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ORIGINAL PAPER

Effect of tafamidis on global longitudinal strain and myocardial work in transthyretin cardiac amyloidosis

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See the editorial comment for this article 'Tafamidis and its stabilizing effects on transthyretin tetramers, the heart and eventually, scientific evidence', by René Rettl and Diana Bonderman, https://doi.org/10.1093/ehjci/jeac077.

Aims In patients with transthyretin amyloid cardiomyopathy (ATTR-CM), the effect of tafamidis on myocardial function using serial speckle tracking echocardiography has not been reported. The purpose of this study was to describe the natural history of myocardial function in untreated ATTR-CM and determine the effect of tafamidis on myocardial functional parameters over 12 months of treatment.

Methods and results A total of 45 subjects with ATTR-CM were retrospectively studied: 23 treated with tafamidis and 22 untreated. Two-dimensional speckle tracking echocardiography was analysed at baseline and 1 year. Serial longitudinal, circumferential, and radial strain, twist, torsion, and myocardial work were measured. Over 1 year, absolute global longitudinal strain (GLS) deteriorated more in the untreated group by a median of 1.1% [inter-quartile range (IQR) 0.95] compared with 0.3% (IQR 1) in the tafamidis group ($P = 0.02$). Myocardial work index and efficiency also deteriorated to a greater degree: 142.5 mmHg% (IQR 197) and 4% (IQR 8), respectively, in the untreated group compared with 61.5 mmHg% (IQR 210) and 1% (IQR 7) in the tafamidis group ($P = 0.04$). There were no significant between group differences in left ventricular ejection fraction (LVEF), tissue Doppler velocities, circumferential or radial strain, LV twist or torsion at 1 year. The stabilization effect of tafamidis on myocardial function at 1 year did not differ according to baseline GLS, LVEF, or National Amyloidosis Centre disease stage.

Conclusions In ATTR-CM, tafamidis resulted in a lesser deterioration in GLS, myocardial work index, and efficiency over a 12-month period compared with a cohort not treated with tafamidis.

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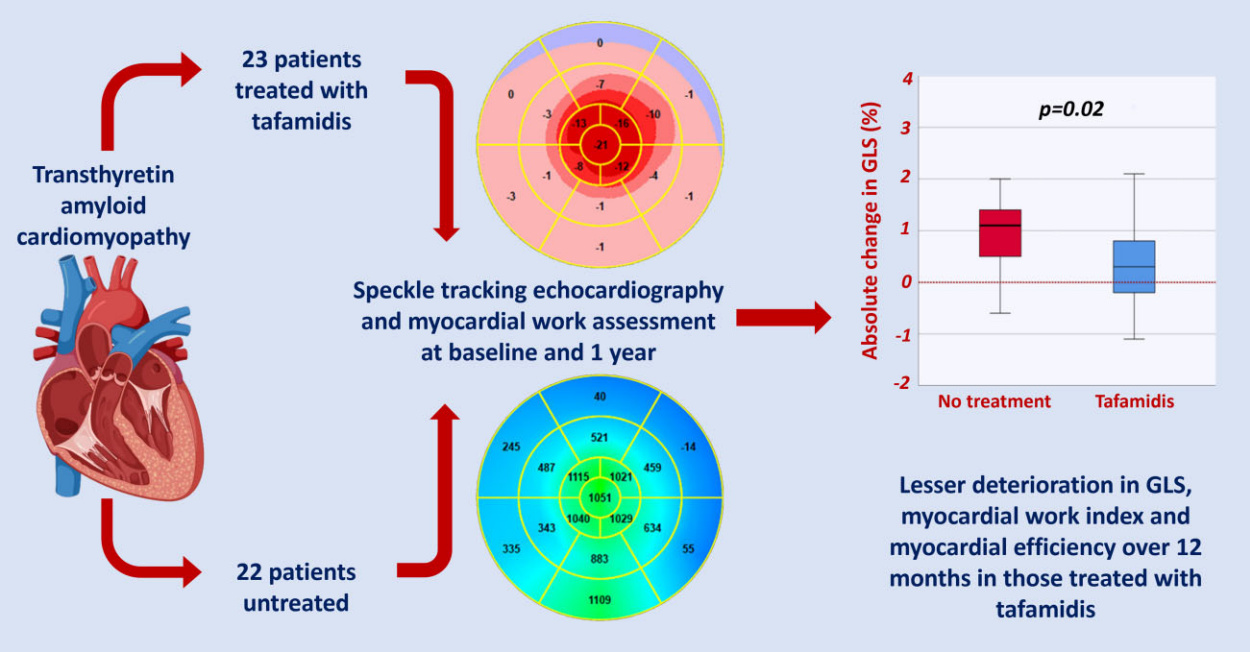
Graphical Abstract



Keywords transthyretin amyloidosis • tafamidis • strain echocardiography • myocardial work index

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is associated with a poor quality of life and high mortality at a median of 31–69 months from diagnosis depending on subtype.[1] Tafamidis is approved for both wild-type and hereditary ATTR-CM following a placebo-controlled, randomized control trial which demonstrated a reduction in all-cause mortality, lower rates of cardiovascular-related hospitalizations, functional decline, and improved quality of life in those treated with tafamidis.[2] To date, no echocardiographic markers of treatment response have been identified for treatment with tafamidis. Timely identification of treatment response is important to allow early detection of treatment non-responders who may warrant consideration for alternative, combination, or investigational therapies.

Speckle tracking echocardiography is commonly used for the diagnosis and longitudinal surveillance of ATTR-CM. Abnormalities in strain imaging, most commonly reported as global longitudinal strain (GLS), serve as an early disease marker and have been shown to be abnormal at an earlier disease stage than left ventricular ejection fraction (LVEF) which is often preserved until the late stages of the disease.[3]

Strain imaging relies on measurement of myocardial deformation by speckle tracking echocardiography, which allows angle-independent assessment of the complex architecture of the LV by examining longitudinal, circumferential, and radial mechanics. Although strain is more sensitive to subtle changes in myocardial function than LVEF and a sensitive tool for long-term surveillance across the cardiomyopathy spectrum,[4] it is influenced by loading conditions and heart rate. A validated method of non-invasive myocardial work assessment derived from the integration of speckle tracking echo and simultaneous blood pressure data overcomes the load dependency of strain by incorporating after-load.[5] This load-independent method holds promise as a more sensitive measure with improved accuracy in longitudinal surveillance of cardiac amyloidosis and sensitivity for detection of changes during treatment.

The natural history of serial changes in the combination of left ventricular (LV) longitudinal, circumferential, and radial strain, twist and non-invasively derived myocardial work in ATTR-CM not treated with amyloid-specific therapy have not been reported. We hypothesized that advanced echocardiography using speckle tracking and non-invasively derived myocardial work indices can be used to demonstrate the transthyretin stabilization effect of tafamidis.

In this study, we aimed to comprehensively demonstrate the natural history of changes in myocardial function by 2D speckle-tracking echocardiography over a 1-year period in untreated ATTR-CM compared with a similar cohort treated with tafamidis.

Methods

Study population

This study retrospectively evaluated subjects with transthyretin cardiac amyloidosis attending the Amyloidosis Program at the Brigham and Women's Hospital, Boston, MA between December 2009 and August 2021. A cohort of 272 consecutive patients was screened. Patients who

received tafamidis or no amyloid-specific therapy and had 2D transthoracic echocardiography performed at baseline and after 12 months were included ($n = 50$). In our centre, patients with ATTR-CM routinely have 2D echocardiography performed on an annual basis. Patients with greater than mild aortic stenosis at baseline or 1 year were not eligible for inclusion and those receiving an alternative ATTR-CM therapy including diflunisal, tauroursodeoxycholic acid (TUDCA), doxycycline, patisiran, inotersen, or participating in a clinical trial of a TTR stabilizer or silencer were excluded. Four patients were excluded due to non-diagnostic quality imaging and one patient was excluded due to new atrial fibrillation with rapid ventricular conduction at the time of follow-up echocardiogram. Forty-five patients were included in the final analysis (22 received no treatment and 23 received tafamidis).

The diagnosis of ATTR-CM was established based on the presence of heart failure symptoms in conjunction with a characteristic echocardiogram and/or cardiac MRI. Cardiac transthyretin deposition was confirmed by either (i) endomyocardial or extracardiac biopsy with typing of amyloid by immunohistochemistry or mass spectrometry or (ii) Perugini grade 2–3 myocardial uptake on PYP SPECT scintigraphy in the absence of a monoclonal gammopathy or elevated free light chains in serum and urine detected by immunofixation.[6] All patients underwent genotyping for a variant in the TTR gene.

Medical history, implantable cardiac device details, and biomarker data were ascertained from review of the electronic medical record and device interrogation records. Serum biomarker data was collected at baseline and at 1 year. All patients were classified by the National Amyloid Centre (NAC) staging system using estimated glomerular filtration rate (eGFR) and serum N-terminal pro-brain natriuretic protein (NTproBNP) levels at the time of baseline echocardiogram.[7]

The study was approved by the Mass General Brigham Institutional Review Board and conducted in accordance with institutional guidelines. The study complied with the Declaration of Helsinki Informed consent was not required. The data underlying this article will be shared on reasonable request to the corresponding author.

Estimation of myocardial function by echocardiography

Using a commercially available ultrasound system, 2D echocardiography with spectral and colour Doppler imaging and speckle tracking imaging was performed in all subjects according to standard American Society of Echocardiography recommendations.[8,9] Conventional analysis of the LV included measurements of wall thickness and cavity dimensions at end-diastole, LVEF, and diastolic function.

Deformation analysis of the left ventricle based on 2D speckle tracking imaging was performed off-line using automated function imaging by dedicated commercially available software as previously described (EchoPACS version 203, GE Vingmed Ultrasound AS, Horten, Norway).[4,10] Circumferential and radial strain were measured from short-axis views of the basal and apical LV.

LV twist was defined as the maximum difference between peak apical and basal rotation during the ejection phase of LV systole and expressed in degrees.[11] Torsion was defined as the base–apex gradient of rotation angle along the long axis of the LV, measured as twist/base–apex length measured at end-diastole from the four-chamber view and expressed in degrees/cm.[10,12]

For myocardial work assessment, brachial blood pressure readings were taken at the start of image acquisition. Incorporating this into strain analysis, the software calculated the following MW parameters: global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE) as previously described.[13]

Paired data was available for longitudinal strain calculation in all patients. Paired data for twist/torsion weas available for 71% (diagnostic quality apical images were absent in the remainder). For myocardial work analysis, blood pressure values were available for 71/90 echoes (79%). For 50 of these echoes, a blood pressure measurement was also recorded during same day clinical assessment and good correlation was found between BP readings at time of echo and clinic assessment (Supplementary data online, *Figure S1*). Therefore in the absence of a recorded BP at time of echo, a same day clinic visit BP was available for 14 further echoes and this was used for myocardial work assessment. In total, myocardial work was analysed in 93% (same day blood pressure measurement was absent in the remainder).

All analyses were performed by one experienced physician. To ensure reproducibility, GLS, and CS were remeasured in a random sample of 10 anonymized studies by a second experienced operator blinded to treatment and echo timing to determine inter-observer variability. Inter-observer intra-class correlation coefficient (ICC) was 0.98, 95% confidence interval (CI) 0.93–0.99 with a mean GLS difference of 0.12%, standard deviation (SD) 0.59 (Supplementary data online, *Table S1* and *Figure S2*). For CS, the ICC was 0.89, 95% CI 0.74–0.98 with a mean difference of 1.04%, SD 2.77 (Supplementary data online, *Table S1* and *Figure S3*).

Statistical analysis

Continuous variables are presented as mean and standard deviation or median and inter-quartile range as appropriate. Categorical variables are presented as frequencies and percentages. Normality was determined using the Shapiro–Wilk test. Continuous variables, including the magnitude of change in echocardiographic parameters between baseline and follow-up, were compared between the tafamidis and untreated groups using the unpaired Student's *t*-test, Mann–Whitney *U* test, or χ^2 test as appropriate. Bivariate correlation analysis was performed using Spearman's rho for non-normally distributed data. A sensitivity analysis was performed excluding patients who underwent cardiac device implantation between baseline and 1-year echocardiography to determine any bias that have been introduced by device implantation. Intra- and inter-observer ICCs were calculated with a two-way random model using an absolute agreement definition and Bland–Altman plots. All statistical tests were two-sided and a *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (version 27, IBM Corp., Armonk, NY, USA).

Results

Baseline clinical characteristics

Baseline demographic and clinical variables of the 22 untreated and 23 tafamidis-treated subjects are shown in *Table 1*. The majority of subjects in this study were older males with wild-type ATTR-CM. There were no significant differences in baseline clinical characteristics or biomarkers between the no tafamidis and tafamidis cohorts. Three patients (7%) had hereditary ATTR-CM, all due to the Val142Ile mutation (one in the untreated group and two in the tafamidis group).

In the tafamidis group, five patients were taking tafamidis for a median of 302 days [inter-quartile range (IQR) 392] prior to their baseline echo. The remainder of this group started treatment at a median of 7 days (IQR 46) after their baseline echo. All patients were treated with tafamidis meglumine 61 mg daily. No patients discontinued tafamidis treatment due to adverse effects and compliance was confirmed at ≥ 1 intervening visit between baseline and 1 year.

Table 1 Baseline clinical and biomarker characteristics

	No tafamidis ($n = 22$)	Tafamidis ($n = 23$)	*P*-value
Age at baseline echo (years)	78.24 (±6.67)	79.13 (±6.00)	0.64
Male	20 (91%)	23 (100%)	0.14
BSA (m^2)	1.93 (±0.20)	1.93 (±0.16)	0.85
Wild type ATTR	21 (95%)	21 (91%)	0.58
NAC Stage			
I	9 (41%)	8 (35%)	0.57
II	5 (23%)	6 (26%)	0.87
III	4 (18%)	7 (30%)	0.39
Systolic blood pressure	120 (29)	121 (24)	0.84
Diastolic blood pressure	70 (12)	68 (19)	0.64
Atrial fibrillation or flutter at baseline echocardiogram	9 (41%)	10 (43%)	0.56
Myocardial infarction	3 (14%)	4 (17%)	0.78
Cardiac device	6 (27%)	8 (35%)	0.32
Dual chamber pacemaker	1 (5%)	4 (17%)	0.17
CRT-P	2 (9%)	2 (9%)	0.96
ICD	1 (5%)	0	0.30
CRT-D	1 (5%)	1 (4%)	0.97
His bundle pacing	0	1 (4%)	0.32
NTproBNP (ng/L)	2807 (3599)	2607 (5331)	0.83
Creatinine (mg/dL)	1.33 (0.57)	1.32 (0.81)	0.40
BUN	29.25 (±15.18)	29.62 (±14.78)	0.94
eGFR (mL/min/1.37 m^2)	52.78 (31.76)	52.10 (37.18)	0.36
ACEi/ARB	6 (27%)	5 (22%)	0.54
Beta blocker	12 (55%)	9 (39%)	0.17
MRA	6 (27%)	6 (26%)	0.78

Values are frequency (percentage), median (inter-quartile range), or mean (± standard deviation).

Baseline echocardiographic characteristics

Baseline echocardiographic variables stratified by treatment groups are shown in *Table 2*. No patient in either group had greater than mild aortic stenosis or greater than moderate mitral regurgitation at baseline. The untreated cohort had a lower median right ventricular s' velocity compared with the tafamidis cohort but otherwise there were no significant differences between baseline echocardiographic measurements. There were no differences between global or regional longitudinal, circumferential, or radial strain.

Across both study groups, analysis of myocardial work by speckle tracking echocardiography incorporating brachial artery blood pressure reveals ATTR-CM is a condition with low baseline GWI (1002 mmHg%, SD 392.65, reference range 1896 ± 308), low global constructive work (1075 mmHg%, IQR 612, reference range 2232 ± 331), and low global work efficiency (88%, SD 4.6, reference range 94–97).[14]

During the 1-year period between serial echocardiograms, three patients had a cardiac device implanted (1 dual chamber pacemaker, 1 CRT-D, and 1 secondary prevention ICD). No patients had a myocardial infarction and none underwent cardiac surgery or percutaneous valve intervention between baseline and 1-year echo which may have impacted myocardial function and echocardiographic measurements.

Changes at 1 year

The mean time between baseline and follow-up echo was 380 days (±46) with no difference between the untreated and tafamidis groups ($P = 0.88$). There was no difference in the extent of change in LV wall thickness, cavity dimensions, LVEF, or tissue Doppler parameters at 1 year between either group (*Table 3*). No patient developed greater than mild aortic stenosis or greater than moderate mitral regurgitation over a 12-month period.

Absolute GLS deteriorated in the untreated group by an absolute mean of +1.1% (IQR 0.95) compared with +0.3% (IQR 1) in the tafamidis group ($P = 0.02$; *Figure 1*). Relatively, this represents a 9.41% (IQR 10.15) deterioration in the untreated group compared with 2.7% (IQR 11.56) in the treated group. When longitudinal strain was averaged by long-axis echocardiographic view, there was a greater deterioration in the 2 chamber values in the untreated group (+1.65% compared with +0.59%, $P = 0.02$). While there was a greater numerical deterioration in basal and apical radial strain, LV twist and torsion in the untreated cohort, these differences did not reach statistical significance.

There was no correlation between the LVEF or GLS at baseline and the magnitude of change in GLS over 1 year in either group (*Figure 2*). When stratified by NAC stage at baseline, there was no difference in the change in GLS at 1 year in either the untreated or tafamidis groups ($P = 0.80$ and 0.87, respectively).

Table 2 Baseline echocardiographic parameters stratified by treatment

	No tafamidis ($n = 22$)	Tafamidis ($n = 23$)	*P*-value
2D measurements			
LVEDD (mm)	41.5 (10.25)	42 (11)	0.74
LVESD (mm)	31 (9)	34 (11)	0.50
IVS (mm)	17 (4.75)	18 (6)	0.52
PW (mm)	17 (5.5)	16 (4)	0.60
LVEF (%)	48 (±12.6)	45.8 (±12.6)	0.57
Tissue Doppler measurements			
E velocity (m/s)	0.92 (0.36)	0.85 (0.36)	0.85
E' lateral (m/s)	0.06 (0.02)	0.05 (0.03)	0.79
E' septal (m/s)	0.04 (0.03)	0.04 (0.02)	0.69
Average *E*/*E*'	20.00 (6.49)	21.07 (18.61)	0.54
RV *S*' (m/s)	0.08 (0.03)	0.09 (0.06)	**0.005**
Speckle-tracking measurements			
GLS (%)	-9.9 (±2.86)	-11.13 (±3.63)	0.21
4-chamber LS (%)	-8.59 (3.59)	-11.93 (5.40)	0.23
3-chamber LS (%)	-9.99 (±3.39)	-11.2 (±3.88)	0.27
2-chamber LS (%)	-9.95 (5.13)	-10.02 (5.71)	0.47
Basal LV LS (%)	-3.72 (±3.22)	-4.36 (±3.24)	0.51
Mid LV LS (%)	-8.77 (±3.52)	-9.47 (±4.19)	0.55
Apical LV LS (%)	-14.32 (±3.21)	-15.86 (±5.33)	0.25
Basal CS (%)[a]	-6.2 (±3.31)	-7.87 (±2.76)	0.10
Apical CS (%)[b]	-11.35 (6.43)	-13.40 (5.70)	0.39
Basal RS (%)[a]	9.64 (±6.84)	12.06 (± 6.98)	0.29
Apical RS (%)[b]	20.12 (27.56)	24.53 (10.29)	0.60
Twist (°)[b]	9.11 (7.73)	10.57 (7.44)	0.57
Torsion (°/cm)[b]	1.08 (1.05)	1.16 (0.78)	0.76
Myocardial work measurements			
Myocardial work index (mmHg%)[c]	948.1 (±362.4)	1054.3 (±421.3)	0.38
Myocardial efficiency (%)[c]	88 (±4.39)	87.41 (±4.89)	0.73
Myocardial constructive work (mmHg%)[c]	1075 (556)	1136 (644)	0.35
Myocardial wasted work (mmHg%)[c]	78 (67)	94 (112)	0.47

Values are median (inter-quartile range) or mean (± standard deviation). *P*-values in bold indicate significant values.
[a]Data available for 38 patients (untreated 19, tafamidis 19).
[b]Data available for 35 patients (untreated 16, tafamidis 19).
[c]Data available for 43 patients (untreated 21, tafamidis: 22).

Baseline and 1-year indices of myocardial work were measured in 20 untreated and 22 tafamidis-treated patients. There was a lesser decline in myocardial work index over 1 year in the tafamidis cohort compared with those who were not treated with tafamidis (-61.50 mmHg% vs. -142.50 mmHg%; $P = 0.04$, *Figure 1*). The decline of myocardial efficiency was also less in the tafamidis group (-1% vs. -4%; $P = 0.04$). There was a greater increase in myocardial wasted work and greater decline in myocardial constructive work in the no tafamidis cohort but these differences did not reach statistical significance.

When change in LS was analysed by LV segment, a deterioration (less negative values) occurred at 1 year in 15/17 segments in the untreated group compared with 9/17 segments in the tafamidis group (*Figure 3*). A deterioration was seen in 15 vs. 11 segments in the untreated and tafamidis groups for myocardial work index and 14 vs. 5 segments for myocardial work efficiency, respectively.

The above analyses were repeated excluding the three patients who underwent device implantation between baseline and 1 year echo. There were no significant differences in findings compared with the original results.

Neurohormonal antagonist use, blood pressure, and the presence of an intra-ventricular conduction abnormality were analysed at baseline and 12 months (Supplementary data online, *Table S2*). There were no significant changes in angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, or mineralocorticoid receptor antagonist use over 12 months in either group. Blood pressure and the proportion of patients with right or left bundle branch

Table 3 Change in echocardiographic parameters between baseline and 1 year follow up stratified by treatment

	No tafamidis ($n = 22$)	Tafamidis ($n = 23$)	*P*-value
2D measurements			
LVEDD (mm)	-0.50 (6.30)	0 (4)	0.85
LVESD (mm)	1.5 (5.50)	0 (3)	0.08
IVS (mm)	0.23 (±2.88)	-0.68 (±4.86)	0.45
PW (mm)	1 (6)	1 (4)	0.49
LVEF (%)	-1 (9)	0 (6)	0.27
Tissue Doppler measurements			
E velocity (m/s)	0.02 (0.19)	0 (0.33)	0.63
Lateral e' (m/s)	-0.01 (0.02)	0 (0.01)	0.63
Septal e' (m/s)	0 (0.02)	0 (0.01)	0.26
Average *E*/e'	0.67 (8.62)	0 (5.95)	0.44
RV S' (m/s)	0 (±0.02)	0 (±0.03)	0.45
Speckle tracking measurements			
GLS (%)	1.1 (0.95)	0.30 (1)	**0.02**
4-chamber LS (%)	0.65 (1.02)	0.68 (2.57)	0.87
3-chamber LS (%)	0.87 (±1.98)	-0.17 (±1.79)	0.22
2-chamber LS (%)	1.65 (±1.44)	0.59 (±1.45)	**0.02**
Basal LS (%)	1.23 (±1.83)	0.06 (±2.41)	0.07
Mid LS (%)	1.33 (2.88)	0.50 (1.50)	0.11
Apical LS (%)	1.50 (±2.23)	0.92 (±2.19)	0.39
Basal CS (%)[a]	0.91 (±3.89)	0.53 (±3.24)	0.75
Apical CS (%)[b]	-1.20 (8.18)	-0.90 (9.95)	0.77
Basal RS (%)[a]	-2.11 (6.69)	-1.75 (8.20)	1.00
Apical RS (%)[b]	-4.51 (±15.37)	-1.05 (±16.78)	0.54
LV twist (°)[b]	-1.49 (±7.76)	1.6 (±7.96)	0.28
LV torsion (°/cm)[b]	-0.23 (±0.93)	0.19 (±0.80)	0.18
Myocardial work measurements			
Myocardial work index (mmHg%)[c]	-142.5 (197)	-61.5 (210)	**0.04**
Work efficiency (%)[c]	-4 (8)	-1 (7)	**0.04**
Myocardial wasted work (mmHg%)[c]	17.6 (±72.5)	9.8 (±79.4)	0.74
Myocardial constructive work (mmHg%)[c]	-141.6 (±177.9)	-31.8 (±207)	0.07

Values are median (inter-quartile range) or mean (± standard deviation). *P*-values in bold indicate significant values.
[a]Data available for 37 patients (untreated 19, tafamidis 18).
[b]Data available for 34 patients (untreated 16, tafamidis 18).
[c]Data available for 42 patients (untreated 20, tafamidis 22).

block were not significantly different at baseline or 12 months between the untreated and tafamidis groups.

Discussion

In this study, we comprehensively describe the natural history of serial changes in myocardial function and myocardial work index and efficiency over a 1-year period among a cohort of patients with ATTR-CM who did not receive amyloid-specific therapy. We also demonstrate the ability of both longitudinal strain and non-invasive myocardial work assessment to detect the clinical effect of tafamidis on myocardial function. Our study shows several novel findings: (i) in a cohort with ATTR-CM who did not receive amyloid-specific therapy, GLS, myocardial work index, and efficiency deteriorates over a 12 month period; (ii) tafamidis resulted in a lesser deterioration in GLS, myocardial work index, and efficiency over a 12-month period compared with an untreated cohort; and (iii) the stabilization effect of tafamidis does not differ according to baseline GLS, LVEF, or NAC disease stage.

To the best of our knowledge, the natural history of serial changes in myocardial function on comprehensive echocardiography including strain and myocardial work in an untreated cohort with ATTR-CM has not previously been reported. We have demonstrated that, in these patients, GLS is reproducible and in absolute terms, deteriorates by a median of 1.1% over a 1-year period while myocardial work index and efficiency decreases by 142.5 mmHg% and 4%, respectively, over the same time period. No significant change was detected in radial or circumferential strain, LV twist, or torsion in this untreated cohort. These data highlight the potential utility of GLS and

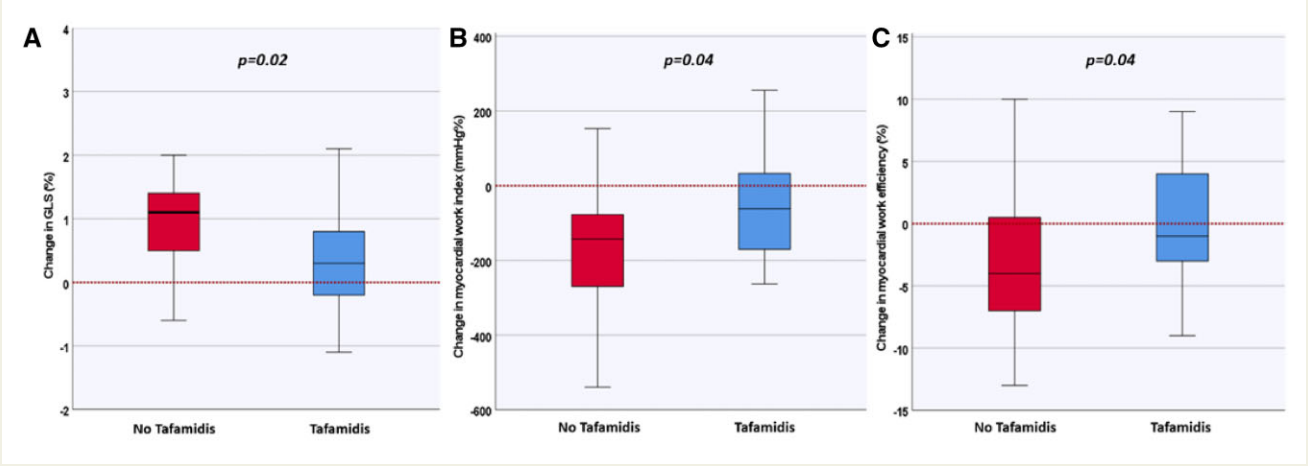


Figure 1 Boxplots showing change in (*A*) GLS at 1 year, (*B*) global myocardial work index at 1 year, and (*C*) myocardial work efficiency at 1 year stratified by treatment.

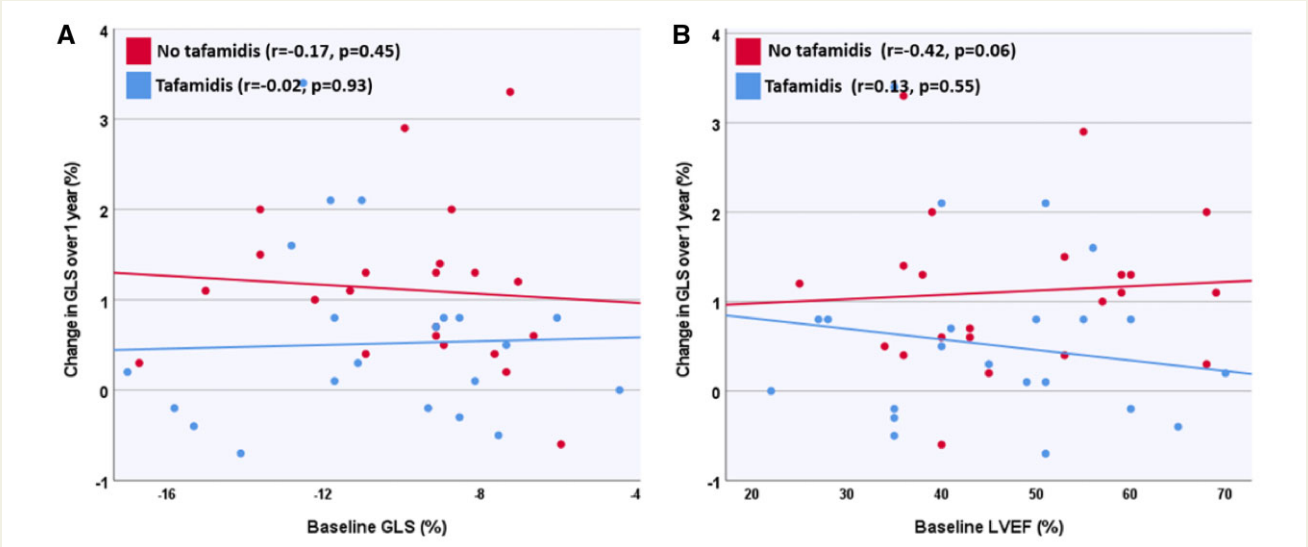


Figure 2 Scatter plots showing correlation of change in GLS at 1 year stratified by treatment group and (*A*) baseline GLS; (*B*) baseline LVEF.

myocardial work assessment in longitudinal surveillance of myocardial function in ATTR-CM.

Echo, clinical, and biomarker indicators of treatment response have been established in light chain amyloidosis.[15] However, the use of similar markers in the treatment of ATTR-CM has been more limited, in particular in relation to tafamidis. The utility of NTproBNP as a measure of disease progression has been shown in the placebo arm of the ATTR-ACT trial.[2] However, its use is limited by biological variability, renal dysfunction, volume status, and the presence of atrial fibrillation.[16] Demonstration of stabilization of serum prealbumin (TTR) levels has been reported as a potential marker of treatment response to tafamidis, but this represents an indirect biochemical stabilizing effect of tafamidis on transthyretin, and does not address the effect on the heart.[17] A phase 2, open-label study showed that treatment with tafamidis 20 mg daily in ATTR-CM was effective in achieving TTR stability as early as 6 weeks.[18] In that study, LV strain was not analysed but there were no significant changes in echocardiographic measures of wall thickness, LVEF, and tissue Doppler diastolic assessment between baseline and after 12 months of treatment, in keeping with our findings. TTR or pre-albumin is also a negative acute phase reactant and marker of protein nutrition, which is often disordered in heart failure-related cachexia and therefore may limit its specificity for monitoring treatment response in ATTR-CM if used in isolation.[19] Notably, none of the biomarkers provide specific information about changes in cardiac structural or functional phenotype after tafamidis therapy.

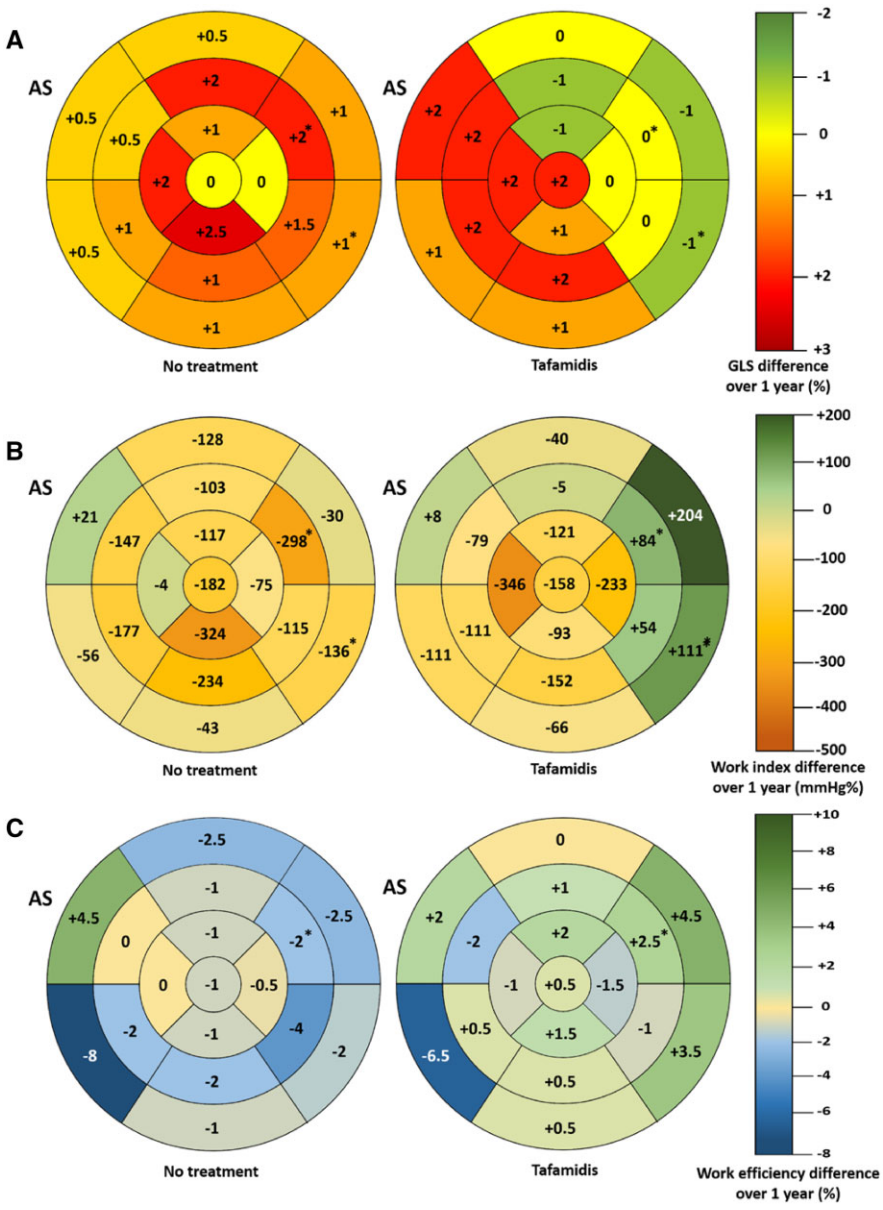


Figure 3 Seventeen segment LV bullseye plots showing segmental (*A*) change in peak systolic longitudinal strain, (*B*) change in myocardial work index, and (*C*) myocardial work efficiency over 1 year stratified by treatment. Negative GLS and positive work index and efficiency differences (green) indicate improvement in parameter. *$P < 0.05$.

Serial cardiac magnetic resonance imaging-derived extracellular volume (ECV) estimation has been shown to decrease by a mean of 6.2% in 6/16 patients during treatment of hereditary ATTR-CM with a combination of the RNA interfering therapeutic patisiran and the TTR stabilizer diflunisal, suggesting regression of amyloid deposition and that ECV may track response to treatment.[20] However, ECV may track the structural changes in ATTR-CM in comparison with GLS and MW which are functional measures. Limited access to MRI and the high implantable cardiac device rate in this population (31% in our study) may limit wider adoption of ECV for the purpose of treatment surveillance.

Data on serial strain assessment in the monitoring of ATTR-CM disease progression are limited. Serial GLS measurements were reported in the ATTR-ACT trial, however, these were not standardized by vendor or centrally analysed. They showed a greater deterioration in mean GLS from baseline to 30 months of 1.46% [standard error (SE) 0.28] in the pooled tafamidis cohort compared with 2.16% (SE 0.33) in the placebo arm.[2] The deterioration seen in the placebo arm is in line with our findings,; however, it is not possible to extrapolate the findings in the treatment arm due to the pooled nature of the treatment arm. Our GLS findings are similar to those previously reported in a substudy of the APOLLO randomized control trial

examining the effect of patisiran on cardiac parameters in hereditary ATTR-CM, which found a deterioration in absolute GLS of 1.46% in the placebo group compared with 0.08% in the treatment group at 18 months ($P = 0.015$).[21] Treatment with the TTR stabilizer diflunisal over 1 year in a cohort of wild-type ATTR-CM also resulted in a change of GLS of +0.1% compared with +1.2% in an untreated cohort ($P = 0.03$).[22]

A novel aspect to our work is the use of non-invasively estimated myocardial work in ATTR-CM. Assessment of myocardial work can overcome the after-load-dependent limitation of GLS by integrating LV after-load into longitudinal strain analysis.[13] This may allow for greater standardization of serial echocardiographic measurements. MW assessment in heart failure with preserved ejection fraction, in particular reduced myocardial efficiency, is closely associated with reduced exercise capacity, blunted LV contractile response to exercise, and greater pulmonary congestion[23] and has been shown to indicate worse prognosis in STEMI patients.[24] In ATTR-CM, LV myocardial work index, and apical–basal segmental work ratio have been shown to be significant predictors of all-cause mortality compared with GLS or LS apex-base ratio.[25] The potential utility of serial MW assessment has not previously been demonstrated in untreated ATTR-CM or during tafamidis treatment. Our data showed that myocardial work index and efficiency both declined at a slower rate over 1 year with tafamidis treatment despite no change in LVEF, providing incremental insights into myocardial mechanics as well as an easily obtained marker of response to TTR stabilizer therapy (*Figure 4*).

We have shown that tafamidis treatment over a 1-year period significantly slows the rate of deterioration in GLS and myocardial work indices when compared with a well-matched untreated cohort, suggesting that these reproducible parameters may be used to indicate TTR stabilization and a favourable response to treatment at 1 year. This stabilization effect was similar across the spectrum of baseline GLS, LVEF, and disease stage as measured by the prognostically important NAC staging system. Our study was not designed to determine whether the stabilization effect of tafamidis may be evident on echocardiography earlier than 1 year. Similar to unanswered questions surrounding stabilization of serum TTR levels, it is not known if the stabilization effect persists and is linear beyond 12 months and how these findings correlate with clinical outcomes. Extrapolating from the ATTR-ACT and APOLLO trial findings, an absolute GLS change of ≥+1% over 6–12 months has previously been proposed as a marker of disease progression in ATTR-CM.[16] However, both inter-observer and inter-vendor variability as well as variance in cardiac rhythm, image acquisition, and quality can impact serial strain measurement. Currently, there are insufficient data relating to clinical outcomes to determine the magnitude of change in GLS which is clinically significant on an individual patient basis, as opposed to a group response.

Accepting the relatively small cohort, an interesting finding from this study is that the magnitude of change in GLS over 1 year in those treated with tafamidis did not correlate with baseline GLS or LVEF. This suggests a treatment effect may exist even in more advanced ATTR-CM as defined by echocardiography.

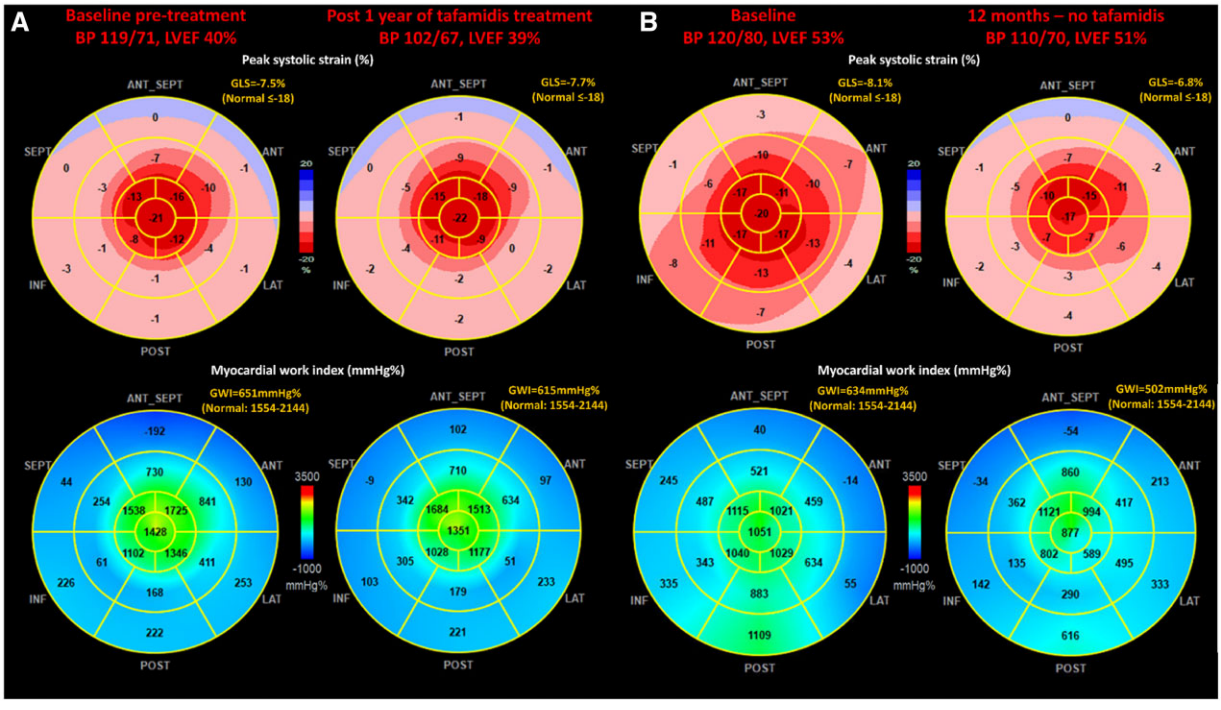


Figure 4 Comparison of change in longitudinal strain and myocardial work index over 1 year. Polar plots of global longitudinal strain and myocardial work index values at baseline (left) and at 1 year (right) in (*A*) a 71 year old male with wild type ATTR-CM treated with tafamidis and (*B*) a 75 year old male with wild-type ATTR-CM not treated with tafamidis. While baseline and 1 year LVEF are similar in both patients, there is less deterioration in strain echo parameters in the patient treated with tafamidis. Normal values from Manganaro *et al.*[14]

Limitations

Our study has a number of limitations. The overall cohort size is relatively small which may have limited statistical power to detect a greater difference in regional and per segment echo parameters and increases the probability of a Type II error. However, the greater deterioration in strain and myocardial work parameters is consistent with the clinical effects of tafamidis and with limited data previously described with strain imaging. A larger treatment cohort and longer analysis period were not possible as tafamidis was approved in May 2019 and the onset of the COVID-19 global pandemic adversely affected our annual surveillance protocol. Although the study sample was retrospectively assessed, we do not believe that this would have produced any selection bias, as all patients who had appropriately timed pairs of echocardiograms were enrolled, and (unlike diflunisal) there are no contraindications to tafamidis use such as heart failure that would result in a less sick population being studied in the treated group. Serial LV twist could only be calculated in 76% due to an absent, off-axis, or poor quality apical short-axis view which may have limited the ability to detect a significant difference between groups.

The proportion of female patients and those with hereditary ATTR-CM was small and therefore the study findings may not be generalizable to these patient groups. As the tafamidis group was treated with tafamidis meglumine 61 mg daily, these results should not be extrapolated to patients treated with alternative non-bioequivalent dosing. Serial strain analysis was performed in a standardized fashion using a single vendor software to remove the potential for inter-vendor variability (EchoPACS version 203, GE Vingmed Ultrasound AS, Horten, Norway). Although the method and software we used have been shown good agreement with other vendors for GLS assessment, our results may not apply when serial measurements are performed on platforms and software by difference vendors.[26] The reproducibility of circumferential strain was limited due to the frequent off-axis nature and endocardial dropout on apical short axis images and variation in apical slice location. However, this reinforces the use of longitudinal strain as a more reproducible serial measurement.

Conclusions

In conclusion, we report that treatment with tafamidis in ATTR-CM lessens deterioration of cardiac function measured by GLS and non-invasively measured myocardial work index and efficiency over 1 year when compared with an untreated cohort. This effect was independent of baseline LVEF, GLS, or NAC disease stage. These early findings provide evidence for the utility of comprehensive serial speckle tracking echocardiography and myocardial work indices to demonstrate a response to treatment and supports incorporation of these measures in future studies of treatment surveillance in ATTR-CM.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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