ESC European Society of Cardiology

European Heart Journal (2017) **38**, 2879–2887
doi:10.1093/eurheartj/ehx350

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement

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Received 2 January 2017; revised 25 April 2017; editorial decision 1 June 2017; accepted 5 June 2017; online publish-ahead-of-print 1 August 2017

See page 2888 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx513)

Aims Transthyretin cardiac amyloidosis (ATTR-CA) has been reported in patients with aortic stenosis (AS) but its prevalence and phenotype are not known. We examine elderly patients with severe symptomatic AS undergoing transcatheter aortic valve replacement (TAVR) and determine the prevalence and phenotype of ATTR-CA non-invasively.

Methods and results We performed technetium-99m pyrophosphate (^{99m}Tc-PYP) cardiac scintigraphy prospectively on patients who underwent TAVR, to screen for ATTR-CA. Transthoracic echocardiography and speckle-strain imaging were performed. We assessed the association of several parameters with ATTR-CA using multivariable logistic regression and constructed receiver operating curves to evaluate the best predictors of ATTR-CA. Among 151 patients (mean age 84 ± 6 years, 68% men), 16% ($n = 24$) screened positive for ATTR-CA with ^{99m}Tc-PYP scintigraphy. Compared with patients without ATTR-CA, ATTR-CA patients had a thicker interventricular septum (1.3 vs. 1.1 cm, $P = 0.007$), higher left ventricular (LV) mass index (130 vs. 98 g/m^2, $P = 0.002$), and lower stroke volume index (30 vs. 36 mL/m^2, $P = 0.009$). ATTR-CA patients had advanced diastolic dysfunction with higher *E/A* ratio (2.3 vs. 0.9, $P = 0.001$) and lower deceleration time (176 vs. 257 ms, $P < 0.0001$); impairment in systolic function with lower ejection fraction (48% vs. 56%, $P = 0.011$), myocardial contraction fraction (26 vs. 41, $P < 0.0001$), and average of lateral and septal mitral annular tissue Doppler S' (4.0 vs. 6.6 cm/s, $P < 0.0001$). While ATTR-CA patients had more impaired global longitudinal strain (-12 vs. -16%, $P = 0.007$), relative apical longitudinal strain was the same regardless of ATTR-CA diagnosis (0.98 vs. 0.98, $P = 0.991$). Average S' best predicted ATTR-CA in multivariable logistic regression (odds ratio 16.67 per 1 cm/s decrease with AUC 0.96, 95% confidence interval 0.90–0.99, $P = 0.002$) with a value ≤6 conferring 100% sensitivity for predicting a positive ^{99m}Tc-PYP amyloid scan.

Conclusions Transthyretin cardiac amyloidosis is prevalent in 16% of patients with severe calcific AS undergoing TAVR and is associated with a severe AS phenotype of low-flow low-gradient with mildly reduced ejection fraction. Average tissue Doppler mitral annular S' of < 6 cm/s may be a sensitive measure that should prompt a confirmatory ^{99m}Tc-PYP scan and subsequent testing for ATTR-CA. Prospective assessment of outcomes after TAVR is needed in patients with and without ATTR-CA.

Keywords Transthyretin cardiac amyloidosis • Aortic stenosis • TAVR • Low-flow low-gradient • Strain

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Introduction

Aortic stenosis (AS) is present in up to 3% of patients ≥75 years old[1] and in symptomatic patients, confers a mean survival of 1.8 years when medically managed.[2,3] Several flow-gradient patterns of severe AS have been elucidated,[4] each with different management strategies because the degree of ventricular recovery after aortic valve replacement (AVR) and clinical outcomes differ.[5,6] Among patients with an aortic valve area (AVA) ≤1.0 cm^2, specific subgroups include Stage D1: 'High-gradient AS' with a mean gradient (MG) ≥40 mmHg or peak velocity (V_{max}) ≥4 m/s; Stage D2: 'Classical low-flow, low-gradient (LF-LG) AS with reduced left ventricular ejection fraction' (LVEF) (MG <40 mmHg or V_{max} <4 m/s with LVEF <50%); and Stage D3: 'LF-LG AS with normal LVEF or paradoxical low-flow AS' (MG <40 mmHg or V_{max} ≤4 m/s with LVEF ≥50%).[4] Despite benefiting from AVR compared with medical therapy, patients with low-flow AS have the worst outcomes, but the reasons for this discrepancy are not fully elucidated.

In low-flow AS with or without a preserved LVEF (Stages D2 and D3), the reduced forward stroke volume may occur in the setting of severe concentric remodelling, diastolic dysfunction, reduced longitudinal myocardial shortening and atrial fibrillation.[7] These findings bear a striking resemblance to transthyretin cardiac amyloidosis (ATTR-CA), the most common cause of restrictive cardiomyopathy in older adults.[8] In ATTR-CA, extracellular deposition of fibrils composed of destabilized wild-type (ATTRwt) or mutant (ATTRm) transthyretin protein leads to diastolic dysfunction, arrhythmias, and clinical heart failure.[9] ATTRwt deposits have been reported in 25% of surgically removed heart valves from adults >80 years old.[10] Identifying ATTR-CA among patients with severe AS may be important as there are a number of disease modifying therapies for ATTR-CA in clinical trials.[9]

Classically, a low electrocardiographic voltage-mass ratio (VMR)[11] and echocardiographic parameters[12–14] have characterized cardiac amyloidosis. Myocardial contraction fraction (MCF), a novel volumetric measure of myocardial shortening, may also be useful in identifying this disease.[15] However, these are not sufficiently sensitive or specific to know that cardiac amyloidosis is not being missed. Nuclear cardiac imaging with bone seeking radioisotopes such as technetium-99m pyrophosphate (^{99m}Tc-PYP) have shown excellent diagnostic accuracy for ATTR-CA.[16–18] A recent multicentre international collaboration validated these radioisotopes for the non-invasive diagnosis of ATTR-CA, with a reported 100% specificity when combined with the absence of a monoclonal protein to rule out light-chain (AL) amyloid, the other major form of cardiac amyloidosis.[19]

In this study, we used ^{99m}Tc-PYP cardiac imaging to examine elderly patients with severe AS undergoing transcatheter aortic valve replacement (TAVR) and determine the prevalence and phenotype of ATTR-CA non-invasively.

Methods

Study design and population

We prospectively recruited patients with severe calcific AS undergoing TAVR at Columbia University's Centre for Interventional Vascular Therapy between December 2014 and July 2016. Patients provided informed consent in accordance with Columbia's IRB. Inclusion criteria were patients ≥65 years old with severe symptomatic AS. Exclusion criteria included patients with AS due to congenital or rheumatic heart disease, patients unable to provide informed consent or lie still for 10 min under the camera. Patients underwent transthoracic echocardiography with strain rate imaging at the time of TAVR evaluation and a ^{99m}Tc-PYP scan within 30 days after TAVR. Echocardiographers and nuclear cardiologists were blinded to patients' clinical information.

Clinical and laboratory measures

Biochemistry analyses were measured prior to TAVR and included troponin I, brain natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), and modified body mass index (mBMI) [albumin x BMI] reflecting autonomic dysfunction and malabsorption.[20] In patients who scanned positive for ATTR-CA, we ruled out AL cardiac amyloid by a normal serum free light chain ratio (0.26–1.65) on Freelite assay and absence of an abnormal monoclonal band on immunofixation of serum or urine.

Technetium-99m pyrophosphate planar cardiac imaging for diagnosis of transthyretin cardiac amyloidosis

All patients underwent a ^{99m}Tc-PYP cardiac scan within 30 days after TAVR according to previously described technique[21]: myocardial tracer uptake was analysed using the semi-quantitative visual score (range 0–3) and quantitative heart-to-contralateral (H/CL) ratio of total counts in a region of interest (ROI) over the heart divided by counts in an identical size ROI over the contralateral chest to normalize for soft tissue and ribs. ATTR-CA was defined by diffuse ^{99m}Tc-PYP uptake, visual score ≥2 and H/CL ≥1.5 based on prior multicentre data on the accuracy of ^{99m}Tc-PYP for diagnosis of ATTR-CA.[18]

Echocardiography and speckle strain imaging

Doppler echocardiography was performed using commercially available ultrasound systems at the time of TAVR evaluation. Standard measurements of cardiac size and function, and classification of LV geometry were performed per American Society of Echocardiography guidelines.[22] Pulse wave and tissue Doppler were used to assess diastolic and biventricular function in the apical four-chamber view. Average mitral annular s' was calculated from tissue Doppler at the lateral and septal mitral annulus. Myocardial contraction fraction was calculated as the ratio of stroke volume to myocardial volume, which were calculated from linear dimensions in the parasternal long-axis view.[15] Speckle strain imaging was performed using TomTec Image-ArenaTM software in patients with adequate endomyocardial border definition from transthoracic echocardiography in the 4-, 3-, and 2-chamber apical views. Regional longitudinal strain (LS) was determined in 17 segments of the LV as per ASE guidelines.[22] 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)/2].[13] The VMR was calculated as the ratio of electrocardiographic voltage by Sokolov Lyon criteria to the echocardiographically derived cross sectional area.[11]

Statistical analysis

Analyses were performed using Statistical Analysis Software (SAS) (v9.4, Cary, NC, USA) and R (R Core Team 2014). Continuous variables were presented as mean ± SD or median and categorical variables were summarized as counts (frequency percentages). χ^2 or Fisher exact test (for small cell counts) compared categorical variables and Wilcoxon

rank-sum tests compared continuous variables between patients with and without ATTR-CA. Two-sided *P*-values were used throughout all analyses. Univariable and multivariable logistic regressions evaluated for factors associated with the outcome of ATTR-CA. All non-collinear variables with $P < 0.25$ in univariable analysis were included in a multivariable regression model, and several model selection methods were employed (backward, forward, and stepwise). Internal validation of the final model was assessed using bootstrap method (1000 repetitions) with the optimism corrected C-statistic.[23] Using systolic or diastolic echocardiographic parameters as well as the VMR as diagnostic markers for ATTR-CA, we estimated and compared the area under the corresponding receiver operating curve (ROC) curve (C-statistic) with corresponding 95% confidence interval (CI). Reproducibility of echocardiographic strain rate imaging was assessed in terms of inter- and intra-observer variability using interclass correlation values for the global LS for a subset of subjects ($n = 20$).

Results

Patient population

The study population (*Table 1*) included 151 patients. They were elderly (mean age 84 ± 6 years), 68% men, with severe cardiac symptoms (75% had New York Heart Association functional class >2) and frequent comorbid conditions. On average, cardiac biomarkers were elevated, troponin I 0.07 (0.02–0.22) ng/mL and BNP 305 (146–847) pg/mL, with mean LVEF 55 ± 15%.

Transthyretin cardiac amyloidosis prevalence and phenotype among patients undergoing transcatheter aortic valve replacement

Transthyretin cardiac amyloidosis was found in 24 subjects (16%, 95% CI 10–23%) (*Figure 1A*, *Table 1*). Compared with patients without ATTR-CA, those with ATTR-CA were more likely to be male, with 22% of male subjects screening positive for ATTR-CA (95% CI 14–31%). Subjects with ATTR-CA had lower systolic blood pressure before TAVR and higher BNP but had no difference in troponin I, eGFR, or mBMI compared with subjects without ATTR-CA. With respect to conduction disease, patients with ATTR-CA also had lower VMR and higher incidence of right bundle branch block but did not have an increased need for placement of a permanent pacemaker after TAVR implantation compared with patients without ATTR-CA.

Echocardiographic features of transthyretin cardiac amyloidosis in transcatheter aortic valve replacement patients

Baseline echocardiographic assessment (*Table 2*) showed patients with ATTR-CA had a similar AVA and a trend towards lower MG and lower peak velocity compared with subjects without ATTR-CA. A greater percentage of patients with ATTR-CA had heart failure with mid-range ejection fraction[24] (48% vs. 56%, $P = 0.011$) with lower average mitral annular S' (4.0 ± 1.1 vs. 6.6 ± 1.5 cm/s, $P < 0.0001$) and reduced MCF (26 ± 10 vs. 41 ± 16, $P < 0.0001$). In addition, they had a thicker interventricular septal wall (1.3 ± 0.3 vs. 1.1 ± 0.2 cm, $P = 0.007$), higher LV mass index (130 ± 44 vs. 98 ± 25 g/m^2, $P = 0.002$), with lower stroke volume index (SVI) (30 ± 11 vs. 36 ± 10 mL/m^2, $P = 0.009$) consistent with increased incidence of concentric hypertrophy (37.5% vs. 12.1%, $P = 0.0009$) (*Figure 2*). Patients with ATTR-CA were nearly 3× more likely to have low-flow low-gradient AS (Stage D2) (29.2% vs. 10.5%, $P = 0.045$) than patients without ATTR-CA. Patients with ATTR-CA had a higher *E/A* ratio [2.3 (1.10–3.10) vs. 0.9 (0.70–1.70), $P = 0.001$] and lower deceleration time [176 (144–198) vs. 257 (209–313) ms, $P < 0.0001$] consistent with grade III diastolic dysfunction. Strain rate imaging revealed more severe impairment in global LS in patients with ATTR-CA compared with patients without ATTR-CA (-12 vs. -16%, $P = 0.007$), which persisted throughout the LV basal, mid, and apical segments (*Figure 3*). However, no significant difference in relative apical LS was observed in patients with and without ATTR-CA (0.98 vs. 0.98, $P = 0.991$). Corresponding bulls-eye plots of segmental strain revealed a patchy distribution of impaired LS consistent with severe AS.[13]

Using logistic regression models, significant univariable predictors of ATTR-CA included older age, male gender, a higher natriuretic peptide level, a lower LVEF, increased left atrial dimension, an interventricular septal wall thickness of ≥1.2 cm, a SVI <35 mL/m^2, decreased MCF, a lower average mitral annular S' and higher *E/A* ratio (*Table 3*). In multivariable logistic regression using forward, backward, and step-wise selection models that considered all non-collinear significant univariable predictors of ATTR-CA, only average mitral annular S' remained significantly associated with ATTR-CA with odds ratio 5.0 per 1 cm/s decrease, 95% CI 2.56–9.09, $P < 0.0001$. In bootstrap validation, the final model generated an optimism-corrected area under the curve (AUC) almost identical to the value obtained using original data (0.947). In ROC analysis, while deceleration time, MCF, *E/A* ratio, and VMR predicted ATTR-CA with AUCs ranging 0.6–0.8, the average tissue Doppler mitral annular S' was the strongest predictor with an AUC 0.95, $P < 0.0001$ (*Figure 1B*). Dichotomizing the average mitral annular S' around the population median of ≤6 vs. >6 cm/s was 100% sensitive but only 57% specific for ATTR-CA by ^{99m}Tc-PYP scan.

It should be noted that five patients who had a positive ^{99m}Tc-PYP scan who met formal diagnostic criteria for ATTR-CA also had an abnormal monoclonal protein by international consensus criteria.[19] Of these, two had a known lymphoproliferative disorder, e.g. monoclonal gammopathy of undetermined significance based on bone marrow biopsy and were followed by a haematologist. All five patients ultimately chose not to undergo tissue biopsy to rule out the possibility of AL CA.

Discussion

This prospective cohort study is the first to report: (i) a 16% prevalence of ATTR-CA in elderly patients undergoing TAVR, (ii) an echocardiographic phenotype of low-flow low-gradient AS with reduced LVEF and severe diastolic dysfunction in this patient population, and (iii) reduced myocardial systolic mechanics with average tissue Doppler mitral annular S' independently associated with ATTR-CA.

Implications for severe as

The 16% prevalence of ATTR-CA that we report corroborates the 6–12% reported in smaller retrospective studies in patients with severe AS.[25,26] The slightly higher prevalence is likely because our study population was older and exclusively underwent TAVR, not surgical

Table 1 Baseline characteristics in elderly patients with severe symptomatic AS with and without ATTR-CA

	All ($n = 151$)	No ATTR-CA ($n = 127$)	ATTR-CA ($n = 24$)	*P*-value
Socio-demographic variables				
Age, years	83.7 ± 6.2	83.3 ± 6.3	86.3 ± 5.7	0.038
Race				
White	141 (93.4%)	118 (92.9%)	23 (95.8%)	
Black	6 (4.0%)	5 (3.9%)	1 (4.2%)	0.678
Asian	4 (2.7%)	4 (3.2%)	0 (0%)	
Male sex	102 (67.6%)	80 (63.0%)	22 (91.7%)	0.005
BMI, kg/m^2	26.8 ± 5.0	27.0 ± 5.3	25.5 ± 2.7	0.225
Modified BMI, kg·g/m^2·dL	106.1 ± 24.6	107.6 ± 25.2	98.1 ± 19.9	0.084
New York Heart Association (*N*, %)				
I	8 (5.3%)	8 (6.3%)	0 (0%)	
II	30 (19.9%)	24 (18.9%)	6 (25%)	0.195
III	99 (65.6%)	81 (63.8%)	18 (75%)	
IV	14 (9.3%)	14 (11.0%)	0 (0%)	
Severe symptomatic AS stage				
D1: High gradient AS	117 (79.1%)	102 (82.2%)	15 (62.5%)	
D2: Low-flow, low-gradient AS with reduced LVEF	20 (13.5%)	13 (10.5%)	7 (29.2%)	0.045
D3: Low-flow, low-gradient AS with normal LVEF	11 (7.4%)	9 (7.3%)	2 (8.3%)	
Clinical and ECG parameters				
Hypertension	129 (85.4%)	107 (84.3%)	22 (91.7%)	0.530
Coronary artery disease	96 (63.6%)	78 (61.4%)	18 (75%)	0.252
Cerebrovascular disease	19 (12.6%)	17 (13.4%)	2 (8.3%)	0.739
Atrial fibrillation/flutter	64 (42.4%)	54 (42.5%)	10 (41.7%)	0.938
Carpal tunnel syndrome	11 (7.3%)	7 (5.5%)	4 (16.7%)	0.075
Systolic blood pressure, mmHg	140.9 ± 25.4	143.6 ± 25.1	125.3 ± 21.5	0.009
Diastolic blood pressure, mmHg	64.5 ± 13.9	65.1 ± 14.3	61.1 ± 10.6	0.310
Low voltage	7 (4.9%)	4 (3.33%)	3 (12.5%)	0.091
Voltage-to-mass ratio	1.3 ± 0.8	1.4 ± 0.8	1.0 ± 0.6	0.028
QRS duration, ms	113.4 ± 31.0	110.7 ± 30.7	127.4 ± 29.8	0.017
Right bundle branch block	28 (19.4%)	19 (15.8%)	9 (37.5%)	0.023
Need for permanent pacemaker post-TAVR	22 (14.9%)	18 (14.4%)	4 (17.4%)	0.751
Laboratory values				
Troponin I, ng/mL	0.07 (0.02–0.22)	0.06 (0.02–0.14)	0.11 (0.05–0.40)	0.430
Troponin T, ng/dL	0.07 (0.05–0.11)	0.06 (0.05–0.08)	0.18 (0.06–0.33)	0.181
BNP, pg/mL	304.5 (146–847)	275 (124–722)	522 (302–1023)	0.041
NT pro-BNP, ng/dL	2003 (714–3226)	1896 (514–2932)	3220 (1092–19 007)	0.148
Estimated GFR, mL/min	67.7 ± 29.2	69.6 ± 29.8	57.6 ± 23.8	0.066
Albumin, g/dL	4.0 ± 0.5	4.0 (3.6–4.3)	3.9 (3.6–4.1)	0.134
Presence of Clone	19 (32.2%)	14 (30.4%)	5 (38.5%)	0.738
^{99m}Tc-PYP cardiac imaging				
Visual score ≥2	24 (15.9%)	0 (0%)	24 (100%)	<0.0001
Heart-to-contralateral ratio	1.2 ± 0.2	1.1 ± 0.1	1.7 ± 0.2	<0.0001

Values are presented as mean ± SD, median (inter-quartile range), or *n* (%).
ATTR-CA, transthyretin cardiac amyloidosis; BNP, brain natriuretic peptide; ^{99m}Tc-PYP, technetium pyrophosphate; BNP, brain natriuretic peptide; GFR, glomerular filtration rate; ECG, electrocardiogram; BMI, body mass index; AS, aortic stenosis; LVEF, left ventricular ejection fraction; SD, standard deviation.

AVR. Our findings also corroborate the 13% reported prevalence in a population of hospitalized patients with heart failure with preserved ejection fraction (HFpEF) and increased wall thickness.[27] Given the high prevalence of calcific AS in the general population and the increasing frequency of TAVR in high and intermediate surgical risk older adults, it may be prudent to screen patients in whom there is suspicion of concomitant severe AS and ATTR-CA because management and prognosis of ATTR-CA differs from that for other cardiomyopathies. Prior reports have suggested the potential detrimental impact of ATTR-CA in patients with severe AS. At 2-year follow-up

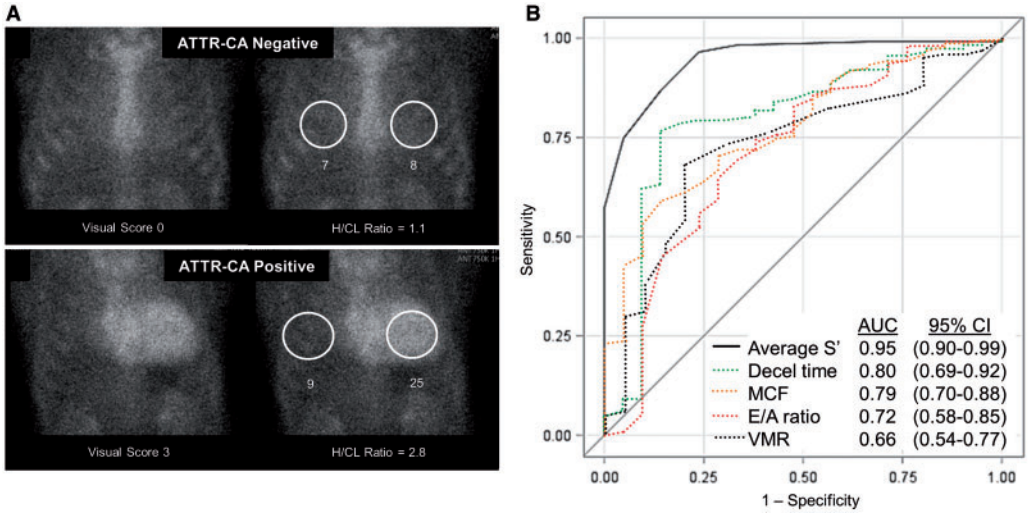

Figure 1 Predictors of ATTR-CA in elderly patients undergoing transcatheter aortic valve replacement. Quantitative assessment of technetium-99m pyrophosphate myocardial uptake (*A*) is shown in a patient with (bottom) and without ATTR-CA (top) with corresponding H/CL ratio. ROC curves for predictors of ATTR-CA (*B*). DT, deceleration time; H/CL, heart-to-contralateral ratio; MCF, myocardial contraction fraction; VMR, voltage-mass ratio; ATTR-CA, transthyretin cardiac amyloidosis.

Table 2 Baseline echocardiographic parameters in patients with severe AS with and without ATTR-CA

	All (*n* = 151)	No ATTR-CA (*n* = 127)	ATTR-CA (*n* = 24)	*P*-value
2D and Doppler variables				
Aortic valve area, cm^2	0.77 ± 0.18	0.77 ± 0.19	0.80 ± 0.16	0.358
Mean gradient, mmHg	40.1 ± 13.9	41.1 ± 13.8	35.2 ± 13.9	0.060
Peak velocity, cm/s	4.2 ± 0.7	4.3 ± 0.7	4.0 ± 0.7	0.078
LV ejection fraction, %	54.8 ± 15.0	56.1 ± 14.1	47.6 ± 17.6	0.011
Interventricular septal wall, cm	1.1 ± 0.3	1.1 ± 0.2	1.3 ± 0.3	0.007
LV posterior wall, cm	0.9 ± 0.3	0.9 ± 0.2	1.1 ± 0.4	<0.001
LV mass index, g/m^2	103.1 ± 31.3	97.9 ± 25.4	129.8 ± 43.6	0.002
Relative wall thickness	0.40 ± 0.10	0.38 ± 0.12	0.49 ± 0.21	0.017
Stroke volume index, mL/m^2	34.7 ± 9.9	35.7 ± 9.6	29.9 ± 10.5	0.009
Myocardial contraction fraction, %	38.6 ± 15.7	41.0 ± 15.5	26.4 ± 10.1	<0.0001
Left atrial dimension, cm	4.5 ± 0.7	4.4 ± 0.7	5.0 ± 0.7	0.002
Diastolic function				
E wave, cm/s	93.7 ± 31.1	95.4 ± 31.1	84.4 ± 30.7	0.140
A wave, cm/s	84.3 ± 37.8	90.7 ± 36.0	50.7 ± 28.8	<0.0001
E/A ratio	1 (0.75–2.10)	0.90 (0.70–1.70)	2.30 (1.10–3.10)	0.001
Deceleration time, ms	250 (191–306)	257 (209–313)	176 (144–198)	<0.0001
E/e' ratio	16 (12–20)	16 (12–20)	19 (15–26)	0.075
LA volume index, mL/m^2	50.2 ± 17.1	49.2 ± 17.2	55.5 ± 15.8	0.108
Tissue Doppler and strain systolic function				
Average mitral annular S', cm/s	6.2 ± 1.7	6.6 ± 1.5	4.0 ± 1.1	<0.0001
Right ventricular S', cm/s	10.9 ± 3.1	11.3 ± 2.9	8.5 ± 2.8	<0.0001
Basal LS (%)	-14.0 ± 4.6	-14.8 ± 4.2	-11.6 ± 5.0	0.007
Mid LS (%)	-14.0 ± 4.6	-14.8 ± 4.2	-11.6 ± 5.0	0.008
Apical LS (%)	-13.8 ± 4.6	-14.6 ± 4.3	-11.4 ± 4.9	0.009
Global LS (%)	-14.9 ± 4.7	-15.7 ± 4.3	-12.4 ± 5.2	0.007
Relative apical LS	0.98 ± 0.04	0.98 ± 0.03	0.98 ± 0.06	0.991

Values are presented as mean ± SD or median (inter-quartile range).
ATTR-CA, transthyretin cardiac amyloidosis; LA, left atrium; LS, longitudinal strain; LV, left ventricular; AS, aortic stenosis; 2D, two dimensional; SD, standard deviation.

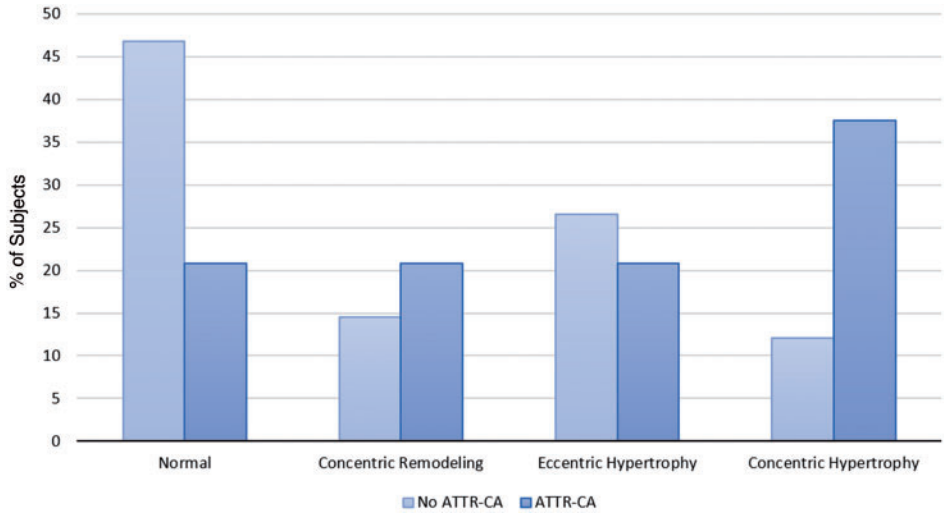

Figure 2 Left ventricular geometry among patients undergoing transcatheter aortic valve replacement with and without ATTR-CA. *P*-value comparing patients with ATTR-CA vs. no ATTR-CA. ATTR-CA, transthyretin cardiac amyloidosis.

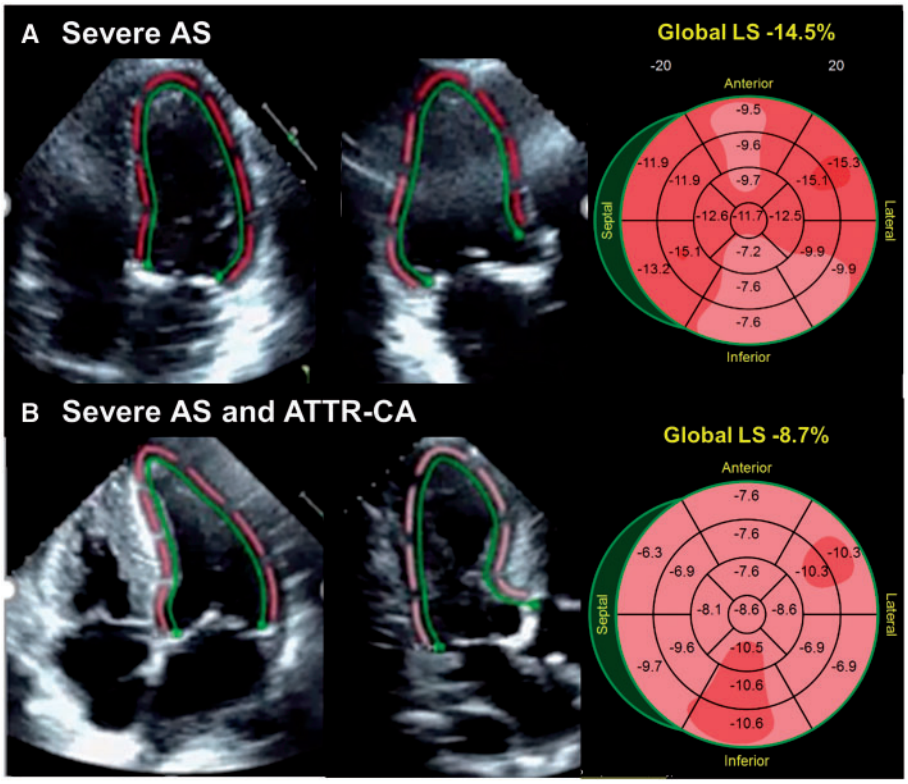

Figure 3 Speckle-strain imaging in elderly patients with severe symptomatic AS with and without ATTR-CA. Bullseye plots demonstrate relative apical sparing is the same whether amyloid is present or not. AS, aortic stenosis; ATTR-CA, transthyretin cardiac amyloidosis.

Table 3 Predictors of ATTR-CA among elderly patients undergoing TAVR

	N	OR	95% CI	C-statistic	*P*-value
Univariable					
Age, per 1 year increase	151	1.09	(1.01–1.18)	0.635	0.034
Gender, male vs. female	151	6.46	(1.45–28.72)	0.643	0.014
Modified BMI, per 1 kg·dL/m^2·g increase	151	0.98	(0.96–1.00)	0.603	0.085
Coronary artery disease, yes vs. no	151	1.89	(0.70–5.08)	0.568	0.210
Elevated BNP[a], yes vs. no	119	2.96	(1.07–8.19)	0.627	0.037
Systolic blood pressure, per 1 mmHg increase	151	1.00	(0.98–1.02)	0.466	0.893
QRS duration, per 1 ms increase	142	1.02	(1.01–1.03)	0.672	0.021
Albumin, per 1 g/dL increase	151	0.55	(0.22–1.36)	0.597	0.195
Mean gradient, per 1 mmHg increase	148	0.97	(0.93–1.00)	0.617	0.061
LVEF, per 1% decrease	151	1.04	(1.01–1.06)	0.640	0.014
LA dimension, per 1 mm increase	141	1.10	(1.03–1.17)	0.702	0.003
IVSD ≥1.2 vs. <1.2 cm	147	4.10	(1.52–11.03)	0.664	0.005
SV index <35 vs. ≥35 mL/m^2	147	4.53	(1.68–12.21)	0.676	0.003
Severe symptomatic AS stage				0.605	0.058
Stage D2 vs. D1	148	3.66	(1.26–10.64)		0.017
Stage D3 vs. D1	148	1.51	(0.30–7.68)		0.619
MCF, per 1 unit decrease	147	1.10	(1.05–1.15)	0.789	<0.0001
Average mitral annular S', per 1 cm/s decrease	136	5.0	(2.56–9.09)	0.947	<0.0001
E/A ratio, per 1 unit increase	136	2.08	(1.39–3.11)	0.719	0.0004
Model selection: 'final' model[b]					
Average mitral annular S', per 1 cm/s decrease	136	5.0	(2.56–9.09)	0.719	<0.0001

ATTR-CA, transthyretin cardiac amyloidosis; TAVR, transcatheter aortic valve replacement; OR, odds ratio; CI, confidence interval; BNP, brain natriuretic peptide; BMI, body mass index; LVEF, left ventricular ejection fraction; LA, left atrium; AS, aortic stenosis; IVSD, interventricular septum at diastole.
[a]Elevated BNP was designated for patients if BNP ≥300 pg/mL or NT proBNP ≥2000 pg/mL.
[b]The 'final' model shows the unanimous recommendations of several model building strategies (backward, forward, and stepwise) that considered all non-collinear predictors with $P < 0.25$ from univariable regression.

among 146 patients who underwent surgical AVR, the presence of ATTR-CA was associated with death with a hazard ratio of 9.5 (95% CI 2.5–35.8, $P = 0.001$).[26] In a retrospective study of 171 patients with ATTR-CA with and without AS, mortality was the same irrespective of AVR, suggesting that ATTR-CA may have a deleterious contribution to outcomes.[28] Whether ATTR-CA affects mortality synergistically with severe AS or as the primary driver needs further exploration in large cohorts.

The current study also suggests that ^{99m}Tc-PYP cardiac imaging can be used to screen for ATTR-CA in at risk populations. In Europe, ^{99m}Tc-DPD cardiac imaging has proven to be an effective screening tool for ATTR-CA, both among patients undergoing TAVR and HFpEF.[25,27] Screening for ATTR-CA may identify ATTR-CA early in the setting of severe AS and/or HFpEF when emerging therapies may have greater benefit. Our data suggest that echocardiography may be an initial screen for ATTR-CA in this high risk, older population, with severe calcific AS. Patients diagnosed with ATTR-CA had specific features including male sex, concentric LV hypertrophy, severe diastolic dysfunction, and reduced myocardial mechanics (*Figure 4*). One would expect a Stage D3 low-flow AS with a preserved LVEF phenotype initially in patients with both AS and ATTR-CA that transitions to Stage D2 low-flow low-gradient AS with a low LVEF as systolic dysfunction ensues. The best independent echocardiographic predictor of ATTR-CA was an average mitral annular S' ≤6 cm/s. The high sensitivity (100%) of a low mitral annular S ≤6 cm/s may enable clinicians to rule out ATTR-CA in subjects with velocities >6 and consider further testing with ^{99m}Tc-PYP cardiac imaging in the rest. While endomyocardial biopsy and tissue typing with histological staining and precursor protein confirmation using mass spectrometry remain the gold standard for diagnosis of ATTR-CA,[29] these procedures often delay diagnosis and may not be appropriate in frail elderly adults, including those already undergoing TAVR. A positive radioisotope scan, such as ^{99m}Tc-PYP, in the absence of an abnormal monoclonal protein is 100% specific for ATTR-CA without the need for invasive heart biopsy. Furthermore, ^{99m}Tc-PYP cardiac imaging may have prognostic in addition to diagnostic importance in patients with ATTR-CA.[18]

Potential mechanism of non-apical sparing in concomitant severe as and amyloid

Speckle strain imaging has demonstrated impaired LS at the base and mid LV with sparing of the apical segments as a predictive feature of cardiac amyloidosis.[13] Cardiac magnetic resonance imaging data have demonstrated that the base and mid-LV segments are twice as thick in amyloid compared with non-amyloid controls, whereas apical thickness only increased by 26%.[13] The apical sparing phenotype in ATTR-CA may reflect lower extracellular amyloid deposition at the apex, less resistance to myocardial deformation, and increased myocyte contraction relative to the other segments. In our cohort of patients with

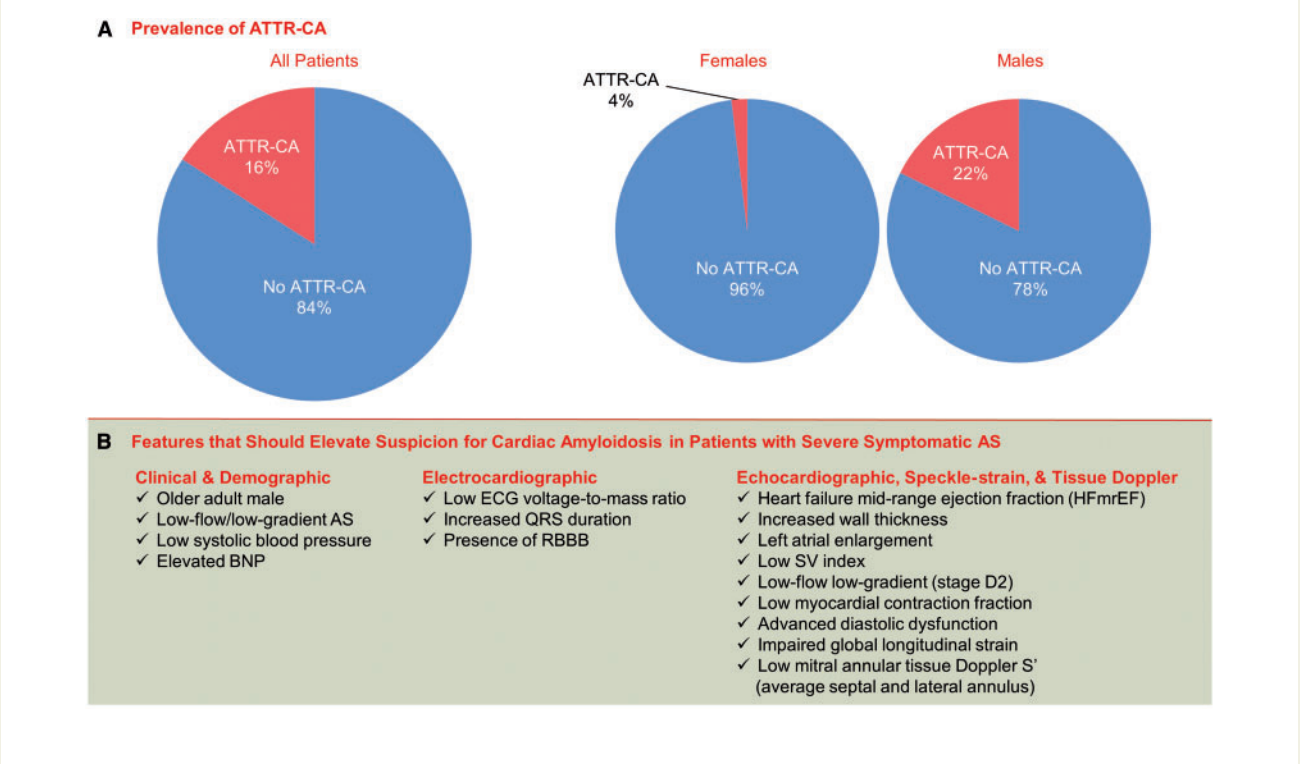

Figure 4 Prevalence and phenotype of ATTR-CA among patients undergoing transcatheter aortic valve replacement at our institution. ATTR-CA, transthyretin cardiac amyloidosis.

concomitant severe, symptomatic AS and ATTR-CA, apical sparing by speckle strain could not predict ATTR-CA. It is possible that the stress and afterload imposed on the ventricle by a severely calcified and stenotic aortic valve masks the sparing of apical strain that is otherwise detected in a patient with pure ATTR-CA without AS.

Limitations

This study was subject to the referral bias of an academic medical centre. Strain analysis was not performed universally as it could only be obtained in patients with adequate endocardial wall definition. While all patients underwent a ^{99m}Tc-PYP scan, cardiac biopsy was not performed given safety risks in this frail older population already undergoing TAVR. However, ^{99m}Tc-PYP is an excellent test for diagnosing advanced forms of ATTR-CA and may replace the need for endomyocardial biopsy.[19] In the current study, of the five patients with ATTR-CA who had an abnormal monoclonal protein, two met the formal diagnostic criteria and had a known MGUS, but ultimately all five chose not to undergo tissue biopsy to formally rule out AL cardiac amyloidosis. The diagnostic utility of ^{99m}Tc-PYP cardiac imaging in early disease has not yet been studied, raising the possibility that ATTR-CA could have been missed among severe AS patients with early cardiac amyloidosis.

Conclusions

In this study of elderly patients with severe calcific AS undergoing TAVR, ATTR cardiac amyloidosis was prevalent at a rate of 16% and associated with a phenotype of low-flow, low gradient AS with a reduced LVEF. An average tissue Doppler mitral annular S' of 6 cm/s or lower may be a sensitive measure that should prompt a confirmatory ^{99m}Tc-PYP scan and subsequent testing for ATTR-CA. Prospective assessment of outcomes after TAVR is needed in patients with and without ATTR-CA.

Acknowledgements

We thank David and Landon Storrs for their generous gift to support Cardiac Amyloidosis research. We also thank the Nurse Practitioners of the Heart Center Critical Care Unit and the Physician Assistants of the Heart Valve Team for their extraordinary care of these patients.

Conflict of interest: A.C. received salary support from the ACC/Merck and New York Academy of Medicine Fellowships in Cardiovascular Disease. S.K. receives consulting fees from Edwards Lifesciences and Medtronic but not in the past 12 months. R.H. is part of the Core Lab consortium for the PARTNER Trial but receives no direct compensation from industry. M.S.M. receives funding from an NIH K24 AG036778 Midcareer Mentoring Award in Geriatric Cardiology and his institution receives funding for research and serving on advisory boards and DSMBs from Pfizer Inc., Alnylam Pharmaceuticals Inc., ISIS Pharmaceuticals and Prothena Inc. D.L.N., N.H., O.K.K., A.D., J.R., C.C., T.N., T.V., I.G., M.B.L., S.B., and R.M. have no disclosures.

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