Reverse Remodeling Following Valve Replacement in Coexisting Aortic Stenosis and Transthyretin Cardiac Amyloidosis

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ABSTRACT

Background: Dual pathology of severe aortic stenosis (AS) and transthyretin cardiac amyloidosis (ATTR) is increasingly recognized. Evolution of symptoms, biomarkers and myocardial mechanics in AS-ATTR following valve replacement is unknown. We aimed to characterize reverse remodeling in AS-ATTR and compare to lone AS.

Methods: Consecutive patients referred for transcatheter aortic valve replacement (TAVR) underwent ATTR screening by blinded 99mTc-DPD bone scintigraphy (Perugini Grade-0 negative, 1–3 increasingly positive) prior to intervention. ATTR was diagnosed by DPD and absence of monoclonal protein. Reverse remodeling was assessed by comprehensive evaluation before TAVR and at 1 year.

Results: 120 patients (81.8±6.3 years, 51.7% male, 95 lone AS, 25 AS-ATTR) with complete follow-up were studied. At 12-months (interquartile range 7-17) following TAVR, both groups experienced significant symptomatic improvement by New York Heart Association (NYHA) functional class (both $p<0.001$). Yet, AS-ATTR remained more symptomatic (NYHA ≥III: 36.0% versus 13.8, $p=0.01$) with higher residual NT-proBNP levels ($p<0.001$). Remodeling by echocardiography showed left ventricular mass regression only for lone AS ($p=0.002$), but not AS-ATTR ($p=0.5$). Global longitudinal strain (LS) improved similarly in both groups. Conversely, improvement of regional LS showed a base-to-apex gradient in AS-ATTR, whereas all but apical segments improved in lone AS. This led to the development of an apical sparing pattern in AS-ATTR only after TAVR.

Conclusions: Patterns of reverse remodeling differ from lone AS to AS-ATTR, with both groups experiencing symptomatic improvement by TAVR. Following AS treatment, AS-ATTR transfers into a lone ATTR cardiomyopathy phenotype.

Key words: ATTR, TAVI, echocardiography, amyloid

CLINICAL PERSPECTIVES

Both, lone aortic stenosis (AS) and dual AS and transthyretin cardiac amyloidosis (AS-ATTR), experience significant symptomatic improvement by transcatheter aortic valve replacement (TAVR). After TAVR, AS-ATTR resembles an ATTR cardiomyopathy phenotype with higher symptomatic burden, higher cardiac biomarkers and left ventricular mass, and new-onset apical sparing by echocardiography when compared to lone AS.

Future studies are required to clarify whether treatment of the residual amyloid component achieves additional prognostic improvements.

ABBREVIATIONS

AS	-	Aortic stenosis
ATTR	-	Transthyretin-related cardiac amyloidosis
DPD	-	^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid
MCF	-	Myocardial contraction fraction
NT-proBNP	-	N-terminal pro-brain natriuretic peptide
NYHA	-	New York Heart Association functional class
TAVR	-	Transcatheter aortic valve replacement

INTRODUCTION

Calcific aortic stenosis (AS) and transthyretin (ATTR) cardiac amyloidosis are both conditions commonly affecting the elderly. Bone scintigraphy using amyloid-avid tracers (99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid, DPD; 99mTc-pyrophosphate; or 99mTc-hydroxymethylene diphosphonate) represents the key imaging modality for non-invasive ATTR diagnosis. [1] Recent studies have used this technology to screen AS patients and demonstrated that AS and ATTR may coexist in 8 to 16%. [2-5] While the dual burden of AS and ATTR might suggest adverse prognostic implications, it has been shown that AS-ATTR and lone AS patients benefit equally from transcatheter aortic valve replacement (TAVR). [3] Hence, it appears that the remaining amyloid component following the treatment of stenosis does not impact short- to mid-term mortality. With increased recognition and valvular treatment of AS-ATTR, the disease course after TAVR becomes a key issue. Novel ATTR-specific treatments are now available, with the potential to further improve prognosis in AS-ATTR on top of valvular replacement. Yet, a more profound understanding of ATTR evolution following left ventricular unloading by TAVR is necessary and currently lacking. The present study was therefore designed to characterize functional, biomarker, and morphological reverse remodeling after successful TAVR in AS-ATTR compared to lone AS.

METHODS

The authors declare that all supporting data are available within the article (and its online supplementary files).

Study population

This prospective cohort study enrolled consecutive adult patients with severe AS referred for TAVR at the Vienna General Hospital, a university-affiliated tertiary center, between October 2017 and March 2019. Patients with complete baseline and follow-up data were considered for the present study (**Figure 1**). All patients underwent cardiac amyloidosis screening including 99mTc-DPD bone scintigraphy, urine and serum free light chain assessment, and endomyocardial biopsy if indicated. Wild-type transthyretin cardiac amyloidosis was identified and light chain (AL) cardiac amyloidosis excluded in accordance with expert consensus recommendations. [6] Patients were stratified according to the presence of concomitant ATTR (lone AS versus AS-ATTR). Baseline assessment beyond ATTR screening included demographic data, clinical and laboratory analysis, electrocardiography, as well as transthoracic echocardiography with strain analysis prior to TAVR. Follow-up was performed at 12 months after TAVR and patients had functional status, laboratory exam, electrocardiography and echocardiography collected. Mortality was captured via the National Death Registry. All participants provided written informed consent and the study was approved by the local ethics committee (EK 2218/2016).

Laboratory assessment

All patients had N-terminal pro-brain natriuretic peptide (NT-proBNP) serum levels measured at baseline and follow-up. Additional routine laboratory examination among others included a full blood count, electrolytes, and serum creatinine. For genetic testing in patients with ATTR, the complete coding regions of the TTR gene were amplified by polymerase chain reaction

assay. Amplified DNA fragments were directly sequenced using an ABI 3130xl Genetic Analyzer (Applied Biosystems).

DPD Bone Scintigraphy

DPD bone scintigraphy was performed in all patients using a General Electric (GE) Infinia Hawkeye 4/ GE Discovery 670 hybrid gamma camera 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. Planar whole-body images were performed at 3 hours. Additional SPECT/CT of the chest at 3 hours was performed in all patients.

DPD scans were analyzed blinded to the clinical data by two readers (CN, RC) according to the Perugini classification, [1] 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. Patients with grade 1 uptake were only considered as having "early ATTR infiltration", when cardiac tracer origin was clearly confirmed by SPECT/CT AND no evidence of monoclonal protein was present. Additional testing in grade-1 patients (n=7) included cardiac magnetic resonance imaging with contrast yielding signs suggestive of CA (positive late enhancement, elevated extracellular volume fraction, n=6), and endomyocardial biopsy revealing underlying ATTR (n=1, this patient had monoclonal protein by serum analysis).

Echocardiography

All patients underwent a comprehensive transthoracic echocardiogram (TTE) using the latest high-end equipment (Vivid E95, GE-Healthcare). Only subjects with complete echocardiographic assessment at baseline and follow-up were considered for the present study. AS severity, any concomitant valve pathology and ventricular function were assessed in

accordance with the EAE/ASE guidelines. [7-10] Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane. LV mass was calculated using the formula from Devereux et al. [11] 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 using the EchoPAC™ software (GE-Healthcare). [12] 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 indexed the stroke volume to the myocardial volume, was calculated as previously described. [2] 'Classical' and 'paradoxical' low-flow, low gradient was defined according to current guidelines. [10]

Statistical analysis

All statistical analyses were computed using SPSS 26 (IBM SPSS, USA) and R (version 4.1.2). 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 Wilcoxon rank sum test. Chi-square tests or Fisher exact tests were used for categorical variables as appropriate. Changes between pre-TAVR and post-TAVR visits were compared using the Wilcoxon signed rank test, McNemar's test, and the Stuart Maxwell test where appropriate. Trajectories of NYHA functional class were visualized using Alluvial plots. A two-sided p-value ≤ 0.05 was considered statistically significant.

RESULTS

STUDY POPULATION

Consecutive patients referred for TAVR were prospectively recruited and underwent comprehensive cardiac amyloidosis screening as detailed above. TAVR survivors were invited

to return for on-site follow-up which was performed at 12.2 months (interquartile range [IQR] 7.3 to 17.3). Time to follow-up was the same in lone AS and AS-ATTR (p=0.5). Only patients returning for follow-up and with sufficient echo quality enabling strain analysis were included in the final analysis (**Figure 1**). A greater proportion of AS-ATTR patients had complete follow-up as compared with lone AS patients (83.3% versus 51.4%, p=0.001). Among those without follow-up, NT-proBNP was higher, pacemaker use, renal function and prevalence of angina were lower, and one-year mortality higher compared to those with complete follow-up (**Table S1**). One-year mortality was significantly lower among patients returning for follow-up (5.0% versus 41.4%; p<0.001). Out of 34 deaths observed in patients without follow-up 8 were periprocedural (during index hospitalization or within 30 days of TAVI). Among the 207 patients who received valve replacement, mortality after 3 years was similar between lone AS and AS-ATTR (log-rank, p=0.6; **Figure S1**). Patients with complete follow-up data were stratified according to the presence of concomitant ATTR. In total, 95 lone AS (79.2%) and 25 AS-ATTR patients (20.8%) were studied. Among AS-ATTR, distribution according to Perugini classification was as follows: 7 grade-1, 13 grade-2, and 5 grade-3. In total, 11 ATTR patients (10 grade-2/3, 1 grade-1) received ATTR-specific treatment (all Tafamidis) following TAVR on a named patient program.

BASELINE FINDINGS

Baseline demographic, clinical, functional, laboratory and echocardiographic characteristics are shown in **Tables 1** and **2.** AS-ATTR patients (all wild-type by genetic testing) on average were 3 years older (84.7 y/o [IQR 81.0 to 88.3] versus 81.9 [IQR 77.9 to 85.2], p=0.009), had a higher prevalence of carpal tunnel syndrome (25.0% versus 1.1, p<0.001), and higher surgical risk (EuroSCORE II 4.7 [IQR 4.0 to 5.0] versus 4.1 [IQR 3.9 to 4.6], p=0.04) as compared to lone AS. Moreover, there was a strong trend towards more male (68.0% versus 47.4, p=0.06),

and a higher prevalence of atrial fibrillation (60.0% versus 41.1, p=0.09) in AS-ATTR, whereas other cardiovascular risk factors were the same in both groups.

Symptoms and laboratory assessment. At baseline, AS-ATTR patients tended to be more symptomatic with a higher proportion of subjects in NYHA class III or IV compared to lone AS (79.2% versus 59.8, p=0.08). Also, NT-proBNP serum levels were significantly increased in ATTR-CA: 3377 pg/mL [IQR 1513 to 6953] versus 1365 [IQR 577 to 3140], p=0.006.

Remodeling by echocardiography. Baseline echocardiography revealed a higher prevalence of both classical (28.0% versus 17.0) and paradoxical low-flow low-gradient AS (24.0% versus 8.5) among AS-ATTR compared to lone AS (p trend =0.03). Accordingly, mean (p=0.014) and peak (p=0.004) gradients as well as transvalvular flow velocity (p=0.005) were significantly lower in AS-ATTR. Owing to the dual burden of infiltration and afterload, myocardial thickening was significantly increased in AS-ATTR compared to lone AS (septum thickness: 17mm [IQR 14 to 20] versus 15mm [IQR 13 to 17], p=0.04; LV mass index: 161 g/m^2 [IQR 127 to 198] versus 131 [IQR 112 to 160], p=0.007). While ventricular dimensions were comparable between groups, AS-ATTR showed larger atria (LA: 64mm [IQR 57 to 68] versus 58 [IQR 52 to 64], p=0.03; RA: 60mm [IQR 53 to 70] versus 55 [IQR 50 to 62]; p=0.04), and more severe functional mitral as well as tricuspid regurgitation (≥moderate: 58.3% versus 22.4 and 56.6% versus 21.4 for mitral and tricuspid, respectively; both p<0.001). LV function was significantly impaired in AS-ATTR compared to lone AS, as determined by lower ejection fraction (52% [IQR 41 to 64] versus 62% [IQR 57 to 70], p=0.007), myocardial contraction fraction (0.14 [IQR 0.10 to 0.19] versus 0.22 [IQR 0.18 to 0.28], p<0.001), and global LS (-10.3 [IQR -15.6 to -7.1] versus -18.0 [IQR -20.6 to -13.8], p=0.001). Importantly, regional strain analysis revealed homogenously impaired contractility in AS-ATTR versus lone AS for apical, midventricular, and basal segments. Consequently, strain ratios commonly used to describe an "apical sparing" pattern were the same between groups (all n.s.). Finally, right

ventricular function (TAPSE) was decreased (p=0.007), and diastology (E/A ratio) trended to be worse in AS-ATTR as compared to lone AS (p=0.09).

INTERVENTION

In total, 95.0% of patients underwent TAVR. Six patients (4 lone AS, 2 ATTR-AS) initially referred for TAVR had a surgical valve replacement according to reconsideration of the heart team and were included in the final analysis. Among TAVR recipients, the proportion of transfemoral access, balloon-expandable prosthesis, and immediate post-interventional valve competency as well as trans-prosthetic gradients were comparable between lone AS and AS-ATTR (all n.s., **Table S2**).

REVERSE REMODELING AT ONE YEAR AFTER AVR

Lone AS. The changes from pre- to postinterventional parameters are summarized in **Table 2**. After a median of one year following TAVR, there was a marked symptomatic improvement (NYHA ≥III: 59.8% to 13.8, p<0.001, **Figure 2**), accompanied by a significant reduction in NT-proBNP levels (1365 pg/mL [IQR 577 to 3140] to 780 pg/mL [IQR 328 to 2016], p<0.001). Left ventricular end-diastolic and end-systolic volumes declined significantly (both p<0.001), as did left (p=0.006) and right atrial size (p=0.014). As expected, LV hypertrophy declined from pre to post intervention, as determined by interventricular septum thickness (15 mm [IQR 13 to 17] to 14 mm [IQR 13 to 16], p<0.001) and LV mass index regression (131 g/m^2 [IQR 112 to 160] to 119 g/m^2 [IQR 102 to 150], p=0.007; **Figure 3**). There was no significant change in LVEF from pre- to post-TAVI in either group; however, baseline EF was lower in the AS-ATTR group. GLS improved significantly pre- to post-TAVI in both the lone AS group (-18.0 [IQR -20.6 to -13.8] to -19.2 [-21.6 to -16.7], p<0.001) and the AS-ATTR group (-10.3 [IQR -15.6 to -7.1] to -15.2 [-18.4 to -11.0], p<0.001); however, the GLS was significantly lower in the AS-ATTR group pre-TAVI. Most interestingly, this improvement of global contractility in lone AS was carried by improvement of basal (-11.7% [IQR -14.6 to -9.9] to -14.9% [IQR -

17.0 to -12.0]) and midventricular strain (-16.7% [IQR -18.5 to -11.6] to -18.2% [IQR -20.8 to -16.0], both p<0.001), whereas apical contractility remained unchanged (p=0.5). Of note, stroke volumes and myocardial contraction fraction decreased from pre- to post-intervention.

AS-ATTR. Patients with dual pathology (n=25) on average experienced marked symptomatic improvement from pre to post intervention (NYHA ≥III: 79.2% to 36.0, p=0.008, **Figure 2**). NT-proBNP levels numerically decreased as well (3377 pg/mL [IQR 1513 to 6953] to 1930 pg/mL [IQR 1211 to 3977], p=0.3), but changes did not reach level of significance. Interestingly, LV thickening remained unchanged, as demonstrated by similar septum thickness (17 mm [IQR 14 to 20] to 16 mm [IQR 13 to 20], p=0.6) and LV mass index (161 g/m^2 [IQR 127 to 198] to 160 g/m^2 [IQR 135 to 221], p=0.5) from before to after TAVR (**Figure 4**). LV end-diastolic and end-systolic volumes declined significantly (both p=0.02), and marked improvements were observed regarding mitral regurgitation severity (≥II: 58.3% to 20.8, p=0.01) and peak tricuspid regurgitation velocity (3.4 m/s [IQR 2.7 to 3.9] to 3.0 m/s [IQR 2.7 to 3.6], p=0.006). Systolic LV function also improved post intervention. While changes in ejection fraction did not reach significance (52% [IQR 41 to 64] to 56% [IQR 48 to 67], p=0.24), enhanced global LS did (-10.3% [IQR -15.6 to -7.1] to -15.2% [-18.4 to -11.0], p=0.01). Improved contractility was most pronounced in apical (-16.6% [IQR -21.7 to -10.1] to -21-5% [IQR -25.5 to -16.5], p=0.016), followed by midventricular segments (-10.0% [IQR -13.6 to -7.3] to -14.8% [IQR -17.2 to -9.7], p=0.027), whereas basal contractility did not change significantly (p=0.25).

Lone AS versus AS-ATTR. With similar decline in NT-proBNP levels from pre to post intervention (pΔ for lone AS versus AS-ATTR =0.8), AS-ATTR patients had higher residual NT-proBNP at follow-up (p<0.001). Also, AS-ATTR remained more symptomatic post intervention than lone AS (NYHA III: 36.0% versus 13.8, p=0.01). With similar decline of transvalvular gradients and LV volumes (pΔ all n.s.), LV mass index regression was only

observed in lone AS (p=0.007), but not in AS-ATTR (p=0.5; pΔ for lone AS versus AS-ATTR =0.06). Also, despite more severe mitral regurgitation among AS-ATTR compared to lone AS at baseline, this was no longer significant at follow-up (p=0.8), due to marked MR regression in dual AS-ATTR after TAVR. Most strikingly, differences in remodeling patterns were observed between groups. Global LS improved to a similar extent in both groups. However, while in lone AS, apical LS remained unchanged post TAVR, these segments displayed significantly improved contractility in AS-ATTR following intervention (pΔ for lone AS versus AS-ATTR =0.04). Conversely, basal contractility only improved in lone AS, but remained unchanged in AS-ATTR (pΔ for lone AS versus AS-ATTR =0.19). Improvement of midventricular LS was similar in both groups. As a result, regional strain ratios formerly identical between lone AS and dual AS-ATTR, showed highly significant differences at follow-up indicative of an "apical spring" pattern in AS-ATTR (e.g., apical/(mid+basal): 0.92 [IQR 0.81 to 1.00] versus 0.73 [IQR 0.63 to 0.81] for AS-ATTR versus lone AS, p<0.001; pΔ=0.01). Results remained more or less unchanged when lone AS was compared to AS-ATTR with grade-2/3 uptake only **(Table S3)**. An analysis confined to patients with low-flow, low-gradient is shown in **Table S4.**

DISCUSSION

In this study we firstly describe functional, morphological, and biomarker trajectories in dual pathology AS-ATTR following valve replacement. We show that TAVR significantly improves dyspnea in AS-ATTR with beneficial effects on cardiac remodeling; yet, these patients on average remain more symptomatic with higher residual NT-proBNP levels than lone AS. We also demonstrate strikingly different patterns of reverse remodeling with LV mass regression only occurring in lone AS but not in dual AS-ATTR. At 1-year post-TAVR, AS-ATTR resembles "lone ATTR" cardiomyopathy by morphology, symptoms, and contractility pattern - highlighting the need for consideration of ATTR-specific therapies.

Since the coexistence of AS and ATTR was firstly described in 2016, [13, 14] we have certainly come a long way in better characterizing this dual pathology. We and others have shown that concomitant cardiac amyloidosis may be present in up to 16% of elderly TAVR candidates, [2-5] which implies a substantially higher prevalence than seen in non-cardiac bone-scintigraphy referrals of the same age. [15] ATTR cardiomyopathy is a condition typically characterized by restrictive physiology and associated low stroke volumes, which – together with frequent neural involvement - predispose for hypotension and intolerance to heart failure medication. The initial perception of futility of AS intervention in dual AS-ATTR was disproven by studies demonstrating survival up to 3 years of TAVR that was indistinguishable from lone AS. [2-4, 16] Yet, it is hard to believe that the remaining amyloid component would be entirely insignificant in terms of functional performance and long-term clinical outcomes – important data, that is currently lacking. We now show that despite significant symptomatic improvement after TAVR, AS-ATTR patients retain a higher dyspnea burden and higher cardiac biomarker levels than lone AS. This persistent heart failure phenotype may partly be held accountable for the increased frequency of heart failure hospitalizations compared to lone AS observed by others. [16]

Persistence of myocardial infiltration was also highlighted by differences in LV mass regression observed between groups. The concept of reverse remodeling following afterload removal has previously been studied for lone AS. Here, LV hypertrophy regressed by up to 30% at 1 year, [17-19] encompassing both cell and extracellular matrix regression. [19] Data from the present study are consistent with these findings as LV mass in lone AS decreased significantly from pre to post intervention. Conversely, a lack of mass reduction was observed for dual AS-ATTR. This could be due to two underlying mechanisms. First, the contribution of AS-related afterload to LV thickening may be less pronounced relative to infiltration, with little potential of regression after TAVR. Second, hypertrophy may indeed regress, but is

counteracted by ongoing amyloid deposition resulting in persistence of LV thickening. Drawing a definite conclusion solely based on data from echocardiography is impossible; cardiac magnetic resonance has the potential to unveil underlying pathophysiological mechanisms and respective studies, therefore, are highly warranted.

Another interesting aspect of reverse remodeling was evolution of LV contractility highlighted by distinct regional strain patterns for both groups (**Figure 5).** Lone AS patients undergoing either surgical or transcatheter aortic valve replacement have previously been shown to experience significant improvement in GLS (reported mean improvements -1.2 to -2.4; present study: -1.9), [20-22] whereas ejection fraction remained unchanged, [20, 21] just as seen for lone AS in the present study. In these patients, regional LS improved across domains of basal and mid-ventricular segments, whereas apical LS remained the same. This is likely due to preserved apical contractility pre-TAVR rather than failure of recovery post-TAVR, as previously proposed. [21] In contrast, AS-ATTR had improved GLS, but displayed a base-to-apex gradient with respect to mechanical recovery. Improvement in regional LS was highest in apical, followed by mid-ventricular segments, whereas basal LS remained unchanged. This increasing "contractile reserve" from base to apex is likely based on and inversely correlated with an apex-to-base gradient of amyloid mass. [23] In other words, apical segments with the lowest amyloid burden exhibit the highest potential of improved contractility after TAVR. As a consequence, AS-ATTR patients develop a pattern of relative apical sparing only after removal of the afterload component. Of note, stroke volumes decreased from pre- to post-intervention in lone AS. This failure of flow recovery has been previously described and hypothetically linked to irreversible heart damage preceding AVR. [24]

These new findings may entail important clinical implications. We show that AS-ATTR transfers into an ATTR cardiomyopathy phenotype after AS treatment (more symptomatic, higher biomarkers, higher LV mass, and more apical sparing compared to lone

AS). The remaining amyloid component warrants consideration of ATTR-specific treatment. Even more so, as systemic amyloidosis screening approaches of AS patients are increasingly implemented and ATTR, thereby, is recognized at earlier stages, [25] where dedicated drugs are believed to be most effective. [26] Yet, at this point, the effect of amyloid-targeting therapies in AS-ATTR is unknown and needs to be evaluated by future studies (ideally in a randomized controlled fashion).

LIMITATIONS

This study included consecutive patients referred for potential TAVR, thereby avoiding selection bias. Following AS treatment, AS-ATTR were managed by both the valve and cardiac amyloidosis clinic, receiving close follow-up. Lone AS patients were also invited to receive on-site follow-up. However, our interventional cardiology unit serves a large population covering a vast supply territory and some patients preferred to receive further check-up by their resident cardiologist/primary care physician – visits that were not eligible for the sake of data consistency. Hence, this is not a prevalence or outcome study – aspects of dual AS-ATTR that have been addressed by previous research. [2-5, 16] Out of 7 grade-1 patients, 6 declined to undergo endomyocardial biopsy due to inherent risks. Yet, comprehensive multimodality imaging (including CMR signs suggestive of CA) and laboratory analysis (absence of monoclonal protein) ensured grade-1 uptake was most likely caused by underlying ATTR. Censoring by mortality may have filtered lower risk patients, but did most likely not affect comparison of lone AS and AS-ATTR, as similar survival rates for both groups have been previously demonstrated. [2-4, 16] Given the small number of patients receiving ATTR-specific medication, this study was underpowered to assess the impact of ATTR treatment. Tissue doppler measurements were not consistently available post-TAVR and were therefore not

included. Finally, the single-center character is a limitation; but at the same time, it guaranteed adherence to a constant clinical routine and consistency of data quality (e.g., strain assessment).

CONCLUSIONS

Dual pathology AS-ATTR experiences functional improvement after AS treatment, and transfers into an ATTR cardiomyopathy phenotype with higher symptomatic burden, higher cardiac biomarkers and more LV thickening compared to lone AS. Also, an apical sparing pattern develops in AS-ATTR only following afterload removal. The remaining amyloid component is likely amenable to ATTR-specific treatment, but this has to be proven by future research.

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Disclosures:

Dr. Nitsche reports speaker fees from Pfizer. The remaining authors have nothing to disclose.

Supplemental Materials

Figure S1

Tables S1-S4

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TABLES

Table 1: Baseline clinical characteristics.

	Lone AS n=95 (79.2%)	AS-ATTR n=25 (20.8%)	*P*-value
Age, y	81.9 (77.9 to 85.2)	84.7 (81.0 to 88.3)	0.009
Male sex, %	47.4	68.0	0.06
BMI, kg/m^2	26.2 (23.5 to 29.7)	27.3 (23.6 to 29.1)	0.84
Pacemaker carrier, %	21.1	20.0	0.91
Comorbidities			
CAD, %	55.8	68.0	0.27
PAD, %	13.7	4.0	0.18
COPD, %	18.4	8.3	0.24
Hypertension, %	93.7	88.0	0.34
Atrial fibrillation, %	41.1	60.0	0.09
Diabetes mellitus, %	27.4	24.0	0.74
Hyperlipidemia, %	77.9	64.0	0.15
CTS, %	1.1	25.0	<0.001
Risk scores			
EuroSCORE II	4.1 (3.9 to 4.6)	4.7 (4.0 to 5.0)	0.042
STS Score	3.5 (2.3 to 4.8)	4.2 (3.1 to 5.8)	0.10
Symptoms			
Asymptomatic	3.3	0.0	0.37
Dyspnea	90.2	95.8	0.38
Angina	36.3	25.0	0.30
Syncope	9.9	8.3	0.82
AS stage			0.026
High gradient	74.5	48.0	
LFLG + EF <50%	8.5	24.0	
LFLG + EF ≥50%	17.0	28.0	
Medication			
Diuretic, %	51.6	64.0	0.27
ACEi/ARB, %	75.8	60.0	0.12

Spironolactone, %	23.2	40.0	0.09
Betablocker, %	66.3	72.0	0.59
ATTR-specific drug, %	0.0	44.0*	<0.001

*) all Tafamidis

AS indicates aortic stenosis; ATTR, transthyretin cardiac amyloidosis; BMI, body mass index; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; CTS, carpal tunnel syndrome; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; STS, Society of Thoracic Surgeons; LFLG, Low-Flow Low-Gradient; EF, ejection fraction; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker;

Table 2: Remodeling from pre- to post-TAVR.

	Lone AS n=95 (79.2%)			AS-ATTR n=25 (20.8%)		
Parameter	Pre-TAVR	Post-TAVR	Change	Pre-TAVR	Post-TAVR	Change
Symptomatic remodeling						
NYHA[*,†]						
I	8.7	48.8	+40.1	0.0	24.0	+24.0
II	31.5	37.5	+6.0	20.8	40.0	+19.2
III	53.3	13.8[*]	-39.5	66.7	36.0[†,‖]	-30.7
IV	6.5	0.0	-6.5	12.5	0.0	-12.5
Biomarker remodeling						
NT-pro BNP, pg/mL	1365 (577 to 3140)	780 (328 to 2016)[*]	-271 (-1000 to 83)	3377 (1513 to 6953)[§]	1930 (1211 to 3977)[‖]	-86 (-2755 to 695)
GFR, ml/min/1.73m^2	60 (47 to 73)	52 (44 to 63)[*]	-3 (-15 to 5)	55 (44 to 80)	54 (37 to 72)	-4 (-15 to 8)
Echocardiographic remodeling						
LV diameter, mm	45 (40 to 49)	44 (40 to 49)	0 (-4 to 4)	41 (37 to 49)	42 (37 to 48)	-1 (-3 to 3)
RV diameter, mm	32 (28 to 36)	33 (29 to 36)	-1 (-4 to 3)	36 (30 to 42)	34 (30 to 41)	-1 (-2 to 3)
LA diameter, mm	58 (52 to 64)	57 (50 to 61)[*]	-2 (-7 to 3)	64 (57 to 68)[§]	63 (56 to 68)[‖]	-1 (-5 to 3)
RA diameter, mm	55 (50 to 62)	53 (49 to 60)[*]	-2 (-6 to 2)	60 (53 to 70)[§]	59 (52 to 64)[‖]	-1 (-4 to 4)
IVS, mm	15 (13 to 17)	14 (13 to 16)[*]	-1 (-3 to 1)	17 (14 to 20)[§]	16 (13 to 20)[‖]	0 (-1 to 1)
AV MPG, mmHg	46 (38 to 55)	9 (6 to 13)[*]	-37 (-45 to -25)	37 (28 to 46)[§]	7 (5 to 12)[†]	-30 (-40 to -20)
AV PPG, mmHg	73 (64 to 88)	17 (11 to 25)[*]	-60 (-69 to -41)	60 (42 to 74)[§]	14 (9 to 22)[†]	-43 (-68 to -35)
AV Vmax, m/s	4.3 (4.0 to 4.7)	2.1 (1.7 to 2.5)[*]	-2.2 (-2.8 to -1.5)	3.9 (3.3 to 4.3)[§]	1.9 (1.5 to 2.4)[†]	-2.0 (-2.7 to -1.5)

TAPSE, mm	2.5 (2.1 to 2.8)	1.9 (1.6 to 2.2)	-0.5 (-0.9 to -0.1)	2.1 (1.6 to 2.5)[§]	1.8 (1.1 to 2.1)	-0.3 (-0.9 to 0.2)
MR≥II, %	22.4	18.1	-4.3	58.3	20.8[†]	-37.5[‡]
TR≥II, %	21.4	23.4	+1.9	56.6	40.0	-16.6
Peak TR velocity, m/s	2.8 (2.0 to 3.1)	2.8 (2.5 to 3.2)	0.0 (-0.4 to 0.5)	3.4 (2.7 to 3.9)[§]	3.0 (2.7 to 3.6)[†]	-0.6 (-1.0 to -0.2)[‡]
LVEF, %	62 (57 to 70)	64 (57 to 69)	1 (-7 to 9)	52 (41 to 64)[§]	56 (48 to 67)[‖]	3 (-5 to 15)
LVEDV, ml	79 (56 to 103)	61 (47 to 88)[*]	-8 (-39 to 0)	80 (61 to 101)	60 (49 to 95)[†]	-13 (-20 to 2)
LVESV, ml	26 (19 to 42)	21 (15 to 31)[*]	-6 (-18 to 0)	34 (22 to 65)	27 (19 to 45)[†,‖]	-7 (-21 to 0)
MCF	0.22 (0.18 to 0.28)	0.18 (0.13 to 0.24)[*]	-0.04 (-0.10 to 0.04)	0.14 (0.10 to 0.19)[§]	0.13 (0.10 to 0.19)[‖]	-0.02 (-0.07 to 0.06)
SV, ml	51 (36 to 60)	38 (29 to 50)[*]	-9 (-23 to 4)	39 (35 to 44)[§]	34 (27 to 50)	-9 (-15 to 14)
LV mass	250 (209 to 294)	225 (177 to 271)[*]	-17 (-64 to 13)	292 (245 to 381)[§]	317 (256 to 403)[‖]	15 (-31 to 47)[‡]
LV mass index, g/m^2	131 (112 to 160)	119 (102 to 150)[*]	-9 (-34 to 8)	161 (127 to 198)[§]	160 (135 to 221)[‖]	9 (-19 to 24)
E deceleration time, ms	225 (160 to 281)	246 (201 to 289)	5 (-29 to 67)	205 (149 to 279)	270 (215 to 345)	34 (-16 to 96)
E/A ratio	0.8 (0.7 to 1.0)	0.8 (0.7 to 1.3)	0.0 (-0.2 to 0.2)	2.1 (0.6 to 2.7)	0.7 (0.6 to 2.0)	0.0 (-1.0 to 0.2)
Apical LS, %	-24.3 (-28.8 to -18.1)	-24.2 (-28.1 to -19.7)	0.0 (-3.6 to 3.2)	-16.6 (-21.7 to -10.1)[§]	-21.5 (-25.5 to -16.5)[‖]	-3.8 (-9.3 to 0.4)[‡]
Mid LS, %	-16.7 (-18.5 to -11.6)	-18.2 (-20.8 to -16.0)[*]	-1.5 (-4.5 to 0.0)	-10.0 (-13.6 to -7.3)[§]	-14.8 (-17.2 to -9.7)[†,‖]	-1.5 (-4.6 to -0.3)
Basal LS, %	-11.7 (-14.6 to -9.9)	-14.9 (-17.0 to -12.0)[*]	-2.6 (-5.1 to 0.0)	-6.8 (-10.6 to -4.3)[§]	-10.0 (-12.5 to -5.0)[‖]	-0.3 (-3.5 to 0.8)
GLS, %	-18.0 (-20.6 to -13.8)	-19.2 (-21.6 to -16.7)[*]	-1.0 (-4.0 to 0.0)	-10.3 (-15.6 to -7.1)[§]	-15.2 (-18.4 to -11.0)[†,‖]	-1.2 (-4.9 to 0.0)
Apical/(mid+basal)	0.81 (0.74 to 0.98)	0.73 (0.63 to 0.81)[*]	-0.12 (-0.25 to 0.02)	0.90 (0.74 to 1.29)	0.92 (0.81 to 1.00)[‖]	0.10 (-0.16 to 0.39)[‡]
Cut-off ≥1.0, %	23.8	4.9[*]	-18.9	42.9	28.0[‖]	-14.9
Apical/basal	1.89 (1.63 to 2.48)	1.61 (1.32 to 1.93)[*]	-0.34 (-0.72 to 0.02)	1.96 (1.17 to 3.15)	2.15 (1.87 to 2.34)[‖]	0.20 (-0.31 to 0.84)[‡]
(Apical+mid)/basal	3.26 (2.82 to 3.98)	2.81 (2.53 to 3.38)[*]	-0.47 (-1.00 to 0.04)	3.35 (2.26 to 4.97)	3.60 (3.20 to 3.82)[‖]	0.46 (-0.24 to 1.11)[‡]

1

*) Lone AS pre-TAVR versus post-TAVR: p≤0.05

†) AS-ATTR pre-TAVR versus post-TAVR: p≤0.05

‡) Differences in pre- to post-TAVR changes for lone AS versus AS-ATTR: p≤0.05

§) Lone AS pre-TAVR versus AS-ATTR pre-TAVR: p≤0.05

‖) Lone AS post-TAVR versus AS-ATTR post-TAVR: p≤0.05

NYHA indicates New York Heart Association functional class; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; GFR, glomerular filtration rate; LV, left ventricular; RV, right ventricular; LA, left atrial; RA, right atrial; IVS, interventricular septum; AV, aortic valve; MPG, mean pressure gradient; PPG, peak pressure gradient; Vmax, peak velocity; TAPSE, tricuspid annular plane systolic excursion; MR, mitral regurgitation; TR, tricuspid regurgitation; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; MCF, myocardial contraction fraction; SV, stroke volume; LS, longitudinal strain; GLS, global longitudinal strain;

FIGURE LEGENDS

Figure 1. Patient sample.

AS indicated aortic stenosis; ATTR, transthyretin cardiac amyloidosis; AVR, aortic valve replacement; DPD, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid bone scintigraphy; SPECT/CT, single-photon emission computed tomography/ computed tomography; TAVR, transcatheter aortic valve replacement;

Figure 2. Evolution of functional status from before to after transcatheter aortic valve replacement (TAVR) for lone aortic stenosis (AS) and dual AS and transthyretin cardiac amyloidosis (AS-ATTR). New York Heart Association (NYHA) functional class improved similarly in both groups. However, post-TAVR more AS-ATTR remained in NYHA class III as compared to lone AS.

Figure 3. Mechanical reverse remodeling in lone AS.

A 85 y/o male with severe high-gradient aortic stenosis (AS) and without evidence of concomitant transthyretin cardiac amyloidosis (negative bone scan) experienced a 16% regression of left ventricular mass index (LVMi) at 1 year after valve replacement. Trajectories of contractility showed an improvement of global longitudinal strain (GLS) at follow-up carried by improved basal and midventricular segments, whereas apical longitudinal strain remained more or less the same. Pre indicates prior to valve replacement; post, after valve replacement; MPG, mean transvalvular pressure gradient; Vmax, maximum transvalvular flow velocity; IVS, interventricular septum thickness; LVEDD, left ventricular end-diastolic diameter; PWT, posterior wall thickness;

Figure 4. Mechanical reverse remodeling in dual AS-ATTR.

A 86 y/o male with severe paradoxical low-flow low-gradient aortic stenosis (CA) and concomitant transthyretin cardiac amyloidosis (confirmed by positive bone scintigraphy and negative light-chain assessment) received transcatheter aortic valve replacement. At 1 year, no regression in left ventricular mass index (LVMi) was observed. Global longitudinal strain improved from pre to post TAVR (-7.4% to -9.4%). Recovery of contractility was highest in apical, followed by mid-ventricular segments and remained unchanged in basal segments, creating a base-to-apex gradient. For abbreviations see Figure 3.

Figure 5. Patterns of reverse remodeling.

AS indicates aortic stenosis; TAVR, transcatheter aortic valve replacement; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association functional class;