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ORIGINAL ARTICLE

Impact of tafamidis on myocardial function and CMR tissue characteristics in transthyretin amyloid cardiomyopathy

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Abstract

Aims Tafamidis improves clinical outcomes in transthyretin amyloid cardiomyopathy (ATTR-CM), yet how tafamidis affects cardiac structure and function remains poorly described. This study prospectively analysed the effect of tafamidis on 12-month longitudinal changes in cardiac structure and function by cardiac magnetic resonance (CMR) compared with the natural course of disease in an untreated historic control cohort.

Methods and results ATTR-CM patients underwent CMR at tafamidis initiation and at 12 months. Untreated patients with serial CMRs served as reference to compare biventricular function, global longitudinal strain (GLS), LV mass and extracellular volume fraction (ECV). Thirty-six tafamidis-treated (n = 35; 97.1% male) and 15 untreated patients (n = 14; 93.3% male) with a mean age of 78.3 ± 6.5 and 76.9 ± 6.5, respectively, and comparable baseline characteristics were included. Tafamidis was associated with preserving biventricular function (LVEF (%): 50.5 ± 12 to 50.7 ± 11.5, P = 0.87; RVEF (%): 48.2 ± 10.4 to 48.2 ± 9.4, P = 0.99) and LV-GLS (−9.6 ± 3.2 to −9.9 ± 2.4%; P = 0.595) at 12 months, while a significantly reduced RV-function (50.8 ± 7.3 to 44.2 ± 11.6%, P = 0.028; P (change over time between groups) = 0.032) and numerically worsening LVGLS (−10.9 ± 3.3 to −9.1 ± 2.9%, P = 0.097; P (change over time between groups) = 0.048) was observed without treatment. LV mass significantly declined with tafamidis (184.7 ± 47.7 to 176.5 ± 44.3 g; P = 0.011), yet remained unchanged in untreated patients (163.8 ± 47.5 to 171.2 ± 39.7 g P = 0.356, P (change over time between groups) = 0.027). Irrespective of tafamidis, ECV and native T1-mapping did not change significantly from baseline to 12-month follow-up ($P > 0.05$).

Conclusions Compared with untreated ATTR-CM patients, initiation of tafamidis preserved CMR-measured biventricular function and reduced LV mass at 12 months. ECV and native T1-mapping did not change significantly comparable to baseline in both groups.

Keywords Cardiac amyloidosis; Cardiac magnetic resonance imaging; ECV; Feature tracking; GLS; Tafamidis; Transthyretin

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Introduction

Cardiac amyloidosis is a protein-misfolding disease characterized by the deposition of amyloid fibrils in the cardiac extracellular space. Progressive amyloid deposition disrupts cardiac structure and function, and eventually a restrictive cardiomyopathy develops,[1] which is associated with high cardiovascular morbidity and mortality.[2] Transthyretin (TTR) is the precursor protein most commonly found in cardiac amyloidosis.[3,4] Among the TTR-targeting therapies developed, tafamidis has emerged as the current standard-of-care,[5,6] significantly reducing morbidity and mortality in patients with TTR amyloid cardiomyopathy (ATTR-CM).[5] Global parameters of biventricular function, ventricular and atrial strain have been established as follow-up parameters to determine ATTR-CM disease staging,[7,8] while

CMR-measured extracellular volume fraction (ECV) and tissue mapping have been suggested as more sensitive parameters to evaluate disease progression and efficacy of therapeutic intervention.[9–11] Yet, due to the limited availability of CMR in many countries and differing regional access to tafamidis, very limited data are available that describes how cardiac structure and function evolve once tafamidis therapy is initiated.

The aim of the present study was to evaluate how cardiac remodelling, function, feature tracking-based strain, and ECV evolve during the first 12 months of tafamidis therapy in patients with ATTR-CM, and to compare these changes to a historical patient cohort, who underwent repeat CMR, but for whom TTR-targeting therapy was not yet available.

Methods

Study design

Eligible patients with ATTR-CM consecutively referred to the Department of Cardiology, Bern University Hospital, Inselspital, Bern, Switzerland, between July 2019 and September 2021 were enrolled into the 'Bern Cardiac Amyloidosis REgistry' (B-CARE). Patients were included in the prospective tafamidis cohort if a TTR-targeting therapy with 61 mg tafamidis once daily was newly initiated and continued for ≥12 months (12 M) and if they underwent CMR at the time of therapy initiation and at 12 months. A historical reference patient cohort, without access to TTR-targeting-therapy prior to its' availability was retrospectively enrolled and included, if a baseline CMR at the time of diagnosis and a repeat CMR to monitor ATTR-CM with a minimum of 6 months between CMRs was available. Exclusion criteria were evidence of amyloid light chain (AL) amyloidosis or the lack of adequate CMR imaging within a predefined timespan (tafamidis cohort: baseline CMR < 6 months prior to or >1 month after treatment initiation; follow-up CMRs 12 ± 6 months). For study participants, yearly clinical, laboratory and longitudinal CMR-imaging follow-up data was collected for the B-CARE registry. The design of the study was approved by the local ethics committee, meeting the criteria outlined in the Declaration of Helsinki. Participants provided written, informed consent and the study was registered with ClinicalTrials.gov (NCT04776824). All data were entered into a dedicated RedCap online database at the University of Bern, Switzerland.

Diagnosis of ATTR-CM

Laboratory testing for monoclonal immunoglobulins (to exclude AL amyloidosis) included serum gel electrophoresis, serum immunofixation and serum free light-chain assays. In patients without evidence of a monoclonal immunoglobulin, the diagnosis of ATTR-CM was made non-invasively, if bone scintigraphy showed moderate or strong myocardial 99mTechnetium-3,3-diphosphono-1,2-propanodicarboxylic (DPD) tracer uptake (Perugini grade II or III). Alternatively, ATTR-CM was diagnosed upon detection of TTR amyloid deposits in biopsy specimen. If biopsy specimen were assessed from extracardiac locations, cardiac imaging (echocardiography or CMR) suggestive of cardiac amyloidosis was required for the diagnosis.[12] In patients with monoclonal gammopathy, hematologic consultation and, if required, tissue biopsy was performed to exclude AL and confirm TTR amyloidosis.

Transthyretin-stabilizing therapy with tafamidis

Tafamidis therapy was initiated, if patients fulfilled the inclusion criteria of the ATTR-ACT study[5]: (1) NYHA functional class I–III, (2) a prior heart failure hospitalization or requirement for a diuretic, (3) NT-proBNP >600 pg/mL, (4) GFR > 25 mL/min/1.73 m^2, (5) 6-min walk test >100 m, and (6) life expectancy >2 years. For all patients, tafamidis was prescribed at a standard dose of 61 mg once daily.

Cardiac magnetic resonance image acquisition and analysis

CMR imaging was performed on a 1.5- and 3.0 Tesla scanner (Aera and Magnetom Trio, Siemens Healthineers, Erlangen, Germany) as previously described.[13,14] In brief, steady-state free precession cine images were acquired in 2-, 3-, and 4-chamber view (CV) and an 8–14 matching short axis (SAX) stack (8 mm slice thickness with no interslice gap) covering both ventricles from base to apex. Image post-processing was performed in a core laboratory following standardized protocols by investigators blinded to clinical patient characteristics using the application CVI42 (Circle Cardiovascular Imaging, Version 5.13.8, Calgary, Canada). Contouring of the endo- and epicardial borders was manually corrected, if required. Left- (LV) and right ventricular (RV) volumes and ejection fraction (EF) were obtained in a SAX stack after exclusion of papillary muscles from the myocardium. Feature tracking-based strain analysis was performed in 2-, 3- and 4-CV to derive LV global longitudinal strain (GLS), in the SAX to obtain LV global circumferential (GCS) and radial strain (GRS), and in 4-CV to obtain RV GLS.[13] The presence of late gadolinium enhancement (LGE) in the LV was visually evaluated after bodyweight-adjusted gadolinium administration (cumulative dose 0.15–0.2 mmol/kg). Furthermore, native and post-contrast T1-mapping was assessed, and extracellular volume fraction (ECV) derived with the patient's same day haematocrit. If haematocrit was not available, a synthetic

haematocrit was approximated from the linear relationship between haematocrit and native T1 of the blood pool to calculate ECV.[15] Native T1 relaxation times were only provided for patients that underwent both scans at 1.5T scanners (n = 46). Patients that underwent the baseline CMR (n = 2) or FU-CMR (n = 2) on a 3.0 Tesla scanner were not considered for the statistical analysis of native T1 values. Left ventricular filling pressures were estimated as recently described by Garg et al: PCWP = 6.1352 + (0.07204*LA ESV) + (0.02256*LV mass).[16]

Statistical analysis

Patient characteristics were presented as frequencies and percentages or as mean ± standard deviation whenever appropriate. Highly skewed variables, such as NT-proBNP were provided as the median and interquartile range (IQR). χ^2 tests were used to compare the distribution of categorical variables in patients with and without TTR-stabilizing treatment. Continuous variables were compared by independent t-tests and Mann–Whitney U tests. Mean changes over time were analysed by one-way repeated measures analyses of variance (ANOVAs) with the within-subject factor time (baseline, 12 months). To estimate the treatment effect, we conducted ANOVAs with the between-subject factor 'treatment'. If the Mauchly sphericity test yielded a significant result, indicating a violation of sphericity assumption, we applied a Huynh-Feldt correction to account for the mild violation ($\varepsilon > 0.75$). A significant time*group interaction in ANOVA indicates that the change over time in the dependent variable differs across the treatment groups, suggesting distinct trends between the tafamidis and reference cohort. Results were considered statistically significant if the two-sided P-value was <0.05. Statistical analysis was performed with IBM SPSS Statistics 25 (IBM Corp., Armon, New York, USA) and R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 143 consecutive patients diagnosed with ATTR-CM were enrolled in the B-CARE registry between July 2019 and September 2021 and evaluated for study participation (see *Figure 1*). Among patients receiving TTR-targeting therapy (73; 51%), baseline CMR at therapy initiation was available for 60 patients (82%) of whom 36 patients underwent follow-up CMR at 12 months. CMR follow-up outside of the defined time window (12 ± 6 months) was the most common reason for study exclusion (n = 16), followed by death (n = 7), implantation of a CMR-incompatible device (n = 5), and discontinuation of tafamidis (n = 2), respectively. Among 70 patients without TTR-stabilizing therapy who comprised the historical reference cohort, 55 patients (78%) underwent a baseline CMR, while both baseline and follow-up CMR was available for 15 patients (21%).

Baseline patient characteristics

Detailed clinical baseline characteristics are shown in *Table 1*. The diagnosis of ATTR-CM was generally made non-invasively by bone-scintigraphy [tafamidis cohort: 34/36 (94.4%); reference cohort: 15/15 (100%)], after laboratory tests excluded AL amyloidosis. Two patients in the tafamidis cohort (5.6%) were diagnosed by endomyocardial biopsy. At the time of baseline CMR, the prevalence of cardiovascular risk factors

Figure 1 Study CONSORT flow chart. ATTR-CM, transthyretin amyloid cardiomyopathy; CMR, cardiac magnetic resonance imaging; DPD, 99mTechnetium-3,3-diphosphono-1,2-propanodicarboxylic acid bone scintigraphy; FU, follow-up.

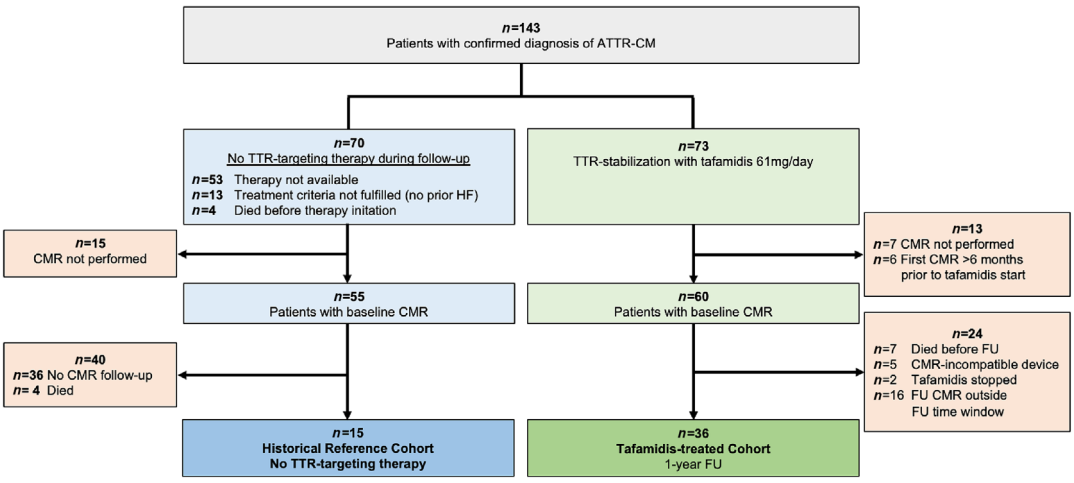


Table 1 Patient characteristics at baseline

	Reference cohort (n = 15)	Tafamidis cohort (n = 36)	P-value
Demographics			
Gender (male), *n* (%)	14 (93.3)	35 (97.2)	0.51
Age (years), mean ± SD	76.9 ± 6.5	78.3 ± 6.5	0.51
Medical history, *n* (%)			
Arterial hypertension	9 (60.0)	26 (72.2)	0.51
Diabetes mellitus	5 (33.3)	7 (19.4)	0.30
Coronary artery disease	5 (33.3)	9 (25.0)	0.73
NHYA class			
I	2 (13.3)	8 (22.2)	0.76
II	8 (53.3)	18 (50)	
III	5 (33.3)	10 (27.7)	
ATTR characteristics, *n* (%)			
History of carpal tunnel syndrome	2 (13.3)	12 (33.3)	**0.011**
History of polyneuropathy	2 (13.3)	6 (16.7)	0.83
Conduction system disease	8 (53.3)	21 (58.3)	0.94
Biomarkers			
Creatinine (mmol/L), mean ± SD	112.9 ± 34.1	102.9 ± 32.9	0.37
eGFR (mL/min), mean ± SD	57.3 ± 20.5	62.0 ± 21.3	0.51
NT-proBNP median (IQR)	1562 (1339–3788)	1621 (859–3169)	0.81
Medication, *n* (%)			
ACE inhibitor/AT1 antagonist	9 (60.0)	20 (55.6)	0.88
Beta-blocker	6 (40.0)	16 (44.4)	0.77
Mineralocorticoid receptor antagonist	4 (26.7)	6 (17.1)	0.46
SGLT2 inhibitor	2 (13.3)	0	
Diuretic	13 (86.7)	17 (47.2)	**0.009**
CMR characteristics			
LVEDV/BSA (mL/m^2)	83.4 ± 16.6	83.3 ± 21.7	0.98
LVSV/BSA (mL/m^2)	45.1 ± 8.3	40.6 ± 9.7	0.12
LVEF (%)	55 ± 9.2	50.5 ± 12.0	0.20
LV mass (g)	163.8 ± 47.5	184.7 ± 47.7	0.16
LV mass/BSA (g/m^2)	87.2 ± 21.2	96.6 ± 21.8	0.16
RVEF (%)	50.8 ± 7.3	48.2 ± 10.4	0.37
LVGLS	−10.9 ± 3.3	−9.6 ± 3.3	0.19
LVGRS	21.4 ± 8.7	20.2 ± 7.9	0.63
LVGCS	−14 ± 3.9	−13.3 ± 4.0	0.58
RVGLS	−18.7 ± 4.5	−17.2 ± 4.4	0.31
Native T1 on 1.5 Tesla scanner (ms)[a]	1099.7 ± 74	1101.5 ± 58.7	0.94
ECV (%)	49.8 ± 14	47.4 ± 8.0	0.24
Estimated PCWP (mmHg)	17.6 ± 4.3	17.9 ± 2.7	0.73

ACE, angiotensin converting enzyme; AT1, angiotensin II receptor type 1; ECV, extracellular volume fraction; EDV, end diastolic volume; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LV/RV, left/right ventricle; PCWP, pulmonary capillary wedge pressure.
[a]Native T1 times for the patients scanned on 3T were 1381 (patient in the reference cohort) and 1376 ms (patient in the tafamidis cohort). These patients were not considered when analysing between-group differences.

(arterial hypertension and diabetes mellitus), coronary and valvular heart disease was similar across groups ($P > 0.05$ for all). While diuretics were more commonly prescribed for patients in the historical reference cohort (86.7% vs. 47.2%; P = 0.009), comparable NYHA functional class, and lack of significant differences in NT-proBNP levels [median (IQR) tafamidis: 1621 (859–3169) pg/mL vs. reference cohort: 1562 (1339–3788) pg/mL, P = 0.806] and renal function (eGFR; tafamidis: 62.0 ± 21.3 mL/min; reference: 57.3 ± 20.5 mL/min; P = 0.511). Baseline CMR showed similar LV mass, LV- and RV EF and LV stroke volume index ($P > 0.05$ for all) between groups (*Table 1*). Tissue mapping did not reveal any differences in global native T1 values or ECV at baseline, and extensive LGE was present in all patients.

12-month longitudinal follow-up

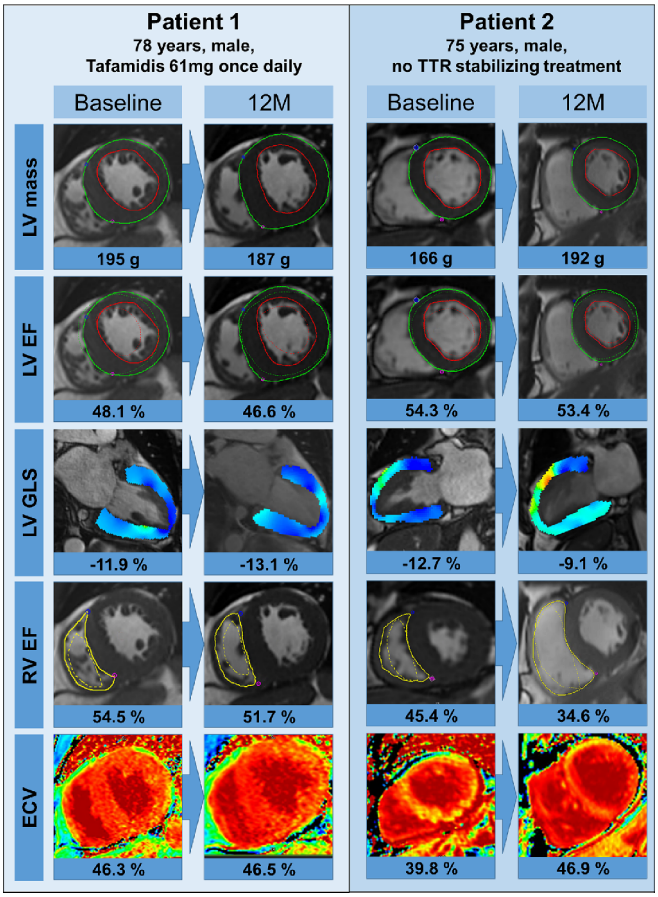
In the tafamidis cohort, 12-month follow-up CMR was performed a median 395 days (IQR 272–497) after the baseline CMR, whereas in the reference cohort, follow-up CMR was conducted at a median 429 (IQR 252–969) days after baseline evaluation. Repeated measure analysis of variance was used to compare within- and between group changes between baseline and follow-up CMR between tafamidis-treated and historical reference cohort (see *Table 2*, *Figures 2*, *3*, and *4*). While LV mass numerically, but non-significantly increased from baseline to 12 months (163.8 ± 47.5 to 171.2 ± 39.7 g, P = 0.356) in the untreated historic reference cohort, LV mass significantly decreased in the tafamidis cohort [184.7 ± 47.7 to 176.5 ± 44.3 g; P = 0.011; P (time*group interaction) = 0.015

Table 2 Longitudinal changes from baseline to 12-month follow-up (12 M)

	Reference cohort (n = 15)			Tafamidis cohort (n = 36)			P (time* group interaction)
	Baseline	12 M	P	Baseline	12 M	P	
CMR volumetry (mean ± SD)							
LVEDV/BSA (mL/m^2)	83.4 ± 16.6	80.4 ± 18.6	0.15	83.3 ± 21.7	83.7 ± 23.8	0.75	0.18
LVSV/BSA (mL/m^2)	45.1 ± 8.3	40.6 ± 11.4	0.084	40.6 ± 9.7	41.3 ± 11.3	0.64	0.054
LVEF (%)	55 ± 9.2	51 ± 10.3	0.15	50.5 ± 12	50.7 ± 11.5	0.87	0.096
LV mass (g)	163.8 ± 47.5	171.2 ± 39.7	0.36	184.7 ± 47.7	176.5 ± 44.3	**0.011**	**0.027**
LV mass/BSA (g/m^2)	87.2 ± 21.2	91.2 ± 19.6	0.39	96.6 ± 21.8	93.3 ± 21.1	0.056	0.066
RV EF (%)	50.8 ± 7.3	44.2 ± 11.6	**0.028**	48.2 ± 10.4	48.2 ± 9.4	0.99	**0.032**
LA ESV/BSA (mL/m^2)	55.9 ± 15.7	57.3 ± 25.5	0.51	57.3 ± 25.5	55.7 ± 25.3	0.40	0.33
CMR global strain (%), mean ± SD							
LVGLS	−10.9 ± 3.3	−9.1 ± 2.9	0.097	−9.6 ± 3.2	−9.9 ± 2.4	0.60	**0.048**
LVGRS	20.6 ± 8.3	17.7 ± 7.2	0.20	20.2 ± 7.9	21.2 ± 7.7	0.32	0.065
LVGCS	−13.6 ± 3.7	−12.2 ± 3.7	0.17	−13.3 ± 3.7	−13.8 ± 3.7	0.32	0.076
RVGLS	−18.7 ± 4.5	−16.7 ± 5.4	0.33	−17.2 ± 4.5	−16.7 ± 5.4	0.52	0.36
Further CMR parameter (mean ± SD)							
Native T1 (ms)[a]	1099.7 ± 74	1111.3 ± 58.5	0.71	1099 ± 59	1090.9 ± 46.5	0.42	0.43
ECV (%)	49.8 ± 14	51.2 ± 12.6	0.40	47.3 ± 8.3	49.4 ± 9.2	0.065	0.73
Estimated PCWP (mmHg)	17.6 ± 4.3	17.6 ± 4.4	0.93	17.9 ± 2.7	18 ± 3.1	0.94	0.92
NYHA class							
I	7%	13%	0.90	23%	20%	0.12	N/A
II	38%	62%		43%	70%		
III	54%	25%		33%	10%		
Biomarkers							
Creatinine (mmol/L), mean ± SD	126.4 ± 38.1	158.9 ± 56.8	0.096	103.0 ± 30.9	108.8 ± 35.8	0.11	**0.023**
eGFR (mL/min), mean ± SD	53.0 ± 19.6	45.6 ± 13.3	0.34	60.1 ± 21.9	60.2 ± 18.2	0.99	0.30
NT-proBNP, median	1562 (1339–3788)	1990 (1453–5452)	0.78	1562 (878–3104)	2284 (1174–3133)	0.23	0.31

ACE, angiotensin converting enzyme; AT1, angiotensin II receptor type 1; ECV, extracellular volume fraction; EDV, end diastolic volume; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LV/RV, left/right ventricle; PCWP, pulmonary capillary wedge pressure.
*Four patients that underwent either the baseline (n = 2) or FU scan (n = 2) on a 3T scanner were excluded from this analysis.

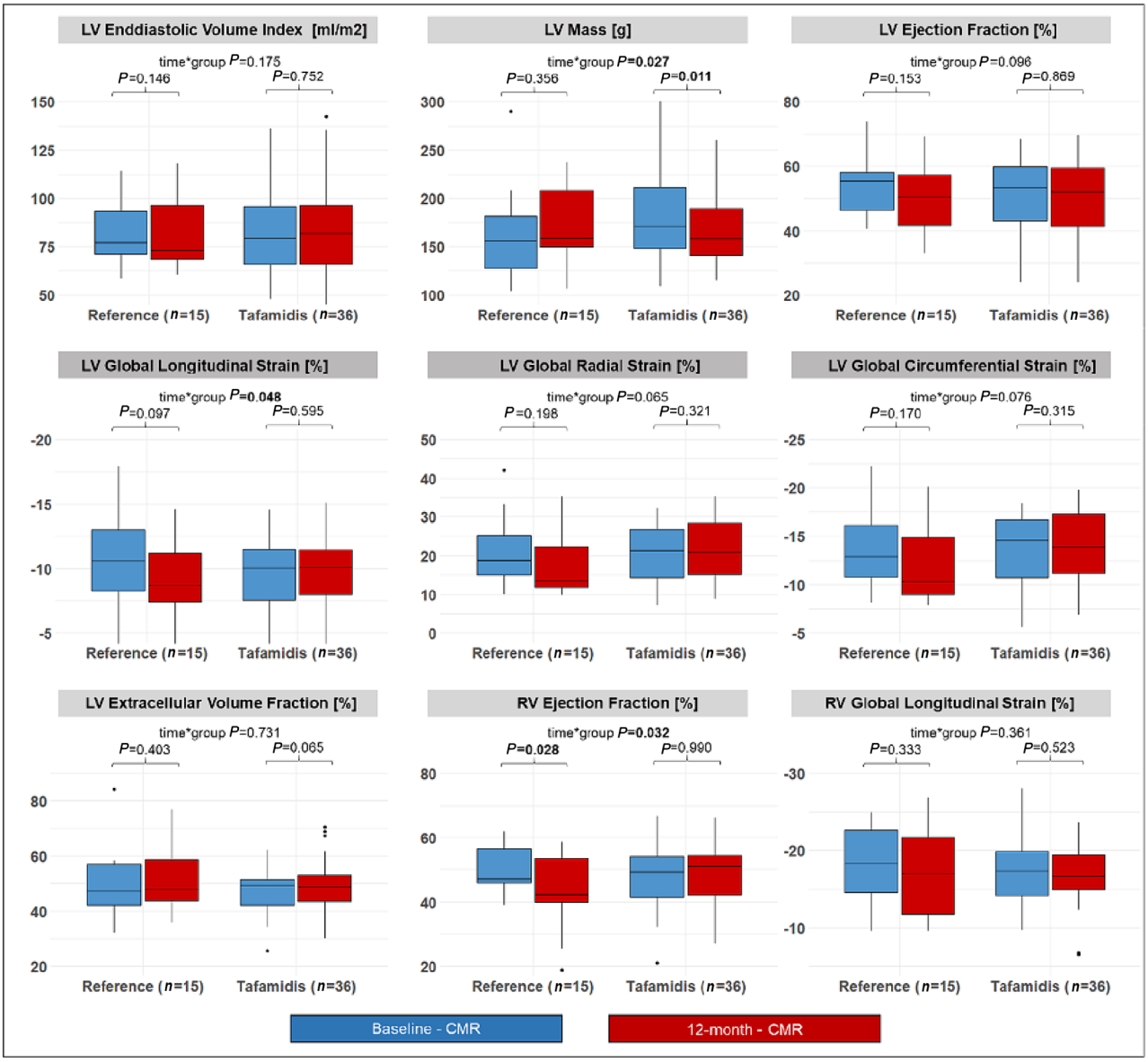
Figure 2 Comparison of a patient receiving tafamidis vs. historical reference patient without TTR-stabilizing therapy. CMR, cardiac magnetic resonance imaging; ECV, extracellular volume fraction; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle.



(comparing differential change between tafamidis and reference cohort between baseline and follow-up)]. LVGLS remained unchanged in the tafamidis cohort (−9.6 ± 3.2 to −9.9 ± 2.4%; *P* = 0.595), while a longitudinal within-group comparison revealed a trend towards worsening LVGLS in the historic reference cohort (−10.9 ± 3.3 to −9.1 ± 2.9%; *P* = 0.097). Comparing the within-group changes in LVGLS from baseline to 12 month follow-up CMR between the tafamidis and historic reference cohort, a significant difference suggesting better preservation of LVGLS with tafamidis therapy was observed (*P* (time*group interaction) = 0.048). Tafamidis treatment was further associated with preserving RVEF (48.2 ± 10.4 to 48.2 ± 9.4%; *P* = 0.990), while a significant decline in RVEF was observed without treatment in the historical reference cohort (50.8 ± 7.3 to 44.2 ± 11.6%; *P* = 0.028) at CMR follow-up. Comparing the within-group changes over time, ANOVA revealed significant differences in RVEF change over time between the tafamidis and reference cohort (*P* (time*group interaction) = 0.032). LVEF and LV stroke volume did not significantly change between baseline and follow-up, yet appeared more stable with tafamidis (LVEF: 50.5 ± 12 to 50.7 ± 11.5%; *P* = 0.869; LVSVi: 40.6 ± 9.7 to 41.3 ± 11.3 mL/m^2, *P* = 0.643) compared with historical reference cohort patients (LVEF 55 ± 9.2 to 51 ± 10.3%; *P* = 0.153; LVSVi: 45.1 ± 8.3 to 40.6 ± 11.4 mL/m^2, *P* = 0.084). Longitudinal changes between groups did not reveal significant differences at 12 months (*P* (time*group interaction) = 0.054 for LV stroke volume and *P* = 0.096 for LVEF, respectively). CMR-estimated PCWP pressures were comparable between groups at baseline and remained unchanged irrespective of tafamidis treatment at follow-up (see *Table 2*). When comparing ECV, no significant differences were seen within each cohort (tafamidis: 47.3 ± 8.3 to 49.4 ± 9.2%, *P* = 0.065 and untreated: 49.8 ± 14 to 51.2 ± 12.6%, *P* = 0.403) or when comparing the developments over time between tafamidis-treated and historical reference cohort (*P* (time*group interaction) = 0.731).

Clinical status (NYHA functional class) and NT-proBNP levels remained comparable at 12-month follow-up regard-

Figure 3 12-month (12 M) longitudinal changes of cardiac structure and function in tafamidis-treated and untreated ATTR-CM. CMR, cardiac magnetic resonance imaging; LV, left ventricle; RV, right ventricle.

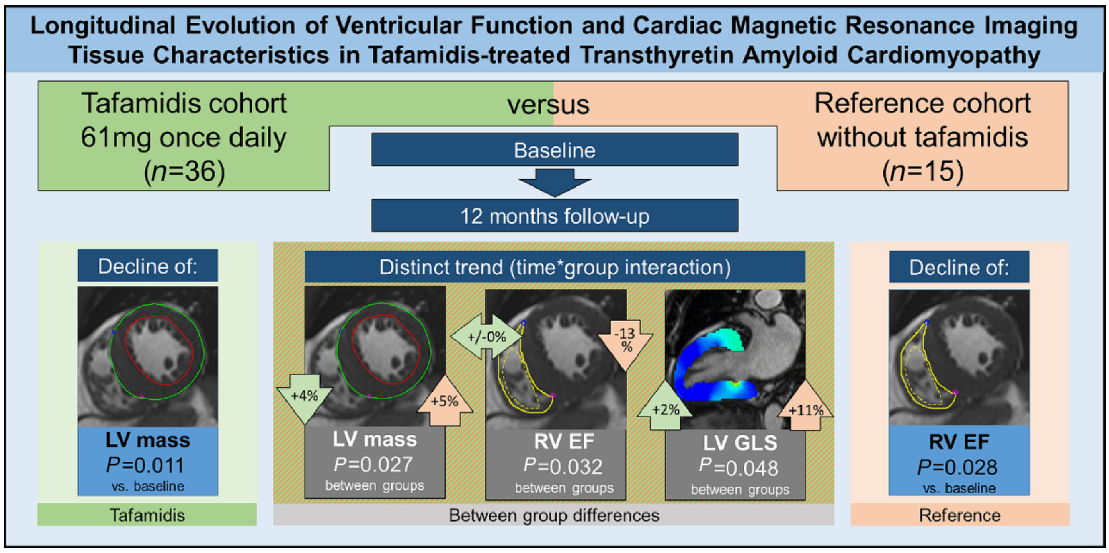


less of TTR-targeting therapy (*Table 2*). Yet, when comparing renal functional parameters over time, tafamidis was associated with a better preservation of kidney function (creatinine: *P* (time*group interaction) = 0.023), resulting from a numerically bigger rise in creatinine levels in the historical reference cohort (126.4 ± 38.1 to 158.9 ± 56.8 mmol/L; *P* = 0.096; GFR: 53.0 ± 19.6 to 45.6 ± 13.3 mL/min, *P* = 0.34), compared with tafamidis-treated patients (103.0 ± 30.9 to 108.8 ± 35.8; *P* = 0.11, GFR: 60.1 ± 21.9 to 60.2 ± 18.2 mL/min, *P* = 0.99), respectively.

Discussion

This prospective, observational cohort study used repeat CMR to evaluate the early effects of TTR-stabilization by tafamidis on CMR-measured cardiac structure and function. The patients included in the tafamidis and the untreated historic reference cohort exhibited similar signs of advanced ATTR-CM, such as increased LV mass and ECV at baseline, and cardiorenal biomarkers suggested similar ATTR-CM National Amyloidosis Centre (NAC) disease stages[17] at the time of baseline CMR. Left untreated, significant maladaptive

Figure 4 Structural and function changes with tafamidis therapy compared with untreated ATTR-CM. ATTR-CM, transthyretin amyloid cardiomyopathy; ECV, extracellular volume fraction; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle; SV, stroke volume.



cardiac remodelling was observed, as LV mass increased, and RV function significantly decreased between baseline and repeat CMR in the reference cohort. On the contrary, serial CMR showed that tafamidis was associated with a reduction in LV mass, preservation of RVEF and LVGLS, and prevention of significant worsening in global parameters of LV function at 12-month follow-up. Our results are in line with echocardiographic data from the randomized ATTR-ACT trial, which showed an attenuated decline in LV systolic and diastolic function with tafamidis therapy compared with placebo.[18]

LV mass was reduced significantly with tafamidis therapy over the 12-month study period. While a beneficial effect of tafamidis had previously been suggested based on longitudinal comparisons between treated and untreated patients, significant differences were mainly attributed to a significant increase in LV mass in untreated patients.[19,20] Whether the observed reduction of LV mass with tafamidis was a result of reduced amyloid fibril deposition and amyloid clearance or other mechanisms such as reverse remodelling is unclear and requires further study.

As suggested by the limited data available, tafamidis therapy did not lead to significant changes in ECV or non-contrast T1 mapping times between treatment initiation and 12-month follow-up.[19,20] As significant 15–20% reductions in ECV, a global marker of amyloid load associated with clinical outcomes,[21,22] have been described after 12 months with novel TTR-depleting antibodies[23] or to a lesser degree with the RNA interference therapeutic patisiran,[11] this repeat finding suggests that TTR-stabilization may be a less efficient therapeutic option when reversing maladaptive cardiac modelling is the desired target. Yet, as tafamidis, like patisiran, also ameliorates worsening of cardiorenal biomarkers and exercise capacity, TTR-stabilization may suffice to prevent significant clinical disease progression and adverse clinical outcomes in many ATTR-CM patients.

Due to the high cost of tafamidis, economic considerations play a major role in deciding whether to initiate and continue targeted therapy in ATTR-CM patients. Currently, initiation and discontinuation of TTR-stabilizing therapy solely relies on clinical parameters. Our current findings and the available data suggest that adverse cardiac remodelling with TTR-stabilization is significantly attenuated and may therefore occur at a rate too slow to uncover clinically meaningful differences with repeat CMR monitoring. However, the more rapid cardiac structural changes observed with anti-ATTR antibodies may provide a timely opportunity to evaluate the potential of CMR as a tool to monitor ATTR-CM disease progression and response to therapy.

Limitations

The following limitations need to be considered: The study was designed as an unblinded, non-randomized, prospective cohort study and performed at a single tertiary centre. Study data are thus subject to multiple biases (referral bias, selection bias, and survival bias) that cannot be controlled for. Sample size was low, and statistical power limited, making random errors and chance findings more likely. Adjustment for multiple testing was not performed. To select patients for the current study, we specified a time window for base-

line and follow-up CMRs and standardized follow-up accordingly. For the retrospective reference cohort, this was not feasible, and thus, there is a greater variation in CMR follow-up times making interpretation of changes over time between the tafamidis and the historical reference cohort more challenging and subject to bias. Four patients underwent CMR imaging on a 3.0 Tesla scanner, with 3 patients crossing over between 1.5 and 3.0 scanners between serial CMRs. Longitudinal comparison of T1 mapping times was therefore not feasible in these patients and instead ECV was used to monitor disease stability in these patients.

Conclusions

Compared with untreated patients with ATTR-CM, initiation of tafamidis therapy was associated with preservation of biventricular function and a reduction of LV mass, both indicative of delayed disease progression at 12 months. ECV and native T1 mapping did not change significantly over 12 months, irrespective of tafamidis treatment. Adequately powered long-term studies are required to identify optimal CMR markers to monitor treatment efficacy and to define the ideal timing for follow-up CMRs in ATTR-CM patients treated with tafamidis or other TTR-targeting therapies.

Conflict of interest

Dr. Dobner received a research grant for the Bern Amyloidosis Registry (B-CARE) (NCT04776824) on behalf of the institution (Inselspital Bern) from Pfizer. Dr. Bernhard reports a career development grant from the Swiss National Science Foundation. Y. Safarkhanlo received research funding from the Center for Artificial Intelligence in Medicine Research Project Fund University Bern, outside of the submitted work. Dr. Gräni received research funding from the GAMBIT foundation for the current study. Further Dr. Gräni received funding from the Swiss National Science Foundation, Innosuisse and from the Center for Artificial Intelligence in Medicine Research Project Fund University Bern, outside of the submitted work. All other authors report no conflicts.

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Conflict of Interest

The authors declare no conflict of interest.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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