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ORIGINAL ARTICLE
Cardiomyopathy

Impact of Tafamidis on Echocardiographic Cardiac Function of Patients With Transthyretin Cardiac Amyloidosis

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Background: The efficacy of a therapy for patients with transthyretin amyloid cardiomyopathy (ATTR-CM) has not been proven, but tafamidis has been associated with favorable outcomes. However, echocardiographic details of the association of tafamidis with cardiac morphology remain undetermined. Moreover, whether the efficacy of tafamidis varies with the degree of cardiac involvement remains unknown. Using echocardiography, this study investigated the impact of tafamidis on the cardiac morphology of patients with ATTR-CM.

Methods and Results: Of 52 consecutive patients with biopsy-proven ATTR-CM at Kobe University Hospital, we included 41 for whom details of follow-up echocardiographic examinations after the administration of tafamidis were available. All patients underwent standard and speckle-tracking echocardiography before and a mean (±SD) of 16±8 months after the administration of tafamidis. No significant changes were observed in any representative echocardiographic parameters after the administration of tafamidis. Furthermore, there were no significant changes observed in subgroup analyses (e.g., left ventricular [LV] ejection fraction ≥50% vs. <50%; LV mass index <150 vs. ≥150 g/m^2; New York Heart Association Class I–II vs. Class III; age ≥80 vs. <80 years).

Conclusions: Tafamidis may prevent worsening of various representative echocardiographic parameters of patients with ATTR-CM. This effect is also seen in patients with relatively advanced disease and in those who are elderly.

Key Words: Echocardiography; Tafamidis; Transthyretin amyloid cardiomyopathy

Cardiac amyloidosis is characterized by the extracellular deposition, in the heart, of misfolded proteins with the pathognomonic histological property of green birefringence when viewed under cross-polarized light after staining with Congo red.[1] Transthyretin (TTR) amyloidosis (ATTR) is characterized by disintegrated liver-derived TTR that accumulates as amyloid fibrils in the myocardium, leading to progressive heart failure (HF) with high morbidity and mortality, especially if left untreated.[2–4] ATTR can be either variant ATTR (ATTRv), with a pathogenic mutation in the *ATTR* gene, or wild-type ATTR (ATTRwt), without any mutation.[5] Although considered a rare disease, recent findings suggest that ATTR is underappreciated as a cause of common cardiac diseases or syndromes.[2] The survival of patients with ATTRwt was thought to be over 60 months,[6,7] but more recent studies have revealed that the median survival after diagnosis is only 43–47 months.[8,9] In addition, the mean survival after diagnosis of ATTRv is approximately 10 years in endemic areas[10] and approximately 7 years for late-onset disease in non-endemic areas[11] when left untreated.

Although there is no proven therapy for patients with ATTR cardiomyopathy (ATTR-CM), a multicenter double-blind placebo-controlled randomized study performed in 2018 (ATTR-ACT Study) showed that tafamidis meglumine, a TTR stabilizer, was associated with reductions in all-cause mortality, cardiovascular-related hospitalizations, and in the declines in functional capacity and quality of life compared with placebo for patients with ATTR-CM.[12] As a result of these findings, tafamidis meglumine is currently the only drug approved for patients with both wild-type

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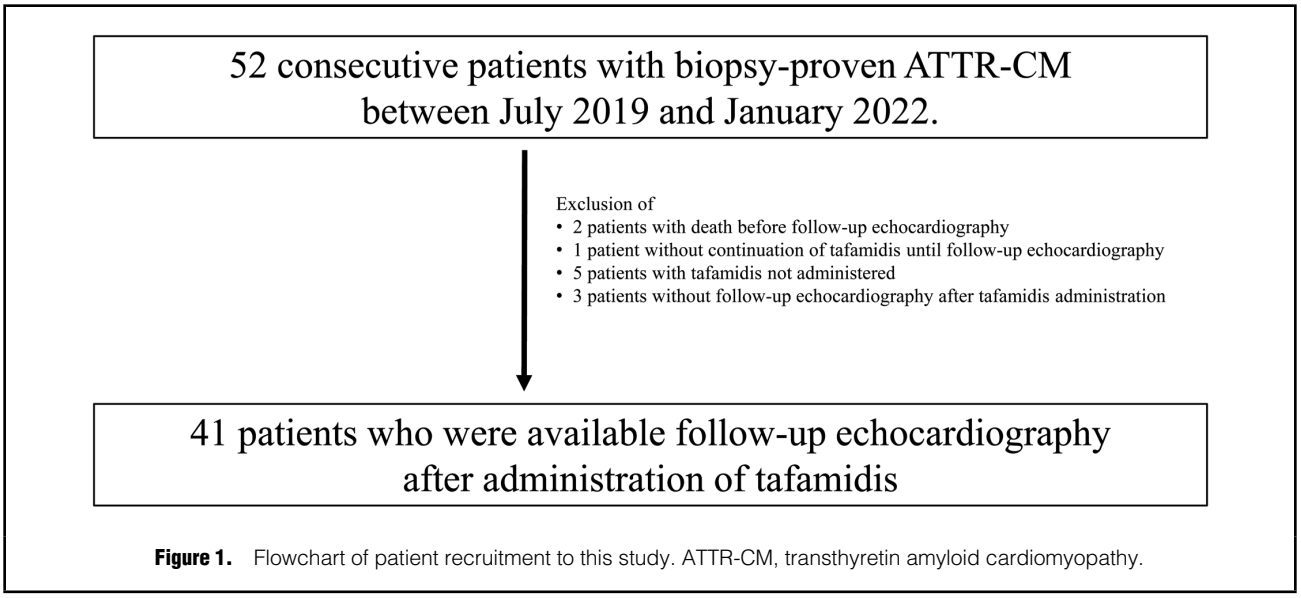

Figure 1. Flowchart of patient recruitment to this study. ATTR-CM, transthyretin amyloid cardiomyopathy.

(ATTRwt-CM) and variant (ATTRv-CM) ATTR-CM, and should be considered for patients whose survival can be reasonably expected.[3,4] Although there have been a few studies into the effect of tafamidis on cardiac function in ATTR-CM, echocardiographic details of the association of tafamidis with cardiac function remain undetermined. In addition, whether the efficacy of tafamidis varies with the degree of cardiac involvement remains unknown.

Thus, the aim of the present study was to investigate, using echocardiography, the effect of tafamidis on cardiac morphological exacerbations of patients with ATTR-CM who were treated with tafamidis.

Methods

Study Population

We retrospectively studied 52 consecutive patients with biopsy-proven ATTR-CM at Kobe University Hospital between July 2019 and January 2022. All patients underwent endomyocardial or extracardiac biopsy, and TTR deposition was confirmed by either endomyocardial or extracardiac biopsy, with amyloid typing by immunohistochemistry or mass spectrometry. Cardiac TTR deposition was confirmed by either endomyocardial biopsy or evidence of Grade 2–3 myocardial uptake on ^{99m}Tc-pyrophosphate (PYP) scintigraphy. Moreover, all patients underwent genotyping for any variants of the *TTR* gene. After the exclusion of 2 patients who died before follow-up echocardiography, 1 patient who was unable to continue tafamidis until the follow-up echocardiography, 5 patients who were not administered tafamidis, and 3 patients without follow-up echocardiography after tafamidis administration, 41 patients with ATTR-CM were included in the study (**Figure 1**).

This study was approved by the Ethics Committee of Kobe University Hospital Clinical and Translational Research Center (No. B220072) and was conducted in accordance with the Declaration of Helsinki.

Standard Echocardiographic Examination

All patients underwent transthoracic echocardiography before and a mean (±SD) of 16±8 months after the administration of tafamidis. For each patient, the most recent follow-up echocardiography data were selected for analysis in this study. All echocardiographic data were obtained using a commercially available echocardiographic system. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the European Association of Cardiovascular Imaging.[13] Specifically, left ventricular (LV) mass was estimated using the formula proposed by Devereux et al,[14] and the LV mass index (LVMI) was calculated for each subject by dividing LV mass by body surface area.

Speckle-Tracking Strain Analysis

Speckle-tracking strain analysis was performed for each patient using a single dedicated software program to evaluate LV longitudinal function, which was assessed in terms of LV global longitudinal strain (GLS; AutoStrain; TOMTEC-ARENA: TOMTEC Imaging Systems GmbH, Munich, Germany). Briefly, apical 4-, 2- and long-axis views, obtained as Digital Imaging and Communications in Medicine (DICOM)-formatted file images, were uploaded onto a personal computer for subsequent off-line GLS analysis. Longitudinal speckle-tracking strain was calculated using an automated contouring detection algorithm, and regions of interest were manually adjusted if necessary. Longitudinal strain results were visualized by color coding in the individual clips and combined in a bull's eye plot. GLS was then determined as the averaged peak longitudinal strain of 18 LV segments and is expressed as an absolute value in accordance with current guidelines.[13] For quantitative assessment of apical sparing by means of speckle-tracking strain (relative apical sparing), the following formula was used: mean apical longitudinal strain/(mean mid-longitudinal strain + mean basal longitudinal strain).[15]

Comparison of Echocardiographic Parameters Before and After Tafamidis Administration

Standard echocardiographic parameters and speckle-tracking parameters obtained before and after the administration of

Table 1. Baseline Patient Characteristics (n=41)	
Clinical characteristics	
Age (years)	75.6±6.9
Male sex	37 (90.2)
BMI (kg/m^2)	21.7±3.4
SBP (mmHg)	123.2±24.3
DBP (mmHg)	71.2±14.0
Heart rate (beats/min)	70.1±10.3
Blood examinations	
Hemoglobin (g/dL)	13.2±2.6
BUN (mg/dL)	23.9±8.8
Creatinine (mg/mL)	1.22±0.38
eGFR (mL/min/1.73 m^2)	47.9±13.4
BNP (pg/mL)	271.9 [139.4–364.6]
AST (U/L)	28.0±10.8
ALT (U/L)	21.7±10.1
LDL-C (mg/dL)	113.8±43.9
Comorbidities	
Hypertension	22 (53.7)
Diabetes	8 (19.5)
Dyslipidemia	14 (34.1)
Obesity (BMI ≥25 kg/m^2)	5 (12.9)
Atrial fibrillation	20 (54.1)
Paroxysmal	8 (21.6)
Chronic	12 (32.4)
Echocardiographic parameters	
LVEF (%)	52.9±11.2
LVMI (g/m^2)	154.1±44.5
LA volume index (mL/m^2)	53.0±17.7
GLS (%)	11.6±3.9
Relative apical sparing	1.51±0.79
NYHA Functional Class	
I	6 (14.6)
II	27 (65.9)
III	8 (19.5)
IV	0 (0.0)
TTR phenotype	
Wild-type	34 (82.9)
Variant	7 (17.1)
Medications	
ACEI/ARB	20 (48.8)
β-blockers	27 (65.9)
MRA	15 (36.6)
SGLT2 inhibitors	2 (4.9)
Calcium channel blockers	6 (14.6)
Sacubitril/valsartan	3 (7.3)
Diuretics	26 (63.4)

Continuous variables are presented as the mean±SD for normally distributed data and as the median [interquartile range] for non-normally distributed data. Categorical variables are presented as n (%). ACEI, angiotensin-converting enzyme inhibitor; ALT, Alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2; TTR, transthyretin.

tafamidis were compared for all patients. The primary endpoint was a comparison of important echocardiographic parameters comprising LV ejection fraction (LVEF), LVMI, the ratio of peak early diastolic mitral flow velocity and pulsed-wave Doppler-derived early diastolic velocity from the septal mitral annulus (E/e′), LA volume index, GLS, and relative apical sparing. The secondary endpoint was a comparison of other echocardiographic parameters. In addition to comparisons in the entire patient group, comparisons were also made in the following patient subgroups: (1) LVEF ≥50% vs. <50%; (2) LVMI <150 g/m^2 (the median value in this study) vs. LVMI ≥150 g/m^2; (3) New York Heart Association Class I–II vs. NYHA Class III; and (4) age ≥80 vs. <80 years.

Statistical Analysis

Continuous variables are expressed as the mean±SD in the case of normally distributed data and as median values with the interquartile range for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. Parameters between 2 subgroups were compared using paired t-tests. Proportional differences were evaluated using Fisher's exact test. In all cases, $P<0.05$ was considered statistically significant. All analyses were performed using MedCalc version 19.6 (MedCalc Software, Mariakerke, Belgium).

Results

The baseline clinical and echocardiographic characteristics of the 41 patients with ATTR-CM are summarized in **Table 1**. Cardiovascular events occurred in 4 patients, including 2 patients with cardiac death and 2 patients with HF hospitalization. The mean patient age was 75.6±6.9 years, 37 (90.2%) patients were male, mean LVEF was 52.9±11.2%, mean LVMI was 154.1±44.5 g/m^2, and none of the patients was classified as NYHA Class IV. Thirty-four (82.9%) patients were diagnosed with ATTRwt-CM; the remaining 7 (17.1%) patients were diagnosed with ATTRv-CM.

Comparison of Echocardiographic Parameters in All Patients

Table 2 shows a comparison of echocardiographic parameters for all patients before and after the administration of tafamidis. Cardiac morphology worsened only slightly with the administration of tafamidis, and there were no significant changes observed in any of the echocardiographic parameters (primary and secondary endpoints) before and after tafamidis administration.

Figure 2 shows representative images of ATTR-CM with representative echocardiographic data from 5 years and immediately before tafamidis administration and at 12 months after tafamidis administration. Cardiac morphology deteriorated over the 5 years prior to tafamidis administration, but the deterioration was suppressed after tafamidis administration.

Comparison of Echocardiographic Parameters in Patients With LVEF ≥50% and <50%

Echocardiographic parameters before and after the administration of tafamidis in patients with LVEF ≥50% and <50% are presented in **Table 3**. There were no significant changes in the primary endpoint in the 2 groups. No significant changes were observed in the secondary endpoint in the 2 groups before and after administration of tafamidis,

Table 2. Echocardiographic Parameters of All Patients

	All patients (n=41)		P value
	Baseline	Follow-up	
Primary endpoint			
Left ventricle			
LVEF (%)	52.9±11.2	51.7±12.3	0.638
LVMI (g/m^2)	154.1±44.5	154.7±45.7	0.956
E/e′	18.3±6.1	19.0±11.4	0.734
Left atrium			
LA volume index (mL/m^2)	53.0±17.7	49.0±17.1	0.299
Speckle-tracking parameters			
GLS (%)	11.6±3.9	10.7±3.9	0.310
Relative apical sparing	1.51±0.79	1.36±0.74	0.380
Secondary endpoint			
Left ventricle			
LV end-diastolic volume (mL)	69.2±20.7	69.1±22.6	0.975
LV end-systolic volume (mL)	33.6±16.8	34.8±21.1	0.769
IVS thickness (mm)	15.3±3.4	15.5±3.0	0.776
Posterior wall thickness (mm)	16.2±3.3	15.0±3.1	0.105
Right ventricle			
RV end-diastolic area (cm^2)	13.8±3.6	12.9±3.0	0.268
RV end-systolic area (cm^2)	8.8±3.0	8.4±2.7	0.578
RV fractional area change (%)	37.5±7.8	36.0±9.0	0.447
RV basal diameter (mm)	32.5±5.3	31.2±5.2	0.425
RV mid-diameter (mm)	22.0±5.0	22.0±4.8	0.971
RV longitudinal diameter (mm)	67.7±7.4	67.2±9.0	0.823
TAPSE (mm)	14.3±4.3	15.5±4.6	0.271
Right atrium			
RA area (cm^2)	16.5±4.5	18.5±6.0	0.347
Valvular heart disease			
Mitral regurgitation (≥moderate)	5 (12.2)	6 (14.6)	0.750
Aortic regurgitation (≥moderate)	4 (9.8)	3 (7.3)	0.697
Aortic stenosis (≥moderate)	1 (2.4)	1 (2.4)	1.000
Tricuspid regurgitation (≥moderate)	2 (4.9)	5 (12.2)	0.241

Unless indicated otherwise, data are given as the mean±SD or n (%). e′, pulsed-wave Doppler-derived early diastolic velocity from the septal mitral annulus; E, peak early diastolic mitral flow velocity; IVS, interventricular septum; LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion. Other abbreviations as in Table 1.

with the exception of a significant difference in tricuspid annular plane systolic excursion in the LVEF ≥50% group.

Comparison of Echocardiographic Parameters in Patients With LVMI <150 and ≥150 g/m^2

The median LVMI of 150 g/m^2 for this study population was used to divide patients into 2 subgroups. Echocardiographic parameters before and after the administration of tafamidis in patients with LVMI <150 and ≥150 g/m^2 are presented in **Table 4**. There were no significant changes in any of the echocardiographic parameters (primary and secondary endpoints) in the 2 groups from before to after administration of tafamidis.

Comparison of Echocardiographic Parameters in Patients With NYHA Class I–II and Class III

Echocardiographic parameters before and after the administration of tafamidis in patients with NYHA Class I–II and Class III are presented in **Table 5**. There were no significant changes in either the primary or the secondary endpoint in the 2 groups from before to after the administration of tafamidis, with the exception of a significant difference in posterior wall thickness in the NYHA Class III group.

Comparison of Echocardiographic Parameters in Patients Aged ≥80 and <80 Years

Echocardiographic parameters before and after the administration of tafamidis in patients aged ≥80 and <80 years are presented in **Table 6**. There were no significant changes in any of the echocardiographic parameters (primary and secondary endpoints) in the 2 groups from before and to after the administration of tafamidis.

Discussion

The findings of this study demonstrate that the administration of tafamidis resulted in no further deterioration of representative echocardiographic parameters for patients with ATTR-CM during a follow-up period of 16±8 months. It was especially noteworthy that tafamidis prevented a worsening of the representative echocardiographic parameters, even in patients with relatively advanced disease

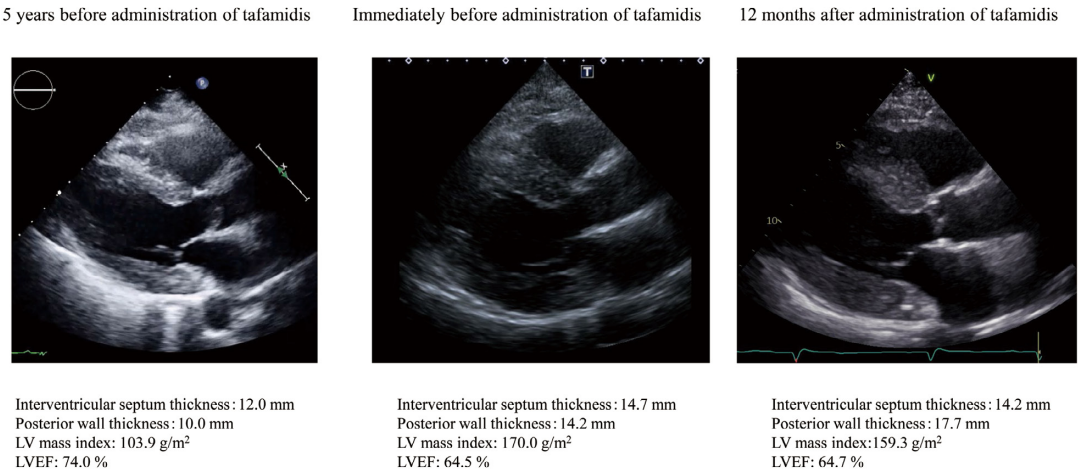

Figure 2. Representative echocardiographic images and data obtained from 5 years before, immediately before, and 12 months after the administration of tafamidis to a 74-year-old woman with wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM). Cardiac morphology worsened during the 2 years prior to tafamidis administration, but this deterioration was suppressed after tafamidis administration. LV, left ventricle; LVEF, left ventricular ejection fraction.

Table 3. Changes in Echocardiographic Parameters in Patients With LVEF ≥ 50% and <50%

	LVEF ≥50% (n=23)			LVEF <50% (n=18)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
Primary endpoint						
Left ventricle						
LVEF (%)	60.8±6.1	59.6±7.0	0.551	42.8±7.3	41.4±9.8	0.651
LVMI (g/m²)	147.0±46.4	142.2±35.8	0.697	163.2±41.3	170.5±52.6	0.643
E/e′	17.7±5.2	18.9±12.7	0.682	18.9±7.1	19.0±9.9	0.979
Left atrium						
LA volume index (mL/m²)	50.4±16.4	48.0±17.3	0.628	56.4±19.2	50.3±17.3	0.326
Speckle-tracking parameters						
GLS (%)	13.8±2.7	12.5±2.6	0.117	8.7±3.2	8.3±4.0	0.751
Relative apical sparing	1.46±0.45	1.32±0.76	0.462	1.58±1.10	1.42±0.72	0.599
Secondary endpoint						
Left ventricle						
LV end-diastolic volume (mL)	64.8±18.3	62.7±14.8	0.673	74.9±22.5	77.2±28.2	0.786
LV end-systolic volume (mL)	25.7±8.9	25.4±7.7	0.907	43.8±19.1	46.9±26.3	0.680
IVS thickness (mm)	15.8±3.8	15.4±2.7	0.704	14.7±2.8	15.6±3.5	0.383
Posterior wall thickness (mm)	16.2±3.4	14.8±3.4	0.143	16.1±3.3	15.2±3.5	0.436
Right ventricle						
RV end-diastolic area (cm²)	12.1±3.1	11.9±2.3	0.826	15.9±3.1	14.2±3.4	0.150
RV end-systolic area (cm²)	7.0±2.1	7.1±1.7	0.914	10.8±2.5	9.9±3.0	0.365
RV fractional area change (%)	42.2±5.9	40.3±8.7	0.448	32.1±6.0	30.8±6.4	0.565
RV basal diameter (mm)	30.4±4.7	29.6±3.7	0.589	35.0±4.9	33.2±6.3	0.387
RV mid-diameter (mm)	19.2±3.9	20.4±4.3	0.368	25.4±4.2	24.0±4.8	0.398
RV longitudinal diameter (mm)	66.1±7.2	67.0±8.6	0.735	69.5±7.4	67.5±9.8	0.520
TAPSE (mm)	14.6±3.5	17.6±4.5	0.026	13.5±5.0	13.0±3.5	0.743
Right atrium						
RA area (cm²)	14.7±2.4	17.6±7.3	0.050	18.1±5.4	19.5±4.5	0.587
Valvular heart disease						
Mitral regurgitation (≥moderate)	0 (0.0)	2 (8.7)	0.155	5 (27.8)	4 (22.2)	0.710
Aortic regurgitation (≥moderate)	2 (8.7)	2 (8.7)	1.000	2 (11.1)	1 (5.6)	0.560
Aortic stenosis (≥moderate)	0 (0.0)	0 (0.0)	1.000	1 (5.6)	1 (5.6)	1.000
Tricuspid regurgitation (≥moderate)	1 (4.3)	1 (4.3)	1.000	1 (5.6)	4 (22.2)	0.157

Unless indicated otherwise, data are given as the mean±SD or n (%). Abbreviations as in Tables 1,2.

Table 4. Changes in Echocardiographic Parameters in Patients With LVMI <150 and ≥150 g/m²

	LVMI <150 g/m² (n=21)			LVMI ≥150 g/m² (n=20)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
Primary endpoint						
Left ventricle						
LVEF (%)	55.0±10.7	55.2±9.8	0.956	50.7±11.5	48.0±13.8	0.504
LVMI (g/m²)	120.2±19.1	126.5±28.6	0.402	189.8±34.2	184.2±41.6	0.648
E/e′	15.9±4.7	13.9±5.5	0.211	20.9±6.4	24.3±13.6	0.327
Left atrium						
LA volume index (mL/m²)	51.9±20.6	48.4±20.8	0.590	54.3±14.6	49.6±12.8	0.294
Speckle-tracking parameters						
GLS (%)	13.0±3.7	12.4±23.9	0.547	10.1±3.5	9.0±4.1	0.384
Relative apical sparing	1.25±0.38	1.06±0.34	0.130	1.82±0.98	1.67±0.91	0.630
Secondary endpoint						
Left ventricle						
LV end-diastolic volume (mL)	62.5±13.0	59.8±13.9	0.530	76.3±24.8	78.7±26.2	0.763
LV end-systolic volume (mL)	28.5±10.1	26.6±7.3	0.483	39.0±20.6	43.5±27.0	0.552
IVS thickness (mm)	13.8±2.8	14.1±2.6	0.673	16.9±3.3	17.0±2.8	0.963
Posterior wall thickness (mm)	14.2±2.6	13.5±2.6	0.415	18.2±2.6	16.6±2.9	0.060
Right ventricle						
RV end-diastolic area (cm²)	13.3±3.8	11.7±1.9	0.149	14.4±3.5	14.0±3.5	0.763
RV end-systolic area (cm²)	8.2±2.8	7.5±1.4	0.360	9.4±3.1	9.2±3.4	0.902
RV fractional area change (%)	39.0±7.3	36.1±8.2	0.271	36.0±8.2	35.9±10.0	0.987
RV basal diameter (mm)	31.7±6.1	31.3±5.3	0.837	33.5±4.3	31.2±5.4	0.158
RV mid-diameter (mm)	22.5±5.9	22.8±4.4	0.900	21.7±4.3	21.3±5.3	0.805
RV longitudinal diameter (mm)	65.1±7.9	64.4±8.9	0.814	70.4±6.0	69.9±8.6	0.836
TAPSE (mm)	16.1±4.3	17.0±4.3	0.518	12.4±3.5	13.9±4.5	0.293
Right atrium						
RA area (cm²)	15.2±5.3	16.6±3.8	0.584	17.3±4.2	20.5±7.3	0.329
Valvular heart disease						
Mitral regurgitation (≥moderate)	1 (4.8)	2 (9.5)	0.560	4 (20.0)	4 (20.0)	1.000
Aortic regurgitation (≥moderate)	1 (4.8)	1 (4.8)	1.000	3 (15.0)	2 (10.0)	0.643
Aortic stenosis (≥moderate)	1 (4.8)	1 (4.8)	1.000	0 (0.0)	0 (0.0)	1.000
Tricuspid regurgitation (≥moderate)	1 (4.8)	1 (4.8)	1.000	1 (5.0)	4 (20.0)	0.159

Unless indicated otherwise, data are given as the mean±SD or n (%). Abbreviations as in Tables 1,2.

(LVEF <50%, LVMI ≥150 g/m², and NYHA Class III) and in elderly patients (age ≥80 years).

Effect of Tafamidis on Cardiac Function in Patients With ATTR-CM

Some very recent studies have investigated the effects of tafamidis on cardiac function in ATTR-CM patients.[16–18] Giblin et al investigated the effect of tafamidis on cardiac function using speckle-tracking in 45 patients with ATTR-CM (23 treated with tafamidis, 22 untreated).[18] In that study, there was less deterioration of GLS in patients treated with tafamidis than in untreated patients.[18] Ochi et al reported that there was no significant deterioration in high-sensitivity cardiac troponin T levels, plasma B-type natriuretic peptide concentrations, LVEF, interventricular septum wall thickness, or GLS 18 months after the administration of tafamidis.[16] A subanalysis of the long-term efficacy of tafamidis as part of an ATTR-ACT Study was published most recently. In that report, mortality was significantly better for the group treated continuously with tafamidis (median follow-up 58.5 months) than for the placebo group (median follow-up 57.1 months). However, the echocardiographic details of the association of tafamidis with cardiac function remain undetermined.

Recent Topics Regarding ATTR-CM

Recent topics of interest include the finding that ATTR-CM is found in a substantial percentage of patients with HF with preserved ejection fraction (HFpEF), as well as those with aortic stenosis (AS) who have been referred for transcatheter aortic valve replacement (TAVR). Specifically, ATTR-CM was found in 13–14% of patients with HFpEF[19,20] and in 12–16% of patients with severe AS who had been referred for TAVR.[21,22] Given the high prevalence of AS in the general population and the increasing frequency of the use of TAVR for older adults at high and intermediate surgical risk, as well as the fact that more than half of HF patients are currently HFpEF, the screening of such patients for ATTR-CM is important because early detection may result in a greater benefit from emerging therapies. In particular, because there is currently no established medical treatment for patients with HFpEF, unlike for those with HF with reduced ejection fraction, the early diagnosis of ATTR-CM among patients with HFpEF may

Table 5. Changes in Echocardiographic Parameters in Patients With NYHA Class I–II and Class III

	NYHA Class I–II (n=33)			NYHA Class III (n=8)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
Primary endpoint						
Left ventricle						
LVEF (%)	55.2±9.4	54.0±10.8	0.627	43.4±13.5	42.1±14.3	0.857
LVMI (g/m^2)	147.3±43.4	149.7±46.3	0.828	182.1±39.9	175.0±39.0	0.724
E/e′	17.7±5.7	17.5±10.0	0.932	20.6±7.1	20.1±9.2	0.892
Left atrium						
LA volume index (mL/m^2)	53.1±17.4	48.7±16.8	0.305	52.9±20.3	50.2±19.6	0.792
Speckle-tracking parameters						
GLS (%)	12.0±4.1	11.1±3.9	0.346	9.6±1.9	9.0±3.6	0.663
Relative apical sparing	1.48±0.81	1.33±0.74	0.443	1.65±0.73	1.49±0.74	
Secondary endpoint						
Left ventricle						
LV end-diastolic volume (mL)	65.6±15.9	63.3±13.7	0.522	83.9±31.2	92.9±35.5	0.601
LV end-systolic volume (mL)	29.5±9.3	29.4±10.3	0.943	50.4±28.5	57.5±36.5	0.673
IVS thickness (mm)	15.1±3.5	15.5±3.3	0.660	16.0±3.1	15.5±1.5	0.695
Posterior wall thickness (mm)	15.7±3.3	14.9±3.4	0.323	17.9±2.7	15.3±2.0	0.047
Right ventricle						
RV end-diastolic area (cm^2)	13.2±3.5	12.6±2.7	0.459	16.1±3.3	14.5±4.1	0.444
RV end-systolic area (cm^2)	8.1±2.7	7.9±2.3	0.788	11.1±2.7	10.4±3.8	0.687
RV fractional area change (%)	39.3±7.3	37.3±8.6	0.349	31.2±6.5	30.3±9.5	0.826
RV basal diameter (mm)	31.7±5.4	30.9±5.1	0.587	35.5±3.7	32.7±6.1	0.314
RV mid-diameter (mm)	21.2±4.7	21.9±4.6	0.590	25.2±5.2	22.7±6.4	0.441
RV longitudinal diameter (mm)	66.4±7.7	67.1±8.7	0.911	72.3±3.3	72.1±9.9	0.956
TAPSE (mm)	14.8±4.6	15.9±4.8	0.348	12.5±2.0	13.8±3.3	0.413
Right atrium						
RA area (cm^2)	16.3±4.6	17.7±5.6	0.524	20.2±4.7	21.8±4.6	0.532
Valvular heart disease						
Mitral regurgitation (≥moderate)	1 (3.0)	3 (9.1)	0.309	4 (50.0)	3 (37.5)	0.641
Aortic regurgitation (≥moderate)	2 (6.1)	2 (6.1)	1.000	2 (25.0)	1 (12.5)	0.553
Aortic stenosis (≥moderate)	0 (0.0)	0 (0.0)	1.000	1 (12.5)	1 (12.5)	1.000
Tricuspid regurgitation (≥moderate)	2 (6.1)	4 (12.1)	0.399	0 (0.0)	1 (12.5)	0.334

Unless indicated otherwise, data are given as the mean±SD or n (%). Abbreviations as in Tables 1,2.

be important to reap the potential benefit of treatment with tafamidis meglumine.

Clinical Implications

Increased awareness of ATTR-CM among physicians with access to recently validated diagnostic imaging methods is leading to a reduction in diagnostic delays, with a resulting increase in the proportion of patients diagnosed with early-stage ATTR-CM. A recent retrospective multicenter observational study showed that the mid-term term natural history of patients with early stage ATTR-CM, defined as a furosemide equivalent diuretic requirement of <0.75 mg/kg and an N-terminal pro B-type natriuretic peptide (NT-proBNP) concentration of ≤500 ng/L, or ≤1,000 ng/L in the presence of atrial fibrillation, was significantly better than that of patients with non-early stage ATTR-CM, and, despite significant cardiovascular morbidity, was comparable to that of the general population.[23] Moreover, the effectiveness of tafamidis, especially for cardiovascular-related hospitalized patients with NYHA Class III at baseline, was not validated by the findings of the ATTR-ACT Study, which suggests the importance of early admission, diagnosis, and treatment of patients with ATTR-CM.[24] Despite improvements in the accuracy of diagnosis of ATTR-CM, it remains a difficult condition to diagnose and not all physicians pay attention to its possible presence. The present study showed that the administration of tafamidis resulted in no further overall deterioration of various echocardiographic parameters for patients with ATTR-CM, and a similar benefit of tafamidis even in patients with relatively advanced disease, such as those with LVEF <50%, LVMI ≥150 g/m^2, and NYHA Class III. Furthermore, a similar effect of tafamidis was observed in the group of patients aged ≥80 years, a more common elderly age group among patients with ATTRwt-CM. Patients with ATTR-CM at relatively advanced stages or elderly patients may be less likely to receive tafamidis, but our findings show that the progression of cardiac morphology may be prevented by tafamidis administration even in these patient groups, so that an indication for tafamidis may be considered even in patients whose disease is relatively advanced at the time of initial diagnosis.

Study Limitations

This study included a small number of patients in a single-

Table 6. Changes in Echocardiographic Parameters in Patients Aged ≤79 and ≥80 Years

	Age ≤79 years (n=27)			Age ≥80 years (n=14)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
Primary endpoint						
Left ventricle						
LVEF (%)	52.6±12.7	50.9±14.0	0.636	53.4±7.9	53.2±8.3	0.936
LVMI (g/m^2)	153.9±45.0	152.1±46.0	0.885	154.5±45.2	159.6±46.3	0.770
E/e′	17.6±6.1	18.4±10.7	0.738	19.5±6.1	20.1±13.0	0.893
Left atrium						
LA volume index (mL/m^2)	48.7±13.0	43.6±13.2	0.160	61.5±22.7	59.5±19.5	0.803
Speckle-tracking parameters						
GLS (%)	11.6±3.7	10.8±3.9	0.427	11.5±4.2	10.6±3.8	0.545
Relative apical sparing	1.34±0.53	1.22±0.55	0.406	1.84±1.09	1.64±0.97	0.614
Secondary endpoint						
Left ventricle						
LV end-diastolic volume (mL)	73.3±22.6	73.6±24.3	0.960	61.3±13.9	60.2±16.3	0.853
LV end-systolic volume (mL)	36.2±19.5	38.3±24.6	0.738	28.5±7.8	28.2±9.1	0.928
IVS thickness (mm)	14.8±3.4	15.2±2.8	0.649	16.4±3.2	16.2±3.3	0.895
Posterior wall thickness (mm)	15.7±3.4	14.5±2.9	0.157	17.0±3.1	16.0±3.5	0.408
Right ventricle						
RV end-diastolic area (cm^2)	14.3±3.6	13.0±3.3	0.210	12.9±3.6	12.8±2.7	0.918
RV end-systolic area (cm^2)	9.2±3.1	8.5±3.2	0.441	7.9±2.5	8.2±1.9	0.761
RV fractional area change (%)	36.7±8.2	36.2±10.0	0.834	39.0±7.1	35.7±7.5	0.269
RV basal diameter (mm)	33.5±5.1	31.3±6.2	0.179	30.6±5.3	31.2±3.0	0.736
RV mid-diameter (mm)	22.5±5.6	22.4±5.7	0.971	21.2±3.7	21.2±2.8	0.997
RV longitudinal diameter (mm)	69.3±5.8	68.1±8.7	0.609	64.7±9.3	65.6±9.8	0.815
TAPSE (mm)	15.0±4.6	15.3±3.9	0.791	13.2±3.6	15.9±5.8	0.179
Right atrium						
RA area (cm^2)	17.2±4.7	18.5±7.2	0.706	15.7±4.6	18.6±5.2	0.323
Valvular heart disease						
Mitral regurgitation (≥moderate)	4 (14.8)	4 (14.8)	1.000	1 (7.1)	2 (14.2)	0.558
Aortic regurgitation (≥moderate)	3 (11.1)	2 (7.4)	0.646	1 (7.1)	1 (7.1)	1.000
Aortic stenosis (≥moderate)	0 (0.0)	0 (0.0)	1.000	1 (7.1)	1 (7.1)	1.000
Tricuspid regurgitation (≥moderate)	2 (7.4)	3 (11.1)	0.646	0 (0.0)	2 (14.2)	0.153

Unless indicated otherwise, data are given as the mean±SD or n (%). Abbreviations as in Tables 1,2.

center retrospective study. Moreover, a control group could not be established in this study because only 5 patients were not administered tafamidis, but they were also not administered a placebo. Although ATTR-CM is a rare disease and tafamidis for the treatment of ATTR-CM has only been on the market for a few years, recent findings suggesting that this disease is underappreciated as a cause of common cardiac diseases or syndromes. This indicates that further prospective multicenter studies with larger patient populations and including placebo-controlled groups are needed to validate our findings. In particular, the number of patients in the subgroup comparison in the present study was even smaller, so that future comparisons between larger numbers of patients with propensity score matching are also needed.

Conclusions

Cardiac morphology, as assessed by representative echocardiographic parameters, worsened only slightly following the administration of tafamidis to patients with ATTR-CM, and this effect was also seen in patients with relatively advanced disease and elderly patients. Our findings may provide new insights into the management of patients with ATTR-CM.

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IRB Information

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