Circulating secretoneurin concentrations in patients with moderate to severe aortic stenosis

Jon Brynildsen MD[a]; Peder L. Myhre MD, PHD[a]; Magnus N. Lyngbakken MD, PhD[a]; Lars Gunnar Klaeboe MD[b], Mats Stridsberg MD, PhD[c]; Geir Christensen MD, PhD, MHA[d]; Thor Edvardsen MD, PhD[b]; Torbjørn Omland MD, PhD, MPH[a]; Helge Røsjø MD, PhD[e].

[a] Department of Cardiology, Division of Medicine, Akershus University Hospital, Lørenskog, Norway and Center for Heart Failure Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[b] Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway and Center for Heart Failure Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

[c] Department of Medical Sciences, Uppsala University, Uppsala, Sweden

[d] Institute for Experimental Medical Research, Oslo University Hospital, Ullevål and Center for Heart Failure Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[e] Division of Research and Innovation, Akershus University Hospital, Lørenskog, Norway and Center for Heart Failure Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Corresponding author and requests for reprints should be addressed to:

Helge Røsjø, MD, PhD, Division of Research and Innovation, Akershus University Hospital, Sykehusveien 25, 1478 Lørenskog, Norway

Phone: +47 67 96 00 00 Fax: +47 67 96 21 90. E-mail: helge.rosjo@medisin.uio.no

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ABSTRACT

Background: Secretoneurin (SN) concentrations provide important prognostic information in patients with myocardial dysfunction. Whether preoperative SN concentrations improve risk assessment in patients with moderate to severe aortic stenosis (AS) is unknown.

Methods: We included 57 patients with moderate to severe AS referred for presurgical evaluation. All patients were examined with comprehensive echocardiography, electrocardiogram (ECG), and biochemical measurements and compared to 10 age- and sex-matched healthy subjects.

Results: Median (quartile 1-3) SN concentrations were 141 (121-163) pmol/L in AS patients and 132 (106-148) pmol/L in control subjects (p=0.17). Lower estimated creatinine clearance and use of diuretics, but not standard ECG or echocardiographic indices and cardiac biomarkers, were associated with increasing SN concentrations. Fifteen patients (26%) died during 3.5 years median follow-up. SN concentrations were higher in non-survivors than survivors: 156 (133-209) vs. 140 (116-155) pmol/L, p=0.007. Higher SN concentrations were associated with increased risk of mortality also after adjustment for established risk indices, biomarkers, and status regarding valvular surgery: hazard ratio per $_{ln}$SN 15.13 (95% CI 1.05-219.00); p=0.046. Receiver operating characteristics area under the curve for SN to predict mortality was 0.74 (95% CI 0.60-0.88) compared to 0.73 (0.59-0.87) for high-sensitivity cardiac troponin T and 0.67 (0.51-0.82) for N-terminal pro-B-type natriuretic peptide. The previously identified cut-off of SN >204 pmol/L in cardiac surgical patients predicted mortality also in this cohort.

Conclusions: SN concentrations improve risk assessment in patients with moderate to severe AS by providing additional prognostic information to established risk indices such as echocardiography, ECG, and established cardiac biomarkers.

Key words: aortic stenosis, biomarkers, secretoneurin, cardiac surgery, echocardiography

Abbreviations: AS, aortic stenosis; AUC, area under the curve; CgA, chromogranin A; CgB, chromogranin B; CI, confidence interval; cTnT, cardiac troponin T; CV, coefficient of variation; ECG, electrocardiogram; hs-cTnT, high-sensitivity cardiac troponin T; ln, natural logarithm; LoD, limit of detection; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile; RIA, radioimmunoassay; ROC, receiver operating characteristics; SgII, secretogranin II; SN, secretoneurin; TAVI, transcatheter aortic valve implantation.

1. INTRODUCTION

Aortic stenosis (AS) is an important cause of cardiovascular mortality with increasing age [1, 2], and there is no curative therapy besides aortic valve replacement [3]. Clinical examination and echocardiography are important tools to diagnose AS, to follow disease progression, and to select patients that may benefit from intervention [3]. Electrocardiogram (ECG) and circulating biomarkers have also been proposed for risk assessment, especially in patients with low physical activity [4-7]. Still, prognostication in elderly patients with moderate to severe AS is imperfect and new risk markers could therefore prove clinically valuable [8].

Secretoneurin (SN) is a 33-amino acid peptide that is cleaved from the pro-hormone secretogranin II (SgII) [9]. SN concentrations increase in cardiac cells during myocardial dysfunction and exert beneficial effects on the myocardium by protecting against myocardial ischemia/reperfusion injury, cardiomyocyte apoptosis, and myocardial remodeling [10-12]. Recent data have also suggested that SN may influence cardiomyocyte Ca^{2+}-handling and stabilize cardiomyocyte Ca^{2+}-homeostasis, which should be of value to protect against life-threatening arrhythmias [13, 14]. We have also found increased circulating SN concentrations in subjects with different types of dysfunctional cardiomyocyte Ca^{2+} handling [15]. The association between SN concentrations and cardiomyocyte Ca^{2+} handling can possibly explain the strong prognostic information from SN measurements in patients with myocardial dysfunction. We and other groups have demonstrated that SN concentrations provide incremental prognostic information to established risk indices in patients with cardiovascular disease [13, 16, 17], in patients undergoing cardiac surgery [18], and in critically ill patients with infections [19, 20]. However, there is no information in the literature whether SN concentrations may improve risk prediction in patients with moderate to severe AS. Accordingly, in this study we hypothesized (i) that SN concentrations are not closely

correlated with established clinical, echocardiographic, ECG, and laboratory variables and (ii) that SN concentrations provide additional prognostic information to established risk indices in patients with moderate to severe AS.

2. MATERIAL AND METHODS

2.1. Patient cohort and control subjects

The study was conducted at Oslo University Hospital, Rikshospitalet, Oslo, Norway, which is a tertiary surgical center, from May 2005 to April 2009. A total of 57 consecutive patients with a previously confirmed diagnosis of moderate to severe AS were included at a presurgical evaluation visit prior to final surgical decision, and followed regardless of surgery or not. Transcatheter aortic valve implantation (TAVI) was not available as a routine procedure in this center during the time of patient inclusion. Patients with aortic regurgitation equal to or over grade 3 were not included. Ten age- and sex-matched controls from outside of the hospital with no previous history or current symptoms of cardiovascular disease were also recruited. Medical records were used to collect information regarding current symptoms, medication, and medical history. New York Heart Association (NYHA) functional class was determined by two independent physicians (TE, TO) and discrepancies between the two (4.7%) were resolved by consensus. The primary outcome of the study was all-cause mortality obtained from electronic hospital records synchronized with the Norwegian National Registry per August 1, 2012. The study was approved by the Regional Ethics Committee of the South-Eastern of Norway and conducted according to the Declaration of Helsinki. All patients provided written informed approval before attending the study.

2.2. Echocardiography

Echocardiography is a non-invasive imaging method to visualize cardiac structure and function by ultrasound, normally transthoracic. Patients and control subjects were examined by echocardiography in supine left lateral position using a standard transthoracic echocardiography protocol according to guidelines [21] with Vivid 7 (GE Vingmed, Horten, Norway). All recordings were stored and later reviewed with EchoPAC software (GE Vingmed Ultrasound) by one researcher (TE) who was blinded to concentrations of circulating biomarkers, but not ECG recordings. Left ventricular (LV) structure was determined by LV dimension, septal and posterior wall thickness and mass as recommended [21]. Systolic function was assessed by cardiac index and by calculating LV ejection fraction (LVEF) by the modified Simpson's rule and by determining fractional shortening. Cardiac index was identified by dividing cardiac output (stroke volume x heart rate) in L/min with the patient's body size (m^2). Fractional shortening was identified by calculating the degree of shortening of the left ventricular diameter between end-diastole and end-systole. Diastolic function was determined by pulsed Doppler transmitral early peak (E), late peak (A), E deceleration time and early diastolic tissue velocity (e') recorded at the base of the septal and lateral mitral annulus. By measuring the velocity through the aortic valve and calculating the mean pressure gradient and aortic valve area we estimated the aortic valvular orifice narrowing.

2.3. Electrocardiogram

ECGs were recorded with standardized 12-lead ECG and interpreted for research purposes by one researcher (JB), blinded to concentrations of circulating biomarkers and echocardiographic data. We measured heart rate, PQ interval, and QRS duration manually. Corrected QT (QTc) interval was calculated by QT interval and heart rate with an online

calculator [22]. Bundle branch block was defined by American Heart Association guidelines [23].

2.4. Biochemistry

Blood samples were obtained by venipuncture at the time of echocardiography. Blood samples were directly put on ice and centrifuged for 30 minutes before plasma separation and then stored at -80°C before shipment to Akershus University Hospital. SN concentrations were measured with an in-house radioimmunoassay (RIA) in Li-heparin plasma at the Department of Medical Sciences, Uppsala University, Uppsala, Sweden. This assay binds to epitopes in the N-terminal region of SN (secretogranin II 154-165) as previously reported [24]. The SN assay has a limit of detection (LoD) of 50 pmol/L, and the coefficient of variation (CV) is 9% in the lower range (110 pmol/L) and 4% in the upper range (380 pmol/L). Risk groups defined in a previous study on patients undergoing cardiac surgery [18] were also assessed in this cohort; <124 pmol/L for low-risk, 124-204 pmol/L for intermediate-risk, and >204 pmol/L for high-risk. Chromogranin A (CgA) concentrations were measured by a commercially available RIA (EuroDiagnostica AB, Malmö, Sweden) [25], with an LoD of 0.80 nmol/L and with a CV of 13% in the lower range (3.1nmol/L) and 9% in the upper range (17.0 nmol/L). Chromogranin B (CgB) concentrations were measured with an in-house RIA at Uppsala University Hospital, Sweden, as previously reported [26], with an LoD of 0.80 nmol/L and a CV of 17% in the lower range (1.40 nmol/L) and 8% in the upper range (6.40 nmol/L). Cardiac troponin T (cTnT) was measured on an autoanalyzer (Cobas e411, Roche Diagnostics, Basel, Switzerland) with a highly sensitive assay (TNT hs STAT, Roche Diagnostics) with an LoD of 5 ng/L and a CV of 10% at 13 ng/L and 99th percentile 14 ng/L. NT-proBNP concentrations were measured with the proBNP II assay (Roche Diagnostics) with an LoD of 5 ng/L. CV for the proBNP II assay is 4.5 at 120 ng/L

and 4.0 at 580 ng/L in the laboratory at Akershus University Hospital. Creatinine concentrations were measured with an enzymatic assay at the hospital laboratory at Oslo University Hospital, Rikshospitalet, Oslo, Norway (Roche Diagnostics). We used the Cockcroft-Gault formula to calculate creatinine clearance [27].

2.5. Statistics

All continuous variables are reported as median (quartile [Q] 1-3) and we used the Kolmogorov-Smirnov test to assess distribution and the Mann-Whitney *U*-test to compare groups. Categorical variables are reported as absolute numbers and percentages and the Pearson Chi-Square test or the Fisher´s exact test was used to compare groups. Spearman rank correlation was used to calculate correlation coefficients. Linear regression analyses were used to identify variables associated with biomarker concentrations and logistic regression models to identify variables associated with aortic stenosis and mortality. We used the Youden J index to calculate the optimal SN concentration cut-off for assessment of long-term mortality. Predictors of mortality were assessed by Kaplan-Meier plots and the log-rank test with SN divided by optimal cut-off concentration and prespecified risk-categories. Cox proportional hazard regression models were used to assess time to all-cause mortality, and all variables in Table 1 were tested in univariable Cox proportional hazard regression models. Variables with p-value <0.05 in univariate regression models were taken into multivariable regression models with backwards selection. Due to collinearity we performed multivariable linear regression in separate models. We used receiver operating characteristics (ROC) to calculate the area under the curve (AUC) with 95% confidence interval (CI). Due to non-normal distributions, estimated creatinine clearance, SN, CgA, CgB, high-sensitivity cTnT (hs-cTnT), and NT-proBNP concentrations were logarithmically transformed with the natural logarithm (ln) prior to all regression analyses. For statistical calculations we used IBM SPSS

Statistics 25 (IBM Corp, Armonk, NY, USA) and MedCalc Statistical Software version 14.10.2 (MedCalc Software, Ostend, Belgium).

3. RESULTS

3.1. Baseline characteristics of patients with aortic stenosis and controls

The 57 patients with AS had a median age of 77 (Q1-3 70-80) years, 31 patients (54.4%) were female, and the median BMI was 25.6 (Q1-3 23.4-27.9) kg/m^2. Patients in the control group (n=10) had similar age, sex, and BMI as the patients with AS, but not echocardiographic indices reflective of moderate to severe AS (**Supplementary Table 1**). Median SN concentration was 141 (Q1-3 121-163) pmol/L in patients with AS and 132 (106-148) pmol/L in the control subjects (p=0.17). Concentrations of hs-cTnT and CgA were not increased in AS patients, while CgB and NT-proBNP concentrations were significantly higher in AS patients compared to the healthy control subjects (**Supplementary Table 1**).

3.2. SN concentrations and long-term mortality in patients with aortic stenosis

A total of 15 patients (26%) with AS died during a median follow-up of 3.5 (Q1-3 2.9-3.8) years. Clinical characteristics, biomarker concentrations, and echocardiographic and ECG indices for survivors and non-survivors are presented in **Table 1** and **Supplementary Table 2**. We found a number of established clinical risk variables to be higher among non-survivors.

Circulating SN concentrations were also higher in non-survivors compared to survivors: 156 (Q1-3 133-209) pmol/L versus 140 (116-155) pmol/L, p=0.007 (**Table 1**). The optimal cut-off based on the Youden J index for SN in discriminating long-term mortality was 147 pmol/L. This cut-off yielded a sensitivity of 67% (95% CI 38-88%), specificity of 74% (58-86%), positive likelihood ratio of 2.6 (1.4-4.7), and negative likelihood ratio of 0.5 (0.2-0.9) in

predicting mortality. Patients with SN concentrations above the optimal cut-off (n=21, 37%) had worse prognosis than patients with SN concentrations below the cut-off (**Figure 1**; p=0.005 with the log-rank test). hs-cTnT concentrations also separated AS patients with a poor and favorable outcome (p=0.009), while CgA, CgB, or NT-proBNP concentrations did not differ between survivors and non-survivors (**Table 1**). In multivariable Cox proportional hazard analysis that adjusted for clinical characteristics, established cardiac biomarkers and echocardiographic parameters, higher concentrations of SN were associated with increased risk of mortality: hazard ratio per $_{ln}$SN 15.13 (95% CI 1.05-219.00), p=0.046 (**Table 2** and **Supplementary Table 3)**. Patients with SN concentrations above the optimal cut-off (147 pmol/L) experienced ~7 times increased risk of mortality compared to patients below the optimal cut-off in adjusted models: HR 6.83 (1.74-26.81), p=0.006. The ROC-AUC to predict mortality was 0.74 (95% CI 0.60-0.88) for SN, 0.73 (0.59-0.87) for hs-cTnT and 0.67 (0.51-0.82) for NT-proBNP. SN concentrations above the previously identified cut-off of SN >204 pmol/L in cardiac surgical patients predicted mortality also in this cohort (log-rank test; p<0.001; **Supplementary Figure 1**).

3.3. Variables associated with high SN concentrations

Patients with SN concentrations above the optimal cut-off of 147 pmol/L were older, had lower estimated creatinine clearance, more frequent use of diuretics, higher concentrations of hs-cTnT and NT-proBNP, and higher maximal aortic valve velocity (**Table 3**). Higher concentrations of SN correlated with lower estimated creatinine clearance and heart rate, use of diuretics or aldosterone antagonists, and higher concentrations of CgA and hs-cTnT (**Supplementary Table 4**). In multivariable linear regression analysis, lower estimated creatinine clearance and the use of diuretics were associated with higher SN concentrations (r^2=0.24, **Supplementary Table 5**).

4. DISCUSSION

In this prospective cohort of patients with moderate to severe AS referred for presurgical evaluation, we found that SN concentrations were associated with mortality and not closely correlated with established risk indices. Hence, SN measurements seem to identify a subgroup of AS patients with poor prognosis that is not identified by clinical risk factors, echocardiographic indices, ECG indices, and established cardiac biomarkers.

Cardiac biomarkers have been proposed as additional tools for selecting patients with AS for intervention [3]. We and other groups have demonstrated that both hs-troponin and NT-proBNP provide incremental prognostic information to established risk models in cardiac surgical patients and patients with valvular heart disease [5, 28-30]. However, based on current knowledge, troponins primarily reflect cardiac injury and B-type natriuretic peptides are considered biomarkers reflective of cardiomyocyte strain [31, 32]. Given the complex and integrated pathophysiology of patients with AS [13, 19, 33, 34], biomarkers that provide additional prognostic information to established risk indices such as echocardiography, ECG, and established cardiac biomarkers, should have potential to improve risk assessment in AS. SN is such a novel and promising circulating cardiovascular biomarker that has been found associated with cardiomyocyte Ca^{2+} handling [13, 15] and systemic stress pathways [19, 33]. SN is expressed and secreted in many tissues throughout the body [35-37], including the myocardium [13], and is eliminated by the kidneys [38]. We have previously shown that SN does not seem closely correlated with established risk indices in patients with acute myocardial dysfunction, severe infections, and in patients that undergo cardiac surgery [13, 17-20], thereby providing incremental prognostic value to established risk indices across a spectrum of conditions with myocardial dysfunction.

In line with previous results, we found no close correlations between circulating SN concentrations and established risk indices. As previously reported for patients with acute heart failure, we did not find universally increased SN concentrations in patients with moderate to severe AS compared to age- and gender-matched controls. In contrast, we find that SN concentrations are specifically increased among AS patients with the worst prognosis, thereby providing a signal of especially increased risk in a subgroup of AS patients. We also validate previous data on cut-offs for risk based on SN measurements [18] as we in this cohort identified SN concentration 147 pmol/L to discriminate long-term mortality, which is within the range of previously established cut-offs of 122 pmol/L and 175 pmol/L for SN in cohorts of critically ill patients [17, 19]. We also used this cohort of patients with valvular heart disease to validate an SN concentration of 204 pmol/L as a discriminator of high risk cardiac surgical patients. Of note, although SN concentrations correlated with CgA and CgB concentrations, we found SN to provide superior prognostic information to other granin proteins. This is also in line with previous data in critically ill patients with infections [19]. Given the lack of associations between SN and echocardiographic and ECG indices and cardiac biomarkers, and no difference in SN concentration between AS patients and healthy control subjects, SN does not seem to reflect structural heart disease *per se*. In contrast, we believe SN reflects additional pathophysiology that seems to influence outcome in patients with myocardial dysfunction [10, 13, 17]. Based on other studies [13, 15, 19, 33], SN concentrations seem to integrate information on systemic stress pathways, cardiomyocyte Ca^{2+} handling, and renal dysfunction, although this study was not designed to validate this model. Accordingly, there is still a need for additional experimental and clinical studies to determine the exact pathophysiology associated with high SN concentrations in patients with myocardial dysfunction.

4.1. Strengths and limitations

This study has some strengths and limitations. One strength is the extensive phenotyping of these patients, as well as comprehensive phenotyping of the control subjects including a standardized echocardiographic examination. We also have prospective data and our results validate previously reported data. Limitations include a single-center study restricted to patients with moderate to severe AS and the lack of TAVI procedure during the study period. Accordingly, our findings should be validated in other, larger cohorts. The relatively low number of events may have undermined the power to detect subtle clinical associations in adjusted analyses, but we believe this will rather attenuate the association between SN and mortality and not explain the results of this study. The number of controls in this study is small and a validation cohort should aim to have a higher number of controls. Finally, we do not have information on the cause of death. However, the main cause of death will most likely be cardiovascular given the advanced cardiac disease and age in our patients.

5. CONCLUSION

In conclusion, we found preoperative concentrations of SN to provide incremental prognostic information to established risk indices in patients with moderate to severe AS. Moreover, SN was not closely correlated to established risk indices, which supports SN as a biomarker that reflects additional pathophysiology of relevance for outcome in patients with moderate to severe AS.

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DECLARATIONS OF INTEREST

JB, MNL, LGK, TE: These authors declare that they have no conflicts of interests. HR, GC, and TO are partners in a patent (PCT/GB0818650.4) filed by the University of Oslo regarding the use of secretoneurin as a biomarker in patients with cardiovascular disease and patients with critical illness. HR, GC, and TO have financial interests in CardiNor AS, which holds the license to commercialize secretoneurin. MS, TO, and HR have also received personal fees from CardiNor AS. TO has served on advisory boards and received speaker´s honoraria and travel funding from Roche Diagnostics and Roche Diagnostics provided hs-TnT and NT-proBNP kits at a reduced price via Akershus University Hospital. PLM, TO and HR have also received personal fees from Novartis.

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AUTHOR CONTRIBUTION STATEMENT

JB: data analysis, writing up the first draft of the paper, critical review of paper, approval of final version; PLM: data analyses, critical review of paper, approval of final version; MNL: data analyses, critical review of paper, approval of final version; LGK: patient recruitment, critical review of paper, approval of final version; MS: biochemical analyses, critical review of paper, approval of final version; GC: study design, critical review of paper, approval of final version; TE: patient recruitment, echocardiographic examination, critical review of paper, approval of final version; TO: study design, critical review of paper, approval of final version; HR: study design, critical review of paper, approval of final version.

PATIENT CONSENT

All patients provided written informed approval before attending the study.

ETHICAL APPROVAL

The study was approved by the Regional Ethics Committee of the South-Eastern of Norway and conducted according to the Declaration of Helsinki.

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FIGURE CAPTION

Figure 1 Cumulative survival in patients with aortic stenosis according to the optimal cut-off concentration (147 pmol/L) for secretoneurin measured prior to aortic valve replacement surgery.

Subtitle Figure 1. *The event rate in the group above cut-off was compared to the event rate in the group below cut-off by the log-rank test. Below optimal cut-off corresponds to secretoneurin concentrations equal or below 147 pmol/L (blue solid line) and above cut-off corresponds to secretoneurin concentrations above 147 pmol/L (red striped line).*

Table 1 Baseline characteristics of aortic stenosis patients according to long-term survival

	Survivor (n=42, 73.7%)	**Non-Survivor (n=15, 26.3%)**	**P**
Age (years)	76.0 (69.8-80.0)	78.0 (76.0-81.0)	0.15
Female sex	26 (61.9%)	5 (33.3%)	0.07
Body mass index (kg/m^2)	26.1 (23.7-28.1)	24.2 (21.7-27.5)	0.20
New York Heart Association Functional Class			0.10
I	2 (4.8%)	4 (26.7%)	
II	26 (61.9%)	6 (40.0%)	
III	13 (31.0%)	5 (33.3%)	
IV	1 (2.4%)	0 (0.0%)	
Estimated creatinine clearance (ml/min)	71.8 (54.5-88.1)	68.5 (41.2-77.7)	0.11
Systolic blood pressure (mmHg)	143 (128-161)	137 (130-155)	0.65
Diastolic blood pressure (mmHg)	80 (70-91)	79 (65-85)	0.35
History of			
Coronary artery disease	19 (45.2%)	9 (60.0%)	0.33
Heart Failure	39 (92.9%)	10 (66.7%)	0.02
Hypertension	25 (59.5%)	4 (26.7%)	0.04
Diabetes Mellitus	6 (14.3%)	2 (13.3%)	1.00
Atrial fibrillation	11 (26.2%)	1 (6.7%)	0.15
Chronic obstructive pulmonary disease	2 (4.8%)	3 (20.0%)	0.11
Medication			
Beta blocker	20 (47.6%)	7 (46.7%)	1.00
Calcium blocker	8 (19.0%)	1 (6.7%)	0.42
Angiotensin-converting-enzyme inhibitor/ Angiotensin II receptor blockers	17 (40.5%)	4 (26.7%)	053
Acetylsalicylic acid	22 (52.4%)	10 (66.7%)	0.38
Warfarin	10 (23.8%)	1 (6.7%)	0.26
Diuretics	18 (42.9%)	7 (46.7%)	0.80
Statins	25 (59.5%)	9 (60.0%)	0.97
Aldosterone antagonist	3 (7.1%)	3 (20.0%)	0.18
Circulating biomarkers			
SN (pmol/L)	140 (116-155)	156 (133-209)	0.007
CgA (nmol/L)	6.4 (4.9-8.2)	7.4 (5.9-9.6)	0.12
CgB (nmol/L)	1.9 (1.8-2.0)	2.0 (1.8-2.3)	0.14
cTnT (ng/L)	17.2 (12.1-24.2)	27.3 (16.1-42.2)	0.009
NT-proBNP (ng/L)	694 (283-2251)	1362 (614-3983)	0.06
Echocardiographic variables			
Left ventricular end-diastolic dimension (mm)	50.5 (47.0-55.3)	56.0 (49.0-57.0)	0.15
Interventricular septal end-diastolic dimension (mm)	12.0 (11.0-13.3)	12.0 (11.0-13.0)	0.54
Left ventricular end-diastolic posterior wall dimension (mm)	10.0 (9.0-11.3)	9.0 (8.0-11.0)	0.06
Left ventricular relative wall thickness	0.44 (0.40-0.49)	0.39 (0.32-0.45)	0.03
Left ventricular mass (g)	228.9 (174.3-272.4)	219.1 (178.1-272.5)	0.94

Left ventricular ejection fraction (%)	61.0 (52.5-64.0)	53.0 (40.0-66.0)	0.25
Fractional shortening (%)	40.0 (34.5-46.0)	31.0 (25.0-47.0)	0.13
Left ventricular cardiac index ($L/min/m^2$)	2.6 (2.2-3.0)	2.7 (2.4-3.0)	0.94
Aortic valve area (cm^2)	0.65 (0.50-0.80)	0.70 (0.50-1.00)	0.36
Aortic valve $velocity_{max}$ (m/s)	4.6 (3.9-5.3)	4.3 (3.1-5.3)	0.37
Aortic valve replacement Surgery	31 (73.8%)	3 (20.0%)	<0.001
Type of surgery			0.001
No surgery	11 (26.2%)	12 (80.0%)	
AVR	19 (45.2%)	2 (13.3%)	
AVR+CABG	12 (28.6%)	1 (6.7%)	

CgA indicates chromogranin A; CgB, chromogranin B; hs-cTnT, high-sensitivity cardiac Troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SN, secretoneurin.

Continuous variables are expressed as median (inter quartile range, quartile1-3)
Categorical variables are expressed as number (percentage, %)

Table 2 Predictors of mortality in patients with aortic stenosis

	HR	95% CI	P	Wald
Univariate analyses				
Age (per one year)	1.06	0.99-1.14	0.09	2.82
Female sex	0.38	0.13-1.13	0.08	3.04
Body mass index (per one kg/m^2)	0.91	0.80-1.04	0.91	1.94
New York Heart Association Functional Class (I/II vs III/IV)	1.13	0.39-3.32	0.82	0.05
Estimated creatinine clearance (per one ml/min)	0.24	0.06-1.04	0.06	3.65
Systolic blood pressure (per mmHg)	0.99	0.97-1.02	0.58	0.31
Diastolic blood pressure (per mmHg)	0.98	0.94-1.01	0.21	1.58
History of:				
Coronary artery disease	1.68	0.60-4.74	0.32	0.98
Heart Failure	0.25	0.09-0.74	0.01	6.28
Hypertension	0.29	0.09-0.90	0.03	4.59
Diabetes Mellitus	0.93	0.21-4.11	0.92	0.01
Atrial fibrillation	0.22	0.03-1.70	0.15	2.09
Chronic obstructive pulmonary disease	3.91	1.09-14.05	0.04	4.37
Medication				
Beta blocker	0.95	0.34-2.62	0.92	0.01
Calcium blocker	0.32	0.04-2.45	0.27	1.20
Angiotensin-converting-enzyme inhibitor/ Angiotensin II receptor blockers	0.58	0.19-1.82	0.35	0.89
Acetylsalicylic acid	1.65	0.56-4.83	0.36	0.84
Warfarin	0.25	0.03-1.91	0.18	1.79
Diuretics	1.12	0.41-3.09	0.83	0.05
Statins	0.96	0.34-2.69	0.94	0.01
Aldosteron antagonist	2.57	0.72-9.16	0.15	2.12
Circulating biomarkers				
SN (per log unit)	4.98	1.33-18.62	0.02	5.70
CgA (per log unit)	1.48	0.81-2.70	0.21	1.60
CgB (per log unit)	9.47	0.87-103.30	0.07	3.40
hs-cTnT (per log unit)	2.85	1.29-6.33	0.01	6.65
NT-proBNP (per log unit)	1.71	1.04-2.81	0.04	4.40
Aortic valve replacement	0.13	0.04-0.46	0.002	10.00
Multivariable analysis (-2 Log Likelihood = 78.7)				
SN (per log unit)	15.13	1.05-219.00	0.046	3.97
NT-proBNP (per log unit)	2.08	1.07-4.08	0.03	4.60
Hypertension	0.21	0.06-0.81	0.02	5.17

CgA indicates chromogranin A; CgB, chromogranin B; hs-cTnT, high-sensitivity cardiac Troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SN, secretoneurin.

Creatinine clearance, SN, hs-cTnT, and NT-proBNP are logarithmically transformed

Table 3 Baseline characteristics of patients with aortic stenosis according to the optimal cut-off concentration of secretoneurin

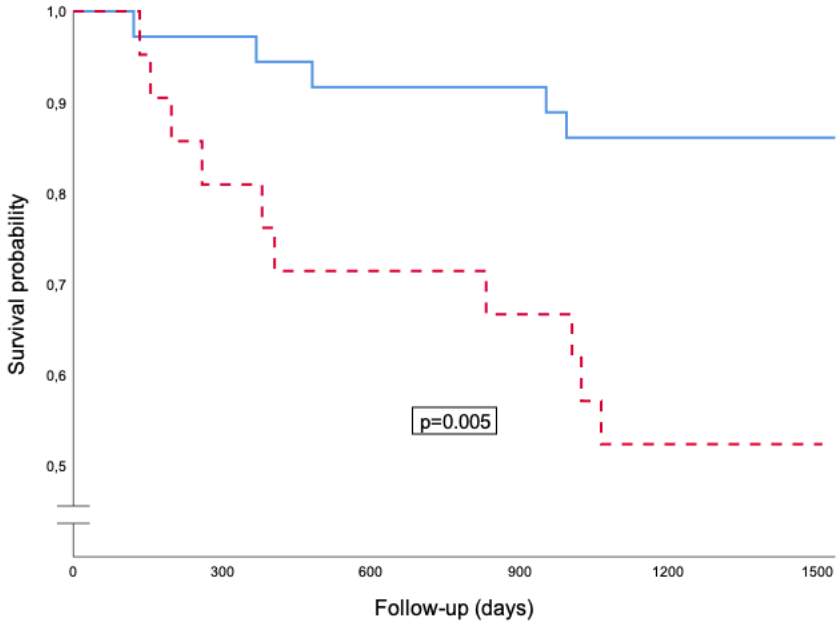
	SN concentration <147 pmol/L (n=36, 63%)	**SN concentration ≥ 147 pmol/L (n=21, 37%)**	**P**
Age (years)	76.0 (69.3-79.0)	79.0 (73.0-82.5)	0.047
Female sex	22 (61.1%)	9 (42.9%)	0.18
Body mass index (kg/m^2)	25.8 (23.3-27.5)	24.6 (23.1-32.0)	0.60
New York Heart Association Functional Class			0.45
I	3 (8.3%)	3 (14.3%)	
II	22 (61.1%)	10 (47.6%)	
III	11 (30.6%)	7 (33.3%)	
IV	0 (0.0%)	1 (4.8%)	
Estimated creatinine clearance (ml/min)	77.2 (56.8-90.4)	52.8 (42.5-77.1)	0.02
Systolic blood pressure (mmHg)	140 (124-155)	148 (134-170)	0.09
Diastolic blood pressure (mmHg)	79 (70-86)	80 (67-95)	0.51
History of			
Coronary artery disease	16 (44.4%)	12 (57.1%)	0.36
Heart Failure	32 (88.9%)	17 (81.0%)	0.41
Hypertension	17 (47.2%)	12 (57.1%)	0.47
Diabetes Mellitus	3 (8.3%)	5 (23.8%)	0.13
Atrial fibrillation	8 (22.2%)	4 (19.0%)	1.00
Chronic obstructive pulmonary disease	2 (5.6%)	3 (14.3%)	0.35
Medication			
Beta blocker	15 (41.7%)	12 (57.1%)	0.26
Calcium blocker	6 (16.7%)	3 (14.3%)	1.00
Angiotensin-converting-enzyme inhibitor/ Angiotensin II receptor blockers	11 (30.6%)	10 (47.6%)	0.20
Acetylsalicylic acid	19 (52.8%)	13 (61.9%)	0.50
Warfarin	7 (19.4%)	4 (19.0%)	1.00
Diuretics	12 (33.3%)	13 (61.9%)	0.04
Statins	20 (55.6%)	14 (66.7%)	0.41
Aldosterone antagonist	2 (5.6%)	4 (19.0%)	0.18
Circulating biomarkers			
CgA (nmol/L)	6.2 (5.0-8.3)	6.7 (5.7-9.4)	0.12
CgB (nmol/L)	1.9 (1.8-2.0)	1.9 (1.8-2.3)	0.16
hs-cTnT (ng/L)	17.0 (11.8-23.4)	25.9 (15.5-40.7)	0.01
NT-proBNP (ng/L)	655 (269-1988)	1362 (538-3072)	0.04
Echocardiographic variables			
Left atrial area (cm^2)	22.8 (15.5-26.7)	21.6 (19.4-28.5)	0.51
Left ventricular end-diastolic dimension (mm)	55.0 (47.0-56.0)	55.0 (48.0-56.5)	0.38
Interventricular septal end-diastolic dimension (mm)	12.0 (11.0-13.0)	12.0 (11.0-15.0)	0.24
Left ventricular end-diastolic posterior wall dimension (mm)	10.0 (8.25-11.0)	10.0 (9.0-12.0)	0.18
Left ventricular relative wall thickness	0.41 (0.38-0.47)	0.45 (0.38-0.49)	0.39
Left ventricular mass (g)	212 (165-272)	241 (189-284)	0.18
Left ventricular ejection fraction (%)	61.0 (50.3-63.8)	58.0 (48.5-65.0)	0.44
Fractional shortening (%)	40.0 (31.0-47.0)	38.0 (28.5-44.0)	0.20
Left ventricular cardiac index (L/min/m2)	2.64 (2.38-3.00)	2.72 (2.16-2.98)	0.52

E/e´	14.8 (12.1-19.8)	18.7 (9.6-25.2)	0.33
E/A ratio	0.82 (0.72-1.05)	0.76 (0.50-1.03)	0.38
Mitral valve deceleration time (ms)	244 (189-299)	207 (156-301)	0.26
Aortic valve area (cm^2)	0.70 (0.60-0.88)	0.60 (0.50-0.80)	0.06
Aortic valve $velocity_{max}$ (m/s)	4.25 (3.76-5.00)	4.95 (4.44-5.44)	0.049
Electrocardiogram variables			
Ventricular frequency (beats/min)	76 (63-89)	70 (63-77)	0.20
Supraventricular tachycardia	9 (25.0%)	1 (4.8%)	0.07
PQ interval (ms)	161 (141-182)	178 (148-198)	0.13
QRS duration (ms)	95 (87-114)	102 (98-109)	0.22
QTc interval (ms)	443 (426-461)	437 (421-450)	0.61
Bundle branch block	3 (8.3%)	3 (14.3%)	0.66
Sokolow-Lyon (mm)	27 (19-35)	26 (20-34)	0.93
Aortic Valve Replacement	23 (63.9%)	11 (52.4%)	0.39

CgA indicates chromogranin A; CgB, chromogranin B; hs-cTnT, high-sensitivity cardiac Troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SN, secretoneurin.

Continuous variables are expressed as median (Q 1-3)
Categorical variables are expressed as absolute number (%)

Figure 1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Survival probability
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Follow-up (days)