommend questioning patients about their sodium intake and providing education regarding liberal sodium/salt intake.[1-4] However, there is a lack of evidence regarding appropriate levels of sodium intake.[22] The recent SODIUM-HF trial which compared low (1.5 g sodium per day) with standard diet in symptomatic HF (NYHA 2 or 3), failed to show a difference in events rates (composite of cardiovascular-related hospitalization, cardiovascular-related emergency department visit, and all-cause death within 12 months), but this trial was underpowered and terminated early due to

interim analysis showing futility and difficulty with running trials during the COVID19 pandemic. [23]This lack of evidence is especially problematic in HFpEF, where virtually no data exist about the detrimental of beneficial effect of high or low sodium intake.[24] Of note, the SODIUM-HF trial predominantly included HFrEF patients.[23] HFpEF is a condition associated with salt and fluid overload (e.g. congestion) as well as drug resistant hypertension, commonly summarized as a salt sensitive state.[24] The PATHWAY II trial illustrated that many patients with drug resistant hypertension exhibit a salt-sensitive phenotype with more pronounced blood pressure reduction when spironolactone is given, especially in patients who have a suppressed plasma renin level, which suggests a state of inappropriate high aldosterone activity.[10]

Our current analysis leverages the systematic baseline questioning of patients enrolled in TOPCAT regarding their sodium intake. Questioning patients about their dietary sodium habits might potentially capture a key element of the pathophysiology of the HFpEF syndrome such as sodium vulnerability. Although sodium intake was not directly measured (eg 24 hours urine collection), it was estimated through a questionnaire with 47% of patients indicating no addition of sodium to their foods whatsoever, 36% indicating light to moderate addition of sodium to their food and 18% of patients admitting to large addition of sodium to their food. While the questionnaire is not reflective of the actual degree (in grams) of sodium addition, it does reflect the patient's actual behavior regarding sodium intake and measuring the actual sodium intake is seldom performed in clinical practice.[25] Interestingly, patients indicating the lowest addition of sodium to their foods exhibited the highest risk for adverse outcome defined as a higher risk for the primary endpoint which was entirely driven by a higher risk to be admitted with heart failure. Importantly, even after adjusting for differences in baseline covariates the increased event rate persisted in patients reported no addition of sodium. Furthermore, categorizing HFpEF patients into similar risk categories (based on 3A3B risk score) illustrated that a low self-reported sodium intake persistently was linked to increased risk

for HF-admission. The data indicate that the acknowledgement of not adding sodium to the food, signals an element about HFpEF-pathophysiology instructive and prognostic. [18] This is in line which a recent analysis from the TOPCAT trial assessing the prognostic role of patients with a low self reported sodium intake, showing that patients with a low sodium intake had worse outcome.[26]

However from the outcome analysis alone (both in our paper and the previous analysis) it is not known if a low sodium intake triggers worsening of heart failure via neuro-hormonal activation or if it is a sign of worse disease with enhanced sodium vulnerability. In that aspect we performed in detail patient phenotyping and leverage the randomized design to determine if the baseline self reported sodium intake interacts with the randomization towards spironolactone and thus interacts with the neuro-hormonal basis of HFpEF. Indeed, some data (mainly documented in HF with reduced ejection fraction) suggests that too stringent sodium restriction might worsen neuro-hormonal (possibly due to volume depletion and/or chloride depletion, which both stimulate the macula densa), we further evaluated patients phenotypes.[27] This because self-reported sodium restriction might also entail learned behavior based on the perceived vulnerability to sodium (indicative of a more volume sensitive disease state). Our data shows that patients indicating a low sodium intake, had more echocardiographic signs of congestion (higher E wave and higher LVEDV) and had a higher estimated plasma volume. Additionally, patients in the low sodium tertile had a higher baseline chloride level. Collectively this argues against the hypothesis of "too stringent sodium restriction induced neurohormonal activation", which could subsequently worsen the disease. This because both volume status and chloride levels were higher in patients reporting a low sodium intake. If low sodium intake itself was the cause of the poor prognosis through neurohormonal activation, patients at baseline might be expected to have chloride and/or volume depletion as these elements stimulate the macula densa for renin release.[28] Our data suggests that acknowledgment of a low self-reported

sodium intake might hint toward a sodium vulnerable state, which would explain the association with the poor clinical outcome.

To further investigate whether such a sodium vulnerable state could potentially be linked to inappropriate aldosterone activity, we assessed electrolyte status. Patients in the lowest sodium tertile had the highest Na/K-ratio. Because aldosterone induces kaliuresis and retains sodium, an elevated plasma volume in the setting of a higher Na/K-ratio suggest an aldosterone effect.[29] However a more firm answer hinting towards a higher aldosterone effect, comes from assessing the treatment response to spironolactone. We document a clear treatment interaction between self-reported sodium intake and the response to spironolactone in terms of the risk of heart failure admission during follow-up, the systolic blood pressure response, patient reported dyspnea and investigator reported lower extremity edema. Patients with a low self-reported sodium intake had greater treatment effect with spironolactone on all these volume-centric endpoints indicative of sodium vulnerability. Interpreting this data in line with the PATHWAY II trial that demonstrated more systolic blood pressure reduction with spironolactone in patients with a potential salt sensitive phenotype, argues that patients who add less sodium to their diet, might suffer from a sodium vulnerable (high level aldosterone state) that incur a larger benefit from aldosterone blockade. Ongoing research is necessary to determine how to best identify such a phenotype. For instance we have previously found that patients with higher aldosterone levels have chronically lower urinary sodium concentrations, which also might hint towards this state of sodium vulnerability.[6;7] Interestingly, simply questioning patients about their ability to tolerate ingestion of sodium might also give insight in to the existence of a sodium vulnerable state.

**Limitations**

Several limitations should be taken into account to appreciate our findings. We do not have a direct measure of plasma renin levels to see if they are suppressed, but interpretation of such data would also be difficult given the high use of ACE-I/ARBs and the difficult pre-analytic requirements with regards to upright resting conditions. Second, interaction analysis for outcome analysis (heart failure admission) with a post-hoc defined covariate (self-sodium intake) should be interpreted carefully, however clear treatment interactions that have a biologic basis, show consistent effects with other metrics (eg blood pressure reduction, edema and dyspnea at follow-up) and show a dose response effect are more credible. Finally, sodium excretion was not measured but the intake was estimated, however questioning patients about sodium intake is a bedrock foundation of every heart failure encounter and sodium intake is seldom quantified in clinical practice.

## CONCLUSION

Patients with HFpEF reporting a lower sodium intake exhibit a higher risk for heart failure admission and presenting with a patient profiling indicative of a more sodium vulnerable state and reflective of the heightened treatment response to spironolactone with greater reduction in heart failure admissions.

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## DISCLOSURE

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**Table 1:** Baseline features of study cohort according to self-reported sodium intake

| Parameters | Low sodium addition tertile (n= 828) | Mid sodium addition tertile (n= 602) | High sodium addition tertile (n= 316) | p-value |
|---|---|---|---|---|
| **Demographics and co-morbidities** | | | | |
| Age, years | 71±10 | 72±9 | 72±10 | 0.372 |
| Male gender, % | 467 (56%) | 284 (47%) | 126 (40%) | <0.001 |
| Caucasian descent, % | 666 (80%) | 462 (77%) | 241 (76%) | 0.146 |
| Hypertension, % | 742 (90%) | 541 (90%) | 287 (91%) | 0.830 |
| Atrial fibrillation, % | 377 (46%) | 236 (39%) | 125 (40%) | 0.032 |
| Diabetes, % | 393 (48%) | 269 (45%) | 117 (37%) | 0.006 |
| Dyslipidemia, % | 597 (72%) | 424 (70%) | 218 (69%) | 0.548 |
| **Physical features** | | | | |
| Height, cm | 169±11 | 165±11 | 164±11 | <0.001 |
| BMI, kg/m² | 34±8 | 33±8 | 34±8 | 0.119 |
| Systolic BP, mmHg | 127±16 | 127±16 | 130±17 | 0.014 |
| **Heart failure features** | | | | |
| LVEF, % | 58±7 | 58±8 | 60±7 | <0.001 |
| NYHA-class<br>NYHA I-II<br>NYHA III-IV | <br>552 (63%)<br>304 (37%) | <br>392 (65%)<br>210 (35%) | <br>219 (70%)<br>96 (31%) | 0.134 |
| Baseline edema, % | 608 (74%) | 428 (71%) | 212 (67%) | 0.094 |
| **Laboratory features** | | | | |
| BNP, pg/ml | 259 (151-444) | 258 (150-478) | 244 (145-407) | 0.767 |
| NTproBNP, pg/ml | 1114 (606-1813) | 915 (606-1812) | 784 (490-1629) | 0.079 |
| eGFR, ml/min/1.73m$^2$ | 63±21 | 66±21 | 64±21 | 0.003 |
| Serum Sodium, mmol/L | 140±3 | 140±3 | 140±8 | 0.275 |
| **Baseline medication use** | | | | |
| ACEi/ARB | 652 (79%) | 477 (79%) | 248 (79%) | 0.971 |
| Beta-blocker | 681 (82%) | 472 (78%) | 220 (70%) | <0.001 |
| Loop diuretic | 762 (92%) | 529 (88%) | 265 (84%) | <0.001 |
| Calcium antagonist | 324 (39%) | 233 (39%) | 117 (37%) | 0.826 |
| Statin | 548 (66%) | 405 (67%) | 182 (58%) | 0.011 |
| Aspirin | 493 (60%) | 347 (58%) | 178 (57%) | 0.592 |

**Abbreviations:** BMI= body mass index, BP= blood pressure, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association class, BNP= brain natriuretic peptide, eGFR= estimated glomerular filtration rate, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker.

**Table 2:** Multivariable adjusted Cox proportional hazard model for sodium addition categories

| Endpoint | Sodium addition category reference | HR, per increment increase | 95% CI | P-value |
|---|---|---|---|---|
| Primary endpoint | low | 0.88 | 0.78-0.99 | 0.041 |
| Heart failure hospitalizations | low | 0.83 | 0.72-0.95 | 0.009 |

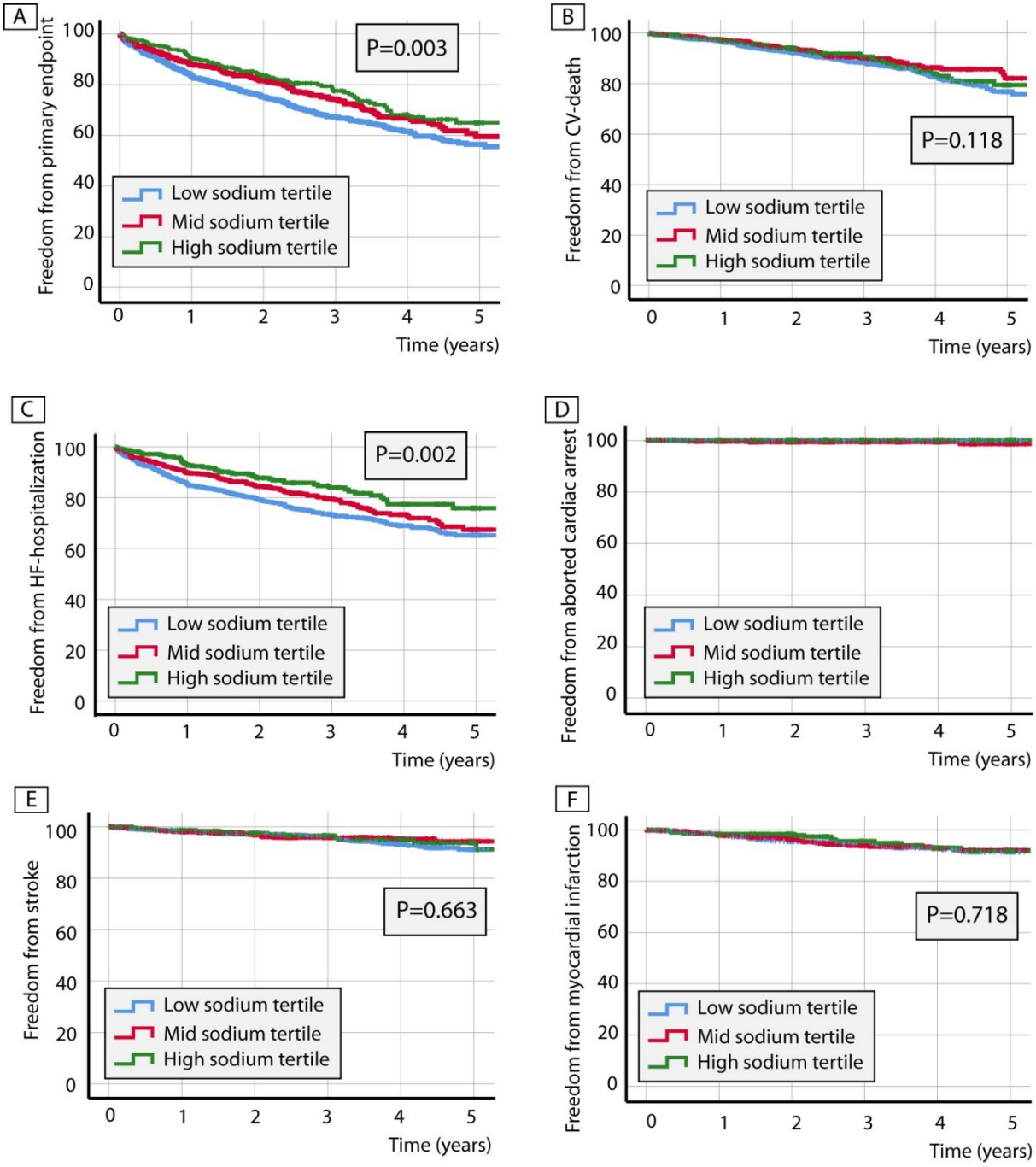
**Explanation:** all models were adjusted for the same covariates which significant differences in baseline table 1 including: Male gender, atrial fibrillation, diabetes mellitus, height, systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate, beta-blocker use, loop diuretic use, and statin use. Additionally models were corrected for the proportion of meals self-prepared. **Abbreviations:** HR= hazard ratio, CI= confidence interval.

**Table 3:** Treatment effect of spironolactone overall and according to the sodium tertiles

| Endpoint | Category | Event rate | HR | 95% CI | p-value | P-interaction |
|---|---|---|---|---|---|---|
| **Primary endpoint** | *Overall* | 516/1744 | 0.82 | 0.69-0.97 | 0.024 | 0.162 |
| | *Low sodium tertile* | 279/827 | 0.78 | 0.62-0.99 | 0.039 | |
| | *Mid sodium tertile* | 160/602 | 0.77 | 0.56-1.05 | 0.099 | |
| | *High sodium tertile* | 77/315 | 1.12 | 0.71-1.74 | 0.630 | |
| **Heart failure hospitalization** | *Overall* | 394/1744 | 0.81 | 0.67-0.99 | 0.040 | 0.030 |
| | *Low sodium tertile* | 216/827 | 0.69 | 0.53-0.91 | 0.009 | |
| | *Mid sodium tertile* | 126/602 | 0.85 | 0.60-1.20 | 0.364 | |
| | *High sodium tertile* | 52/315 | 1.37 | 0.79-2.38 | 0.270 | |

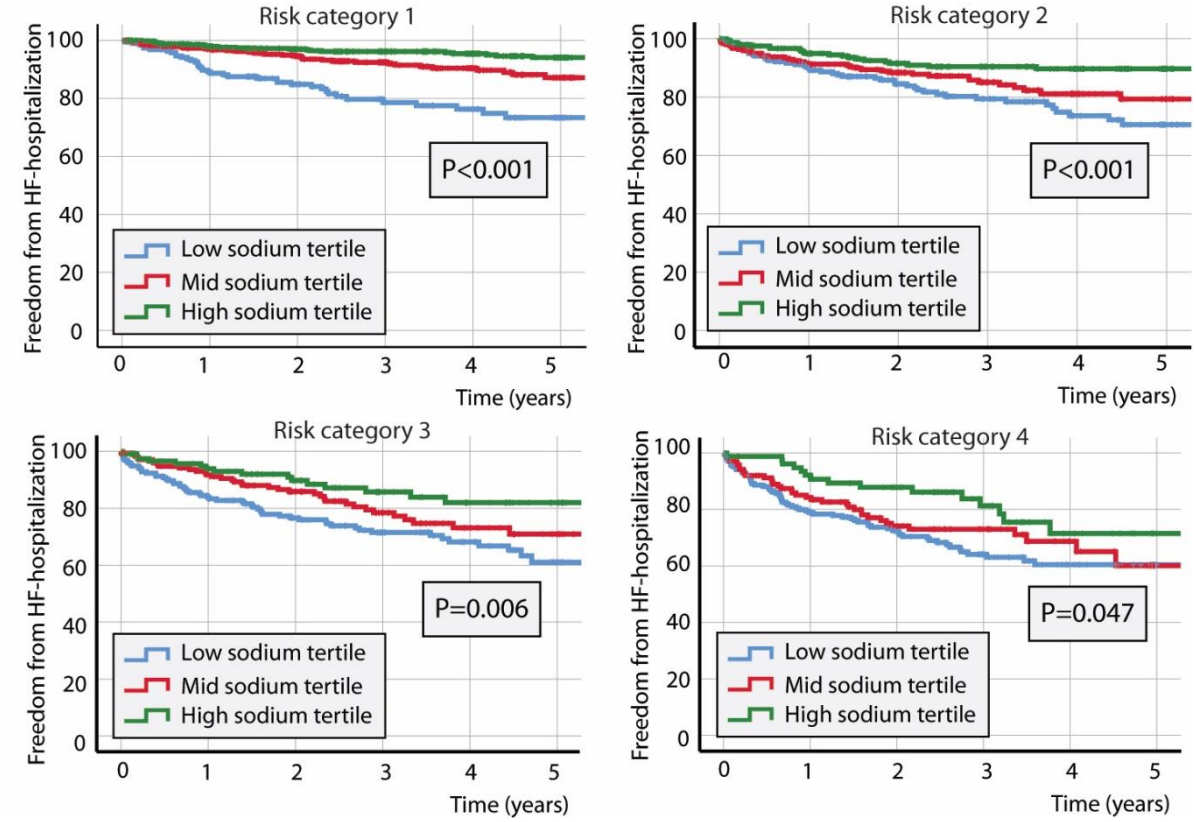
**Abbreviations:** HR= hazard ratio, CI= confidence interval.

**Figure 1:** Kaplan-Meier curves for different endpoints according to sodium addition tertiles



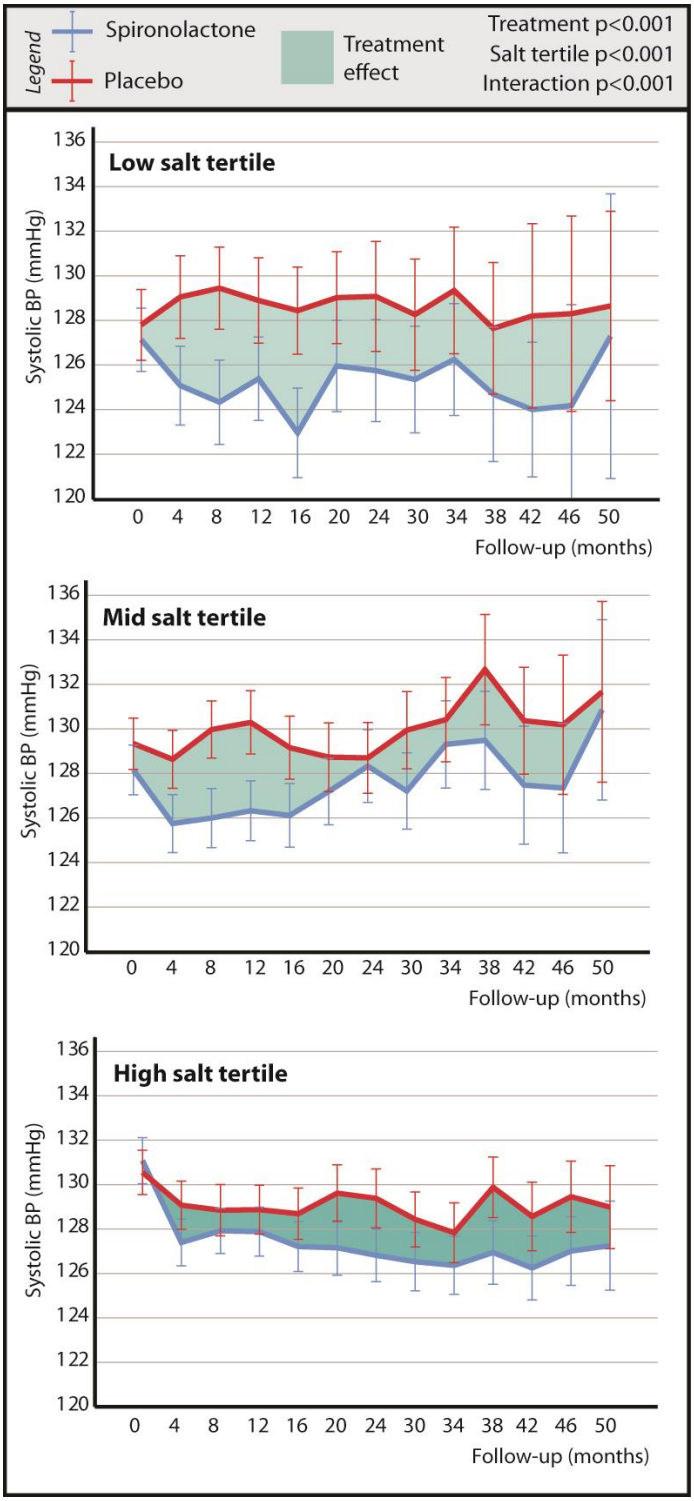

**Abbreviations:** CV= cardiovascular, HF= heart failure. Panel A illustrates the primary endpoint, panel C to D illustrates the individual components of the primary endpoint. Panel E and F illustrates respectively the adjudicated endpoint of stroke and myocardial infarction. For panel D no p-value was calculated as the high self-reported sodium intake subgroups contained 0 events.

**Figure 2:** Kaplan-Meier curves for HF-hospitalization stratified baseline risk




**Abbreviations:** HF= heart failure. **Explanation:** Risk categories were based on the A3B3-score validated in the TOPCAT trial. Risk is based on: age > 75 years (2 points), albumin <3.7 g/dl (1 points), anemia (1 points), BMI <22 kg/m$^2$ (1 points), BNP ≥300 pg/ml (or NT-proBNP≥1400 pg/ml) (1 points), and BUN ≥25 mg/dl (1 points). Generating a risk score ranging from 0 to 7. Because the low number of patients with a risk score of ≥4 these patients were clustered in risk category 4. Risk category 1 reflects a score of 0 or 1 and risk category 2, a score of 2 and category 3 a score of 3.

**Figure 3:** Blood pressure response to spironolactone according to self-reported sodium intake




***Abbreviations:*** *BP= blood pressure.* ***Explanation:*** *results of a linear mixed models for change in blood pressure from baseline (0 months). P-values indicate that patients in the different sodium reported tertiles have different Systolic BP, spironolactone results in a drop in systolic BP and the interaction term indicates a more pronounced drop in systolic BP with spironolactone in patients with a low self-reported sodium intake*

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