Frequency and Impact of Hyponatremia on All-Cause Mortality in Patients With Aortic Stenosis

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Asymptomatic aortic stenosis (AS) is a frequent condition that may cause hyponatremia due to neurohumoral activation. We examined if hyponatremia heralds poor prognosis in patients with asymptomatic AS, and whether AS in itself is associated with increased risk of hyponatremia. The study question was investigated in 1,677 individuals that had and annual plasma sodium measurements in the SEAS (Simvastatin and Ezetimibe in AS) trial; 1,873 asymptomatic patients with mild-moderate AS (maximal transaortic velocity 2.5 to 4.0 m/s) randomized to simvastatin/ezetimibe combination versus placebo. All-cause mortality was the primary endpoint and incident hyponatremia (P-Na^+ <137 mmol/L) a secondary outcome. At baseline, 4% (n = 67) had hyponatremia. After a median follow-up of 4.3 (interquartile range 4.1 to 4.6) years, 140 (9%) of those with initial normonatremia had developed hyponatremia, and 174 (10%) had died. In multiple regression Cox models, both baseline hyponatremia (hazard ratio [HR] 2.1, [95% confidence interval 1.1 to 3.8]) and incident hyponatremia (HR 1.9, [95% confidence interval 1.0 to 3.4], both p ≤ .03) was associated with higher all-cause mortality as compared with normonatremia. This association persisted after adjustment for diuretics as a time-varying covariate. Higher N-terminal pro b-type natriuretic peptide levels and lower sodium levels at baseline was associated with higher risk of incident hyponatremia. Conversely, assignment to simvastatin/ezetimibe protected against incident hyponatremia. In conclusion, both prevalent and incident hyponatremia associate with increased mortality in patients with AS. The prevalence of hyponatremia is around 4% and the incidence about 2% per year, which is comparable to that of older adults without AS. **(Am J Cardiol 2021;141:93−97)**

Hyponatremia is reported in 2% to 7% of healthy older adults but can exceed 40% among those hospitalized.[1,2] Several studies on newly hospitalized patients have shown a strong association between hyponatremia and increased morbidity and mortality.[3] However, it is unclear if this is due to reverse causation since medical conditions and need for drugs that cause hyponatremia is associated with a poor prognosis in itself. Aortic stenosis (AS) is the most common valvular disease in the western world, and older age is the primary risk factor on a population level.[4] Importantly, advancing AS may lead to neurohumoral activation through increased preload, afterload, and reduced renal perfusion. Hence, hyponatremia may evolve due to activation of natriuretic peptides, the renin-angiotensin system, antidiuretic hormone, and changes in catecholamine levels.[5] Yet, it has not been studied whether this potential interplay between AS progression and hyponatremia alter patient prognosis. The primary aim of this study was, therefore, to investigate the impact of hyponatremia on all-cause mortality in patients with asymptomatic AS. A secondary aim was to identify the incidence and risk factors for hyponatremia during follow-up in such patients.

Methods

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial was a multicenter, randomized, double-blind, placebo-controlled study, which investigated if intensive lipid lowering with 40 mg Simvastatin and 10 mg Ezetimibe versus placebo reduce cardiovascular morbidity and mortality in adults with asymptomatic mild-to-moderate AS. The main inclusion criteria were an echocardiographic aortic valve thickening accompanied by a Doppler-measured aortic peak flow velocity ≥2.5 and <4 m/s, normal LV systolic function and no perceived need for lipid-lowering therapy. The findings and study protocol of the main SEAS trial have been published previously

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(http://ClinicalTrials.gov, identifier NCT00092677). In this substudy, we included 1,677 (90%) of the 1,873 SEAS participants who had sodium ascertained at baseline. All patients gave written informed consent, and ethics committees in all participating countries had approved the SEAS study protocol.

Plasma sodium concentration was measured using a potentiometric (Cobas, Roche diagnostics) assay with a reported measuring range of 80-180 mmol/L. Hyponatremia was defined as plasma sodium <137 mmol/L, normonatremia as 137 to 145 mmol/L, and hypernatremia as >145 mmol/L.[6]

Transthoracic echocardiograms were read at the SEAS echocardiography core laboratory at Haukeland University Hospital in Bergen, Norway, blinded to randomization, sodium levels, and time since enrollment, using the American Society of Echocardiography guidelines.

The primary endpoint in this study was all-cause mortality. The secondary endpoint was incident hyponatremia, which was defined as the first blood draw with plasma sodium <137 mmol/L on scheduled in-study visits (baseline, year 1, year 2, year 3, and year 4 of follow-up).

Statistical analysis was performed using the statistical software SAS 9.4 (Cary, NC). Data are given as mean with standard deviations, median with interquartile range, or frequencies. One-way ANOVA, Wilcoxon, and $\chi 2$ were used as appropriate. We checked assumptions and then used Cox regression to calculate hazard ratios for all-cause mortality and incident hyponatremia. Multivariable Cox models for all-cause mortality according to baseline plasma sodium at baseline were adjusted for all of the covariates that varied between categories of plasma sodium (age, sex, hypertension, creatinine, potassium, glucose, high-density lipoprotein, and log-transformed N-terminal pro b-type natriuretic peptide [NT-proBNP]). To identify risk factors for incident hyponatremia, we used an iterative penalized maximum likelihood function (all subsets selection) to identify the combination of covariables that resulted in the optimal model fit. The probability of incident hyponatremia was

Table 1
Baseline characteristics in relation to plasma sodium

Characteristic	Hyponatremia (n = 67*)	Normonatremia (n = 1496*)	Hypernatremia (n = 114*)	p
P-Sodium (mmol/L)	134.0±2.4	142.0±2.0	149.9±1.5	NA
Clinical parameters				
Age (years)	70.2±8.2	67.3±9.8	68.6±8.2	.03
Women	49%	38%	40%	.15
Body Mass Index (kg/m^2)	26.5±4.4	27.0±4.4	27.1±4.7	.65
Heart rate (bpm)	66.5±11.3	64.9±11.3	65.4±10.4	.68
Atrial Fibrillation	6%	9%	11%	.48
Hypertension	69%	51%	54%	.02
Systolic Blood Pressure (mm Hg)	147.4±22.3	144.8±20.1	142.6±18.9	.29
Diastolic Blood Pressure (mm Hg)	80.8±10.9	81.9±10.4	82.1±9.6	.68
Echocardiography				
LV mass index (g/m^2)	100.0±35.3	101.3±31.6	99.0±26.3	.74
LV Ejection fraction (%)	65±8	66±8	66±8	.59
LADV (mm^3)	37 (25-52)	32 (22-46)	31 (19-45)	.42
IVSDD (cm)	1.1±0.3	1.1±0.3	1.1±0.3	.87
Mean gradient (mmHg)	21.3±7.6	22.9±8.9	22.0±8.4	.23
Peak velocity (m/sec)	3.0±0.5	3.1±0.5	3.1±0.5	.31
Biochemistry				
Creatinine (μmol/L)	89.5±15.3	93.4±15.5	97.9±17.8	<.01
eGFR (ml/min/1.73m^2)	69.1±12.2	68.6±12.3	64.4±11.4	<.01
Potassium (mmol/L)	4.5±0.5	4.3±0.4	4.5±0.4	<.01
Hematocrit	41±4%	41±4%	41±4%	.68
Glucose (mmol/L)	4.9±0.8	5.3±0.8	5.2±0.7	<.01
TSH (mIU/L)	1.6 (0.9-2.6)	1.6(1.1-2.4)	1.6(0.8-2.3)	.19
HDL (mg/dl)	30.6±7.2	27±7.2	27±7.2	<.01
HDL (mmol/L)	1.7±0.4	1.5±0.4	1.5±0.4	<.01
LDL (mg/dl)	61.3±16.2	63.1±16.2	64.9±16.2	.38
LDL (mmol/L)	3.4±0.8	3.5±0.9	3.6±0.9	.38
Triglyceride (mg/dl)	23.4±12.6	25.2±12.6	25.2±10.8	.39
Triglyceride (mmol/L)	1.3±0.7	1.4±0.7	1.4±0.6	.39
NT-proBNP (pg/mL)	253 (151-720)	161 (85-344)	167 (91-346)	<.01
Medicine				
Diuretic	39%	23%	29%	<.01
RAS inhibitor	46%	25%	26%	<.01
Ca^{2+}-blocker	19%	18%	11%	.22
Beta-blocker	40%	27%	37%	<.01
Simvastatin/Ezetimibe	48%	50%	52%	.86

Abbreviations: HDL = high-density lipoprotein; IVSDD = intraventricular septal diastolic diameter; LADV = left atrial diastolic volume; LDL = low-density lipoprotein; NA = not applicable; NT-proBNP = N-terminal pro-brain natriuretic peptide; RAS = renin-angiotensin system; TSH = thyroid-stimulating hormone.

* Hyponatremia = P-Na^+ <137 mmol/L, normonatremia = P-Na^+ 137-145 mmol/L, hypernatremia = P-Na^+ >145 mmol/L.

estimated by competing risk regression, using all-cause mortality as a competing event. Three exploratory analyses were performed to discern: (1) if the observed effect estimates on incident hyponatremia were explained by new or add-on diuretic treatment; (2) if the associations with incident hyponatremia were sensitive to whether or not the patient had undergone aortic valve replacement (AVR); and (3) if incident hyponatremia heralds increased risk of all-cause mortality. We accounted for immortal time-bias when using updated data.[7] In a sensitivity analysis, we examined intervals of ±1 standard deviation (SD) and ±2 SD. A 2-tailed p value <0.05 was considered significant.

Results

One thousand six hundred (90%) patients from the SEAS-trial had ascertained plasma sodium at baseline. The range of sodium was 122 to 154 mmol/L (mean 141 ± 2.8 mol/L). The frequency of sodium abnormalities and associated changes in baseline characteristics are given in Table 1. Of note, only 2 patients had severe hyponatremia (sodium <125 mmol/L), and just 5 of those with hypernatremia had sodium ≥150 mmol/L.

After a median follow-up 4.3 (IQR 4.1 to 4.6) years, a total of 174 (10%) had died (13 patients [19%] with hyponatremia, 147 [10%] with normonatremia, and 14 [12%] with hypernatremia, respectively). Low plasma sodium at baseline was associated with a higher risk of all-cause mortality with no apparent risk threshold (Figure 1). In multivariable Cox models, those with hyponatremia at baseline had 2.1-fold (95% confidence interval [CI]: 1.1 to 3.8) higher risk of all-cause mortality (Table 2). In a sensitivity analysis, we investigated the impact of alternative thresholds for hyponatremia based on mean-2 SD in the current

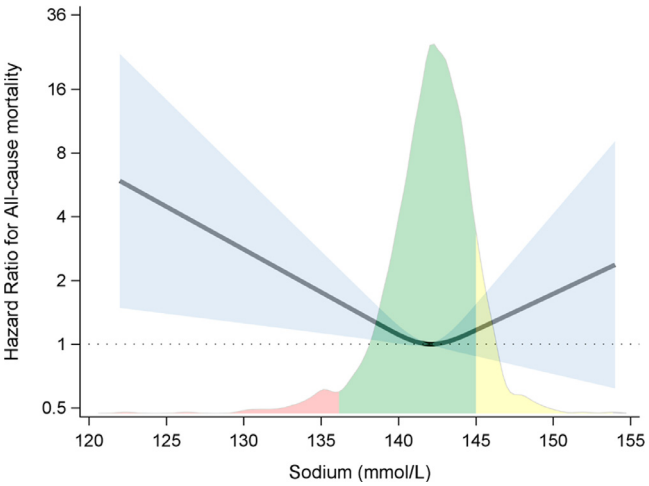

Figure 1. Hazard ratios for all-cause mortality as a function of baseline plasma sodium. The density function in the background reflects the distribution of plasma sodium at baseline. Red corresponds to hyponatremia (Na^+ <137 mmol/L), green to normonatremia (Na^+ 137 to 145 mmol/L) and yellow to hypernatremia (Na^+ >145 mmol/L). The solid dark line reflects hazards ratios for all-cause when entering plasma sodium as a natural cubic spline. Shaded blue areas correspond to 95% confidence intervals for the regression line.

population. Using this definition, a total of 51 patients had a P-Na^+≤ 135 mmol/L, and the Supplemental Table 1 gives an adjusted HR of 2.7 (p < 0.001) for this category on all-cause mortality. In an exploratory analysis, those who were normonatremic at baseline but developed incident hyponatremia had a subsequent higher risk of all-cause mortality (HR 1.9 [95% CI: 1.0 to 3.4], Table 2).

Among the 1,496 patients who were normonatremic at baseline, 140 (9%) developed hyponatremia during follow-

Table 2
Multivariable cox-proportional hazard models for all-cause mortality (top) and incident hyponatremia (bottom)

	Univariate HRs	Multivariate HRs
All-cause mortality (events n = 174)		
Hyponatremia at baseline	2.2 (1.2-3.8, p<.01)	2.1 (1.1-3.8, p=.02)*
Normonatremia at baseline	Ref.	Ref.
Hypernatremia at baseline	1.3 (0.7-2.2, p=.41)	1.3 (0.8-2.3, p=.33)*
Incident hyponatremia‡	2.0 (1.1-3.76, p=.02)	1.9 (1.0-3.4, p=.03)†
Incident hyponatremia (events n=140)		
Pulse (per 10 bpm)	1.2 (1.0-1.4, p=.02)	1.2 (1.0-1.4, p=.02)§
Hypertension (Yes)	1.5 (1.0-2.0, p=.03)	1.3 (0.9-1.9, p=.13)§
LVEF (per 10% higher)	1.2 (0.9-1.4, p=.18)	1.2 (1.0-1.5, p=.05)§
Mean Transaortic gradient (per 10 mm Hg)	1.0 (0.8-1.2, p=.73)	0.9 (0.7-1.1, p=.40)§
Creatinine (per 1 mmol/L)	0.9 (0.8-1.0, p=.02)	0.9 (0.8-1.0, p=.04)§
Glucose (per 1 mmol/L)	1.0 (0.8-1.2, p=.93)	0.9 (0.7-1.1, p=.91)§
ln(NT-proBNP)	1.2 (1.0-1.4, p=.02)	1.3 (1.1-1.5, p=.01)§
Simvastatin/Ezetimibe vs. placebo	0.6 (0.4-0.9, p<.01)	0.6 (0.4-0.8, p<.01)§
P-sodium (per 1 mmol/L higher at baseline)	0.8 (0.7-0.8, p<.01)	0.8 (0.7-0.9, p<.01)§

Abbreviation: ln(NT-proBNP) = natural logarithm of n-terminal pro brain natriuretic peptide, LVEF: left ventricular ejection fraction.

* Multivariate hazard ratios for all-cause mortality in relation to all-cause mortality reflect adjustment by all baseline characteristics (age, sex, hypertension, creatinine, potassium, glucose, high-density lipoprotein, and log-transformed NT-proBNP), which differed between plasma sodium categories (Table 1).

† To avoid overfitting due to low absolute event rates after incident hyponatremia, multivariate hazard ratios for incident hyponatremia (time-varying), and subsequent all-cause mortality reflects adjustment by age (years), sex and stratification by randomized treatment.

‡ Of the 1,449 normonatremic patients, 134 patients developed incident hyponatremia among which 13 (10%) eventually died.

§ Multivariable hazard ratios reflect an adjustment for all variables listed as predictors of incident hyponatremia. These were identified using an iterative procedure that identified the combination of covariates that resulted in the optimal prediction of incident hyponatremia (Bayes information criteria) using an all subsets selection.

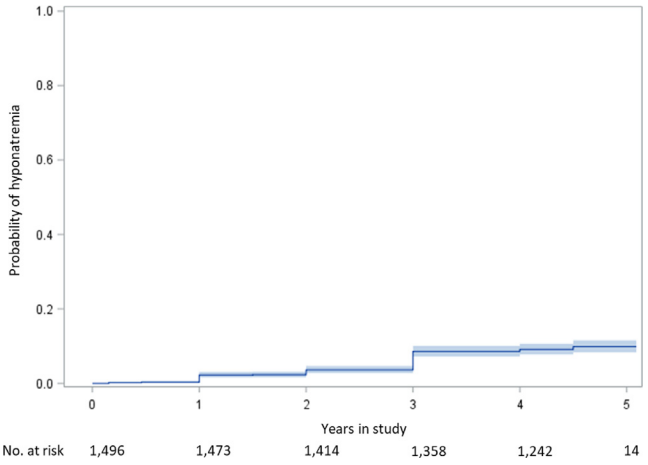

Figure 2. Cumulative incidence of hyponatremia.

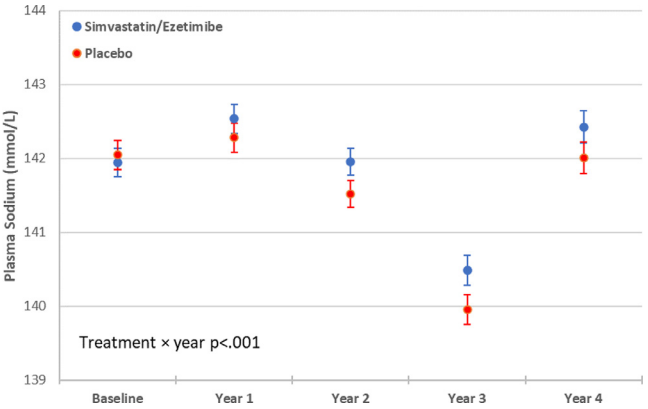

Figure 4. Absolute levels of plasma sodium according to randomized treatment. Filled circles indicate mean with error bars reflecting standard errors of the mean. Blue equals Simvastatin/Ezetimibe combination and red assignment to placebo.

up (Table 2), which translated into an annual rate of about 2% per year (Figure 2). Using model selection by penalized likelihood estimates, we identified lower plasma sodium at baseline (HR 0.8 [95% CI: 0.7 to 0.9] per 1 mmol/L lower P-Na^+) and higher NT-proBNP (HR 1.3 [95% CI: 1.1 to 1.5], per 1 unit increase on natural log-scale) as independently associated with incident hyponatremia. Forcing age and sex into the model did not materially alter these results (Supplemental Table 2). Importantly, randomized treatment with Simvastatin-Ezetimibe protected against incident hyponatremia (HR 0.6 [95% CI: 0.4 to 0.8], Figure 3). The protective effect of Simvastatin-Ezetimibe on incident hyponatremia increased over time and peaked at year 3 (Figure 4), which did not coincide with the immediate reduction in low-density lipoprotein levels in the active-arm. Also, the protective effect was not sensitive to the threshold of hyponatremia as analysis on changes in absolute levels confirmed the findings from the Cox model (Figure 4). Similarly, the observed differences in absolute sodium levels between the study-arms were not explained by concurrent changes in kidney function or blood pressure (Supplemental Figure 1). In exploratory analyses, there were no detectable differences in the patient's plasma sodium on the last blood draw before AVR as compared with the first blood draw after AVR (Supplemental Figure 2). Also, the observed multivariable associations with incident hyponatremia did not appear sensitive to whether patients received new or add-on diuretic treatment during the study (Supplemental Table 3 and Supplemental Table 4).

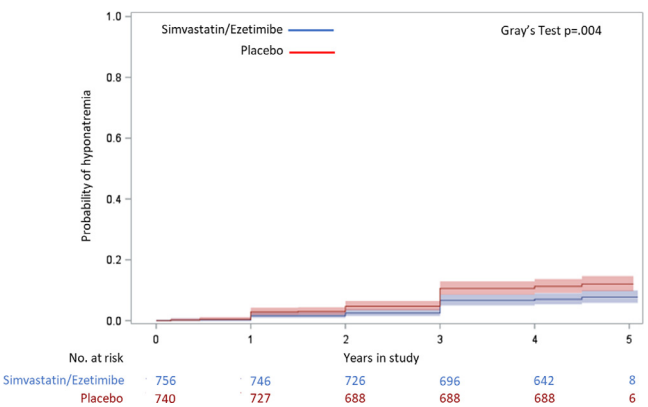

Figure 3. Cumulative incidence of hyponatremia according to randomized treatment.

Discussion

To our knowledge, this is the first report on sodium levels and their prognostic impact in patients with asymptomatic, mild to moderate AS. There are 3 novel findings. First, hyponatremia occurs in ≈2% per year. Second, both prevalent and incident hyponatremia portend increased all-cause mortality. Third, low-normal baseline plasma sodium, higher baseline NT-proBNP, and placebo allocation were independently associated with incident hyponatremia. Importantly, the latter was not attenuated by adjusting for new or add-on diuretic treatment.

The 4% prevalence of hyponatremia at baseline in the current study, matches the 2% to 7% reported in previous studies on healthy older people without AS.[1,2] This argues that non-severe AS does not lead to enough hemodynamic stress to induce hyponatremia.[8] Prior studies have reported that hyponatremia presage all-cause mortality in various clinical populations.[9–12] Here we extend that knowledge into patients with asymptomatic AS. Hyponatremia defined as values below 138 mmol/L has previously been suggested.[13] Our data do not support that there is a particular threshold that defines when low plasma sodium is hazardous.

Baseline hyponatremia was associated with diuretic and renin-angiotensin system inhibitor treatment, but it is not possible to infer what the primary mechanism of incident hyponatremia is. We speculate that a potential factor is subclinical cardiac strain because NT-proBNP was a multivariate predictor of incident hyponatremia. Increased natriuresis through the effects of natriuretic hormones may contribute to hyponatremia in this context,[14] and thus be a mechanistic link to increased mortality. Adjustment for in-study diuretic treatment did not attenuate the effect of NT-proBNP. Hyponatremia may also be associated with heart failure drugs acting on BNP degradation.[15]

How hyponatremia increases mortality risk across various clinical populations is disputed. As such, it is debated whether mild to moderate hyponatremia adversely affects a patient's clinical state per se or whether it is a confounder, which "merely" reflects the patient's clinical or subclinical disease burden.[16] This study supports the latter hypothesis.

A serendipitous finding of the present study was that Simvastatin/Ezetimibe protected against incident hyponatremia. Extreme hyperproteinemia may lead to pseudohyponatremia using an indirect assay. Hence, LDL-lowering could have the influenced sodium assay in the active-arm. Yet, none of the absolute differences in ether albumin, LDL, or triglycerides between the two study arms was of a magnitude to explain the differences in plasma sodium.[17,18]

There are limitations to this study. To rule out an LDL lowering effect on plasma sodium concentration, a direct measurement of plasma sodium would have been required.[19] Finally, our study sample had a low prevalence of severe dysnatremic patients and may not be reproducible in a more diseased study population.

In conclusion, hyponatremia occurred at a rate comparable to that of otherwise healthy older adults without AS; both prevalent and incident hyponatremia are associated with an increased risk of all-cause mortality; incident hyponatremia is more likely to evolve in patients with low-normal plasma sodium or cardiac strain as indicated by elevated NT-proBNP levels. Simvastatin/Ezetimibe was protective against incident hyponatremia. Future studies should therefore investigate whether Simvastatin/Ezetimibe attenuates subclinical cardiac strain to mitigate risk of hyponatremia.

Author Declarations

Dr. Nielsen had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ramberg, Haugaard, Nielsen. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Ramberg, Berg, Greve. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Greve. Administrative, technical, or material support: Wachtell, Nielsen. Study supervision: Greve, Nielsen.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.015.

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