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Christian Nitsche, MD, Paul R. Scully, PhD, Kush P. Patel, MBBS, Andreas Kammerlander, MD, PhD, Matthias Koschutnik, MD, Carolina Dona, MD, Tim Wollenweber, MD, Nida Ahmed, MBBS, George D. Thornton, MBBS, Andrew Kelion, MD, Nikant Sabharwal, MD, James D. Newton, MD, Muhiddin Ozkor, MD, Simon Kennon, MD, Michael Mullen, MD, Guy Lloyd, MD, Marianna Fontana, PhD, Philip Hawkins, FRS, Francesca Pugliese, MD, Leon Menezes, MD, James C. Moon, MD, Julia Mascherbauer, MD, Thomas A. Treibel, PhD

PII: S0735-1097(20)37735-4

DOI: https://doi.org/10.1016/j.jacc.2020.11.006

Reference: JAC 27850

To appear in: *Journal of the American College of Cardiology*

Received Date: 11 August 2020

Revised Date: 26 October 2020

Accepted Date: 4 November 2020

Please cite this article as: Nitsche C, Scully PR, Patel KP, Kammerlander A, Koschutnik M, Dona C, Wollenweber T, Ahmed N, Thornton GD, Kelion A, Sabharwal N, Newton JD, Ozkor M, Kennon S, Mullen M, Lloyd G, Fontana M, Hawkins P, Pugliese F, Menezes L, Moon JC, Mascherbauer J, Treibel TA, Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis, *Journal of the American College of Cardiology* (2020), doi: https://doi.org/10.1016/j.jacc.2020.11.006.

Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis

Brief title: Outcome of cardiac amyloidosis and aortic stenosis

Christian Nitsche, MD[1], Paul R Scully, PhD[2,3], Kush P Patel, MBBS[2, 4], Andreas Kammerlander, MD, PhD[1], Matthias Koschutnik, MD[1], Carolina Dona, MD[1], Tim Wollenweber, MD[5], Nida Ahmed, MBBS[2,4], George D. Thornton, MBBS[2,4], Andrew Kelion, MD[7], Nikant Sabharwal, MD[7], James D. Newton, MD[7], Muhiddin Ozkor, MD[4], Simon Kennon, MD[4], Michael Mullen, MD[4], Guy Lloyd, MD[2,4,6], Marianna Fontana, PhD[8], Philip Hawkins, FRS[8], Francesca Pugliese, MD[4,6], Leon Menezes, MD[4,9], James C Moon, MD[2,4], Julia Mascherbauer, MD[1], Thomas A Treibel, PhD[2,4]

Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria
Institute of Cardiovascular Science, University College London, UK.
Cardiology Department, Guy's and St Thomas' NHS Foundation Trust, UK.
Barts Heart Centre, St Bartholomew's Hospital, UK.
Department of Nuclear Medicine, Medical University of Vienna
Queen Mary University London, UK.
John Radcliffe Hospital, Oxford, UK
National Amyloid Centre, UK
UCL/ULCH NIHR Biomedical Research Centre, UK

Disclosures: All authors report no conflict of interest.

Address for correspondence:
Dr Thomas Treibel
Barts Heart Centre
St. Bartholomew's Hospital,
West Smithfield, London EC1A 7BE
Telephone: +44 203 465 6115
Email: Thomas.Treibel@nhs.net
Twitter: @ThomasTreibel

ABSTRACT

Background: Older patients with severe aortic stenosis (AS) are increasingly identified to have cardiac amyloidosis (CA). It is unknown whether dual AS-CA has worse outcomes or results in futility of transcatheter aortic valve replacement (TAVR).

Objective: To identify clinical characteristics and outcomes of AS-CA compared to lone AS.

Methods: TAVR referrals at three international sites underwent blinded research-corelab 99mTc-DPD bone scintigraphy (Perugini Grade-0 negative, 1–3 increasingly positive) prior to intervention. Transthyretin-CA (ATTR) was diagnosed by DPD and absence of a clonal immunoglobulin, and light-chain-CA (AL) via tissue biopsy. National registries captured all-cause mortality.

Results: 407 patients (83.4±6.5 years, 49.8% male) were recruited. DPD was positive in n=48 (11.8%, Grade-1 3.9%[n=16] Grade-2/3 7.9%[n=32]); AL was diagnosed in one Grade-1. Grade-2/3 patients had worse functional capacity, biomarkers (NT-proBNP/hsTnT), and bi-ventricular remodeling. A clinical score (RAISE) using left-ventricular Remodeling (hypertrophy/diastolic dysfunction), Age, Injury (hsTnT), Systemic involvement, and Electrical abnormalities (RBBB/low-voltages) was developed to predict AS-CA presence (AUC 0.86, 95%CI 0.78-0.94, p<0.001). Heart Team decision (DPD-blinded) resulted in TAVR (333[81.6%]), surgical-AVR (10[2.5%]), or medical management (65[15.9%]). After median 1.7 years, 23% of patients had died. 1-year mortality was worse in all-comers AS-CA (Grade-1-3) than lone AS (24.5 vs 13.9%, *p=0.05*). TAVR improved survival versus medical management with AS-CA survival post-TAVR no different to lone AS (p=0.36).

Conclusion: Dual pathology of AS-CA is common in older AS patients and can be predicted clinically. AS-CA has worse clinical presentation and a trend towards worse prognosis, unless treated. TAVR should therefore not be withheld in AS-CA.

CONDENSED ABSTRACT: Co-existence of cardiac amyloidosis (CA) and severe aortic stenosis (AS) is increasingly recognized, but survival implications of dual pathology AS-CA are still unclear. This multicenter study screened consecutive patients referred for transcatheter aortic valve replacement (TAVR) with bone scintigraphy and identified 48 AS-CA patients (11.8%). AS-CA diagnosis (blinded to the clinical team) could be predicted by a simple clinical score and was associated with worse functional capacity, cardiac remodeling, and a trend towards worse 1-year mortality. TAVR improved survival both in lone AS and AS-CA with no difference between groups (p=0.36), disproving treatment futility in this population.

Key words: aortic stenosis, cardiac amyloidosis, TAVR

ABBREVIATIONS

AS	-	Aortic stenosis
AS-CA	-	Dual aortic stenosis and cardiac amyloid pathology
AL	-	Immunoglobulin light chain cardiac amyloidosis
ATTR	-	Transthyretin-related cardiac amyloidosis
DPD	-	^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid
hsTnT	-	High-sensitivity troponin T
MCF	-	Myocardial contraction fraction
NT-proBNP	-	N-terminal pro-brain natriuretic peptide
TAVR	-	Transcatheter aortic valve replacement
V/M ratio	-	Voltage/mass ratio

Introduction

Degenerative aortic stenosis (AS) affects>3% of people aged 75 years or older. (1) In severe AS with symptoms or cardiac decompensation surgical (SAVR) or transcatheter-based (TAVR) valve replacement are indicated to improve outcome. (2) Morphologically, significant AS is characterized by hypertrophic myocardial remodelling, similar to cardiac amyloidosis (CA). CA is an infiltrative process caused by the myocardial deposition of amyloid fibrils. The two major amyloid proteins found in ventricular myocardium are transthyretin (TTR), which predominantly affects older individuals and, less frequently, immunoglobulin light chain (AL). (3) The co-existence of AS and CA in patients referred for TAVR ranges from 9 to 16%. (4-7) Increased diagnosis of CA is driven by the sensitivity and specificity of bone scintigraphy (99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid, DPD; 99mTc-pyrophosphate; or 99mTc-hydroxymethylene diphosphonate), in particular for ATTR. This is important given the advent of novel CA therapies (8). The survival implications of concurrent AS-CA remain unclear. Three potentially underpowered studies have recently reported no mortality difference of AS-CA as compared to lone AS in cohorts of ~200 patients. (4,6,9) The present multicenter study was therefore designed to evaluate the differential mortality hazard of AS-CA vs. lone AS, and predictors of AS-CA beyond existing diagnostic criteria.

Methods

Study population

This prospective, multicenter study enrolled consecutive adult patients with severe degenerative AS referred for TAVR at three tertiary referral centers: Barts Heart Centre, London (October 2016 to January 2019); John Radcliffe Hospital, Oxford (January 2018 to June 2019);

and Vienna General Hospital (October 2017 to February 2019). This study includes patients from two previous published studies, (4,6) expanding the study cohort, follow-up and implementing blinded core-lab analysis of bone scintigraphy.

To reduce selection bias, recruitment took place after referral to AVR and prior to discussion by the Heart Team meeting. We therefore anticipated some crossover to medical therapy and to surgical valve replacement. All patients underwent blinded 99mTc-DPD bone scintigraphy as well as clinical and laboratory assessment, six-minute walk test, ECG, and transthoracic echocardiography with strain analysis. All-cause mortality was selected as the primary study endpoint, determined using national data via the UK National Health Service Spine and Austrian Death Registry and was 100% complete. Peri-procedural complications were defined using the Valve Academic Research Consortium-2 (VARC-2) criteria. This study complies with the Declaration of Helsinki, relevant local ethics and site approvals were obtained and all patients provided written informed consent.

Laboratory and electrocardiographic assessment

For the detection of pathological light chains underlying AL-CA, laboratory testing included serum immunoglobins and free light chain quantification, and serum/urine immunofixation, which was performed in all DPD positive patients. Additionally, N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity Troponin T (hs-TnT) serum levels were determined in all patients. Electrocardiograms were recorded according to current recommendations. (10) Voltage/mass ratio (VMR) was determined in patients without bundle branch block and paced rhythm by dividing the Sokolow-Lyon index by the LV mass index on echocardiography. The Sokolow-Lyon index was calculated as the sum of precordial voltage (S-

wave in lead V_1 plus R wave in lead V_5 or V_6 [SV_1+RV_5 or V_6]). Low limb lead voltages were defined as all limb leads with an amplitude ≤0.5mV.

Echocardiography

All patients underwent clinical transthoracic echocardiogram (TTE), primarily for assessment of AS severity, any concomitant valve pathology and ventricular function according to the local protocols, written in accordance with international imaging guidelines. (11-14) Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane where possible, or otherwise quantified visually. Stroke volume (SV) was quantified using the left ventricular outflow tract (LVOT) velocity time integral (VTI) and the LVOT diameter and then indexed to body surface area. LV mass was calculated using the formula from Devereux et al. (15) Strain analysis was performed in the 4-, 3-, and 2-chamber apical views. Regional longitudinal strain (LS) was determined in 17 segments of the LV. (16) Global LS was calculated as the average LS of these 17 segments. Relative apical LS was calculated as average apical LS/(average basal LS + average mid LS). Myocardial contraction fraction (MCF), which indexes the SV to the myocardial volume, was calculated as previously described. (17) 'Classical' low-flow, low gradient was defined as an aortic valve area ≤1.0cm^2, with an LVEF <50%, an indexed SV <35ml/m^2, a peak aortic valve velocity <4m/s and a mean gradient <40mmHg; conversely 'paradoxical' low-flow, low-gradient was defined as an LVEF ≥50%, but an indexed SV <35mls/m^2, peak velocity <4m/s and mean gradient <40mmHg. (14) Where equivocal, AS severity was adjudicated using low-dose dobutamine stress echocardiography, and the computed tomography (CT)-derived aortic valve calcium score.

DPD Bone Scintigraphy

Blinded, pre-TAVR DPD bone scintigraphy was performed in all patients, who were scanned using either Phillips Brightview single photon emission computed tomography (SPECT)-CT gamma camera/ Siemens Symbia gamma camera/ Pulse CDC gamma camera (IS2) (London, Oxford), or General Electric (GE) Infinia Hawkeye 4/ GE Discovery 670 hybrid gamma camera (Vienna) following the administration of 700 MBq of 99mTc-DPD. Whole body images were acquired at a scan speed of 10cm/min using low energy high-resolution collimators. (18) Planar whole-body images were performed at 3 hours at all study-sites. Additional SPECT/CT of the chest at 3 hours was performed in London/Oxford.

Blinding pre-procedure.

DPD scans were reported blinded to the clinical data by two readers from each institution (CN, TV, PS, LM) according to the Perugini classification, (19) where grade 0 represents no cardiac uptake with normal bone uptake (i.e. negative) and grades 1-3 represent increasing cardiac uptake with increasing bone attenuation and soft tissue uptake. In discrepant cases (adjudication different to the previous local DPD grade, n=5), which occurred more often in borderline cases without SPECT, the adjudication panel (CN, TV, PS, LM, TAT) re-reviewed the scans and assigned the final diagnosis by consensus.

Diagnosis of cardiac amyloidosis

Referring to the different disease burden in Perugini grade 1 (sub-clinical amyloid deposition) versus Perugini grade ≥2 (clinical amyloidosis), these two conditions were defined as AS-amyloid vs. AS-amyloidosis, respectively. The presence of ATTR was diagnosed in patients with cardiac tracer uptake on bone scintigraphy and unremarkable serum and urine free light chain assessment (8). AL was diagnosed if these were elevated and there was endomyocardial or extracardiac biopsy amyloid of light chain origin. AL amyloidosis was considered possible in

three cases (two grade-1, and one grade-2): In the first grade-1 patient endomyocardial biopsy confirmed ATTR; the second grade-1 died shortly after TAVR with an autopsy diagnosis of AL (AL-kappa positive, TTR negative); the grade-2 patient had a monoclonal gammopathy of undetermined significance with inconclusive bone marrow biopsy, but declined further biopsy. However, given the known coexistence of ATTR and monoclonal protein without cardiac AL amyloidosis (8) and the low percentage of AL with Perugini uptake ≥2 (18) this subject was classified as ATTR.

Statistical analysis

All statistical analyses were computed using SPSS 26 (IBM SPSS, USA). Continuous data are expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR), and categorical variables are presented as numbers and percentages. Differences between groups were analyzed with the Chi-square and Kruskal Wallis test as appropriate. Post-hoc analyses were performed using Dunn-Bonferroni tests for continuous variables. The discriminative power of the novel scoring system was established using receiver operating characteristic (ROC) curve analysis with area under the curve (AUC) and respective 95% confidence intervals (CI). Uni- and multivariate Cox regression analyses were performed for the overall and AVR cohort to evaluate predictors of mortality **(Tables S1-3).** All baseline parameters were proposed for univariate analysis. Multivariate analysis was performed using a stepwise forward selection with the cut-off P-value to enter the multivariate model being ≤ 0.05 in univariate testing and the p-value to remove from multivariate testing being >0.1. To allow better comparison between continuous parameters within the multivariate model, scaled hazard ratios (Z-scores) were created by subtracting the mean from individual values and dividing them by the respective SD. The proportional hazards assumption was tested with the examination of Schoenfeld residuals.

Kaplan-Meier curves were used to evaluate the prognostic significance of CA and AVR. Uni- and multivariate binary logistic analyses were applied to evaluate the association of parameters with the presence of CA. A P-value ≤ 0.05 was considered statistically significant.

Results

Patient Characteristics

407 patients referred for TAVR (mean age 83.4±6.5 years, 49.8% male) were recruited in 3 centers (**Figure 1**). All patients underwent DPD bone scintigraphy performed 16 (IQR 2-50) days prior to AVR. Treatment decision was determined by the multidisciplinary Heart Team. 333 patients (81.6%) underwent TAVR, SAVR was performed in 10 (2.5%) and conservative management or ongoing surveillance was pursued in 65 (15.9%).

Prevalence, Type and Predictors of AS-CA

Cardiac tracer uptake on DPD bone scintigraphy was present in 48 patients (11.8%). Distribution according to Perugini classification was as follows: 16 (3.9%) grade-1 (AS-Amyloid), and 32 (7.9%) grade-2/3 (AS-Amyloidosis). ATTR was found in 47 (all wild-type confirmed by genotyping), and one AL as aforementioned.

Independent predictors of presence of CA by multivariate linear regression analysis were a longer QRS duration (OR 2.51, 95% CI 1.15-5.49, p=0.021), lower voltage/mass-ratio (0.37, 95% 0.16-0.87, p=0.022), and history of carpal tunnel syndrome (1.55, 95% 1.06-2.28, p=0.024).

Lone AS versus AS-Amyloidosis (Grade-2/3 AS-CA)

Patients with AS-Amyloidosis (Grade-2/3 AS-CA; n=32) were 3 years older compared to lone AS (86.6 vs. 83.6, p<0.001) with a trend towards male (male 65 vs. 48%, p=0.06), had higher prevalence of carpal tunnel syndrome (18.8% vs. 1.1, p<0.001) and had a lower prevalence of coronary and peripheral artery disease (p<0.05). Functional capacity was

decreased significantly as measured by shorter 6-minute walk distance (94 [50-225] vs. 194 [82-286] m, p=0.038). Cardiac biomarkers were significantly elevated: NT-proBNP 4855 (1412-7494) versus 1606 (640-3843) ng/dL in lone AS (p=0.001), and hsTnT 49 (33-87) versus 24 (15-39) ng/L (p<0.001; normal hsTnT <14 ng/L).

AS-Amyloidosis was characterized by lower Sokolow-Lyon voltage (1.7 [1.3-2.4] vs. 2.3 [1.7-3.0] mV, p=0.007), and voltage/mass ratio (1.1 [0.8-1.9] vs. 1.8 [1.3-2.8] $mV/g/m^2x10^{-2}$, p=0.001). Higher RBBB prevalence did not reach significance (18.8 vs. 8.7%, p=0.06).

On echocardiographic assessment (**Table 2**) AS-Amyloidosis patients had slightly lower gradients (AV Vmax 3.9 vs. 4.2 m/s, AV peak/mean gradient 60/36 vs. 71/44 mmHg, p<0.05), though with no significant difference in absolute or indexed aortic valve area (AVA, p=0.5; AVAi p=0.3). Low-flow, low-gradient AS (Stage D2 or D3) was more prevalent among AS-Amyloidosis (56.2 vs. 32.9%, p=0.01), equally split between classical and paradoxical low-flow, low-gradient AS. Moreover, AS-amyloidosis exhibited worse cardiac remodeling with greater LV hypertrophy (LV mass index 150 [119-177] vs. 127 [101-151] g/m^2, p=0.006), and worse diastolic dysfunction. LV ejection fraction (LVEF) was not different (p=0.39), whereas indexed stroke volume (SVi) had trend to be lower (35.8 [27.4-44.0] vs. 40.1 [31.4-48.0] mL/m^2, p=0.06). Myocardial contraction fraction, the stroke volume per myocardial volume, was significantly worse (24.5 [20.6-29.3] vs. 33.6 [25.4-45.1] %, p<0.001). Global longitudinal strain was not different (-13.7 [-17.3;-10.2] vs. -15.6 [-19.3;-10.2] , p=0.3), but relative apical sparing was more pronounced in AS-Amyloidosis (1.1 [0.9-1.8] vs. 0.8 [0.7-1.1], p<0.01).

Lone AS versus AS-Amyloid (Grade-1 AS-CA)

Among AS-amyloid patients (Grade-1 AS-CA; n=16), cardiovascular risk profiles were comparable with lone AS apart from a lower prevalence of arterial hypertension. Carpal tunnel

syndrome was more common (20.0 vs. 1.1%, p<0.001). Cardiac markers were the same. With the exception of lower SVi in AS-Amyloid (33 [30-39] vs. 40 [31-48] ml/m^2, p=0.033) echocardiographic parameters did not differ, including LV mass index, LVEF, MCF, E/A-ratio, and strain values. On ECG, AS-amyloid patients displayed longer QRS duration, mainly due to a higher prevalence of RBBB (33.3 vs. 8.7%, p=0.002), and lower Sokolow-Lyon voltage (1.3 [1.0-2.0] vs. 2.3 [1.7-3.0] mV, p=0.002) and voltage mass-ratio (1.2 [0.7-2.0] vs. 1.8 [1.3-2.8] mV/g/m^2x10^{-2}, p=0.02).

RAISE Scoring system for discrimination of lone AS versus AS-CA

To aid clinical AS-amyloid/amyloidosis detection, a scoring system was created across 5 domains: **R**emodeling (LVH/diastolic dysfunction), **A**ge, **I**njury (hsTnT), **S**ystemic (carpel tunnel syndrome), and **E**lectrical (RBBB or low voltages). The RAISE score captures systemic disease (carpal tunnel syndrome, 3 points), disproportionate electrical remodeling (RBBB, 2 points; low voltages or Sokolow/Lyon index <1.9mV, 1 point), disproportionate myocardial remodeling (marked LVH: septal wall thickness≥18mm, 1 point; marked diastolic dysfunction, E/A ratio>1.4, 1 point), chronic myocardial injury (hsTnT>20 ng/l, 1 point) and age (≥85, 1 point). The score was derived in the Vienna cohort with strong discriminative power for the distinction of lone AS and AS-CA (AUC 0.86, 95% CI 0.78-0.94, p<0.001), and then validated in the London cohort (AUC 0.83, 95% CI 0.75-0.92, p<0.001). Scores of ≥2 and ≥3 points had high sensitivity (93.6 / 72.3%), with adequate specificity (52.1 / 83.6%) for the presence of AS-CA, respectively (**Figure 4**). When excluding troponin, AUC was 0.81 (95% CI 0.73-0.88, p<0.001, **Supplemental Figure 1**).

Outcome in AS-CA vs lone AS

After a median of 1.7 (1.3-2.6) years, 97 (24%) out of 407 patients referred for TAVR consideration had died. In this overall cohort, there was a trend towards higher one-year mortality in AS-CA vs. lone AS at 25.0% vs. 13.9% (log-rank, p=0.05, **Figure 2**). When excluding the AL case, unadjusted all-cause mortality of AS-CA was higher (196 deaths/1000 patient years) as compared to lone AS (137 deaths/1000 patient years, p=0.001), with even Grade-1 having significantly higher unadjusted all-cause mortality than lone AS (p<0.001). AVR improved survival both in lone AS and AS-CA compared to medical management (p<0.001 and 0.003, respectively, **Figure 3**). Results remained the same when excluding surgically managed patients (p<0.001 and 0.017, respectively, **Supplemental Figure 2**). There was a trend towards higher levels of intervention in the lone AS cohort (85.0 vs. 72.7% for lone AS vs. AS-CA, p=0.07). Post-AVR, survival was comparable between lone AS and AS-CA (log-rank, p=0.36). No interaction between CA and AVR was identified (p=0.94). One-year mortality was 10.8 (AVR) vs. 31.5% (medical) for the lone AS and 16.2 vs. 54.5% for the AS-CA cohort; this persisted out to two years. ATTR-targeting therapy (tafamidis only) was used in a minority of AS-CA patients (all after AVR, 14.9%, 7/47), and was not associated with a mortality difference (log-rank, p=0.40).

Predictors of outcome.

By multivariate Cox regression analysis, AVR (HR 0.62, 95%CI 0.53-0.73, p<0.001), serum albumin (HR 0.70, 95%CI 0.57-0.85, p=0.001), NT-proBNP (HR 1.40, 95%CI 1.12-1.76, p=0.003), creatinine (HR 1.20, 95%CI 1.04-1.38, p=0.015), and BMI (HR 0.77, 95%CI 0.61-0.97, p=0.018) were independent predictors of mortality for the overall cohort (**Table 3, Supplemental Table 1**). In the intervention sub-group, independent mortality predictors were periprocedural stroke (HR 1.43, 95%CI 1.25-1.63, p<0.001), hematocrit (HR 0.64, 95%CI 0.48-

0.84, p=0.001), serum albumin (HR 0.73, 95%CI 0.58-0.92, p=0.008), peak aortic jet velocity (HR 0.73, 95%CI 0.56-0.95, p=0.018), left atrial diameter (HR 1.34, 95%CI 1.03-1.74, p=0.032), and BMI (HR 0.73, 95%CI 0.54-0.98, p=0.033, **Supplemental Table 2**).

Periprocedural complications

Among patients undergoing TAVR, major adverse events according to VARC-2 occurred at the same rate in lone AS and AS-CA: stroke 2.7 vs. 2.9%, vascular complication 4.7 vs. 2.9%, acute kidney injury 7.5 vs. 6.1%, and pacemaker implantation 6.4 vs. 14.7%, p for all>0.05.

Discussion

In this international multicenter study of older patients with severe AS referred for TAVR, we show that dual pathology of severe AS and cardiac amyloid deposition (AS-CA) confers overall worse disease by functional capacity, cardiac remodeling and biomarkers, and can be predicted by a simple clinical score. Despite blinding clinicians prior to heart team decision, less AS-CA patients underwent TAVR and had overall worse outcomes. However, if AS-CA patients were selected for and received TAVR, their outcomes were indistinguishable from lone AS patients. Medically-managed patients – lone AS or AS-CA – had poor survival in line with previously published data like PARTNER 1B (**Central Illustration**) (20). We therefore conclude that a diagnosis of AS-CA should not preclude patients from TAVR.

We also confirmed that AS-CA is common, affecting 1 in 8 patients referred for TAVR; either amyloid deposition (grade-1) or clinical amyloidosis (grade-2/3). The presence of occult ATTR in AS was firstly described in patients undergoing SAVR in 2016. (21) Since then, data from multiple retro- and prospective studies have been reported, (4-7,22,23) most of which were solely dedicated to ATTR. This study adds to existing data on the prevalence of AS-CA; (4-7) data from our and other studies is ten times higher than in unselected populations where

prevalence in the elderly is <1% in those aged >80. (24) CA in AS is predominantly of the transthyretin-type (ATTR), but light chain amyloidosis (AL) needs to be excluded by concomitant screening for a plasma cell dyscrasia. (25) Although the vast majority of CA patients in the present series had ATTR, one case of AL was identified. Even though interpretation of light chain results is challenging and requires multidisciplinary decision making processes, AL screening is essential in case of suspicion for CA, as it usually requires urgent specific treatment (26).

The perception of futility of aortic valve intervention in AS-CA (27) originated from limited data in small observational studies. (27) In our data we clearly show that TAVR improves outcome in patients with AS-CA, and that on the basis of these data TAVR should not be withheld from patients with dual pathology AS-CA. The clinical picture in AS-Amyloidosis (= Grade-2/3) with lower functional capacity, elevated biomarkers and impaired biventricular function highlights a more decompensated clinical state, which will likely affect outcome, although in our cohort there was no statistical outcome difference in those patients who underwent TAVR. Intriguingly, patients with AS-Amyloid (= Grade-1) also had a worse outcome despite only mild remodeling (with lower SVi) and lower prevalence of electrical disturbances, and can therefore not be considered as clinically irrelevant or benign. Larger prospective studies and registry data is warranted to understand the importance of Grade-1 AS-Amyloid.

Routine screening of elderly patients with severe AS for AS-CA using bone scintigraphy is not feasible in routine clinical practice. But AS-CA patients have distinct clinical risk profiles including older age, history of carpal tunnel syndrome, elevated troponin levels, increased septal thickness and E/A ratio on echocardiography, and RBBB and lower Sokolow criteria on ECG.

Those parameters were integrated in a simple clinical scoring system that can help to identify AS patients with a high likelihood of coexisting CA and guide referral for bone scintigraphy and exclusion of a plasma cell dyscrasia. We propose a stepwise screening process for cardiac amyloidosis in elderly patients with severe AS. The proposed algorithm would allow high-volume TAVR centers to detect CA with a high sensitivity, without overstraining local resources: Based on the data presented (see **Figure 4**), scores of ≥2 points would instigate further screening by bone scintigraphy and light chain assessment. TAVR should not be delayed for AS-CA work-up without evidence of plasma cell dyscrasia, as TAVR improves survival. An alternative approach is the screening by obtaining the extracellular volume fraction (ECV%) from the pre-procedural TAVR cardiac CT (28) – the use of routine cardiac magnetic resonance is not feasible in all-comers for TAVR.

Underlying pathophysiological aspects of AS-CA are still incompletely understood. Despite the limited data on amyloid prevalence in the aging general population, ATTR has a lower prevalence in non-cardiac patients (<1%) and predominantly affects elderly men. (24) AS-CA appears to be different with not only a ten times higher general prevalence, but also near equal gender distribution and predilection for Grade 2/3 tracer uptake in AS (rather than an equal distribution between grades). These observations point towards a causal relationship between AS and amyloid. The increased LV afterload posed by AS has been hypothesized to prime the LV for deposition of amyloid fibrils; (6,29) this may be driven by increased extracellular matrix turnover, low-grade inflammation, chronic subendocardial ischemia and resultant cell death – both fibrosis and amyloid deposition occur with an endo- to epicardial gradient. In particular, the significant shear stresses in AS may cause an increased TTR deposition through a mechano-enzymatic cleavage process. (30) Valve intervention per se may stabilize ATTR by reducing the

shear stresses and thereby the aforementioned mechano-enzymatic cleavage process, (30) like AVR improves gastrointestinal bleeding in Heyde's syndrome by reducing activation of acquired type-2A von Willebrand factor. (31) Alternatively, common upstream pathways may affect both amyloidosis and valve stenosis progression, for example higher levels of systemic inflammation may accelerate aortic valve calcification and drive greater cardiac deposition of amyloidogenic protein. (32) Further research is warranted to strengthen our understanding of underlying mechanisms of AS-CA, especially with respect to amenability to novel TTR therapeutics. Whether patients with AS-CA post-AVR (i.e. afterload is treated) will benefit from novel therapies that stabilize the TTR tetramer (tafamidis)(33) or reduce TTR serum levels (AG10, inotersen, patisiran)(34-36) is unclear. In our study, seven out of 47 patients with ATTR-CA received tafamidis after AVR (on a named patient program in Austria). Survival of the 40 ATTR-therapy-naïve patients was similar to lone AS, parallel to findings in other studies. (6,9) Multi-center registry (AS-Amyloidosis.net) and a larger study of CA patients post-AVR is required to elucidate the benefit of ATTR therapy in this patient cohort, ideally in a randomized controlled trial (AS patients were excluded from previous RCTs in this area).

Limitations

Despite the recruitment of patients prior to heart team recommendations, there may still be a selection bias of those patients who were actually referred to recruiting centers. Blinding pre-procedure was broken for two reasons: seven patients had a plasma cell dyscrasia necessitating unblinding as per protocol. Austrian and UK centers used echocardiographic strain software from different vendors, which might affect comparability of respective data. Dual pathology AS-CA is much rarer in younger patients, (21) and at middle age would be affected by a different valve etiology (likely bicuspid) and amyloid type (AL or hereditary ATTR). These

were not investigated here - prognosis and management strategies are therefore not generalizable to this younger group. As opposed to previous findings, (7) relative apical sparing was more pronounced in AS-CA, whereas global longitudinal strain was comparable between groups. This should be re-evaluated in future studies. Mitral annular S' was not available for the derivation cohort (Vienna) and respective data is therefore not presented. SPECT/CT was not performed in the Vienna cohort – yet, blinded core-lab adjudication ensured that the diagnosis was as accurate as possible. Cause of mortality was not ascertained.

Conclusions

Dual pathology of AS-CA is common in older AS patients referred for possible TAVR. We present a simple clinical scoring system to help identify those where bone scintigraphy is indicated. AS-CA has worse functional capacity, cardiac remodeling pre procedure, and a trend towards worse prognosis if not treated by TAVR. Mortality is however the same if TAVR is performed. Based on this data, TAVR should not be withheld in AS-CA.

Perspectives

Competency in Patient Care and Procedural Skills: Concomitant cardiac amyloidosis (CA) occurs in 1 of 8 patients with severe aortic stenosis (AS) referred for transcatheter aortic valve replacement (TAVR), and is associated with more severe functional incapacity, cardiac remodeling, and adverse prognosis. Following TAVR, the outcomes of patients with concomitant CA was not significantly different from those with AS without CA.

Translational Outlook: Future studies should determine whether ATTR-specific treatment improves survival in patients with AS and ATTR-CA following aortic valve replacement..

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Figure Legends

Figure 1. Patient population. AS indicates aortic stenosis; DPD, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement;

Figure 2. One-year mortality for lone aortic stenosis (AS) and dual AS and cardiac amyloidosis (AS-CA). Among all-comers referred for aortic valve replacement, AS-CA experienced a trend towards higher all-cause mortality at one year.

Figure 3. Time-to-Event Curves for All-cause Mortality. Aortic valve replacement (AVR) improved outcomes for both lone aortic stenosis (AS) and dual pathology aortic stenosis and cardiac amyloidosis (AS-CA). Post-AVR survival of AS-CA was comparable to lone AS.

Figure 4. Scoring System for the discrimination of lone aortic stenosis and dual pathology aortic stenosis and cardiac amyloidosis. AFib indicates atrial fibrillation; BBB, bundle branch block; CTS, carpal tunnel syndrome; hs-TnT, high-sensitive troponin T; IVS, inter-ventricular septum; PM, pacemaker; RBBB, right bundle branch block; SR, sinus rhythm;

Central Illustration: Dual Pathology Aortic Stenosis-Cardiac Amyloidosis. AS indicates aortic stenosis; AVR, aortic valve replacement; CA, cardiac amyloidosis; DPD, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; LVH, left ventricular hypertrophy; MCF, myocardial contraction fraction; RBBB, right bundle branch block; TAVR, transcatheter aortic valve replacement. PARTNER-1B data adapted from *Kapadia SR et. al. Lancet 2015*.(20)

Table 1: Baseline clinical characteristics.

	DPD 0 n=359 (88.2%)	DPD 1 n=16 (3.9%)	DPD 2/3 n=32 (7.9%)	*P*-Value
Age, y	83.6 (72.3-87.6)	85.4 (80.2-89.1)	86.6 (84.1-91.8)[†]	0.001
Sex, male, %	48.2	50.0	65.6	0.167
BMI, kg/m^2	26.4 (23.5-29.7)	27.6 (24.5-30.0)	25.7 (23.2-29.1)	0.429
EuroSCORE II, %	4.2 (3.7-5.1)	4.1 (3.6-4.6)	4.5 (3.9-5.2)	0.297
Systolic BP, mmHg	134 (120-148)	138 (118-162)	126 (110-150)	0.319
Diastolic BP, mmHg	69 (60-79)	80 (58-91)	68 (60-74)	0.244
Arterial hypertension, %	83.4	62.5[*,‡]	90.6	0.046
Pre-interventional PM, %	14.6	6.3	25.0	0.173
Diabetes, %	26.1	18.8	18.8	0.550
Atrial fibrillation, %	36.3	50.0	50.0	0.186
CAD, %	45.9	68.8	21.9[†,‡]	0.005
Previous MI, %	10.3	12.5	6.3	0.724
Previous PCI, %	22.8	37.5	3.1[†,‡]	0.011
PAD, %	11.5	0.0	0.0[†]	0.046
Cerebral OD, %	16.4	0.0	12.5	0.202
CTS, %	1.1	20.0[*]	18.8[†]	<0.001
AS phenotype, %				0.176
D1: High gradient	67.2	53.3	43.8	
D2: LFLG, LVEF≥50%	16.4	26.7	28.1	
D3: LFLG, LVEF<50%	16.4	20.0	28.1	

Asymptomatic, %	7.7	6.7	6.3	0.948
Dyspnea, %	84.3	86.7	90.6	0.620
Angina, %	25.6	13.3	18.8	0.407
Syncope, %	19.1	6.7	12.5	0.324
Hs-TnT, ng/L	24 (15-39)	25 (23-32)	49 (33-87)[†,‡]	<0.001
NT-proBNP, ng/dL	1606 (640-3843)	1632 (933-3619)	4855 (1412-7494)[†]	0.003
Creatinine	1.1 (0.9-1.4)	1.3 (1.1-1.4)	1.1 (0.9-1.3)	0.230
eGFR, ml/min/1.73m^2	62.3 (46.4-77.9	52.5 (39.9-58.3)	61.4 (45.2-73.7)	0.213
Hemoglobin, mg/dl	11.9 (10.4-13.0)	13.3 (11.7-14.0)	11.8 (10.8-13.0)	0.097
Albumin, g/L	40.4 (32.6-40.0)	42.1 (41.9-44.5)	39.0 (35.6-42.0)	0.132
6-MWT, m	194 (82-286)	260 (191-369)	94 (50-225)[†,‡]	0.034

[*)] DPD grade 1 vs. DPD grade 0: p≤0.05
[†)] DPD grade 2/3 vs. DPD grade 0: p≤0.05
[‡)] DPD grade 2/3 vs. DPD grade 1: p≤0.05

DPD indicates ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid bone scintigraphy; BMI, body mass index; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; BP, blood pressure; PM, pacemaker; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; OD, occlusive disease; CTS, carpal tunnel syndrome; LFLG, low-flow low-gradient; LVEF, left ventricular ejection fraction; hs-TnT, high sensitive troponin T; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; eGFR, estimated glomerular filtration rate; 6-MWT, six minute walk test;

Table 2: Baseline echo- and electrocardiographic characteristics.

	DPD 0 n=359 (88.2%)	DPD 1 n=16 (3.9%)	DPD 2/3 n=32 (7.9%)	*P*- Value
BASELINE ECHOCARDIOGRAPHIC PARAMETERS				
LVEDD, mm	45.0 (40.0-50.0)	44.0 (39.0-50.0)	43.0 (38.0-49.0)	0.308
RVEDD, mm	36.0 (31.0-41.0)	36.0 (32.0-44.0)	38.0 (33.0-43.0)	0.158
IVS, mm	14.0 (12.0-16.0)	13.0 (12.0-14.0)	16.0 (14.0-19.0)[†, ‡]	0.012
LA diameter, mm	51.0 (41.0-62.0)	55.0 (42.0-64.0)	56.0 (44.0-66.0)	0.405
AVA, cm^2	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.7 (0.5-0.9)	0.814
AV Vmax, m/s	4.2 (3.9-4.6)	4.0 (3.4-4.7)	3.9 (3.2-4.6)[†]	0.017
AV-PPG, mmHg	71.0 (60.0-84.0)	64.0 (45.0-87.0)	60.0 (42.0-86.0)[†]	0.018
AV-MPG, mmHg	44.0 (35.0-53.0)	39.0 (27.0-49.0)	36.0 (25.0-48.0)[†]	0.017
SVi, ml/m^2	40.1 (31.4-48.0)	33.2 (30.0-39.1)[*]	35.8 (27.4-44.0)	0.021
LVEF, %	58.0 (44.0-64.0)	55.0 (35.0-61.0)	51.0 (42.0-64.0)	0.371
LVEDV, ml	91.0 (68.0-117.0)	87.0 (77.0-107.0)	80.0 (61.0-99.0)	0.201
LVESV, ml	34.0 (22.0-51.0)	33.0 (24.0-65.0)	36.0 (22.0-43.0)	0.819
Peak TR velocity, m/s	3.0 (2.4-3.5)	3.2 (2.0-3.8)	3.4 (2.6-4.1)	0.074
sPAP, mmHg	39.0 (27.0-50.0)	48.0 (18.0-53.0)	49.0 (32.0-61.0)	0.062
E wave deceleration time, ms	217 (166-281)	229 (189-337)	196 (158-246)	0.143
E/A ratio[§]	0.80 (0.68-1.20)	1.35 (0.64-3.09)	1.43 (0.88-2.43)[†]	0.010
TAPSE, mm	2.1 (1.6-2.5)	2.1 (1.6-2.2)	1.8 (1.3-2.3)	0.073
LV mass index, g/m^2	127 (101-151)	120 (91-163)	150 (119-177)[†, ‡]	0.017

MCF, %	33.6 (25.4-45.1)	34.8 (20.5-40.7)	24.5 (20.6-29.3)†	0.001
GLS, %	-15.6 (-19.3; -10.2)	-12.2 (-18.0; -8.6)	-13.7 (-17.3; -10.2)	0.433
Apical LS, %	-21.0 (-26.6; -13.2)	-19.8 (-26.1; -5.8)	-21.5 (-25.2; -16.0)	0.881
Midventricular LS, %	-13.3 (-17.5; -8.8)	-10.2 (-18.7; -7.2)	-10.1 (-13.8; -7.3)	0.214
Basal LS, %	-10.6 (-13.6; -6.5)	-9.3 (-12.0; -5.6)	-7.4 (-10.8; -3.0)	0.072
Apical/(mid+basal)	0.84 (0.69-1.05)	0.87 (0.55-1.61)	1.10 (0.85-1.78)†	0.005
ECG PARAMETERS				
Heart rate, bpm	70 (62-79)	74 (68-83)	68 (60-77)	0.355
Sokolow-Lyon index, mV	2.25 (1.70-2.95)	1.25 (1.03-1.96)*	1.68 (1.33-2.35)†	<0.001
VMR, mV/g/m^{2}x 10^{-2}	1.84 (1.29-2.79)	1.18 (0.66-2.02)*	1.06 (0.83-1.85)†	<0.001
Low voltage limb, %	3.2	0.0	3.1	0.783
QRS duration, ms	96 (86-118)	128 (106-141)*	107 (90-135)	0.005
LBBB, %	8.7	0.0	3.1	0.259
RBBB, %	8.7	33.3*	18.8	0.003

*) DPD grade 1 vs. DPD grade 0: p≤0.05
†) DPD grade 2/3 vs. DPD grade 0: p≤0.05
‡) DPD grade 2/3 vs. DPD grade 1: p≤0.05

§) For patients in sinus rhythm at the time of echocardiography.

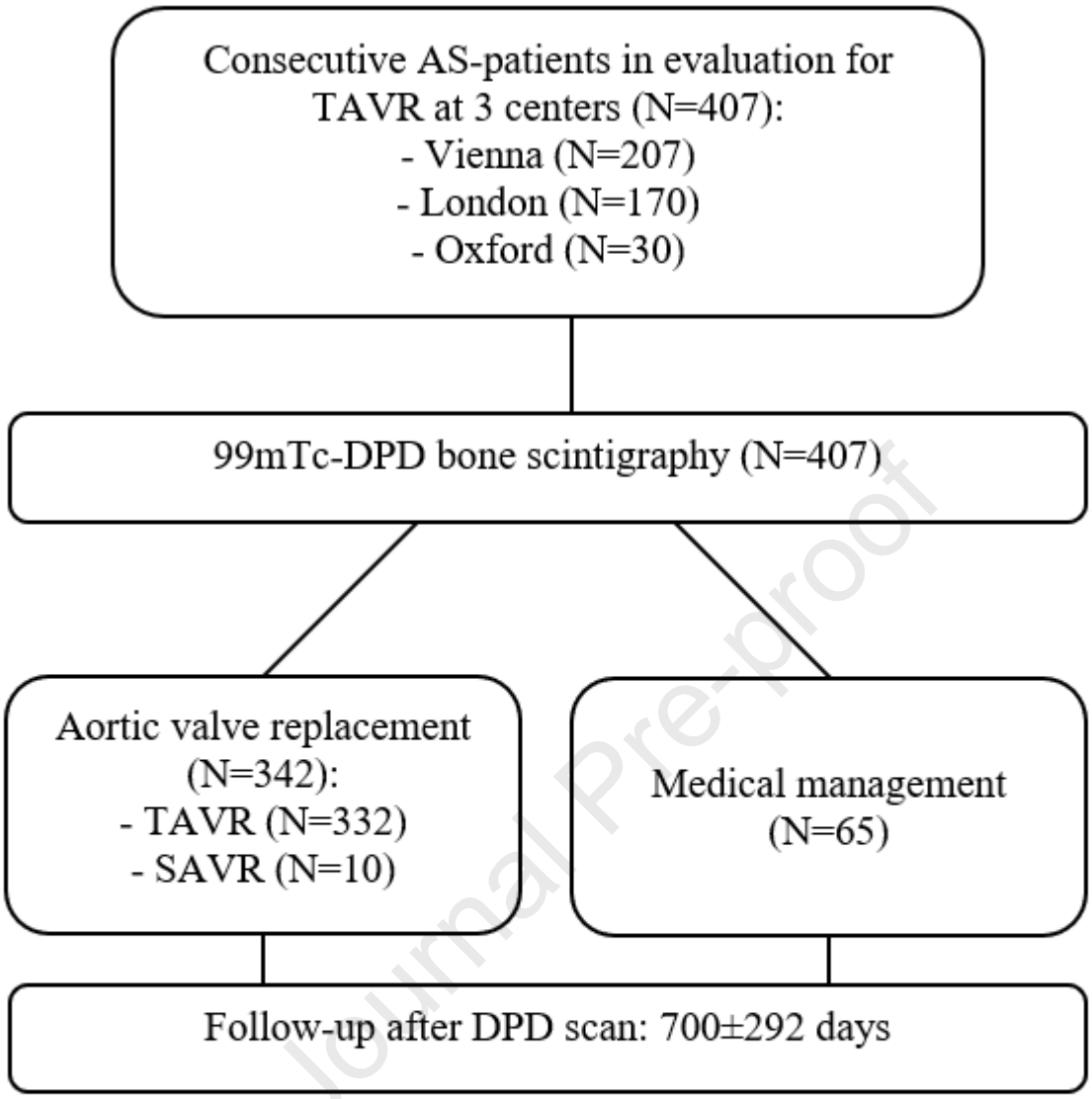
LV, left ventricular; RV, right ventricular; EDD, enddiastolic diameter; IVS, interventricular septum; LA, left atrial; AV, aortic valve; AVA, aortic valve area; Vmax, peak velocity; PPG, peak pressure gradient; MPG, mean pressure gradient; SVi, stroke volume index; EF, ejection fraction; EDV, enddiastolic volume; ESV, endsystolic volume; TR, tricuspid regurgitation; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; MCF, myocardial contraction fraction; LS, longitudinal strain; GLS, global longitudinal strain; VMR, voltage/mass-ratio; LBBB, left bundle branch block; RBBB, right bundle branch block.

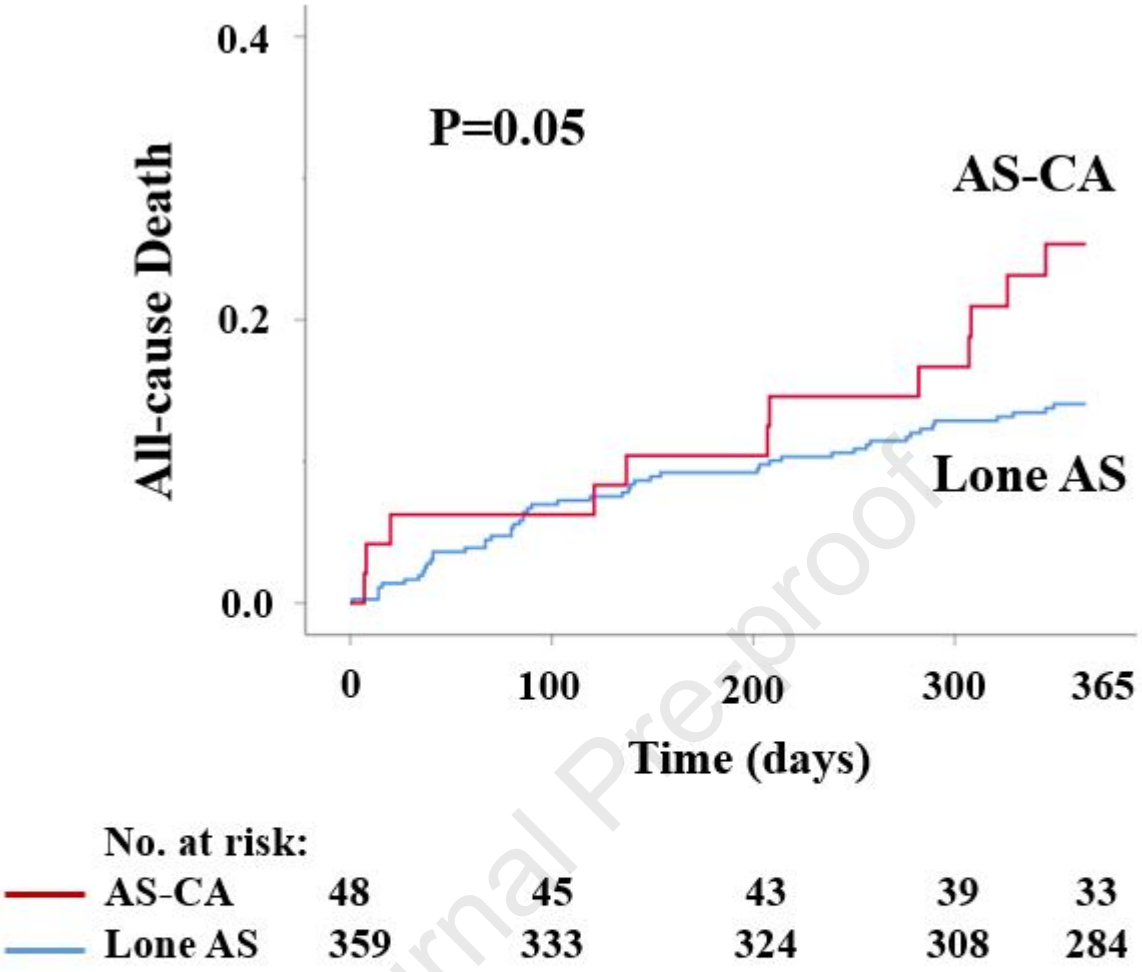
Table 3: Multivariate Cox regression analysis assessing the association of parameters with mortality. Overall cohort.

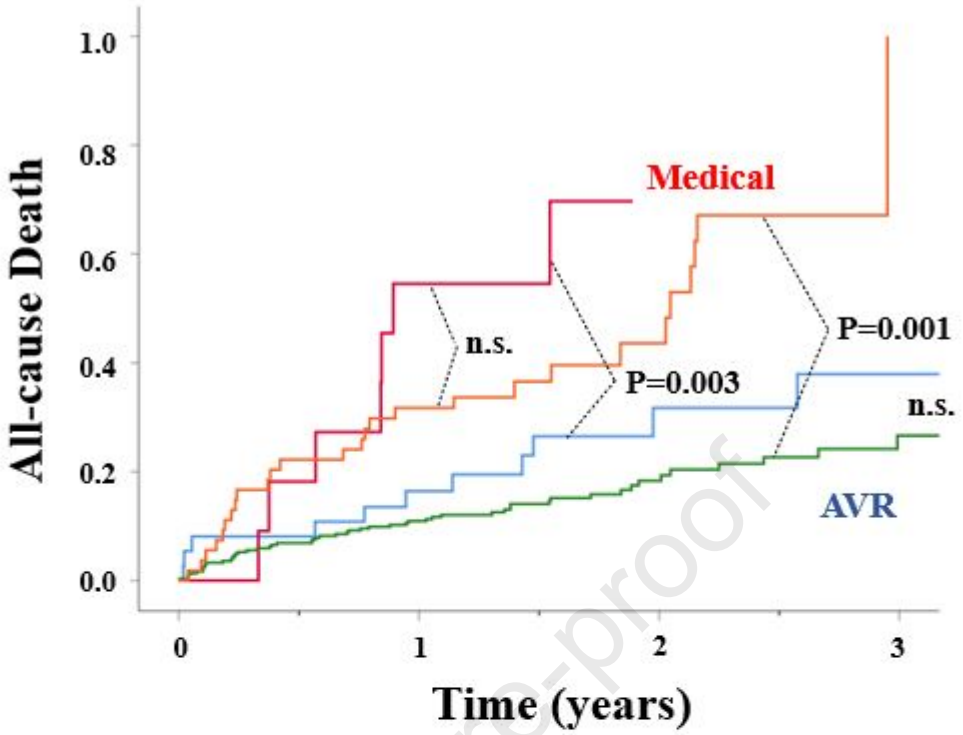
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline clinical parameters				
Aortic valve replacement	0.621 (0.532-0.725)	<0.001	0.617 (0.526-0.723)	**<0.001**
Albumin	0.605 (0.551-0.804)	<0.001	0.699 (0.572-0.854)	**0.001**
NT-proBNP*	1.555 (1.260-1.918)	<0.001	1.401 (1.118-1.755)	**0.003**
Creatinine	1.249 (1.098-1.422)	<0.001	1.196 (1.035-1.383)	**0.015**
BMI	0.721 (0.574-0.905)	0.005	0.765 (0.613-0.965)	**0.018**
Troponin T	1.354 (1.204-1-522)	<0.001		
Hematocrit	0.741 (0.604-0.909)	0.004		
Dual AS-CA	1.145 (0.970-1.352)	0.100		
AV-Vmax	0.673 (0.551-0.823)	<0.001		
AV-MPG	0.666 (0.532-0.834)	0.001		
LVEF	0.825 (0.684-0.995)	0.045		
LVESV	1.270 (1.077-1.498)	0.004		
GLS	1.263 (1.049-1.521)	0.014		
Apical LS	1.260 (1.054-1.505)	0.011		
Midventricular LS	1.237 (1.030-1.486)	0.023		

*) NT-proBNP was graded into quartiles for this analysis

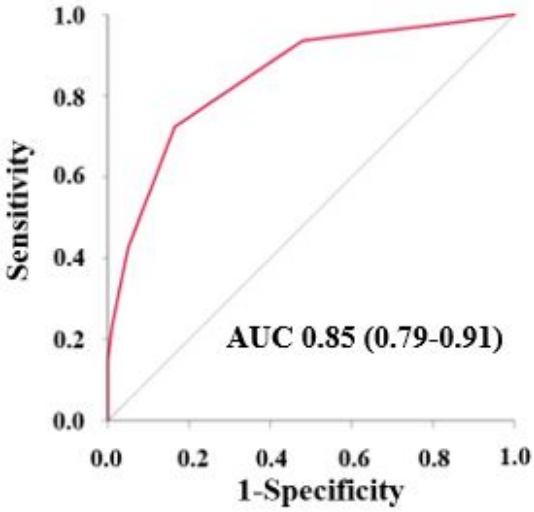
HR indicates hazard ratio; CI, confidence interval; BMI, body mass index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; AS-CA, dual aortic stenosis and cardiac amyloid pathology; LA, left atrial; AV, aortic valve; Vmax, peak velocity; MPG, mean pressure gradient; LV, left ventricular; EF, ejection fraction; ESV, endsystolic volume; GLS, global longitudinal strain







No. at risk:				
AS-CA - Medical	11	4	0	
Lone AS - Medical	54	35	13	0
AS-CA - AVR	37	29	13	6
Lone AS - AVR	305	249	85	30



Parameter	Points
CTS	3
RBBB	2
Age≥85y	1
Hs-TnT>20ng/L	1
IVS≥18mm	1
If in SR*: E/A ratio >1.4	1
If no BBB or PM: Sokolow index <1.9mV	1

*) AUC for AFib sub-cohort: 0.83

Score	Specificity	Sensitivity
≥6 points	100%	14.9%
≥5 points	98.9%	23.4%
≥4 points	95.0%	42.6%
≥3 points	83.6%	72.3%
≥2 points	52.1%	93.6%
≥1 point	16.7%	97.9%

Supplemental material

Table S1: Uni- and multivariate Cox regression analysis assessing the association of parameters with mortality. Overall cohort.

	Univariate analysis			Multivariate analysis*	
	HR (95% CI)	*P*-value	PHA (*P*-value)	HR (95% CI)	*P*-value
Baseline clinical parameters					
Age (per year increase)	1.005 (0.972-1.039)	0.781			
Sex, male	1.683 (1.119-2.530)	**0.012**	0.752		
BMI	0.938 (0.897-0.981)	**0.005**	0.580	0.765 (0.613-0.965)	**0.018**
EuroSCORE II	1.000 (0.992-1.007)	0.944			
BP systolic	0.997 (0.988-1.007)	0.597			
BP diastolic	0.998 (0.980-1.016)	0.831			
Arterial hypertension	1.013 (0.592-1.733)	0.963			
Pacemaker carrier	1.252 (0.740-2.116)	0.402			
Diabetes	1.243 (0.796-1.942)	0.339			
Atrial fibrillation	1.441 (0.963-2.157)	0.076			
Hyperlipidemia	0.548 (0.363-0.826)	**0.004**	0.011‡		
CAD	1.004 (0.689-1.507)	0.985			
Previous MCI	0.883 (0.406-1.729)	0.632			
Previous PCI	1.115 (0.673-1.850)	0.672			
PAD	1.561 (0.851-2.865)	0.151			
Cerebral OD	1.069 (0.605-1.889)	0.818			
CTS	1.043 (0.382-2.843)	0.935			
Asymptomatic	1.388 (0.720-2.677)	0.328			
Dyspnea	0.775 (0.463-1.296)	0.331			
Angina	0.835 (0.513-1.360)	0.469			
Syncope	0.592 (0.329-1.066)	0.081			
Troponin T	1.008 (1.005-1-011)	**<0.001**	0.122		

NT-proBNP[†]	1.492 (1.233-1.805)	**<0.001**	0.231	1.401 (1.118-1.755)	**0.003**
Creatinine	1.395 (1.157-1.683)	**<0.001**	0.670	1.196 (1.035-1.383)	**0.015**
eGFR	0.992 (0.982-1.001)	0.083			
Hemoglobin	0.985 (0.919-1.056)	0.675			
Hematocrit	0.942 (0.905-0.981)	**0.004**	0.533		
Albumin	0.928 (0.896-0.960)	**<0.001**	0.075	0.699 (0.572-0.854)	**0.001**
6-MWT	0.999 (0.997-1.001)	0.466			
Dual AS-CA	1.521 (0.910-2.542)	0.100	0.667		
Aortic valve replacement	0.273 (0.179-0.415)	**<0.001**	0.129	0.617 (0.526-0.723)	**<0.001**
Baseline echocardiographic parameters					
LVEDD	1.009 (0.982-1.036)	0.512			
RVEDD	1.020 (0.994-1.048)	0.132			
LA diameter	1.017 (0.999-1.035)	0.064			
IVS	0.933 (0.862-1.011)	0.089			
AVA	1.513 (0.656-3.491)	0.332			
AV Vmax	0.553 (0.409-0.747)	**<0.001**	0.196		
AV-PPG	0.982 (0.973-0.992)	**<0.001**	0.284		
AV-MPG	0.973 (0.959-0.988)	**0.001**	0.074		
SVi	0.996 (0.979-1.014)	0.686			
LVEF	0.988 (0.976-1.000)	**0.045**	0.505		
LVEDV	1.004 (0.998-1.009)	0.169			
LVESV	1.009 (1.003-1.016)	**0.004**	0.646		
Peak TR velocity	1.138 (0.935-1.386)	0.197			
sPAP	1.009 (0.997-1.022)	0.138			
LV mass index	1.001 (0.996-1.006)	0.593			
MCF	0.369 (0.082-1.650)	0.192			
GLS	1.053 (1.011-1.096)	**0.014**	0.375		
Apical LS	1.033 (1.007-1.058)	**0.011**	0.411		
Midventricular LS	1.046 (1.006-1.088)	**0.023**	0.386		
Basal LS	1.015 (0.976-1.056)	0.455			
Apical/(mid+basal)	0.834 (0.625-1.112)	0.216			

Baseline electrocardiographic parameters		
Heart rate	0.990 (0.974-1.007)	0.243
Sokolow-Lyon index	1.023 (0.773-1.355)	0.872
Low voltage limb	2.145 (0.782-5.882)	0.138
QRS duration	1.003 (0.996-1.011)	0.349
LBBB	0.737 (0.322-1.687)	0.737
RBBB	0.924 (0.465-1.840)	0.823
LAFB	1.511 (0.936-2.441)	0.091

*) Scaled HRs are displayed for multivariate analysis.

†) NTproBNP was graded into quartiles for this analysis.

‡) Hyperlipidemia did not satisfy the proportional hazard assumption and was therefore excluded from multivariate analysis

HR indicates hazard ratio; CI, confidence interval; PHA, proportionate hazard assumption; BMI, body mass index; STS, Society of Thoracic Surgery; BP, blood pressure; PM, pacemaker; CAD, coronary artery disease; MCI, myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; OD, occlusive disease; CTS, carpal tunnel syndrome; hs, high sensitive; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; eGFR, estimated glomerular filtration rate; 6-MWT, six minute walk test; AS-CA, dual pathology of aortic stenosis and cardiac amyloidosis; LV, left ventricular; RV, right ventricular; EDD, enddiastolic diameter; IVS, interventricular septum; LA, left atrial; AV, aortic valve; AVA, aortic valve area; Vmax, peak velocity; PPG, peak pressure gradient; MPG, mean pressure gradient; SVi, stroke volume index; EF, ejection fraction; EDV, enddiastolic volume; ESV, endsystolic volume; TR, tricuspid regurgitation; sPAP, systolic pulmonary artery pressure; MCF, myocardial contraction fraction; LS, longitudinal strain; GLS, global longitudinal strain; VMR, voltage/mass-ratio; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block.

Table S2: Uni- and multivariate Cox regression analysis assessing the association of parameters with mortality. AVR only cohort.

	Univariate analysis			Multivariate analysis*	
	HR (95% CI)	*P*-value	PHA (*P*-value)	HR (95% CI)	*P*-value
Baseline clinical parameters					
Age (per year increase)	0.989 (0.948-1.031)	0.593			
Sex, male	1.785 (1.059-3.010)	**0.030**	0.899		
BMI	0.925 (0.873-0.981)	**0.009**	0.789	0.727 (0.542-0.975)	**0.033**
EuroSCORE II	0.992 (0.965-1.019)	0.545			
BP systolic	0.993 (0.982-1.005)	0.286			
BP diastolic	0.992 (0.971-1.014)	0.481			
Arterial hypertension	1.413 (0.642-3.113)	0.390			
Pre-interventional PM	1.169 (0.574-2.378)	0.667			
Diabetes	1.153 (0.649-2.048)	0.628			
Atrial fibrillation	1.622 (0.973-2.703)	0.064			
Hyperlipidemia	0.811 (0.486-1.352)	0.421			
CAD	1.044 (0.625-1.745)	0.869			
Previous MCI	1.075 (0.488-2.368)	0.857			
Previous PCI	1.289 (0.705-2.358)	0.410			
PAD	1.346 (0.610-2.970)	0.461			
Cerebral OD	1.071 (0.525-2.185)	0.850			
CTS	0.459 (0.064-3.319)	0.441			
Valve-in-valve	2.527 (0.772-8.270)	0.125			
Asymptomatic	0.777 (0.189-3.186)	0.726			
Dyspnea	1.024 (0.439-2.387)	0.956			
Angina	0.783 (0.422-1.453)	0.438			
Syncope	0.622 (0.304-1.272)	0.622			
hs-TnT	1.008 (1.003-1-013)	**0.002**	0.129		
NT-proBNP[†]	1.366 (1.007-1.733)	**0.010**	0.257		

Creatinine	1.456 (1.188-1.783)	**<0.001**	0.701		
eGFR	0.984 (0.972-0.997)	**0.017**	0.673		
Hemoglobin	0.957 (0.883-1.038)	0.291			
Hematocrit	0.907 (0.860-0.957)	**<0.001**	0.590	0.638 (0.484-0.842)	**0.001**
Albumin	0.911 (0.874-0.950)	**<0.001**	0.082	0.731 (0.579-0.923)	**0.008**
6-MWT	1.000 (0.997-1.003)	0.983			
Dual AS-CA	1.050 (0.476-2.313)	0.904			
Baseline echocardiographic parameters					
LVEDD	0.994 (0.959-1.030)	0.983			
RVEDD	1.016 (0.980-1.053)	0.387			
LA diameter	1.032 (1.010-1.055)	**0.005**	0.163	1.337 (1.025-1.744)	**0.032**
IVS	0.969 (0.882-1.065)	0.515			
AVA	1.349(0.445-4.089)	0.597			
AV Vmax	0.586 (0.395-0.869)	**0.008**	0.272	0.725 (0.555-0.946)	**0.018**
AV-PPG	0.984 (0.972-0.997)	**0.013**	0.206		
AV-MPG	0.977 (0.959-0.996)	**0.020**	0.061		
SVi	1.005 (0.983-1.027)	0.677			
LVEF	1.001 (0.984-1.017)	0.922			
LVEDV	1.000 (0.992-1.007)	0.960			
LVESV	1.005 (0.995-1.015)	0.318			
Peak TR velocity	1.070 (0.829-1.382)	0.602			
sPAP	1.010 (0.994-1.025)	0.217			
LV mass index	1.003 (0.996-1.009)	0.401			
MCF	0.312 (0.043-2.261)	0.249			
GLS	1.031 (0.980-1.085)	0.239			
Apical LS	1.018 (0.985-1.052)	0.288			
Midventricular LS	1.018 (0.971-1.068)	0.461			
Basal LS	0.993 (0.943-1.045)	0.786			
Apical/(mid+basal)	0.794 (0.517-1.220)	0.293			
Baseline electrocardiographic parameters					
Heart rate	0.991 (0.972-1.010)	0.350			

Sokolow-Lyon index	0.993 (0.708-1.393)	0.967			
VMR	0.767 (0.550-1.071)	0.229			
Low voltage limb	2.358 (0.731-7.603)	0.151			
QRS duration	1.002 (0.994-1.011)	0.588			
LBBB	1.083 (0.433-2.712)	0.864			
RBBB	0.854 (0.341-2.139)	0.736			
LAFB	1.564 (0.855-2.860)	0.147			
Periprocedural characteristics					
PM dependency	1.249 (0.499-3.122)	0.635			
Major vascular complication	1.822 (0.728-4.558)	0.200			
Major stroke	7.768 (3.513-17.177)	**<0.001**	0.450	1.429 (1.250-1.633)	**<0.001**
Acute kidney injury	1.049 (0.379-2.900)	0.927			

*) Scaled HRs are displayed for multivariate analysis.

†) NTproBNP was graded into quartiles for this analysis.

HR indicates hazard ratio; CI, confidence interval; PHA, proportionate hazard assumption; BMI, body mass index; STS, Society of Thoracic Surgery; BP, blood pressure; PM, pacemaker; CAD, coronary artery disease; MCI, myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; OD, occlusive disease; CTS, carpal tunnel syndrome; hs-TnT, high sensitive troponin T; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; eGFR, estimated glomerular filtration rate; 6-MWT, six minute walk test; AS-CA, dual pathology of aortic stenosis and cardiac amyloidosis; LV, left ventricular; RV, right ventricular; EDD, enddiastolic diameter; IVS, interventricular septum; LA, left atrial; AV, aortic valve; AVA, aortic valve area; Vmax, peak velocity; PPG, peak pressure gradient; MPG, mean pressure gradient; SVi, stroke volume index; EF, ejection fraction; EDV, enddiastolic volume; ESV, endsystolic volume; TR, tricuspid regurgitation; sPAP, systolic pulmonary artery pressure; MCF, myocardial contraction fraction; LS, longitudinal strain; GLS, global longitudinal strain; VMR, voltage/mass-ratio; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block.

Table S3: Uni- and multivariate Cox regression analysis assessing the association of parameters with 1-year mortality. Overall cohort.

	Univariate analysis			Multivariate analysis*	
	HR (95% CI)	*P*-value	PHA (*P*-value)	HR (95% CI)	*P*-value
Baseline clinical parameters					
Age (per year increase)	0.997 (0.958-1.037)	0.873			
Sex, male	1.771 (1.055-2.972)	**0.031**	0.161		
BMI	0.941 (0.889-0.995)	**0.032**	0.127		
EuroSCORE II	1.001 (0.994-1.009)	0.734			
BP systolic	0.996 (0.984-1.008)	0.533			
BP diastolic	0.995 (0.974-1.017)	0.672			
Arterial hypertension	0.792 (0.421-1.491)	0.469			
Pacemaker carrier	0.842 (0.400-1.772)	0.650			
Diabetes	1.179 (0.672-2.067)	0.565			
Atrial fibrillation	1.012 (0.601-1.703)	0.964			
Hyperlipidemia	0.778 (0.469-1.290)	0.330			
CAD	1.012 (0.609-1.683)	0.963			
Previous MCI	0.465 (0.146-1.484)	0.196			
Previous PCI	1.139 (0.626-2.071)	0.671			
PAD	1.449 (0.688-3.051)	0.329			
Cerebral OD	1.874 (0.414-1.844)	0.724			
CTS	0.981 (0.240-4.016)	0.979			
Asymptomatic	1.177 (0.471-2.943)	0.727			
Dyspnea	0.662 (0.351-1.248)	0.202			
Angina	0.966 (0.529-1.763)	0.911			
Syncope	0.792 (0.390-1.611)	0.521			
Troponin T	1.007 (1.004-1-010)	**<0.001**	0.295		
NT-proBNP[†]	1.650 (1.290-2.109)	**<0.001**	0.316	1.492 (1.120-1.988)	**0.006**
Creatinine	1.404 (1.159-1.701)	**0.001**	0.869	1.180 (1.012-1.376)	**0.035**

eGFR	0.986 (0.975-0.998)	**0.025**	0.652		
Hemoglobin	1.013 (0.926-1.107)	0.783			
Hematocrit	0.942 (0.896-0.991)	**0.021**	0.268		
Albumin	0.910 (0.872-0.949)	**<0.001**	0.335	0.644 (0.503-0.825)	**0.001**
6-MWT	0.999 (0.996-1.002)	0.502			
Dual AS-CA	1.849 (0.999-3.471)	**0.050**	0.144		
Aortic valve replacement	0.289 (0.172-0.484)	**<0.001**	0.208	0.626 (0.515-0.760)	**<0.001**
Baseline echocardiographic parameters					
LVEDD	1.010 (0.977-1.044)	0.567			
RVEDD	1.010 (0.977-1.044)	0.551			
LA diameter	1.020 (0.998-1.042)	0.071			
IVS	0.909 (0.825-1.003)	0.057			
AVA	1.258 (0.431-3.673)	0.675			
AV Vmax	0.626 (0.431-0.908)	**0.014**	0.708		
AV-PPG	0.986 (0.975-0.998)	**0.024**	0.551		
AV-MPG	0.983 (0.965-1.000)	0.054			
SVi	1.004 (0.983-1.025)	0.737			
LVEF	0.991 (0.975-1.006)	0.229			
LVEDV	1.003 (0.997-1.010)	0.317			
LVESV	1.010 (1.002-1.017)	**0.013**	0.164		
Peak TR velocity	1.091 (0.844-1.410)	0.505			
sPAP	1.013 (0.999-1.028)	0.060			
LV mass index	1.001 (0.994-1.007)	0.870			
MCF	0.779 (0.128-4.744)	0.787			
GLS	1.0051 (0.997-1.108)	0.063			
Apical LS	1.026 (0.994-1.059)	0.117			
Midventricular LS	1.044 (0.992-1.098)	0.096			
Basal LS	1.037 (0.984-1.093)	0.173			
Apical/(mid+basal)	1.000 (0.744-1.346)	0.998			
Baseline electrocardiographic parameters					
Heart rate	0.993 (0.972-1.015)	0.534			

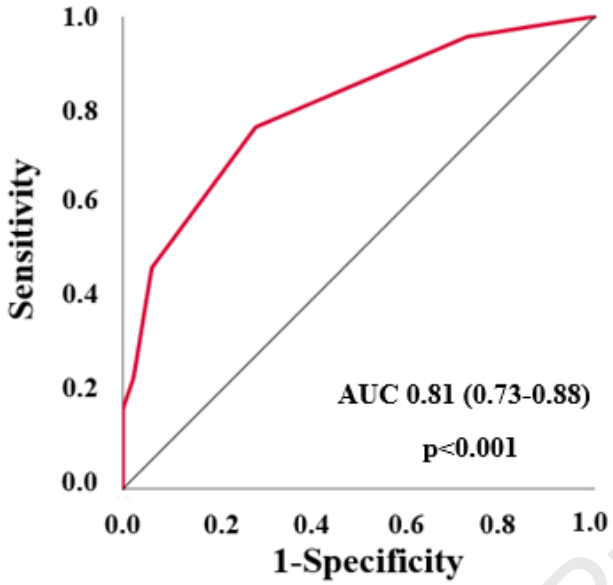
Sokolow-Lyon index	1.224 (0.882-1.700)	0.226
Low voltage limb	1.864 (0.583-5.959)	0.294
QRS duration	0.998 (0.988-1.009)	0.734
LBBB	0.194 (0.027-1.399)	0.104
RBBB	0.809 (0.323-2.026)	0.651
LAFB	1.141 (0.591-2.203)	0.694

*) Scaled HRs are displayed for multivariate analysis.

†) NTproBNP was graded into quartiles for this analysis.

HR indicates hazard ratio; CI, confidence interval; PHA, proportionate hazard assumption; BMI, body mass index; STS, Society of Thoracic Surgery; BP, blood pressure; PM, pacemaker; CAD, coronary artery disease; MCI, myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; OD, occlusive disease; CTS, carpal tunnel syndrome; hs, high sensitive; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; eGFR, estimated glomerular filtration rate; 6-MWT, six minute walk test; AS-CA, dual pathology of aortic stenosis and cardiac amyloidosis; LV, left ventricular; RV, right ventricular; EDD, enddiastolic diameter; IVS, interventricular septum; LA, left atrial; AV, aortic valve; AVA, aortic valve area; Vmax, peak velocity; PPG, peak pressure gradient; MPG, mean pressure gradient; SVi, stroke volume index; EF, ejection fraction; EDV, enddiastolic volume; ESV, endsystolic volume; TR, tricuspid regurgitation; sPAP, systolic pulmonary artery pressure; MCF, myocardial contraction fraction; LS, longitudinal strain; GLS, global longitudinal strain; VMR, voltage/mass-ratio; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block.

Figure S1. Scoring System for the discrimination of lone aortic stenosis and aortic stenosis with positive bone scan results. Troponin not included as a parameter.



Parameter	Points
CTS	3
RBBB	2
Age≥85y	1
IVS≥18	1
E/A ratio>1.4	1
If no BBB or PM: Sokolow index <1.9	1

Score	Sensitivity	Specificity
≥5 points	100%	17.0%
≥4 points	97.8%	23.4%
≥3 points	93.8%	46.8%
≥2 points	71.9%	76.6%
≥1 point	27.0%	95.7%

Figure S2: Time-to-Event Curves for All-cause Mortality comparing patients undergoing transcatheter aortic valve replacement (TAVR) and medical management for lone AS (Panel A) and AS-CA cohort (Panel B).