Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis

Christian Nitsche, MD,[a] Paul R. Scully, PHD,[b,c] Kush P. Patel, MBBS,[b,d] Andreas A. Kammerlander, MD, PHD,[a]
Matthias Koschutnik, MD,[a] Carolina Dona, MD,[a] Tim Wollenweber, MD,[e] Nida Ahmed, MBBS,[b,d]
George D. Thornton, MBBS,[b,d] Andrew D. Kelion, MD,[f] Nikant Sabharwal, MD,[f] James D. Newton, MD,[f]
Muhiddin Ozkor, MD,[d] Simon Kennon, MD,[d] Michael Mullen, MD,[d] Guy Lloyd, MD,[b,d,g] Marianna Fontana, PHD,[h]
Philip N. Hawkins, FMedSci,[h] Francesca Pugliese, MD,[b,g] Leon J. Menezes, MD,[d,i] James C. Moon, MD,[b,d]
Julia Mascherbauer, MD,[a] Thomas A. Treibel, PHD[b,d]

ABSTRACT

BACKGROUND Older patients with severe aortic stenosis (AS) are increasingly identified as having cardiac amyloidosis (CA). It is unknown whether concomitant AS-CA has worse outcomes or results in futility of transcatheter aortic valve replacement (TAVR).

OBJECTIVES This study identified clinical characteristics and outcomes of AS-CA compared with lone AS.

METHODS Patients who were referred for TAVR at 3 international sites underwent blinded research core laboratory ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) bone scintigraphy (Perugini grade 0: negative; grades 1 to 3: increasingly positive) before intervention. Transthyretin-CA (ATTR) was diagnosed by DPD and absence of a clonal immunoglobulin, and light-chain CA (AL) was diagnosed via tissue biopsy. National registries captured all-cause mortality.

RESULTS A total of 407 patients (age 83.4 ± 6.5 years; 49.8% men) were recruited. DPD was positive in 48 patients (11.8%; grade 1: 3.9% [n = 16]; grade 2/3: 7.9% [n = 32]). AL was diagnosed in 1 patient with grade 1. Patients with grade 2/3 had worse functional capacity, biomarkers (N-terminal pro-brain natriuretic peptide and/or high-sensitivity troponin T), and biventricular remodeling. A clinical score (RAISE) that used left ventricular remodeling (hypertrophy/diastolic dysfunction), age, injury (high-sensitivity troponin T), systemic involvement, and electrical abnormalities (right bundle branch block/low voltages) was developed to predict the presence of AS-CA (area under the curve: 0.86; 95% confidence interval: 0.78 to 0.94; p < 0.001). Decisions by the heart team (DPD-blinded) resulted in TAVR (333 [81.6%]), surgical AVR (10 [2.5%]), or medical management (65 [15.9%]). After a median of 1.7 years, 23% of patients died. One-year mortality was worse in all patients with AS-CA (grade: 1 to 3) than those with lone AS (24.5% vs. 13.9%; p = 0.05). TAVR improved survival versus medical management; AS-CA survival post-TAVR did not differ from lone AS (p = 0.36).

CONCLUSIONS Concomitant pathology of AS-CA is common in older patients with AS and can be predicted clinically. AS-CA has worse clinical presentation and a trend toward worse prognosis, unless treated. Therefore, TAVR should not be withheld in AS-CA. (J Am Coll Cardiol 2021;77:128–39) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria; [b]Institute of Cardiovascular Science, University College London, London, United Kingdom; [c]Cardiology Department, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom; [d]Barts Heart Centre, St. Bartholomew's Hospital, London, United Kingdom; [e]Department of Nuclear Medicine, Medical University of Vienna, Vienna, Austria; [f]John Radcliffe Hospital, Oxford, United Kingdom; [g]Queen Mary University London, London, United Kingdom; [h]National Amyloid Centre, London, United Kingdom; and the [i]UCL/ULCH NIHR Biomedical Research Centre, London, United Kingdom.

Degenerative aortic stenosis (AS) affects >3% of people aged 75 years or older (1). In severe AS with symptoms or cardiac decompensation, surgical aortic valve replacement (SAVR) or transcatheter-based aortic valve replacement (TAVR) are indicated to improve outcome (2). Morphologically, significant AS is characterized by hypertrophic myocardial remodeling, similar to cardiac amyloidosis (CA). CA is an infiltrative process caused by myocardial deposition of amyloid fibrils. The 2 major amyloid proteins found in ventricular myocardium are transthyretin (TTR), which predominantly affects older adults, and immunoglobulin light-chain (AL), which occurs less frequently (3). The coexistence 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 (^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD], ^{99m}technetium-pyrophosphate, or ^{99m}technetium-hydroxymethylene diphosphonate), in particular for ATTR. This is important because of the advent of novel CA therapies (8). The survival implications of concurrent AS-CA remain unclear. Three potentially underpowered studies recently reported no mortality difference of AS-CA compared with lone AS in cohorts of approximately 200 patients (4,6,9). Therefore, the present multicenter study was designed to evaluate the differential mortality hazard of AS-CA versus lone AS, as well as predictors of AS-CA beyond the existing diagnostic criteria.

METHODS

STUDY POPULATION. This prospective, multicenter study enrolled consecutive adult patients with severe degenerative AS who were referred for TAVR at 3 tertiary referral centers: Barts Heart Centre, London, United Kingdom (October 2016 to January 2019); John Radcliffe Hospital, Oxford, United Kingdom (January 2018 to June 2019); and Vienna General Hospital, Vienna, Austria (October 2017 to February 2019). This study included patients from 2 previous published studies (4,6), which expanded the study cohort, follow-up, and implementation of the blinded core laboratory analysis of bone scintigraphy.

To reduce selection bias, recruitment took place after referral to AVR and before discussion by the heart team. Therefore, we anticipated some crossover to medical therapy and to surgical valve replacement. All patients underwent blinded DPD bone scintigraphy, as well as clinical and laboratory assessment, a 6-min walk test, electrocardiography, and transthoracic echocardiography with strain analysis. All-cause mortality was selected as the primary study endpoint, was determined using national data via the U.K. National Health Service (NHS Spine), and Austrian Death Registry, and was 100% complete. Periprocedural complications were defined using the Valve Academic Research Consortium-2 criteria. This study complied with the Declaration of Helsinki; relevant local ethics and site approvals were obtained, and all patients provided written informed consent.
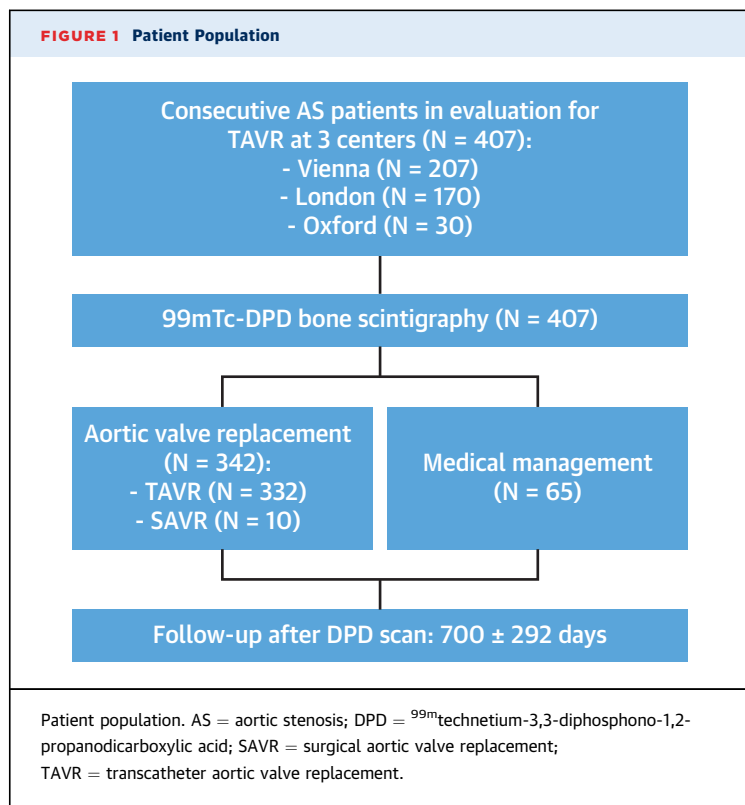
LABORATORY AND ELECTROCARDIOGRAPHIC ASSESSMENT. For detection of pathological light-chains underlying AL-CA, laboratory testing included serum immunoglobins and free light-chain quantification, as well as serum and/or urine immunofixation, which was performed in all DPD-positive patients. In addition, 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 was determined in patients without bundle branch block, and paced rhythm was assessed by dividing the Sokolow-Lyon index by the left ventricular (LV) mass index on echocardiography. The Sokolow-Lyon index was calculated as the sum of pre-cordial 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 of ≤0.5 mV.

ECHOCARDIOGRAPHY. All patients underwent clinical transthoracic echocardiography, 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). LV ejection fraction (LVEF) was calculated using Simpson's biplane test where possible or otherwise quantified visually. Stroke volume (SV) was quantified using the LV outflow tract velocity–time integral and the LV outflow tract 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 the 17 segments of the LV (16). Global LS was calculated as the average LS of these 17 segments. Relative

FIGURE 1   Patient Population

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

apical LS was calculated as average apical LS/(average basal LS + average mid-LS). The myocardial contraction fraction, which indexes SV to the myocardial volume, was calculated as previously described (17). The classic low-flow, low gradient was defined as an aortic valve area of ≤1.0 cm², with an LVEF of <50%, an indexed SV of <35 ml/m², a peak aortic valve velocity of <4 m/s, and a mean gradient of <40 mm Hg. In contrast, the paradoxical low-flow, low-gradient was defined as an LVEF of ≥50% but an indexed SV of <35 ml/m², peak velocity of <4 m/s, and a mean gradient of <40 mm Hg (14). When equivocal, AS severity was adjudicated using low-dose dobutamine stress echocardiography and the computed tomography–derived aortic valve calcium score.

DPD BONE SCINTIGRAPHY. Blinded, pre-TAVR DPD bone scintigraphy was performed in all patients, who were scanned using Phillips Brightview single-photon emission computed tomography–computed tomography gamma camera (Philips Healthcare, Amsterdam, the Netherlands), Siemens Symbia gamma camera (Siemens Healthcare, Erlangen, Germany), and/or Pulse CDC gamma camera (IS2, London, United Kingdom), or the General Electric Infinia Hawkeye 4/GE Discovery 670 hybrid gamma camera (Vienna, Austria) following the administration of 700 MBq of DPD. Whole body images were acquired at a scan speed of 10 cm/min using low-energy, high-resolution collimators (18). Planar whole body images were performed 3 h after tracer administration at all study sites. Additional single-photon emission computed tomography–computed tomography of the chest at 3 h was performed in London and/or Oxford.

BLINDING PRE-PROCEDURE. DPD scans were reported blinded to the clinical data by 2 readers from each institution (C.N., T.V., P.S., L.M.) according to the Perugini classification (19), where grade 0 represented no cardiac uptake with normal bone uptake (i.e., negative) and grades 1 to 3 represented 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 who did not undergo single-photon emission computed tomography, the adjudication panel (C.N., T.V., P.S., L.M., T.A.T.) re-reviewed the scans and assigned the final diagnosis by consensus.

DIAGNOSIS OF CA. Referring to the different disease burden in Perugini grade 1 (subclinical amyloid deposition) versus Perugini grade ≥2 (clinical amyloidosis), these 2 conditions were defined as AS-amyloid versus 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 3 cases (2 in grade 1 and 1 in grade 2). In the first patient in grade 1, endomyocardial biopsy confirmed ATTR; the second patient in grade 1 died shortly after TAVR with an autopsy diagnosis of AL (AL-kappa positive, TTR negative). The patient in grade 2 had a monoclonal gammopathy of undetermined significance with an inconclusive bone marrow biopsy; this patient declined further biopsy. However, because of 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 patient was classified as ATTR.

STATISTICAL ANALYSIS. All statistical analyses were computed using SPSS version 26 (IBM, Armonk, New York). Continuous data are expressed as mean ± SD or as median (interquartile range [IQR]), and categorical variables are presented as numbers and percentages. Differences between groups were analyzed with the chi-square and Kruskal Wallis tests, as appropriate. Post hoc analyses were performed using Dunn-Bonferroni tests for continuous variables. The

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, yrs	83.6 (72.3–87.6)	85.4 (80.2–89.1)	86.6 (84.1–91.8)*	0.001
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, mm Hg	134 (120–148)	138 (118–162)	126 (110–150)	0.319
Diastolic BP, mm Hg	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, pg/ml	1,606 (640–3,843)	1,632 (933–3,619)	4,855 (1,412–7,494)*	0.003
Creatinine, mg/dl	1.1 (0.9–1.4)	1.3 (1.1–1.4)	1.1 (0.9–1.3)	0.230
eGFR, ml/min/1.73 m^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

Values are median (interquartile range) or %. *DPD grade 2/3 versus DPD grade 0: p ≤ 0.05. †DPD grade 1 versus DPD grade 0: p ≤ 0.05. ‡DPD grade 2/3 versus DPD grade 1: p ≤ 0.05.

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

discriminative power of the novel scoring system was established using the receiver-operating characteristic curve analysis with area under the curve (AUC) and respective 95% confidence intervals (CIs). Univariate and multivariate Cox regression analyses were performed for the overall and AVR cohort to evaluate predictors of mortality (Supplemental Tables 1 to 3). All baseline parameters were proposed for univariate analysis. Multivariate analysis was performed using a stepwise forward selection, with the univariate cutoff p value of ≤0.05 used to enter the multivariate model for univariate testing and the p value of >0.1 used for removal from multivariate testing. To allow better comparison between continuous parameters within the multivariate model, scaled hazard ratios (HRs) (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 examination of Schoenfeld residuals. Kaplan-Meier curves were used to evaluate the prognostic significance of CA and AVR. Univariate 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. A total of 407 patients referred for TAVR (mean age: 83.4 ± 6.5 years; 49.8% men) were recruited in 3 centers (Figure 1). All patients underwent DPD bone scintigraphy performed 16 days (IQR: 2 to 50 days) before AVR. Treatment decisions were determined by the multidisciplinary

TABLE 2 Baseline Echocardiographic 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 to 50.0)	44.0 (39.0 to 50.0)	43.0 (38.0 to 49.0)	0.308
RVEDD, mm	36.0 (31.0 to 41.0)	36.0 (32.0 to 44.0)	38.0 (33.0 to 43.0)	0.158
IVS, mm	14.0 (12.0 to 16.0)	13.0 (12.0 to 14.0)	16.0 (14.0 to 19.0)*†	0.012
LA diameter, mm	51.0 (41.0 to 62.0)	55.0 (42.0 to 64.0)	56.0 (44.0 to 66.0)	0.405
AVA, cm²	0.7 (0.6 to 0.8)	0.7 (0.6 to 0.8)	0.7 (0.5 to 0.9)	0.814
AV Vmax, m/s	4.2 (3.9 to 4.6)	4.0 (3.4 to 4.7)	3.9 (3.2 to 4.6)*	0.017
AV-PPG, mm Hg	71.0 (60.0 to 84.0)	64.0 (45.0 to 87.0)	60.0 (42.0 to 86.0)*	0.018
AV-MPG, mm Hg	44.0 (35.0 to 53.0)	39.0 (27.0 to 49.0)	36.0 (25.0 to 48.0)*	0.017
SVi, ml/m²	40.1 (31.4 to 48.0)	33.2 (30.0 to 39.1)‡	35.8 (27.4 to 44.0)	0.021
LVEF, %	58.0 (44.0 to 64.0)	55.0 (35.0 to 61.0)	51.0 (42.0 to 64.0)	0.371
LVEDV, ml	91.0 (68.0 to 117.0)	87.0 (77.0 to 107.0)	80.0 (61.0 to 99.0)	0.201
LVESV, ml	34.0 (22.0 to 51.0)	33.0 (24.0 to 65.0)	36.0 (22.0 to 43.0)	0.819
Peak TR velocity, m/s	3.0 (2.4 to 3.5)	3.2 (2.0 to 3.8)	3.4 (2.6 to 4.1)	0.074
sPAP, mm Hg	39.0 (27.0 to 50.0)	48.0 (18.0 to 53.0)	49.0 (32.0 to 61.0)	0.062
E-wave deceleration time, ms	217 (166 to 281)	229 (189 to 337)	196 (158 to 246)	0.143
E/A ratio§	0.80 (0.68 to 1.20)	1.35 (0.64 to 3.09)	1.43 (0.88 to 2.43)*	0.010
TAPSE, mm	2.1 (1.6 to 2.5)	2.1 (1.6 to 2.2)	1.8 (1.3 to 2.3)	0.073
LV mass index, g/m²	127 (101 to 151)	120 (91 to 163)	150 (119 to 177)*†	0.017
MCF, %	33.6 (25.4 to 45.1)	34.8 (20.5 to 40.7)	24.5 (20.6 to 29.3)*	0.001
GLS, %	−15.6 (−19.3 to −10.2)	−12.2 (−18.0 to −8.6)	−13.7 (−17.3 to −10.2)	0.433
Apical LS, %	−21.0 (−26.6 to −13.2)	−19.8 (−26.1 to −5.8)	−21.5 (−25.2 to −16.0)	0.881
Midventricular LS, %	−13.3 (−17.5 to −8.8)	−10.2 (−18.7 to −7.2)	−10.1 (−13.8 to −7.3)	0.214
Basal LS, %	−10.6 (−13.6 to −6.5)	−9.3 (−12.0 to −5.6)	−7.4 (−10.8 to −3.0)	0.072
Apical/(mid + basal)	0.84 (0.69 to 1.05)	0.87 (0.55 to 1.61)	1.10 (0.85 to 1.78)*	0.005
ECG parameters				
Heart rate, beats/min	70 (62 to 79)	74 (68 to 83)	68 (60 to 77)	0.355
Sokolow-Lyon index, mV	2.25 (1.70 to 2.95)	1.25 (1.03 to 1.96)*	1.68 (1.33 to 2.35)*	<0.001
VMR, mV/g/m² × 10⁻²	1.84 (1.29 to 2.79)	1.18 (0.66 to 2.02)*	1.06 (0.83 to 1.85)*	<0.001
Low voltage limb	3.2	0.0	3.1	0.783
QRS duration, ms	96 (86 to 118)	128 (106 to 141)‡	107 (90 to 135)	0.005
LBBB	8.7	0.0	3.1	0.259
RBBB	8.7	33.3‡	18.8	0.003

Values are median (interquartile range) or %. *DPD grade 2/3 versus DPD grade 0: p ≤ 0.05. †DPD grade 2/3 versus DPD grade 1: p≤0.05. ‡DPD grade 1 versus DPD grade 0: p ≤ 0.05. §For patients in sinus rhythm at the time of echocardiography.

AV = aortic valve; AVA = aortic valve area; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; GLS = global longitudinal strain; IVS = interventricular septum; LA = left atrial; LBBB = left bundle branch block; LS = longitudinal strain; LV = left ventricular; MCF = myocardial contraction fraction; MPG = mean pressure gradient; PPG = peak pressure gradient; RBBB = right bundle branch block; RV = right ventricular; sPAP = systolic pulmonary artery pressure; SVi = stroke volume index; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; Vmax = peak velocity; VMR = voltage/mass ratio; other abbreviation as in Tale 1.

heart team. Of these 407 patients, 333 (81.6%) underwent TAVR; SAVR was performed in 10 (2.5%) patients, and conservative management or ongoing surveillance was pursued in 65 (15.9%) patients.

PREVALENCE, TYPE, AND PREDICTORS OF AS-CA. Cardiac tracer uptake on DPD bone scintigraphy was present in 48 patients (11.8%). Distribution according to the Perugini classification was as follows: 16 (3.9%) patients were in grade 1 (AS-amyloid), and 32 (7.9%) patients were in grade 2/3 (AS-amyloidosis). ATTR was found in 47 patients (all wild-type confirmed by genotyping), and 1 patient had AL, as previously described.

Independent predictors of presence of CA by multivariate linear regression analysis were a longer QRS duration (odds ratio [OR]: 2.51; 95% CI: 1.15 to 5.49; p = 0.021), a lower voltage/mass ratio (OR: 0.37; 95% CI: 0.16 to 0.87; p = 0.022), and history of carpal tunnel syndrome (OR: 1.55; 95% CI: 1.06 to 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 with patients with lone AS (86.6 vs. 83.6 years; p < 0.001), with a trend toward higher percentage in men (men: 65% vs. women: 48%; p = 0.06) (Table 1); patients with

FIGURE 2 Scoring System for the Discrimination of Lone AS and Dual Pathology AS-CA
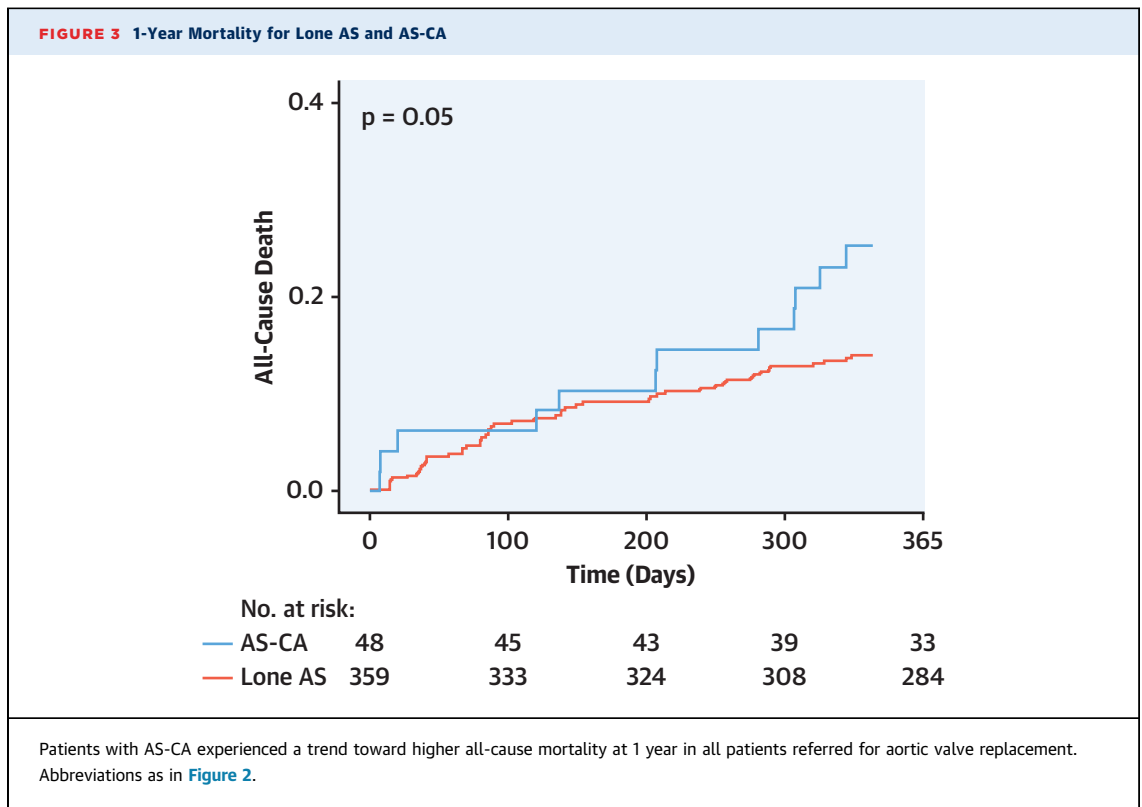

Parameter	Points
CTS	3
RBBB	2
Age ≥85 years	1
Hs-TnT >20 ng/l	1
IVS ≥18 mm	1
If in SR*: E/A ratio >1.4	1
If no BBB or PM: Sokolow index <1.9 mV	1

AUC 0.85 (0.79-0.91)

* 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%

Scoring system for the discrimination of lone AS and dual pathology AS-CA. AFib = atrial fibrillation; AS = aortic stenosis; AUC = area under the curve; BBB = bundle branch block; CA = cardiac amyloidosis; CTS = carpal tunnel syndrome; Hs-TnT = high-sensitivity troponin T; IVS = interventricular septum; PM = pacemaker; RBBB = right bundle branch block; SR = sinus rhythm.

AS-amyloidosis had a 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 a shorter 6-min walk distance (94 m [IQR: 50 to 225 m] vs. 194 m [IQR: 82 to 286 m]; p = 0.038). Cardiac biomarkers were significantly elevated: NT-proBNP: 4,855 ng/dl (IQR: 1,412 to 7,494 ng/dl) versus 1,606 ng/dl (IQR 640 to 3,843 ng/dl) in lone AS (p = 0.001); and hsTnT: 49 ng/l (IQR: 33 to 87 ng/l) versus 24 ng/l (IQR: 15 to 39 ng/l) (p < 0.001; normal hsTnT: <14 ng/l).

AS-amyloidosis was characterized by a lower Sokolow-Lyon voltage (1.7 mV [IQR: 1.3 to 2.4 mV] vs. 2.3 mV [IQR: 1.7 to 3.0 mV]; p = 0.007) and voltage/mass ratio (1.1 mV/g/m^2 × 10^{-2} [IQR: 0.8 to 1.9 mV/g/m^2 × 10^{-2}] vs. 1.8 mV/g/m^2 × 10^{-2} [IQR: 1.3 to 2.8 mV/g/m^2 × 10^{-2}]; p = 0.001). Higher right bundle branch block prevalence did not reach significance (18.8% vs. 8.7%; p = 0.06).

On echocardiographic assessment (Table 2), patients with AS-amyloidosis had slightly lower gradients (aortic valve Vmax 3.9 m/s vs. 4.2 m/s; aortic valve peak/mean gradient 60/36 mm Hg vs. 71/44 mm Hg; p < 0.05), although there was no significant difference in absolute or indexed aortic valve area (p = 0.5 and p = 0.3, respectively). Low-flow, low-gradient AS (stage D2 or D3) was more prevalent among patients with AS-amyloidosis (56.2% vs. 32.9%; p = 0.01) and was equally split between classical and paradoxical low-flow, low-gradient AS. Moreover, patients with AS-amyloidosis exhibited worse cardiac remodeling with greater LV hypertrophy (LV mass index: 150 g/m^2 [IQR: 119 to 177 g/m^2] vs. 127 g/m^2 [IQR: 101 to 151 g/m^2]; p = 0.006) and worse diastolic dysfunction. LVEFs were not different (p = 0.39), whereas indexed SV trended to be lower (35.8 ml/m^2 [IQR: 27.4 to 44.0 ml/m^2] vs. 40.1 ml/m^2 [IQR: 31.4 to 48.0 ml/m^2]; p = 0.06). The myocardial contraction fraction, the SV per myocardial volume,

FIGURE 3 1-Year Mortality for Lone AS and AS-CA

No. at risk:					
— AS-CA	48	45	43	39	33
— Lone AS	359	333	324	308	284

Patients with AS-CA experienced a trend toward higher all-cause mortality at 1 year in all patients referred for aortic valve replacement. Abbreviations as in Figure 2.
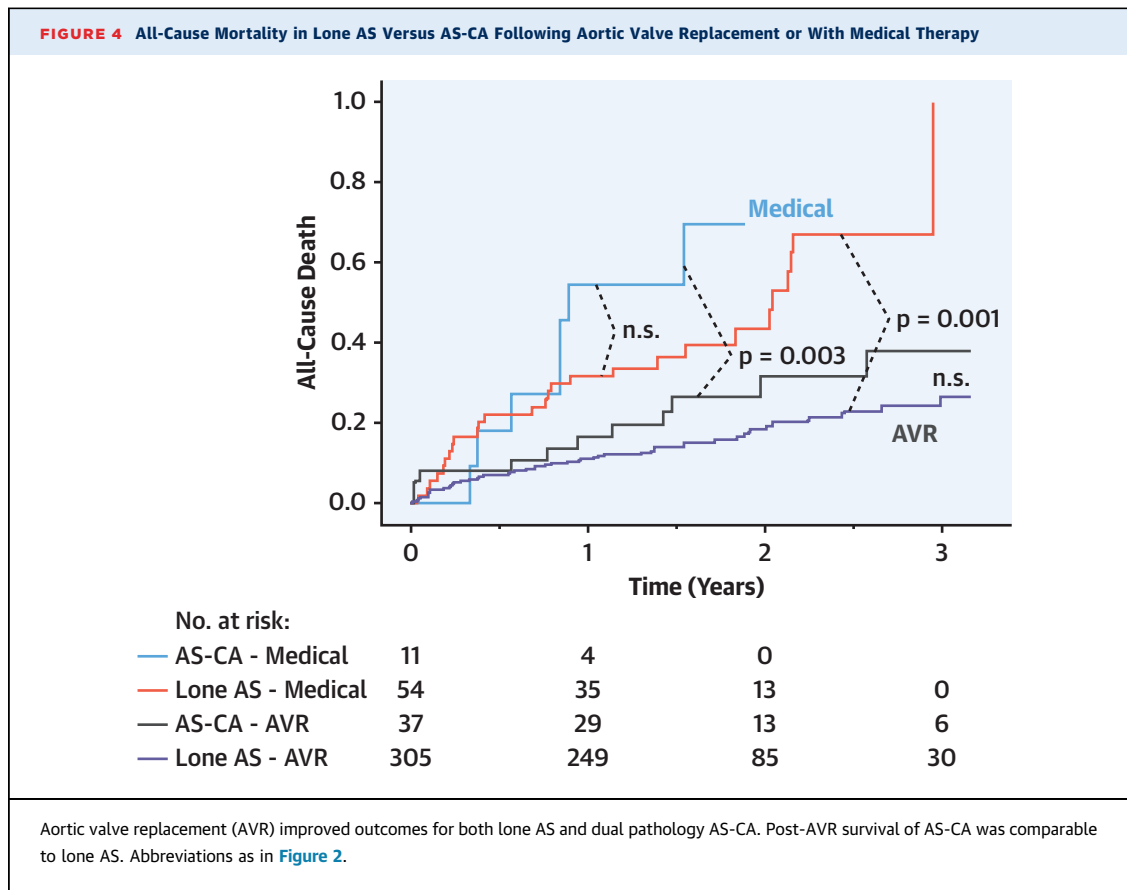
was significantly worse (24.5% [IQR: 20.6% to 29.3%] vs. 33.6% [IQR: 25.4% to 45.1%]; p < 0.001). Global LS was not different (−13.7 [IQR: −17.3 to −10.2] vs. −15.6 [IQR: −19.3 to −10.2]; p = 0.3), but relative apical sparing was more pronounced in AS-amyloidosis (1.1 [IQR: 0.9 to 1.8] vs. 0.8 [IQR: 0.7 to 1.1]; p < 0.01).

LONE AS VERSUS AS-AMYLOID (GRADE 1 AS-CA). Among patients with AS-amyloid (grade 1 AS-CA; n = 16), cardiovascular risk profiles were comparable with lone AS, except for 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 a lower SV index in patients with AS-amyloid (33 ml/m² [IQR: 30 to 39 ml/m²] vs. 40 ml/m² [IQR: 31 to 48 ml/m²]; p = 0.033), echocardiographic parameters did not differ, including LV mass index, LVEF, myocardial contraction fraction, E/A ratio, and strain values. On electrocardiography, patients with AS-amyloid displayed longer QRS duration, mainly due to a higher prevalence of right bundle branch block (33.3% vs. 8.7%; p = 0.002), and a lower Sokolow-Lyon voltage (1.3 mV [IQR: 1.0 to 2.0 mV] vs. 2.3 mV [IQR: 1.7 to 3.0 mV]; p = 0.002) and voltage/mass ratio (1.2 mV/g/m² × 10⁻² [IQR: 0.7 to 2.0 mV/g/m² × 10⁻²] vs. 1.8 mV/g/m² × 10⁻² [IQR: 1.3 to 2.8 mV/g/m² × 10⁻²]; p = 0.02).

REMODELING, AGE, INJURY, SYSTEM, AND ELECTRICAL SCORING SYSTEM FOR DISCRIMINATION OF LONE AS VERSUS AS-CA. To aid clinical AS-amyloid and/or AS-amyloidosis detection, a scoring system was created across 5 domains: remodeling (LV hypertrophy and/or diastolic dysfunction), age, injury (hsTnT), systemic (carpel tunnel syndrome), and electrical (right bundle branch block or low voltages) (RAISE). The RAISE score captures systemic disease (carpal tunnel syndrome, 3 points), disproportionate electrical remodeling (right bundle branch block, 2 points; low voltages or Sokolow-Lyon index <1.9 mV, 1 point), disproportionate myocardial remodeling (marked LV hypertrophy; septal wall thickness ≥18 mm, 1 point; marked diastolic dysfunction, E/A ratio >1.4, 1 point), chronic myocardial injury (hsTnT >20 ng/l, 1 point), and age (85 years or older, 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 to 0.94; p < 0.001) and then validated in the London cohort (AUC: 0.83; 95% CI: 0.75 to 0.92; p < 0.001). Scores of ≥2 and ≥3 points had high sensitivity (93.6% and 72.3%), with adequate specificity (52.1% and 83.6%) for the presence of AS-CA, respectively (Figure 2). When excluding troponin,

FIGURE 4 All-Cause Mortality in Lone AS Versus AS-CA Following Aortic Valve Replacement or With Medical Therapy

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

Aortic valve replacement (AVR) improved outcomes for both lone AS and dual pathology AS-CA. Post-AVR survival of AS-CA was comparable to lone AS. Abbreviations as in **Figure 2**.

the AUC was 0.81 (95% CI: 0.73 to 0.88; p < 0.001) (Supplemental Figure 1).

OUTCOME IN AS-CA VERSUS LONE AS. After a median of 1.7 years (IQR: 1.3 to 2.6 years), 97 (24%) of 407 patients referred for TAVR died. In this overall cohort, there was a trend toward higher 1-year mortality in patients with AS-CA versus patients with lone AS (25.0% vs. 13.9%; log-rank p = 0.05) (**Figure 3**). When excluding the AL case, unadjusted all-cause mortality of AS-CA was higher (196 deaths per 1,000 patient-years) compared with lone AS (137 deaths per 1,000 patient years; p = 0.001), with even those in grade 1 having significantly higher unadjusted all-cause mortality than those with lone AS (p < 0.001). AVR improved survival in patients with lone AS and AS-CA compared with medical management (p < 0.001 and 0.003, respectively) (**Figure 4**). Results remained the same when surgically managed patients were excluded (p < 0.001 and 0.017, respectively) (Supplemental Figure 2). There was a trend toward 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) versus 31.5% (medical) for the lone AS cohort and 16.2% versus 54.5% for the AS-CA cohort; this persisted out to 2 years. ATTR-targeting therapy (tafamidis only) was used in a minority of patients with AS-CA (all after AVR, 14.9%; n = 7 of 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 to 0.73; p < 0.001), serum albumin (HR: 0.70; 95% CI: 0.57 to 0.85; p = 0.001), NT-proBNP (HR: 1.40; 95% CI: 1.12 to 1.76; p = 0.003), creatinine (HR: 1.20; 95% CI: 1.04 to 1.38; p = 0.015), and body mass index (HR: 0.77; 95% CI: 0.61 to 0.97; p = 0.018) were independent predictors of mortality for the overall cohort (**Table 3**, Supplemental Table 1). In the intervention subgroup, independent mortality predictors were peri-procedural stroke (HR: 1.43; 95% CI: 1.25 to 1.63; p < 0.001), hematocrit (HR: 0.64; 95% CI: 0.48 to 0.84; p = 0.001), serum albumin (HR: 0.73; 95% CI: 0.58 to 0.92; p = 0.008), peak aortic jet velocity (HR: 0.73; 95% CI: 0.56 to 0.95; p = 0.018), left atrial diameter (HR: 1.34; 95% CI: 1.03 to 1.74; p = 0.032),

TABLE 3 Multivariate Cox regression Analysis Assessing the Association of Parameters With Mortality in the Overall Cohort

Baseline Clinical Parameters	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
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		
Mid-ventricular LS	1.237 (1.030–1.486)	0.023		

Bold values indicate statistical significance in multivariate testing. *NT-proBNP was graded into quartiles for this analysis.

AS-CA = dual aortic stenosis and cardiac amyloid pathology; CI = confidence interval; HR = hazard ratio; other abbreviations as in **Tables 1 and 2**.

and body mass index (HR: 0.73; 95% CI: 0.54 to 0.98; p = 0.033) (Supplemental Table 2).

PERI-PROCEDURAL COMPLICATIONS. In patients who underwent TAVR, major adverse events according to Valve Academic Research Consortium-2 occurred at the same rate in those with 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 showed that dual pathology of severe AS-CA conferred overall worse disease by functional capacity, cardiac remodeling and biomarkers, and could be predicted by a simple clinical score. Despite blinding clinicians before heart team decisions, fewer patients with AS-CA underwent TAVR and had overall worse outcomes. However, if patients with AS-CA were selected for and received TAVR, their outcomes were indistinguishable from patients with lone AS. Medically managed patients (both patients with lone AS or AS-CA) had poor survival in line with previously published data (e.g., PARTNER 1B trial [20]) (Central Illustration). Therefore, we concluded that a diagnosis of AS-CA should not preclude patients from TAVR.

We also confirmed that AS-CA was common and affected 1 in 8 patients referred for TAVR, either those with amyloid deposition (grade 1) or those with clinical amyloidosis (grade 2/3). The presence of occult ATTR in AS was first described in patients who underwent SAVR in 2016 (21). Since then, data from multiple retrospective and prospective studies were reported, (4-7,22,23), most of which were solely dedicated to ATTR. This study added to the existing data on the prevalence of AS-CA (4-7); data from our study and other studies was 10 times higher than that in unselected populations, in which prevalence in the older adults was <1% in those aged 80 years or older (24). CA in AS is predominantly of the ATTR-type, but AL-amyloidosis needs to be excluded by concomitant screening for plasma cell dyscrasia (25). Although most of the patients with CA in the present series had ATTR, 1 case of AL was identified. Although interpretation of light-chain results is challenging and requires multidisciplinary decision-making processes, AL screening is essential in case of suspicion for CA, because 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. In our data, we clearly showed that TAVR improved 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, highlighted a more decompensated clinical state that would likely affect outcome; although in our cohort, there was no statistical outcome difference in those patients who underwent TAVR. Patients with AS-amyloid (grade 1) also had worse outcomes, despite only mild remodeling (with a lower SV index) and a lower prevalence of electrical disturbances; therefore, AS-amyloid could not be considered as clinically irrelevant or benign. Larger prospective studies and registry data are warranted to understand the importance of grade 1 AS-amyloid.

Routine screening of older adult patients with severe AS or AS-CA using bone scintigraphy is not feasible in routine clinical practice. However, patients with AS-CA have distinct clinical risk profiles, including older age, a history of carpal tunnel syndrome, elevated troponin levels, increased septal thickness and E/A ratio on echocardiography, and right bundle branch block and lower Sokolow criteria on electrocardiography. Those parameters were integrated into a simple clinical scoring system that helped to identify patients with AS with a high

CENTRAL ILLUSTRATION Concomitant Pathology Aortic Stenosis-Cardiac Amyloidosis
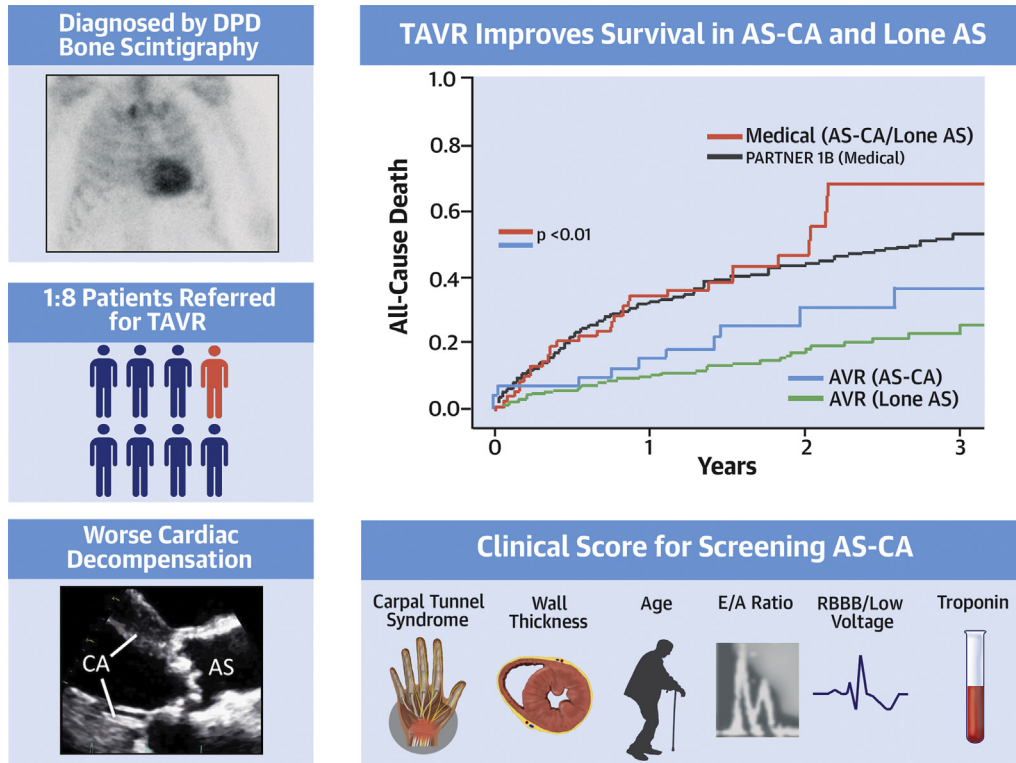
Nitsche, C. et al. J Am Coll Cardiol. 2021;77(2):128–39.

Concomitant pathology aortic stenosis-cardiac amyloidosis. PARTNER 1B data adapted from Kapadia et al. (20). AS = aortic stenosis; AVR = aortic valve replacement; CA = cardiac amyloidosis; DPD = ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; RBBB = right bundle branch block; TAVR = transcatheter aortic valve replacement.

likelihood of coexisting CA and guide referral for bone scintigraphy and exclusion of plasma cell dyscrasia. We proposed a stepwise screening process for CA in older adult patients with severe AS. The proposed algorithm would allow high-volume TAVR centers to detect CA with high sensitivity, without overstraining local resources. Based on the data presented (see **Figure 2**), scores of ≥2 points would instigate further screening by bone scintigraphy and light-chain assessment. TAVR should not be delayed for AS-CA workup without evidence of plasma cell dyscrasia because TAVR improves survival. An alternative approach would be screening by obtaining the extracellular volume fraction from pre-procedural TAVR cardiac computed tomography (28); the use of routine cardiac magnetic resonance is not feasible in all TAVR patients.

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 noncardiac patients (<1%) and predominantly affects older adult men (24). AS-CA appears to be different, with not only a 10× times higher general prevalence, but also near equal sex distribution and predilection for grade 2/3 tracer uptake in AS (rather than an equal distribution between grades). These observations point toward a causal relationship between AS and amyloid. The increased LV afterload posed by AS was hypothesized to prime the LV for deposition of amyloid fibrils (6,29). This might be driven by increased extracellular matrix turnover, low grade inflammation, chronic subendocardial ischemia, and resultant cell death because both fibrosis and amyloid deposition occur with an endocardial to epicardial gradient. In particular, the significant shear stresses in AS could cause an increased TTR deposition through a mechano-

enzymatic cleavage process (30). Valve intervention, per se, might stabilize ATTR by reducing the shear stresses and thereby the aforementioned mechano-enzymatic cleavage process (30), like AVR improves gastrointestinal bleeding in Heyde syndrome by reducing activation of acquired type-2A von Willebrand factor (31). Alternatively, common upstream pathways might affect both amyloidosis and valve stenosis progression; for example, higher levels of systemic inflammation might accelerate aortic valve calcification and drive greater cardiac deposition of amyloidogenic proteins (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, 7 of 47 patients with ATTR-CA received tafamidis after AVR (on a named patient program in Austria). Survival of the 40 therapy-naïve patients with ATTR was similar to lone AS and parallel to findings in other studies (6,9). Multicenter registries (e.g., the Aortic Stenosis & Amyloidosis Registry) and larger studies of patients with CA post-AVR are required to elucidate the benefit of ATTR therapy in this patient cohort, ideally in a randomized controlled trial (patients with AS were excluded from previous randomized controlled trials in this area).

STUDY LIMITATIONS. Despite the recruitment of patients before heart team recommendations, there might still be a selection bias of those patients who were actually referred to recruiting centers. Blinding pre-procedure was broken for 2 reasons: 7 patients had plasma cell dyscrasia that necessitated unblinding, as per protocol. Austrian and U.K. centers used echocardiographic strain software from different vendors, which might have affected 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 in the present study; therefore, prognosis and management strategies were not generalizable to this younger group. As opposed to previous findings (7), relative apical sparing was more pronounced in patients with AS-CA, whereas global

LS was comparable between groups. This should be re-evaluated in future studies. Mitral annular Ś was not available for the derivation cohort (Vienna); therefore, respective data were not presented. Single-photon emission computed tomography/computed tomography was not performed in the Vienna cohort; however, blinded core laboratory 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 patients with AS referred for possible TAVR. We presented a simple clinical scoring system to help identify those in whom bone scintigraphy is indicated. Patients with AS-CA had worse functional capacity, cardiac remodeling pre-procedure, and a trend toward worse prognosis if not treated by TAVR. However, mortality was the same if TAVR was performed. Based on these data, TAVR should not be withheld in AS-CA.

AUTHOR DISCLOSURES

ADDRESS FOR CORRESPONDENCE: Dr. Thomas Treibel, Barts Heart Centre, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, United Kingdom. E-mail: Thomas.Treibel@nhs.net. Twitter: @ThomasTreibel.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Concomitant CA occurs in 1 of 8 patients with severe AS referred for TAVR and is associated with more severe functional incapacity, cardiac remodeling, and adverse prognosis. Following TAVR, the outcomes of patients with concomitant CA were 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.

REFERENCES

1. Coffey S, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. J Am Coll Cardiol 2014;63:2852–61.

2. Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. Circulation 1982;66:1105–10.

3. Gertz MA, Dispenzieri A, Sher T. Pathophysiology and treatment of cardiac amyloidosis. Nat Rev Cardiol 2015;12:91–102.

4. Nitsche C, Aschauer S, Kammerlander AA, et al. Light-chain and transthyretin cardiac amyloidosis in severe aortic stenosis: prevalence, screening possibilities, and outcome. Eur J Heart Fail 2020 Feb 20 [Epub ahead of print].

5. Scully PR, Treibel TA, Fontana M, et al. Prevalence of cardiac amyloidosis in patients referred for transcatheter aortic valve replacement. J Am Coll Cardiol 2018;71:463–4.

6. Scully PR, Patel KP, Treibel TA, et al. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. Eur Heart J 2020;41:2759–67.

7. Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017;38:2879–87.

8. Gillmore JD, Maurer MS, Falk RH, et al. Non-biopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404–12.

9. Rosenblum H, Masri A, Narotsky DL, et al. Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis. Eur J Heart Fail 2020 Jul 30 [Epub ahead of print].

10. Kligfield P, Gettes LS, Bailey JJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2007;49:1109–27.

11. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Rev Esp Cardiol (Engl Ed) 2018;71:110.

12. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.

13. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.

14. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30:372–92.

15. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.

16. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–70.

17. King DL, El-Khoury Coffin L, Maurer MS. Myocardial contraction fraction: a volumetric index of myocardial shortening by freehand three-dimensional echocardiography. J Am Coll Cardiol 2002;40:325–9.

18. Hutt DF, Quigley AM, Page J, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. Eur Heart J Cardiovasc Imaging 2014;15:1289–98.

19. Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. J Am Coll Cardiol 2005;46:1076–84.

20. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2485–91.

21. Treibel TA, Fontana M, Gilbertson JA, et al. Occult transthyretin cardiac amyloid in severe calcific aortic stenosis: prevalence and prognosis in patients undergoing surgical aortic valve replacement. Circ Cardiovasc Imaging 2016;9:e005066.

22. Cavalcante JL, Rijal S, Abdelkarim I, et al. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. J Cardiovasc Magn Reson 2017;19:98.

23. Longhi S, Lorenzini M, Gagliardi C, et al. Coexistence of degenerative aortic stenosis and wild-type transthyretin-related cardiac amyloidosis. J Am Coll Cardiol Img 2016;9:325–7.

24. Longhi S, Guidalotti PL, Quarta CC, et al. Identification of TTR-related subclinical amyloidosis with 99mTc-DPD scintigraphy. J Am Coll Cardiol Img 2014;7:531–2.

25. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail 2019;12:e006075.

26. Gertz MA. Immunoglobulin light chain amyloidosis: 2018 update on diagnosis, prognosis, and treatment. Am J Hematol 2018;93:1169–80.

27. Ternacle J, Krapf L, Mohty D, et al. Aortic stenosis and cardiac amyloidosis: JACC review topic of the week. J Am Coll Cardiol 2019;74:2638–51.

28. Scully PRP KP, Saberwal B. Identifying cardiac amyloid in aortic stenosis - ECV quantification by cardiac CT in TAVR patients. J Am Coll Cardiol Img 2020;13:2177–89.

29. Galat A, Guellich A, Bodez D, et al. Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg? Eur Heart J 2016;37:3525–31.

30. Marcoux J, Mangione PP, Porcari R, et al. A novel mechano-enzymatic cleavage mechanism underlies transthyretin amyloidogenesis. EMBO Mol Med 2015;7:1337–49.

31. Godino C, Lauretta L, Pavon AG, et al. Heyde's syndrome incidence and outcome in patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol 2013;61:687–9.

32. Bois JP, Crowson CS, Khullar T, Achenbach SJ, Krause ML, Mankad R. Progression rate of severity of aortic stenosis in patients with rheumatoid arthritis. Echocardiography 2017;34:1410–6.

33. Maurer MS, Sultan MB, Rapezzi C. Tafamidis for transthyretin amyloid cardiomyopathy. N Engl J Med 2019;380:196–7.

34. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018;379:22–31.

35. Judge DP, Heitner SB, Falk RH, et al. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. J Am Coll Cardiol 2019;74:285–95.

36. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018;379:11–21.

KEY WORDS aortic stenosis, cardiac amyloidosis, TAVR

APPENDIX For supplemental tables and figures, please see the online version of this paper.