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ORIGINAL ARTICLE

Transthyretin cardiac amyloidosis in patients after TAVR: clinical and echocardiographic findings and long term survival

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Abstract

Aims The aim of this study was to examine the prevalence of amyloid transthyretin (ATTR) cardiac amyloidosis in patients 1–2 years after trans-catheter aortic valve replacement (TAVR) and to assess their clinical and echocardiographic outcome and long-term survival.

Methods and results We enrolled 88 patients, mean age 81 years, 534 (390–711) days after TAVR. Patients underwent a Tc99m-PYP scintigraphy for the diagnosis of ATTR cardiac amyloidosis. Eleven (12.5%) participants were diagnosed with ATTR cardiac amyloidosis. Eighty eight per cent of patients without amyloidosis were in New York Heart Association Classes 1–2 after TAVR, compared with 64% patients with ATTR cardiac amyloidosis (P = 0.022). There were no differences in left ventricular (LV) ejection fraction (P = 0.69) between patients with and without ATTR cardiac amyloidosis at enrolment. The LV mass index and pulmonary artery pressure were significantly higher in patients with ATTR cardiac amyloidosis (P = 0.046 and P = 0.002, respectively). Global longitudinal strain and myocardial work efficiency were significantly lower in patients with ATTR cardiac amyloidosis (P = 0.031 and P = 0.048, respectively). We assessed changes in echocardiographic data, from the time of TAVR to enrolment, and as expected, there was a significant decrease in aortic valve gradient in both groups. There was a significant reduction in LV mass and LV mass index and improvement in basal segment LV strain in the ATTR cardiac amyloidosis negative group (P = 0.045, P = 0.046 and 0.023, respectively). However, in the ATTR cardiac amyloidosis group the change in LV mass and LV mass index and LV basal strain values was not significant (P = 0.24, P = 0.13 and P = 0.35, respectively). The were no significant changes in other echocardiographic parameters in both groups. The patients were followed for 1150 (1086–1221) days after enrolment. Twenty seven patients had at least one cardiac hospitalization during of follow up, of them seven were with ATTR cardiac amyloidosis and 20 patients without amyloidosis (P = 0.017). Eighteen patients (20%) died during follow up; 12 (14%) patients died due to cardiac causes. There was no difference in all-cause and cardiac mortality between patients with and without ATTR cardiac amyloidosis (P = 0.6 and P = 0.53, respectively).

Conclusions The long-term survival after TAVR is not significantly affected by the presence of ATTR cardiac amyloidosis. However, the clinical course of these patients and the LV hemodynamic improvement is less favourable. This hypothesis-generating study suggests screening for ATTR cardiac amyloidosis in patients who underwent TAVR and have limited clinical or echocardiographic improvement, because they may potentially improve with new therapies for ATTR cardiac amyolidosis.

Keywords Amyloidosis; Aortic valve intervention; Myocardial strain

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Sara Shimoni and Meital Zikri contributed equally to the paper.
[Correction added on 05 November 2021, after first online publication: The article title has been corrected in this version as well as the author name 'Valeri' has been corrected to 'Valery'.]

Introduction

Amyloidosis is a multi-organ syndrome, with cardiac involvement that usually presents as restrictive cardiomyopathy.[1] Amyloid Transthyretin (ATTR) amyloidosis is a subtype of amyloidosis with abnormal precipitation of transthyretin, a protein that normally acts as transporter for circulating thyroxin and retinol. The gold standard for the diagnosis of ATTR cardiac amyloidosis is the demonstration of ATTR deposits on endomyocardial biopsy.[2] Nuclear cardiac imaging with radioisotopes, such as technetium-99m pyrophosphate (^{99m}Tc-PYP), have shown excellent diagnostic accuracy for ATTR cardiac amyloidosis obviating the need for cardiac biopsy.[3] The prevalence of ATTR cardiac amyloidosis is unknown. Amyloid fibrils are present in the myocardium in approximately 25% of patients 80 years or older in autopsy studies.[4] In patients with heart failure (HF) and preserved left ventricular (LV) function the prevalence of ATTR amyloidosis was reported to be 13.3%.[5] There is accumulating evidence for a pivotal role of oxidative stress, inflammation, and extracellular remodelling in the ATTR cardiac amyloidosis.[6,7]

Degenerative aortic valve (AV) stenosis (AS) is currently the most common valvular heart disease in Western developed countries. Inflammation and oxidative stress play a significant role in pathogenesis of AS.[8] In recent reports on patients with significant AS, the prevalence of ATTR amyloidosis varied from 6% to 16%.[9,10] It is unclear if there is a causative link between AS and ATTR cardiac amyloidosis. Trans-catheter AV replacement (TAVR) is generally indicated for moderate and high-risk AS.[11] There are several reports on possible complications and poor prognosis of AV intervention in patients with AS and ATTR cardiac amyloidosis.[9,12–14] Recently, new studies assessed prospectively the prognosis of patients with ATTR cardiac amyloidosis that underwent TAVR and found that ATTR cardiac amyloidosis does not affect mortality.[15–18] In these studies, the patients were enrolled and the diagnosis was made before performing TAVR. The follow-up data included mortality and hospitalizations. There are no data, however, on the prevalence of ATTR cardiac amyloidosis in a cohort of patients a year or more after TAVR, and there are no data on the clinical and echocardiographic findings in these patients after TAVR. The aim of this study was to examine the prevalence of ATTR cardiac amyloidosis in post-TAVR patients and study their clinical and echocardiographic changes and long-term prognosis.

Methods

Population

The Kaplan Medical Center TAVR registry includes all patients who underwent TAVR since 2010.The patients are followed in the valvular disease clinic and undergo echocardiography every 6–12 months after TAVR, based on their clinical status. From this registry, 267 consecutive patients underwent elective TAVR during the years 2014–2016. The patients were enrolled prospectively during the years 2016–2017. Upon enrolment, patients underwent clinical assessment, echocardiography and ^{99m}Tc-PYP nuclear scintigraphy imaging. Patients were followed prospectively and hospitalization and mortality data was collected.

In addition, retrospective clinical and echocardiographic data was collected from the time before TAVR until enrolment, using the TAVR registry data and from hospital and family physician records. Cardiovascular hospitalizations included hospitalizations for cardiac cause: chest pain, arrhythmia, dyspnoea, and HF. HF hospitalizations were defined as hospitalization due to symptoms and signs of left or right HF.

The study was approved by the local IRB of Kaplan Medical Center (protocol 018-17KMC) and all patients provided written consent form.

Echocardiographic data

Left ventricular dimension was measured in 2-D parasternal long axis view; LV ejection fraction (LVEF) was estimated using the bi-plane Simpson's method; diastolic function was analysed based on mitral Doppler inflow and tissue Doppler imaging (TDI) at the lateral and septal mitral annulus and pulmonary artery pressure (PAP) was calculated by the maximal tricuspid regurgitation velocity. The peak AV pressure gradient was calculated using the Bernoulli equation, and mean AV pressure gradient was calculated by averaging the instantaneous gradients over the ejection period on the continuous-wave Doppler recordings. AV area (AVA) was calculated using the continuity equations previously described.[19,20] LV mass was calculated by Devereux formula.[20]

Strain measurements

Two-dimensional speckle-tracking strain and quantification of myocardial work (MW) analysis were performed offline by using commercially available software (Echo PAC version 202 GE, Horten, Norway). The global longitudinal strain (GLS) was obtained from the apical four-chamber, two-chamber, and long-axis views in an 18-segment LV model. Subsequently, longitudinal strain of all 18 LV segments were averaged to assess the LVGLS and the basal segments, mid segments and apical segments were averaged to assess the basal, mid and apical segments.[21,22] Because all included patients had adequate strain tracking, no patient was excluded form strain analysis.

After calculating GLS and adding the brachial blood pressure and the time of aortic and mitral opening and closure

events by echocardiography, the software derived non-invasive pressure strain loops. When the velocity on AV was above 2 m/s, and in order to correct for underestimation of intraventricular pressure, we added the mean AV pressure gradient to the systolic blood pressure used by the software. The area of the loop indicated the regional and global MW. Using the software, additional indices of MW were obtained including global constructive work (GCW) (the sum of work performed during shortening in systole and the negative work during lengthening in isovolumetric relaxation); global wasted work (GWW) (the sum of negative work performed during lengthening in systole and the work performed during shortening in isovolumetric relaxation); and global work efficiency (GWE) (constructive work divided by the sum of constructive and wasted work).[23]

Technetium-99m pyrophosphate scintigraphy for diagnosis of transthyretin cardiac amyloidosis

99mTc-PYP planar cardiac scan was performed using dual-head SPECT/CT camera (Symbia, Ecam cammera, Siemens) equipped with low-energy, high-resolution collimators. The planar images (anterior and lateral views) were acquired 1–3 h after injection of 10 mCi of 99mTc-PYP. The images were acquired for a total of 750 000 counts with the heart centred in the field of view.

Two nuclear cardiologists blinded to the patients' clinical status independently evaluated cardiac retention of 99mTc-PYP using a semi quantitative visual scoring method (0 = no uptake, 1 = uptake less than ribs, 2 = uptake equal to ribs, 3 = uptake greater than ribs).[3] The scan was defined positive when the score ≥ 2. In six patients with an equivocal ATTR planar scan, in order to minimize the confounding factors of blood pool imaging and increased bone activity, a single photon emission computed tomography (SPECT) gated acquisition was performed after planar scan. Twenty mCi of 99mTc-PYP were injected. SPECT gated scan protocol, with image acquisition of 10 min and eight frames, using a CZT multi detectors camera (D-SPECT camera, Spectra Dynamic was performed. Five SPECT studies were negative, most probably false positive planar study due to blood pool. One patient that had an equivocal ATTR planar scan had a positive SPECT study.

Statistical analysis

All analyses were performed by SPSS version 21, a significance level of $P \leq 0.05$ was considered significant. Continuous variables were presented as mean ± SD or median (25th; 75th inter-quartile range) and dichotomous as a percentage. Clinical and echocardiographic data were compared between the groups using *T* test or chi-squared test for categorical data. Changes in echocardiographic finding in the time between TAVR and patient's enrolment in the study were assessed with paired *T* test.

New York Heart Association (NYHA) class difference between the groups at enrolment and before TAVR was assessed using generalized estimating equations—model of repeated measurements of ordinal variables—order scale.

C statistics was performed in order to determine the echocardiographic strain parameters related to ATTR cardiac amyloidosis and the best cut-off was calculated as maximal sensitivity + specificity − 1. The comparison between the area under the curve (AUC) of different variables was performed with MedCalc software.

The association between count variables (number of hospitalizations − number of events over a period of time) was analysed by using a generalized linear model for Poissonic/negative binomial distribution.

Kaplan–Meier plots were used for drawing survival curve of the different groups, and Cox proportional hazards regression analysis was used to evaluate the association of variables with mortality. To test the association between variables and event-free survival after enrolment, Cox regression for survival analysis was utilized, using the stepwise, forward, likelihood ratio method.

Results

Patient population

Two hundred sixty seven elderly patients underwent elective TAVR during the years 2014–2016 (*Figure 1*). Eighty five patients died before the current study started. Thirty seven patients were not able to consent the study due to cognitive or functional impairment. Additional 47 patients refused to participate in the study and 10 were lost to follow up. The patients not included in the study are a heterogenic group. We compared the baseline parameters (before TAVR) of patients included in the current study and patients that could not be included, and the results are shown in *Table 1*. As can be seen in the table, the populations differ significantly in renal function that is impaired in patients not included and hyperlipidaemia rate that was lower in patients not included. However, all other clinical data do not differ between the populations. The final research population included 88 patients (32.9%).

As seen in *Table* 2, the mean age was 81 years, 55% women. The majority of patients had history of hypertension and dyslipidaemia. Atrial fibrillation was found in 30% of patients and coronary artery disease in 60% of all patients.

The patients underwent PYP scintigraphy between the years 2016 and 2017, at enrolment. The median time from TAVR to enrolment was 534 (390–711) days. Eleven (12.5%) subjects were diagnosed with ATTR cardiac amyloidosis.

Figure 1 Flow diagram of patient recruitment. TAVR, trans-catheter aortic valve replacement.

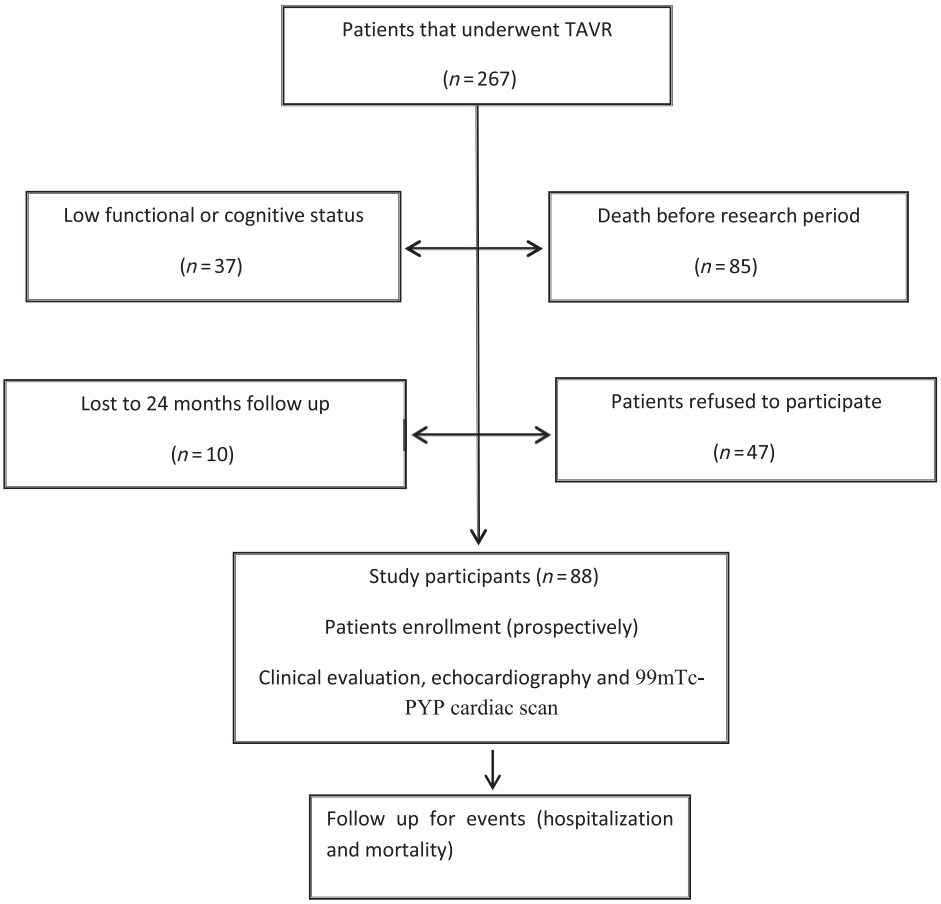

Figure 2 shows an example of a patient with a positive scan for ATTR cardiac amyloidosis. AL amyloidosis was excluded by a negative test for monoclonal gammopathy.

As seen in *Table* 2, there were no significant differences between the groups in regard to age, gender and risk factors. The level of haematocrit was significantly lower in patients with ATTR cardiac amyloidosis. Creatinine level was higher in patients with ATTR cardiac amyloidosis, with borderline statistical significance. The level of troponin was significantly higher in patients with ATTR cardiac amyloidosis. N-terminal pro b-type natriuretic peptide levels were higher in patients with ATTR; however, this difference was not statistically significant. There was no difference in the percentage of self-expandable or balloon expandable valve in each group (P = 0.64).

Clinical findings

Before TAVR, 49% of patients negative for ATTR cardiac amyloidosis and 36% of patients positive for ATTR cardiac amyloidosis were in NYHA Class 2 (P = 0.58). At enrolment, 88% of patients without ATTR cardiac amyloidosis and 64% with ATTR cardiac amyloidosis were in NYHA Classes 1–2 (P = 0.022, *Figure 3A*). In patients with ATTR cardiac amyloidosis, the change in NYHA class was not significant (P = 0.28). Patients with no ATTR cardiac amyloidosis improved significantly from the time of TAVR until enrolment ($P < 0.001$).

Using generalized estimating equations analysis for assessing interaction of time (TAVR to enrolment) and the presence of ATTR cardiac amyloidosis on NYHA class, we found that both parameters were significant ($P < 0.01$ for time and P = 0.014 for ATTR-cardiac amyloidosis). The interaction time * ATTR-cardiac amyloidosis was also significant (P = 0.047).

Echocardiographic measurements before trans-catheter aortic valve replacement

Before TAVR, patients diagnosed later with ATTR cardiac amyloidosis had similar AS severity as subjects with no ATTR car-

Table 1 Baseline characteristics in patients that underwent TAVR in the years 2014–2016

	Included in the study (n = 88)	Not included in the study (n = 179)	
Age	81 (78–85)	82(79–86)	0.3
BMI	28.79 ± 5.05	27.8 ± 5	0.29
Gender male (%)	45%	39%	0.912
Hypertension (%)	93%	90%	0.99
Diabetes mellitus (%)	43.%	42%	0.99
Dyslipidaemia (%)	91%	76%	0.04
Smoking (%)	31.40%	22%	0.7
Atrial fibrillation (%)	29%	33%	0.8
Coronary artery disease (%)	61.20%	50%	0.63
Haemoglobin (g/dL)	11.4 ± 1.59	11.7 ± 1.4	0.23
Haematocrit (vol %)	34.6 ± 5.16	34.9 ± 5.16	0.3
Platelets (K/uL)	195 ± 66	202 ± 59	0.27
Urea (mg/dL)	45.95 ± 24.96	54 ± 29	0.06
Creatinine (mg/dL)	0.944 ± 0.39	1.22 ± 1.1	0.04
Albumin (g/dL)	3.63 ± 0.44	3.8 ± 0.2	0.03
LVEF%	55 ± 10	53 ± 10	0.66
AV peak gradient (mmHg)	75 ± 15	68 ± 13	0.21
AVA (cm^2)	0.71 ± 0.14	0.68 ± 0.16	0.13

AV, aortic valve; AVA, aortic valve area; BMI, body mass index; LVEF, left ventricular ejection fraction.
Comparison between patients included in the study and patients not included.

Table 2 Patient's baseline characteristics at enrolment

	All n = 88	ATTR-CA n = 11	No ATTR-CA n = 77	P value
Clinical parameters				
Gender—men N (%)	39(44.3)	7 (64)	32 (41.6)	0.2
Age, year	81 ± 6.4	81.7 ± 7.86	80.9 ± 6.2	0.70
NYHA classification N (%)				0.022
1	34(39)	1(9)	33 (43)	
2	41(46)	6(55)	35(45)	
3	12(14)	3(27.)	9(12)	
4	1 (1.)	1(9)	0	
Hypertension (%)	94%	100%	93.5%	0.98
Diabetes mellitus (%)	43.%	54.5%	41.5%	0.52
Dyslipidaemia (%)	92%	90%	92%	0.98
Smoking (%)	31%	20%	33%	0.8
Atrial fibrillation (%)	30%	45%	27%	0.29
Coronary artery disease (%)	60%	82%	57%	0.19
Laboratory results				
Haemoglobin (g/dL)	12.18 ± 1.32	11.5 ± 1.9	12.3 ± 1.3	0.08
Haematocrit (vol %)	38.6 ± 4	36.1 ± 4,1	38.95 ± 3.9	0.034
WBC (K/μL)	7.98 ± 1.9	7.1 ± 1.7	8.1 ± 1.8	0.12
Platelets (K/μL)	215 ± 68	210 ± 51	216 ± 70	0.79
Urea (mg/dL)	55.2 ± 23.9	63.8 ± 25	54 ± 24	0.23
Creatinine (mg/dL)	1.1 ± 0.4	1.4 ± 0.6	1.07 ± 0.39	0.056
Troponin I (pg/mL)	13.86 ± 16.9	43.5 ± 9	12.3 ± 14	0.009
NT-pro-BNP (pg/mL)	1511 ± 3056	3963 ± 8411	1259 ± 1814	0.4
Nutritional parameters				
BMI kg/m^2	28.63 + 5	28.39 ± 6.3	28.7 ± 4.8	0.87
Albumin (g/dL)	4.01 ± 0.27	3.95 ± 0.22	4.07 ± 0.27	0.17
ALT—GPT (U/L)	18 + 10.1	15.2 ± 7	18.40 + 10	0.35

ALT-GPT, alanine transaminase; BMI, body mass index; NT-pro-BNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; WBC, white blood cells.

diac amyloidosis. The groups had similar LV diastolic diameter and LVEF. Patients having later a positive scan had a higher LV mass and LV mass index (252 ± 72 g vs 211 ± 55 g, P = 0.036 and 140 ± 34 g/m^2 vs. 119 ± 31 g/m^2, P = 0.06, respectively). There was a trend, but not statistically significant, for higher PAP in the ATTR cardiac amyloidosis group before intervention. The GLS did not differ between the groups before intervention. The basal segments strain was, however, lower in patients diagnosed later with ATTR cardiac amyloidosis and the apical to basal strain ratio was higher

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Figure 2 An example for a patients with a negative (A) and positive (B) ^{99m}Tc-PYP scan for amyloid transthyretin (ATTR) cardiac amyloidosis.

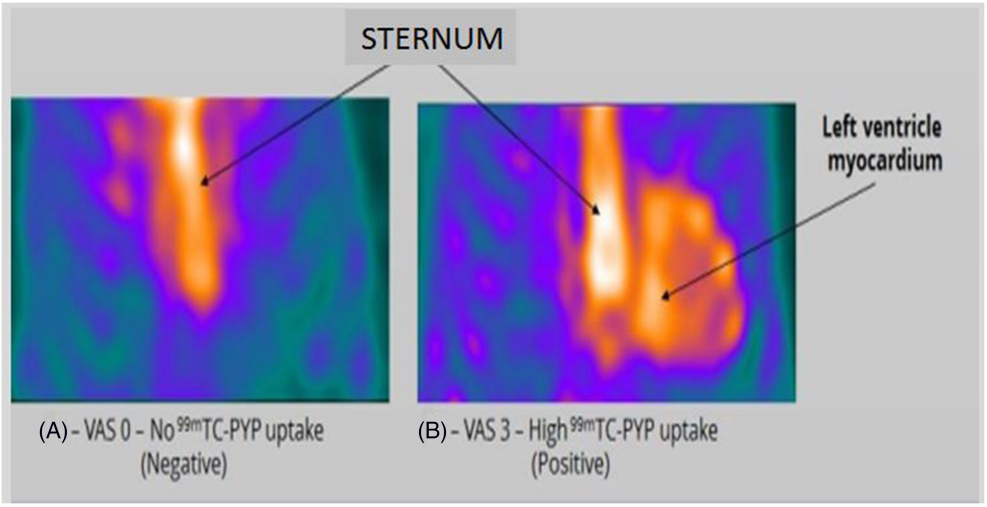
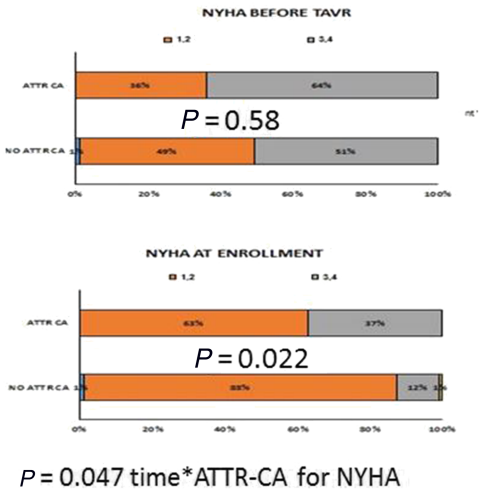


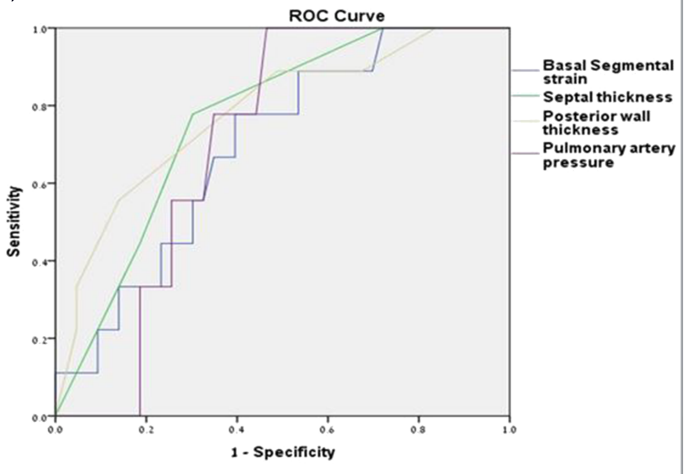
Figure 3 A functional [New York Heart Association (NYHA) class] status at study enrolment and before TVR in patients with and without amyloid transthyretin (ATTR) cardiac amyloidosis. (B) ROC curves and cut-offs for ATTR cardiac amyloidosis diagnosis by echo parameters (septal and posterior wall thickness, pulmonary artery pressure and basal segmental LV strain). (C) An example of Bull's eyes analysis of global strain and myocardial work in a patient with ATTR cardiac amyloidosis.

(A)

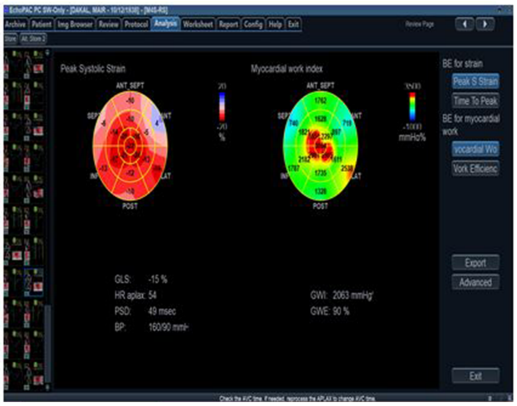


$P = 0.047$ time*ATTR-CA for NYHA

(B)



(C)



	UAC	p	Cut-off	Sensitivity%	Specificity%
LV basal segmental strain	0.72 (0.57-0.87)	0.031	-15.2%	80	61
Septal thickness	0.77 (0.61-0.91)	0.01	13.5(cm)	78	67
Posterior wall thickness	0.77 (0.6-0.94)	0.01	11.5(cm)	89	51
Pulmonary artery pressure	0.72 (0.6-0.83)	0.04	44mmHG	78	63

$P = 0.21$ between the ROC AUC

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(−12.8 ± 2% vs. −14.7% ± 4.2, P = 0.037, and 1.67 ± −0.2 vs. 1.48 ± 0.29, P = 0.051, respectively). No significant differences were observed between the groups in the indices of MW before TAVR, however the ratio of apical segments to basal segments GW was significantly higher in patients diagnosed later with ATTR cardiac amyloidosis (1.86 ± 0.2 vs. 1.48 ± 0.5, P = 0.001).

Echocardiography at enrolment

Echocardiographic data of the patients that were performed at enrolment are seen in *Table* 3. There were no differences in LV size and LVEF between patients with and without ATTR cardiac amyloidosis. The AV pressure gradient was also similar. The LV mass and the septal and posterior wall thickness were significantly higher in patients with ATTR cardiac amyloidosis, (137 ± 35 g/m^2 vs. 113 ± 32 g/m^2, P = 0.046, for LVMi). The MV deceleration time was shorter in patients with ATTR cardiac amyloidosis (214.1 ± 59 ms vs. 261.8 ± 71 ms, P = 0.04). Patients with ATTR cardiac amyloidosis had significantly higher PAP (47.5 ± 4.5mmHG vs. 38 ± 16mmHG, P = 0.002). GLS was significantly lower in patients with ATTR cardiac amyloidosis with higher apical/basal segments strain ratio (−15.9 ± 3% vs. −18.77 ± 5%, P = 0.031, 1.62 ± 0.28 vs. 1.42 ± 0.26, P = 0.04, respectively). ROC curves in *Figure 3B* show echocardiographic parameters that are significantly related to the presence of ATTR cardiac amyloidosis and may be 'red flags' for ATTR cardiac amyloidosis in patients after TAVR. Septal and posterior wall thickness, elevated PAP and basal segmental strain had a significant area under the curve, with no significant difference among them (P = 0.21). Basal segmental strain of ≥ −15.2%, for example, showed sensitivity of 80% and specificity of 61% to identify ATTR cardiac amyloidosis (*Figure 3B*). MW index and global constructive work were lower in patients with ATTR cardiac amyloidosis; however the difference was no statistically significant. The ratio of apical to basal segments MW was higher in patients with ATTR cardiac amyloidosis (1.91 ± 0.5 vs. 1.58 ± 0.26, P = 0.044). MWE was significantly lower in patients with ATTR cardiac amyloidosis compared with patients without ATTR cardiac amyloidosis (0.9 ± 0.09% vs.

Table 3 Echocardiographic parameters before TAVR and at study enrolment (12–24 months)

	Before intervention-(TAVR)			At enrolment (1–2 years after intervention)		
	Positive scan for TTR	Negative scan for TTR	*P* value	Positive scan for TTR	Negative scan for TTR	*P* value
Aortic valve peak gradient (mmHg)	71.50 ± 15.69	76 ± 21	0.42	21.6 ± 16*	20.2 ± 11*	0.73
Aortic valve mean gradient (mmHg)	44.83 ± 8.40	46 ± 16	0.71			
Aortic valve area (cm$^{2)}$	0.72 ± 0.06	0.7 ± 0.16	0.8			
LVEDd (mm)	47 ± 4.47	45 ± 5.5	0.30	45.1 ± 6	44.7 ± 6.5	0.96
Interventricular septal wall thickness (mm)	14.00 ± 1.9	13.0 ± 2.1	0.16	14.33 ± 1.3	12.7 ± 1.7	0.01
Posterior wall thickness (mm)	12.70 ± 1.49	11.8 ± 1.7	0.12	14 ± 2.3	11.3 ± 1.6	0.04
LVM (g)	252 ± 72	211 ± 55	0.036	247 ± 70	201 ± 61*	0.042
LVMi (g/m2)	140 ± 34	119 ± 31	0.06	137 ± 35	113 ± 32*	0.046
LVEF %	54.5 ± 6	53.6 ± 10	0.78	52.8 ± 6.6	53.8 ± 6.6	0.69
SVi (mL/beat/m2)	39.7 ± 7	42.2 ± 12	0.81			
Pulmonary artery systolic pressure (mmHg)	45.7 ± 15	38.9 ± 13	0.13	47.5 ± 4.5	38 ± 16	0.002
Aortic regurgitation grade (%)			0.94			0.96
no or mild	82	81		88	87	
moderate or severe	18	19		12	13	
Mitral E wave (cm/s)	1.11 ± 0.4	0.99 ± 0.4	0.38	1.14 ± 0.36	1.04 ± 0.34	0.41
Deceleration time (ms)	197 ± 77	261 ± 102	0.09	214.1 ± 59	261.8 ± 71	0.041
Mitral A wave (cm/s)	0.86 ± 0.22	1.01 ± 0.4	0.68	0.65 ± 0.36	0.89 ± 46	0.128
e′ (cm/s)	0.072 ± 0.02	0.057 ± 0.03	0.07	0.067 ± 0.019	0.058 ± 0.02	0.2
a′ (cm/s)	0.087 ± 0.026	0.093 ± 0.026	0.17	0.065 ± 0.023	0.081 ± 0.035	0.18
s′ (cm/s)	0.06 ± 0.016	0.062 ± 0.02	0.83	0.063 ± 0.014	0.07 ± 0.02	0.41
GLS (%)	−16.2 ± 2.9	−17.1 ± 5.2	0.46	−15.9 ± 3	−18.77 ± 5	0.031
Basal strain (%)	−12.8 ± 2	−14.7 ± 4.2	0.037	−13.6 ± 3	−16.4 ± 3.6*	0.03
Mid strain (%)	−15.8 ± 2.5	−17 ± 5	0.25	−16.77 ± 3.4	−18.9 ± 4.5	0.172
Apical strain (%)	−21.8 ± 3.8	−21.6 ± 6.9	0.93	−21.6 ± 4.7	−23.5 ± 6.9	0.426
Apical/basal strain ratio	1.67 ± ¯0.2	1.48 ± 0.29	0.051	1.62 ± 0.28	1.42 ± 0.26	0.04
Apical/mid + basal strain ratio	0.75 ± 0.07	0.68 ± 0.1	0.044	0.71 ± 0.09	0.66 ± 0.09	0.087
LVMWI (mmHG%)	2,120 ± 534	2,231 ± 919	0.74	1904 ± 889	2,245 ± 697	0.25
LVGCW (mmHG%)	2,349 ± 446	2,553 ± 993	0.55	2,177 ± 787	2,253 ± 754	0.24
LVMWE (%)	0.94 ± 0.028	0.92 ± 0.07	0.26	0.9 ± 0.09	0.94 ± 0.03	0.048
LVGWW (mmHG%)	103 ± 59	193 ± 72	0.36	225 ± 88	123 ± 77	0.053
Apical/basal GWI ratio	1.86 ± 0.2	1.48 ± 0.5	0.001	1.91 ± 0.5	1.58 ± 0.26	0.044

GLS, global longitudinal strain; LVEDd, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMi, left ventricular mass index; LVMWI-left ventricular myocardial work index, LVGCW-LV global constructive work; LVGWW-LV global wasted work; LVMWE-LV myocardial wasted work; TAVR, trans-catheter aortic valve replacement.
*$P < 0.05$ difference between enrolment and before TAVR.

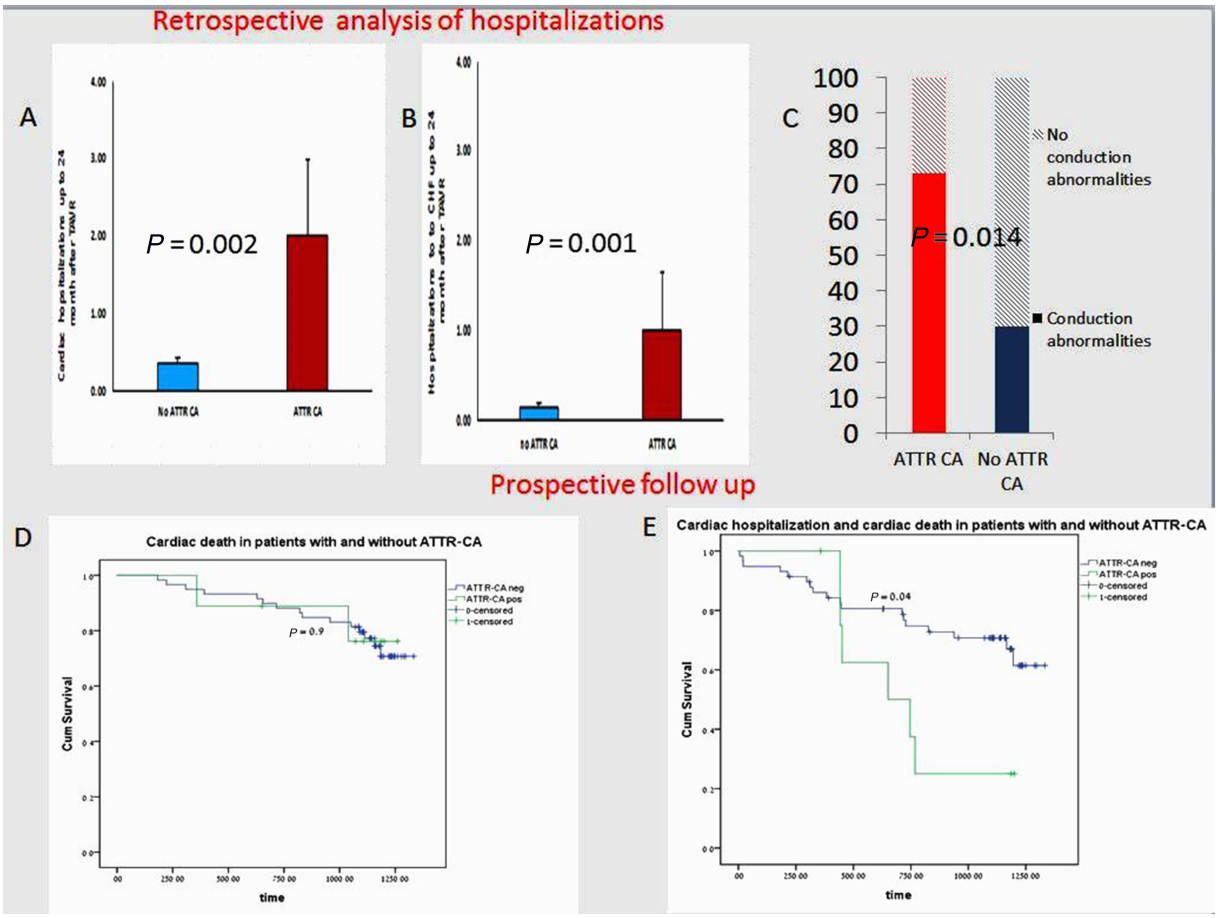
0.94 ± 0.03%, *P* = 0.048). It should be noticed that these patients had also a higher rate of conduction abnormalities. An example showing GLS and MW analysis in a patient with ATTR cardiac amyloidosis is shown in *Figure 3C*.

We assessed changes in echocardiographic data, from the time of TAVR to enrolment, and as expected there was a significant decrease in AV gradient in both groups. There was also a significant reduction in LV mass and LV mass index and improvement in basal segment LV strain in the ATTR cardiac amyloidosis negative group (*P* = 0.045, *P* = 0.046 and 0.023, respectively). However, in the ATTR cardiac amyloidosis group the changes in LV mass and LV mass index and LV basal strain values were not significant (*P* = 0.24, *P* = 0.13 and 0.35, respectively). The were no significant changes in other echocardiographic parameters in both groups.

Hospitalization due to cardiac causes and heart failure from trans-catheter aortic valve replacement to enrolment

We studied retrospectively cardiac hospitalization rate during 24 months after TAVR. There were no significant difference in procedure related hospitalizations in both groups (*P* = 0.7). There were total 37 cardiac hospitalizations, of which 13 were in ATTR cardiac amyloidosis patients. Twenty two of the hospitalizations were due to HF, 11 of which were in the ATTR cardiac amyloidosis group. As seen in *Figure 4A,B*, ATTR cardiac amyloidosis is significantly related to cardiac hospitalizations and HF hospitalizations (*P* = 0.002, and *P* = 0.001, respectively). Patients with ATTR cardiac amyloidosis had 5.1 times more cardiac hospitalizations and 4.8 times more HF hospitalizations than the ATTR cardiac amyloidosis

Figure 4 (A) Rate of cardiac hospitalizations in patients with and without amyloid transthyretin (ATTR) cardiac amyloidosis. (B) Rate of heart failure hospitalizations in patients with and without ATTR cardiac amyloidosis. (C) Conduction abnormalities in patients with and without ATTR cardiac amyloidosis. (D) Kaplan–Meier plot of cardiac death in patients with and without ATTR cardiac amyloidosis. (E) Kaplan–Meier plot of combined cardiac hospitalizations and cardiac death in patients with and without ATTR cardiac amyloidosis.



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negative group. We also assessed other factors that are related to cardiac hospitalizations and found that patients age, presence of diabetes mellitus, atrial fibrillation and CAD were related to cardiac hospitalization (all $P < 0.05$), In addition PAP, LVEF and GLS were related to cardiac hospitalization. After correcting for other confounders, ATTR cardiac amyloidosis remained significantly related to cardiac hospitalization ($P = 0.024$). Other independent factors were LVEF and GLS before TAVR ($P = 0.023$ and $P = 0.009$, respectively).

In addition to hospitalization, conduction disorders (need for permanent pacemaker or new and persistent LBBB) were found in 39% of all patients at enrolment. Eight patients (73%) with ATTR cardiac amyloidosis had conduction abnormalities within a month after TAVR compared with 23 (30%) patients in the control group ($P = 0.014$, *Figure 4C*). Four additional patients underwent pacemaker implantation from the time of TAVR to enrolment; all were negative for ATTR cardiac amyloidosis. So at enrolment, 73% of ATTR cardiac amyloidosis patients and 35% of ATTR cardiac amyloidosis negative patients had conduction abnormalities ($P = 0.023$).

Prospective clinical follow up after enrolment

The median follow up after enrolment was 1,150 (1,086–1,221) days. Twenty seven patients had at least one cardiac hospitalization during follow up, of them 7 were with ATTR cardiac amyloidosis and 20 patients were ATTR cardiac amyloidosis negative ($P = 0.017$). Eighteen patients (20%) died during follow up, 12 (14%) patients died due to cardiac causes, mainly congestive HF, arrhythmia and endocarditis. There was no difference in all-cause mortality and cardiac mortality between patients ATTR cardiac amyloidosis positive and negative ($P = 0.6$ and $P = 0.53$, respectively, *Figure 4D*). As seen in *Table 4*, the independent predictors for all-cause mortality were age and GLS [1.213 95% confidence interval (CI) 1.065–1.382, $P = 0.004$, and 1.128 95% CI 1.004–1.267, $P = 0.043$] and for cardiac mortality the predictor was GLS (1.532 95% CI 1.105–2.125, $P = 0.011$). Using a composite endpoint of cardiac hospitalization or cardiac death, patients with ATTR cardiac amyloidosis had significantly more events (P = 0.04, *Figure 4C*). The other factors related to combined endpoint were NYHA class and LVEF. However, only NYHA class was found to be an independent factor for cardiac hospitalization and death (1.807 95% CI 1.130–2.889, $P = 0.015$).

Discussion

In this study, we evaluated the clinical and echocardiographic findings of patients' diagnosed positive for ATTR cardiac amyloidosis 1 to 2 years [534 (390–711) days] after TAVR. We assessed retrospectively the clinical and echocardiographic finding during the time period from TAVR to the diagnostic PYP scan at enrolment and prospectively after the enrolment. The study main findings are (i) ATTR cardiac amyloidosis was seen in 12.5% of this patients group; (ii) GLS and MWE were lower and LV mass higher in patients with ATTR cardiac amyloidosis compared patients with no ATTR cardiac amyloidosis. (iii) The functional status of patients diagnosed with ATTR cardiac amyloidosis was lower compared with those without ATTR cardiac amyloidosis with significantly higher rate of cardiac hospitalizations; (iv) however, there was no difference in all-cause or cardiac mortality between patients with and without ATTR cardiac amyloidosis during follow up.

Various clinical and echocardiographic 'red flags' were suggested to identify the presence of amyloidosis in patients with AS.[24,25] The studies usually looked on patients with AS before intervention-with dual pathology. None of the studies looked on patient's functional class a year or more after TAVR, when the valvular pathology was treated, and there are no data on the clinical course and echocardiographic findings of these patients. Our study is the first, to our knowledge, that compared the functional class of patients with and without ATTR cardiac amyloidosis after TAVR. Thirty seven per cent of patients with ATTR cardiac amyloidosis were in NYHA functional Class 3 or 4 a year after TAVR, and there was no significant improvement in NYHA class in these patients after TAVR. So it appears that these patients are clinically 'poor responders'.

In addition, these patients showed persistent LV remodelling. There were differences between the groups in systolic function as shown by GLS and basal segmental LS and in diastolic function as shown by shorter mitral E wave deceleration time and higher PAP. In addition, the MWE was lower in patients with ATTR-CA, in line with a recent report on patients with cardiac amyloidosis without AS.[26] An index of basal segmental strain could identify ATTR cardiac amyloidosis in this population with a fair accuracy. Septal and posterior wall thickness and elevated PAP are other echocardiographic signs to suspect ATTR-CA.

The echocardiographic findings together with the lower haematocrit levels and higher creatinine in patients with ATTR cardiac amyloidosis are associated with the lower functional class of these patients.

Wild-type ATTR affects almost exclusively the heart and is frequently associated with AS. In retrospective case series and studies, the mortality of patients with AS and ATTR cardiac amyloidosis was high.[9,14,27,28] Chacko *et al*. assessed echocardiographic parameters in patients with ATTR cardiac amyloidosis and found that the presence of severe AS was independently associated with significantly reduced patient survival, that was significantly worse if treated conservatively.[29] A review of several studies, support the finding of higher risk of mortality in patients with AS and

Table 4 Clinical and echocardiographic predictors of all-cause mortality, cardiac mortality, cardiac hospitalizations and hospitalization or cardiac mortality

All-cause mortality	Univariate analysis		Multivariate analysis		Cardiac mortality	Univariate analysis		Multivariate analysis	
	P	HR (95%CI)	*P*	HR (95%CI)		*P*	HR (95%CI)	*P*	HR (95%CI)
Age	0.006	1.143 (1.039–1.257)	0.004	1.213 (1.065–1.382)	Age	0.027	1.142 (1.106–1.285)	0.056	
Gender	0.171				Gender	0.298			
Hypertension	0.896				Hypertension	0.786			
Diabetes mellitus	0.439				Diabetes mellitus	0.876			
Atrial fibrillation	0.786				Atrial fibrillation	0.343			
Coronary artery disease	0.546				Coronary artery disease	0.509			
NYHA	0.086	1.676 (0.930–3.021)			NYHA	0.106			
ATTR–cardiac amyloidosi	0.6				ATTR-CA	0.763			
Haemoglobin	0.225				Haemoglobin	0.062	0.661 (0.428–1.022)		
Creatinine	0.82				Creatinine	0.114			
LVEF	0.826				LVEF	0.15			
Pulmonary artery pressure	0.006	1.987 (1.214–3.251)	0.643		Pulmonary artery pressure	0.029	1.973 (1.071–3.635)	0.309	
LV mass	0.295				LV mass	0.737			
GLS	0.036	1.130 (1.008–1.127)	0.043	1.128 (1.004–1.267)	GLS	0.011	1.532 (1.010–2.125)	0.024	1.579 (1.061–2.351)
RV strain	0.139				RV strain	0.098	0.901 (0.797–1.019)		
Hospitalizations	*P*	HR (95%CI)	*P*	HR (95%CI)	Hospitalization or cardiac death	*P*	HR (95%CI)	*P*	HR (95%CI)
Age	0.702				Age	0.186			
Gender	0.907				Gender	0.627			
Hypertension	0.663				Hypertension	0.465			
Diabetes mellitus	0.045	2.335 (1.018–5.356)	0.067		Diabetes mellitus	0.092	1.865 (0.902–3.855)		
Atrial fibrillation	0.127				Atrial fibrillation	0.066	1.962 (0.936–4.027)		
Coronary artery disease	0.269				Coronary artery disease	0.127			
NYHA	0.04	2.536 (1.041–6.179)	0.04	2.536 (1.041–6.179)	NYHA	0.013	2.738 (1.241–6.043)	0.015	1.807 (1.130–2.889)
ATTR-CA	0.048	2.566 (1.009–6.524)	0.149		ATTR-CA	0.041	2.367 (1.007–5.163)	0.179	
Haemoglobin	0.448				Haemoglobin	0.289			
Creatinine	0.110				Creatinine	0.078	1.790 (0.936–3.423)		
LVEF	0.119				LVEF	0.035	0.948 (0.901–0.996)	0.079	
Pulmonary artery pressure	0.352				Pulmonary artery pressure	0.132			
LV mass	0.426				LV mass	0.193			
GLS	0.572				GLS	0.297			
RV strain	0.447				RV strain	0.111			

GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricle.

ATTR-CA.[30] Recently, studies with quit similar design showed prospectively that in patients with ATTR cardiac amyloidosis and AS, that undergo AVR, the presence of ATTR cardiac amyloidosis, does not affect survival or combined endpoint of survival and time to first HF hospitalization, in up to 2 years follow up.[15–17,24] Our study is in line with these studies and extends the prospective follow in additional 3 years, showing no difference in mortality over late follow up. However, there was a higher rate of cardiac and HF hospitalizations in patients with ATTR cardiac amyloidosis, similarly to the findings of Rosenblum *et al*. The cardiac death was relatively low, especially compared with hospitalizations number and this can explain the significant difference in combined endpoint result between patients with and without ATTR cardiac amyloidosis, although, the independent predictor for the combined endpoint was NYHA functional class.

Cardiac amyloidosis is a chronic disease. Itzhaki Ben Zudok *et al*. showed that increased wall thickness and diastolic dysfunction develop in cardiac amyloidosis over a time course of several years.[31] In AS patients, however, the echocardiographic findings can be similar. Since the diagnosis of ATTR cardiac amyloidosis was performed at enrolment, we cannot know whether the patients were positive for ATTR cardiac amyloidosis before TAVR, but we assume that these subjects had a milder form of the disease at the time of TAVR. Before TAVR, patients had higher LV mass and lower basal segmental LS. The apical to basal segments GLS and MW ratio was higher in these patients. The findings of relative low MW in basal segments compared with apical segments, in cardiac amyloidosis was recently reported by Clemmensen *et al*.[26] Relative apical sparing is specific for cardiac amyloidosis.[32] In patients with AS and ATTR cardiac amyloidosis, this findings are less specific, because AS also reduces basal strain.[22] In patients with AS, apical sparing is related to worse prognosis and this may be due to undiagnosed amyloidosis.[33] So, although the relative apical sparing is less pronounced in AS and ATTR cardiac amyloidosis patients and may not reach the cut-offs suggested for the diagnosis of cardiac amyloidosis without AS, it should rise a clinical suspicion on the presence of ATTR cardiac amyloidosis in patents with AS before AVR and also after the AV underwent treatment.

Patients with cardiac amyloidosis can present with different degrees of involvement of amyloid infiltration, which might significantly alter the prognosis. ATTR cardiac amyloidosis may be a disease modifier in patients with AS and vice versa.[9,34] Recently, Scully *et al*. suggested that AS primes the myocardium for amyloid deposition and that TAVR may be beneficial in these patients.[16] Our findings show that in ATTR cardiac amyloidosis patients diagnosed after TAVR there was a progression in LV thickness and reduction in LV longitudinal function compared with pre-TAVR study.

Another finding of the study is higher incidence of conduction abnormalities in ATTR cardiac amyloidosis patients. Previous studies showed more frequent conduction abnormalities in patients with ATTR amyloidosis.[1,35] Castano *et al*. suggested that the correlation between late gadolinium enhancement on CMR and conduction abnormalities in patients with AS undergoing TAVR, can be explained by occult amyloidosis.[36] Later, they and others showed higher incidence of right bundle branch block in patients with AS and ATTR cardiac amyloidosis but no significant difference in the need for permanent pacemaker after TAVR.[10,16] We looked on combined endpoint of pacemaker and new LBBB. LBBB was reported more frequently with wild-type ATTR cardiac amyloidosis.[1] The effect of AV intervention on a compromised conduction system due to infiltration explains the higher rate of conduction abnormalities.

Limitations

The main limitation of this research is the relative small study cohort and enrolling only patients in relatively good functional and cognitive status. We do not know the rates of cardial amyloidosis in patients who died before the study period or who were not enrolled. Although the baseline, pre-TAVR data, in these patients does not differ significantly, the renal function in this population is impaired. In addition, the cognitive status of the patients before and after TAVR is not known. Because 32% of patients died within 2 years after TAVR, we cannot extrapolate from the population included to the population that could not be included. In addition, the survival analysis is limited and underpowered due to the small cohort. So although the results go along with other studies, they should be interpreted with caution. Another limitation is the retrospective analysis of the clinical and echocardiographic data before TAVR. However, all the patients are part of the TAVR registry in our institution and all the patients underwent a complete echocardiographic study before the procedure. The forth limitation is that we did not perform genetic testing since it is an elderly population and most probably have wild type ATTR. Another limitation is the assessment of MW analysis from pressure strain loops by echocardiography using echo-PAC software. We added mean aortic pressure gradient to systolic blood pressure for pressure analysis, however the software is not validated in these patients, so the pre TAVR data should be taken with caution. The MW index is relatively high compared with previous reports,[23] however a high proportion of patients were with hypertension and the numbers are quint similar to the preliminary reports on patients before and after TAVR.[37]

Conclusions

Our study adds information on late clinical and echocardiographic follow up of a subgroup of patients with ATTR cardiac amyloidosis that underwent TAVR. The long-term survival is

not significantly affected by the presence of ATTR cardiac amyloidosis, further supporting the need for intervention in these patients. However, these patients showed a less favourable clinical course with poorer functional status and higher rate of hospitalization as compared with patients without ATTR cardiac amyloidosis. The systolic and diastolic function indices as well as MW efficiency are lower in patients with ATTR cardiac amyloidosis. Our results suggest that in patients who underwent TAVR and have limited clinical or echocardiographic improvement, screening for ATTR cardiac amyloidosis should be considered. Future studies are warranted to explore the potential role and the benefit of new and novel cardiac amyloidosis therapies (e.g. tafamidis) in post-TAVR patients with ATTR cardiac amyloidosis, in improving NYHA class and reducing recurrent cardiac hospitalizations.

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