Impact of Afterload and Infiltration on coexisting Aortic Stenosis and Transthyretin Amyloidosis

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Abstract (250 words)

Objective: The coexistence of wild-type transthyretin cardiac amyloidosis (ATTR) is common in patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI). However, the impact of ATTR and AS on the resultant AS-ATTR is unclear and poses diagnostic and management challenges. We therefore used a multi-cohort approach to evaluate myocardial structure, function, stress and damage by assessing age-, afterload- and amyloid-related remodelling on the resultant AS-ATTR phenotype.

Methods: We compared four samples (n=583): 359 patients with AS, 107 with ATTR (97% Perugini grade 2), 36 with AS-ATTR (92% Perugini grade 2) and 81 age- and sex-matched controls. DPD scintigraphy was used to diagnose amyloidosis (Perugini grade 1 was excluded). The primary end-point was NT-proBNP and secondary end-points related to myocardial structure, function and damage.

Results: Compared to older age controls, the three disease cohorts had greater cardiac remodelling, worse function and elevated NT-proBNP/Troponin-T. NT-proBNP was higher in AS-ATTR (2844 (1745, 4635) ng/dL) compared to AS (1294 (1077, 1554)ng/dL; p=0.002) and not significantly different to ATTR (3272 (2552, 4197)ng/dL; p=0.63). The left ventricular mass index in AS-ATTR was lower than ATTR (139 (112, 167) vs 180 (167, 194)g; p=0.013), and non-significantly different to AS (120 (109, 130)g; p=0.179). Diastology, Troponin T and prevalence of carpal tunnel syndrome were statistically similar between AS-ATTR and ATTR and higher than AS.

Conclusions: The AS-ATTR phenotype likely reflects an early stage of amyloid infiltration, but the combined insult resembles ATTR. Even after treatment of AS, ATTR-specific therapy is therefore likely to be beneficial.

Key Questions

What is already known about this subject?

AS-ATTR is common among patients with AS. TAVI reduces mortality and should not be withheld among such patients

What does this study add?

AS-ATTR is a mixed phenotype which is worse than lone AS but is not the summation or even potentiation of the two insults (afterload and infiltration) – it is likely to reflect an early stage of amyloid infiltration. Despite this, the phenotype resembles ATTR in terms of cardiac biomarkers, longitudinal systolic function, diastology and the prevalence of carpal tunnel syndrome. The AS-ATTR phenotype is also broad with majority of features resembling ATTR, a few features resembling AS and some different from both AS and ATTR.

How might this impact on clinical practice?

ATTR-specific therapies are likely to be of benefit among patients with AS-ATTR. Current screening approaches (e.g. screening only males, or low-flow low-gradient AS) may miss patients with AS-ATTR due to its broad and varied phenotype.

Introduction

Severe aortic stenosis (AS) and wild-type transthyretin cardiac amyloidosis (ATTR) are common in the elderly [1,2]. Recent studies have demonstrated that transthyretin amyloid coexists with severe AS at a prevalence of 13-16% [3–5]. Cardiac amyloid is graded with bone scintigraphy using the Perugini system; 0 representing no amyloid, 1-3 representing increasing grades [6]. In AS, a small degree of amyloid (Perugini grade 1) is typically considered bystander, but grade 2 and 3 (AS-ATTR) has been described as having amyloidosis like characteristics including; demographics (older age, marked male predominance), electrocardiography (low voltage), cardiac morphology (unexplained hypertrophy, low-flow, low-gradient AS) and poorer outcomes [3,4,7]. However, studies to date have had three limitations: firstly, some have made the distinction between AS and AS-ATTR in response to clinical suspicion, risking selection bias. Secondly, many studies have reported cases from a single centre/region. Thirdly, comparisons have not been complete: whilst AS has been compared to AS-ATTR [3,8,9], comparisons to ATTR (specifically, wild-type transthyretin cardiac amyloidosis) and older age controls have not been made. A fuller appreciation of AS-ATTR requires this 2x2 matrix comparison of AS (present/absent) and wild-type transthyretin cardiac amyloidosis (present/absent). Biologically, AS and ATTR are both diseases impacting the myocardium through incompletely understood processes affecting both the interstitium and myocytes, with age and sex-specific influences. It is therefore plausible that the resulting phenotype, AS-ATTR, may be the product of a biological interaction between both diseases, sufficient to render AS-ATTR an extreme phenotype from the sum of both diseases. Alternatively, one disease could dominate the clinical phenotype, with the other disease either acting as a bystander or having less impact. Recent advances in diagnostics, particularly bone scintigraphy have underlined the clinical impact of cardiac amyloidosis, whilst new pharmacotherapies now offer symptomatic and

prognostic benefits [10,11]. Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of AS for nearly the last two decades, and has demonstrated improved mortality in cases of AS-ATTR [8,12]. This is intriguing as the amyloid component still remains post-TAVI but does not seem to influence mortality. Studies to date, have not evaluated the effect of amyloid-targeted therapy on outcomes among patients with AS-ATTR. It is therefore important to understand the phenotype of AS-ATTR as its presentation, natural history, response to treatment and prognosis may behave differently in the presence of a potential disease modifier. Clinically this will help define diagnostic and therapeutic pathways, and allow evaluation of associated costs, side effects and complications. Accordingly, we set out to evaluate myocardial structure, function, stress and damage by comparing AS-ATTR to AS and ATTR in patients, and older age controls, in order to understand the relative impact of each individual disease (AS related afterload and amyloid infiltration) on the resulting phenotype.

Methods

Study population

Four prospectively recruited cohorts were combined (total n=583): older age controls from the Southall And Brent REvisited (SABRE) study [13]. AS and AS-ATTR from the Role of Occult Cardiac Amyloid in the Elderly with Aortic Stenosis (ATTRact AS) study and a Vienna General Hospital study and ATTR from the UK National Amyloid Centre (NAC) registry. Table 1 shows the 2x2 matrix cohort model that was used for this study. AS, AS-ATTR and ATTR cohorts consisted of screened patients with complete data. The older age cohort provided age-expected comorbidities, matching that of the patient cohorts. All participants provided informed consent and each study was approved by a local research ethics committee. Patients, as part of the patient and public involvement programme for

valvular heart disease, were involved in the design of this study. Participants had demographic data, cardiac biomarkers (NT-proBNP, high-sensitivity Troponin-T), electrocardiography, echocardiography and clinical data collected. Wild-type transthyretin cardiac amyloidosis was identified in all patients using bone scintigraphy and exclusion of AL amyloidosis in accordance with international guidelines [14].

SABRE cohort

A sample of elderly, European origin patients, without significant valvular heart disease, history of myocardial infarction or known heart failure was selected to provide a population-based, older age control cohort which was matched to the disease cohorts on age and ethnicity. This cohort did not have DPD scintigraphy.

AS-ATTR cohort

This cohort comprised of patients recruited from two prospective observational studies: ATTRact AS (a two-centre (John Radcliff Hospital (JRH), Oxford, UK and St Bartholomew's Hospital (SBH), London, UK), study of patients 75 years or older with severe AS referred for a transcatheter aortic valve implantation (TAVI) recruited between October 2016 and February 2019 (NCT03029026)) and a study from Vienna General hospital (VGH) (recruited consecutive patients referred for a TAVI between October 2017 and January 2019). Consenting patients underwent pre-TAVI ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy to identify coexisting amyloid. Further assessments in positive DPD patients (serum free light chain ratio and monoclonal immunoglobulin in the serum and urine by immunofixation and genotyping) identified wild-type transthyretin cardiac amyloidosis based on international guidelines [14]. For this study we only considered patients with wild-type transthyretin cardiac amyloidosis, Perugini grade 2 and 3, named as AS-ATTR and did

not include those with Perugini grade 1. This resulted in two cohorts: 359 patients with AS and 36 patients with AS-ATTR.

ATTR cohort

The NAC is a tertiary referral centre in the UK. For this study we chose consecutively referred, newly diagnosed patients with wild-type transthyretin cardiac amyloidosis, Perugini grade 2 and 3, (lone-amyloidosis), totalling 107 patients. Diagnosis of wild-type transthyretin cardiac amyloidosis was based on international guidelines [14]. Patients with coexisting mild-moderate AS (n=4) and Perugini grade 1 (n=2) were excluded.

Biomarkers

All subjects had NT-proBNP and high sensitivity Troponin-T (hsTnT) measured at their index consultation.

DPD scintigraphy

All patients (not older age controls) underwent DPD scintigraphy. The imaging protocol at the JRH, NAC and SBH consisted of an early (5 minutes) and late (3 hours) planar whole-body image. Scans were performed using aligned protocols and Perugini scoring; with grade 0 being negative, grade 1 to 3 increasingly positive as previously described [6]. Among positive patients, further assessments (serum free light chain ratio and monoclonal immunoglobulin in the serum and urine by immunofixation) to rule out AL amyloid and genotyping identified wild-type transthyretin cardiac amyloidosis based on international guidelines [14]. Patients with Perugini grade 1 were excluded from this study.

Echocardiography

All patients underwent transthoracic echocardiography by experienced accredited echocardiographers. Different machines and software were used at different sites for image acquisition. Chamber and valve quantification was according to international recommendations [15]. Cardiac parameters were measured using EchoPAC software (GE Healthcare, Wauwatosa, WI, USA). Left ventricular (LV) mass was calculated using methodology described previously [16]. Myocardial contraction fraction (MCF) was derived from the ratio of stroke volume over myocardial volume. Global longitudinal function (GLS) was acquired using strain imaging in the apical 4, 3 and 2 chamber views and is an average of all 17 segments.

Study endpoints

For the purposes of statistical modelling end-points were selected as markers of myocardial damage, structure and function. The primary end-point was NT-proBNP, based on its prognostic value in patients with AS and ATTR. The secondary endpoints used were:

a) left ventricular mass indexed as it is a marker of amyloid burden and a frequent consequence of remodelling in AS.

b) Myocardial contraction fraction (MCF) and global longitudinal strain (GLS) as markers of LV systolic function

c) E/A ratio to assess LV diastolic function

d) Tricuspid annular planar systolic excursion (TAPSE) to assess RV systolic function

e) High sensitivity Troponin T (hsTnT) as a marker of myocardial damage

f) Carpal tunnel syndrome as a marker of systemic ATTR involvement

Statistical analysis

Continuous data describing the sample are summarised as mean ± standard deviation (SD) or median (interquartile range) for skewed data; categorical data are summarised as frequencies (percentages). Results from the four diagnostic groups were compared using multivariable regression modelling with covariate adjustment to control confounding. Results are presented as marginal means and 95% confidence intervals (CI). Covariates were chosen as potential confounders based on *a priori* evidence indicating correlations with both exposure and outcome. Covariates were sex, age, diabetes, hypertension, high cholesterol and chronic kidney disease. Additional sensitivity analyses were performed to check the results of the regression modelling, using augmented inverse-probability weighting (AIPW) to achieve confounder balance across the four groups. AIPW is a statistical approach that combines propensity-based inverse probability weighting (where the contribution of an individual's data is weighted by the propensity score) and regression adjustment. AIPW has the advantage that it is 'doubly robust', such that only one of the two methods need be correctly specified to obtain an unbiased effect estimator [17].

Additional data on comorbidities, ECG and echocardiographic findings are provided in supplemental table 1. These parameters were not included in the main analysis and are presented to provide a more complete description of each cohort, rather than for inferential purposes. All statistical analyses were performed using SPSS statistics software (V26, IBM, Chicago, IL) or Stata SE (15.1, StataCorp LLC, College Station, Texas). For the primary outcome (NT-ProBNP) a two-sided p value of <0.05 was considered significant. Inferences on other outcomes were made based on the means and 95% confidence intervals.

Results

Study population

Baseline characteristics of the four prospective cohorts are shown in table 2, supplementary table 1 and figure 1. Patient demographics for the four cohorts were:

1) Older age controls (AS negative, amyloidosis unlikely) cohort (n=81) was 69% male, median age of 82 (80, 84) years,

2) AS (i.e. amyloidosis negative, severe AS) cohort (n=359) was 49% male, median age of 85 (80, 88) years,

3) AS-ATTR cohort (amyloidosis positive, severe AS) cohort (n=36) was 61% male, median age of 88 (85, 92) years with Perugini grade 2 identified in 33 patients (92%) and grade 3 in 3 patients (8%).

4) ATTR (amyloidosis positive, AS negative) cohort (n=107) was 94% male, median age of 80 (75, 84) years. Perugini grade 2 was identified in 104 patients (97%), grade 3 in 3 patients (3%).

AS-ATTR patients with Perugini grade 1 were excluded from this study (n=16). The AS-ATTR cohort was older than all three other cohorts (p<0.005 for trend) but between AS and ATTR for male predominance (61%; p<0.005 for trend).

Impact on myocardium stress

Patients with AS-ATTR have higher NT-proBNP (2844; 95% CI (1745, 4635)ng/dL) than older age controls (127; 95% CI (100, 162)ng/dL; P<0.001) and AS (1294; 95% CI (1077, 1554)ng/dL; P=0.002) and similar to ATTR (3272; 95% CI (2552, 4197)ng/dL; p=0.63). These results are consistent with the doubly robust analysis (table 2 and supplementary table 2).

Impact of myocardial structure

LVMi in AS-ATTR was greater than in older age controls, similar to AS and lower than ATTR. Doubly robust analysis demonstrated no significant difference between groups except between older age controls and AS-ATTR. However, confidence intervals are wide. (table 2 and supplementary table 2).

Impact of myocardial function

GLS and TAPSE in AS-ATTR was impaired and similar to AS and ATTR. All three patient cohorts had worse function compared to older age controls. However, MCF in AS-ATTR was worse compared to AS and better compared to ATTR, with older age controls demonstrating the best MCF. E/A ratio in AS-ATTR (restrictive diastology) was worse than AS and older age controls and similar to ATTR These results are consistent with the doubly robust analysis except for GLS where confidence intervals for older age controls are wide and for E/A ratio where comparison with AS demonstrates a trend towards significance (p=0.069) (table 2 and supplementary table 2).

Impact on myocardial damage

hsTnT in AS-ATTR was higher than AS and older age controls and similar to ATTR These results are consistent with the doubly robust analysis (table 2 and supplementary table 2).

Systemic impact of ATTR

Carpal tunnel syndrome in AS-ATTR was more frequent compared to AS and similar to ATTR. These results are inconsistent with the doubly robust analysis, however, overall numbers of carpal tunnel syndrome are small limiting statistical power (table 2 and supplementary table 2).

Discussion

Using a multi-centre, multi-cohort approach of over 500 patients, we characterized AS-ATTR by comparing the phenotype to that of AS, ATTR and age- and sex-matched controls. Four main conclusions can be drawn (figure 1); Firstly, despite an equivalent amyloid infiltration bone scintigraphy grade of ATTR, myocardial remodelling (LVMi) in AS-ATTR is similar to AS and less than ATTR, suggesting a lower amyloid burden in AS-ATTR patients, suggesting that they are detected early. Secondly, the impact of dual pathology on the clinical phenotype is increased myocardial stress and damage with NT-proBNP and hsTnT levels similar to patients with ATTR. Thirdly, systolic longitudinal function is impaired in AS-ATTR but similar to the AS and ATTR phenotype. Fourthly, diastology in AS-ATTR is restrictive and closely resembles ATTR. We therefore conclude that the dual insult of AS and ATTR results in a combined phenotype most closely resembling ATTR (rather than a more severe phenotype)- due to a lower amyloid but higher afterload burden.

AS-ATTR poses several challenges, from diagnostics- screening patients with AS for coexisting amyloid to management- timing (either pre or post- aortic valve replacement) and mode of aortic valve interventions (either surgical aortic valve replacement or TAVI) and amyloid-targeted therapy. This makes understanding the relative impact of each contributing pathology very important.

DPD grades are indicative of the distribution of amyloid in the heart relative to other organ systems. Despite comparing patients with only Perugini grade 2 (majority of patients) and 3 and adjusting for several covariates, AS-ATTR had a lower amyloid burden (estimated using LVMi) compared to ATTR. The most plausible reason for this is that the amyloid in AS-ATTR, here discovered by screening, was simply an earlier phase of amyloid compared to ATTR, which was derived from a national referral cohort. Despite the lower amyloid burden,

the dual impact of AS-related afterload and ATTR-related infiltration may be sufficient to drive certain markers of myocardial remodelling to resemble those of ATTR.

Both NT-proBNP and hsTnT have demonstrated prognostic value in patients with AS [18,19] and ATTR [20,21]. In AS-ATTR, the double hit to the myocardium from AS-related afterload and amyloid infiltration significantly increases both biomarkers. However, despite this increase, mortality is similar between AS and AS-ATTR post-TAVI [8,12], suggesting that the AS component of AS-ATTR is the dominant pathology in AS-ATTR. This calls for an evaluation of the biomarkers' prognostic role in AS-ATTR but supports their diagnostic value in discriminating AS-ATTR from AS [12].

Assessment of LV systolic function using left ventricular ejection fraction in patients with cardiac remodelling can be misleading as changes in ventricular capacitance are not accounted for. GLS is a more sensitive marker of LV function and was found to be similar between AS-ATTR and AS and ATTR, indicating that longitudinal deformation is unaffected by dual pathology. However, when indexing stroke volume to the amount of myocardium using MCF, there is a clear difference between all four cohorts with AS-ATTR demonstrating better function than ATTR but worse function than older age controls and AS. This indicates the impact of amyloid in AS-ATTR alters ventricular geometry and reduces function without significantly increasing LVMi. The amyloid component of AS-ATTR also contributes to worse diastolic function compared to AS, resulting in a restrictive physiology- similar to ATTR.

Our study differed from previous descriptions of AS-ATTR, which likely reflects differences in sample selection, study methodology and ascertainment, here exclusively by prospective screening. There are similarities between our data and others on the description of AS-ATTR compared to AS: worse diastolic function and MCF. However, our study has demonstrated

similar GLS and LVMi, higher cardiac biomarkers and more carpal tunnel syndrome in AS-ATTR compared to AS [3,4].

Our findings have important clinical implications. The similarities in cardiac function, biomarkers and carpal tunnel syndrome between AS-ATTR and ATTR suggest that the amyloid component in AS-ATTR plays a key role in the phenotype. And given that the amyloid burden may be lower in AS-ATTR, the phenotype may be more amenable to treatment than previously thought. Although speculative- amyloid stabilizing drugs such as Tafamidis, may have a greater benefit when treating amyloid at an earlier stage than at later stages when the amyloid burden and impact is greater. Therefore, studies evaluating the effect of amyloid-targeted therapy are needed for AS-ATTR [22]. Treating AS-ATTR only with aortic valve replacement would neglect a significant part of phenotype. The subtle differences between AS-ATTR and AS call for a high index of suspicion and screening pathways to identify AS-ATTR in patients with AS. AS-ATTR affects the elderly, where quality of life and symptomatic relief are just as important as mortality benefit; future studies need to consider these outcomes when trialling interventions for AS-ATTR.

Limitations

Ascertainment bias remains in this study due to the different recruitment strategies for each cohort. Although we matched across cohorts using regression and augmented inverse probability weighting, some differences may persist. Despite a relatively high prevalence of coexisting amyloid in patients with AS, the number of patients in this study with AS-ATTR is low; a multi-cohort approach was therefore used to overcome this. Diastolic function was only assessed with one parameter: E/A ratio and further studies need to provide a more detailed analysis of diastology. Pacemaker rates were not compared due to the impact of TAVI on pacemaker need. Lastly, the older age cohort did not have bone scintigraphy, so

some occult amyloid may have been missed- we minimized this by selecting participants without a history of heart failure and given their normal echocardiographic appearance and biomarker levels- ATTR within this cohort was deemed unlikely. This is a cross-sectional study at a single-time point and further longitudinal studies are needed.

Conclusions

AS-ATTR is a mixed phenotype which is worse than lone AS but is not the summation or even potentiation of the two insults (afterload and infiltration). It likely reflects an early stage of amyloid infiltration, but the combined insult in a phenotype resembles ATTR. Even after treatment of AS, ATTR-specific therapy is therefore likely to provide benefit.

Abbreviations

AS- Aortic stenosis

AS-ATTR- coexisting aortic stenosis and transthyretin amyloidosis (grade 2 or 3)

ATTRact AS- Role of Occult Cardiac Amyloid in the Elderly With Aortic Stenosis

hsTnT- high sensitivity Troponin T

LV- left ventricular

LVEF- left ventricular ejection fraction

GLS- global longitudinal function

LVMi- left ventricular mass indexed

MCF- myocardial contraction fraction

NAC- National Amyloid Centre

NS- non significant

NT-proBNP- N terminal pro-brain natriuretic peptide

RV- right ventricular

SABRE- Southall And Brent Study

TAPSE- tricuspid annular planar systolic excursion

Disclosures

Apart from those above, none declared.

Contributorship statement

Conception and study design- KPP, PRS, CN, AK, GL, TAT, JCM, JM, MF, JG, AK, PH, AH, TT. data acquisition-KPP, PRS, CN, AK, GJ, GT, RH, SW, TT, LC, JG, PH, MF, AK, NS, JN, SK, MO, MJM, LM. Data analysis/interpretation- KPP, PRS, CN, AH, PH, TAT, GL, JCM. Drafting manuscript- KPP, PRS, CN, AH, PH, TAT, GL, JCM. Critical revision of manuscript- all authors. final approval of manuscript- all authors.

All authors agree to be accountable for all aspects of this manuscript.

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Figure legends

Figure 1: Characterization of AS-ATTR.

AS-ATTR compared to AS, ATTR and older age controls (not drawn to scale). For some parameters (GLS, TAPSE), AS-ATTR was similar to AS and ATTR, whilst for others it was similar to ATTR and higher than AS (cardiac biomarkers, carpal tunnel syndrome and diastolic dysfunction). AS-ATTR was similar to AS and less than ATTR for LV mass indexed and in between AS and ATTR for MCF. NT-proBNP- N terminal pro- brain natriuretic peptide, hsTnT- high sensitivity Troponin T, LV- left ventricular, LVEF- left ventricular ejection fraction, TAPSE- tricuspid annular plane systolic excursion.

Figure 2: Multi-modality characterization of AS-ATTR.

Echocardiographic and DPD (axial SPECT/CT and planar) images of patients from all four cohorts: older age control, AS, AS-ATTR and ATTR. Echocardiography shows an apical four chamber (A4C) view. Single photon emission computed tomography/ computed tomography (SPECT/CT) shows coronal slices at the level of the heart showing radioisotope uptake superimposed on a CT image. Planar images show cardiac radioisotope uptake relative to bony uptake.

Tables

		Aortic stenosis	
		Present	**Absent**
Amyloidosis	**Present**	AS-ATTR (n=36) 61% male, age 88 (85, 92) years. Perugini grade 2 in 33 patients (92%) and grade 3 in 3 patients (8%)	ATTR (n=107) 94% male, age 80 (75, 84) years. Perugini grade 2 in 104 patients (97%), grade 3 in 3 patients (3%)
	Absent	AS (n=359) 49% male, age 85 (80, 88) years	Older age controls (n=81) 64% male, age 82 (80, 84) years

Table 1: Study population according to the presence or absence of aortic stenosis and amyloidosis.

Table 2: Comparison of AS-ATTR to older age controls, AS and ATTR using regression analysis.

Myocardial factor	Diagnosis	Marginal geometric mean	95% Confidence Interval	P value (versus AS+ATTR)
NT-proBNP	AS + ATTR	2844	(1745, 4635)	NR
	AS	1294	(1077, 1554)	0.002
	ATTR	3272	(2552, 4197)	0.63
	Control	127	(100, 162)	<0.001
LVMi	AS + ATTR	139	(112, 167)	NR
	AS	120	(109, 130)	0.179
	ATTR	180	(167, 194)	0.013
	Control	92	(79, 106)	0.003
MCF	AS + ATTR	0.17	(0.13, 0.22)	NR
	AS	0.3	(0.27, 0.33)	0.001
	ATTR	0.1	(0.09, 0.11)	<0.001
	Control	0.27	(0.24, 0.30)	0.017
GLS	AS + ATTR	-15.1	(-21.6, -8.5)	NR
	AS	-14.8	(-16.5, -13.1)	0.576
	ATTR	-12.2	(-13.5, -10.8)	0.215
	Control	-19.5	(-20.7, -18.2)	0.002
TAPSE	AS + ATTR	1.5	(1.1, 2.0)	NR
	AS	1.9	(1.8, 2.0)	0.332
	ATTR	1.5	(1.4, 1.6)	0.156
	Control	2.4	(2.3, 2.5)	<0.001
TnT	AS + ATTR	50	(30, 83)	NR
	AS	22	(19, 25)	<0.001

	ATTR	49	(43, 56)	0.529
	Control	12	(10, 13)	<0.001
E/A ratio	**AS + ATTR**	3.3	(0.9, 5.7)	NR
	AS	1.1	(0.9, 1.3)	<0.001
	ATTR	2.3	(1.9, 2.8)	0.272
	Control	0.7	(0.7, 0.8)	<0.001
Carpal tunnel syndrome	**AS + ATTR**	1.3	(1.1, 1.6)	NR
	AS	1	(1.0, 1.0)	0.001
	ATTR	1.3	(1.2, 1.4)	0.864
	Control	n/a	n/a	n/a

NT-proBNP- N terminal pro brain natriuretic peptide, hsTnT- high sensitivity Troponin T,

LVMi- left ventricular mass index, MCF- myocardial contraction fraction, GLS- global

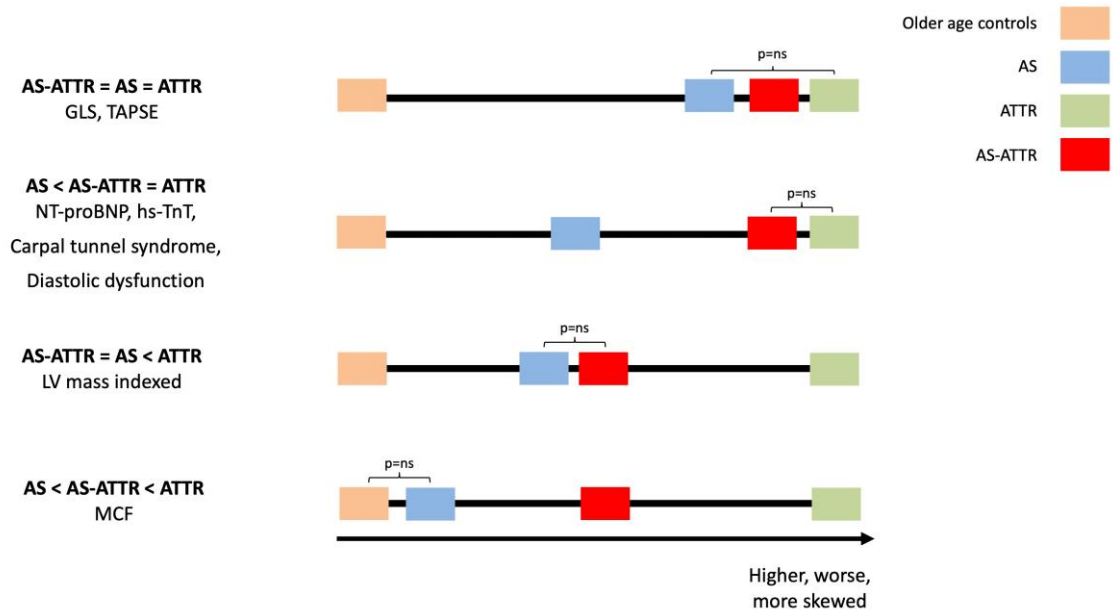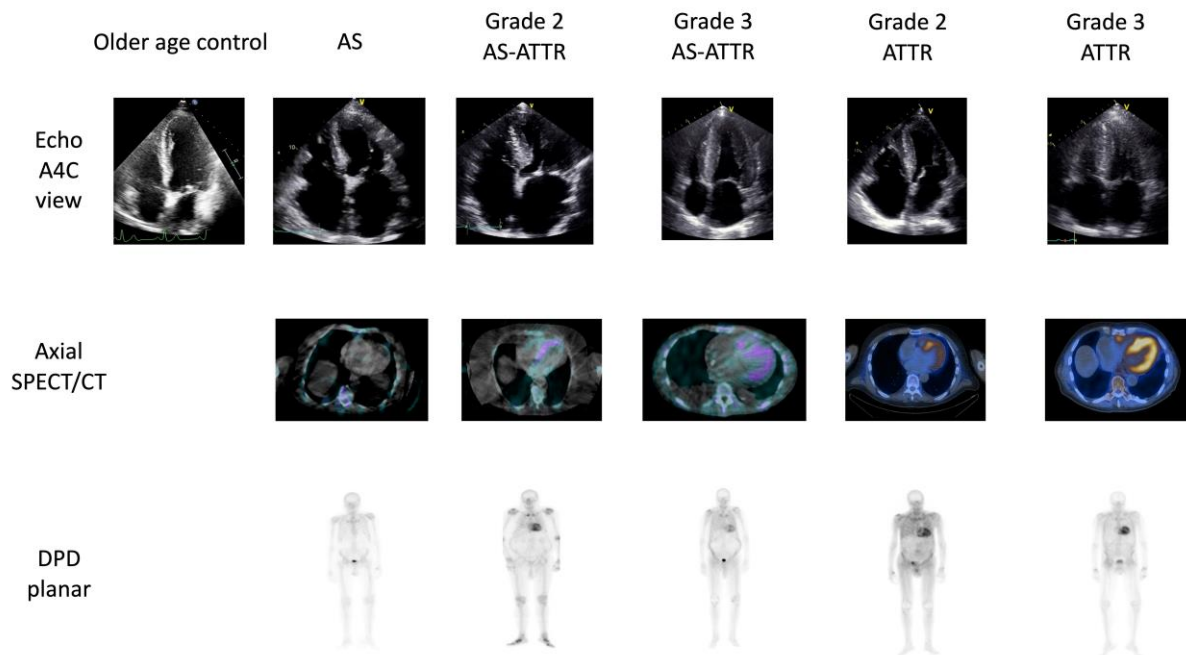longitudinal strain, TAPSE- tricuspid annular planar systolic excursion.

Figure 1

Figure 2