Real-World Diagnostic and Therapeutic Insights in Transthyretin Cardiac Amyloidosis: Experience from the Black Sea Region of Türkiye

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Transthyretin cardiac amyloidosis (ATTR-CM) is an increasingly recognized cause of heart failure with preserved ejection fraction (HFpEF) in older adults.[1,2] However, real-world data from middle-income countries remain limited.[3] In Türkiye, diagnostic pathways generally follow international guideline recommendations, but access to disease-modifying therapies is strongly influenced by national reimbursement rules, which require specific biomarker thresholds and defined disease stages.[4] Tafamidis, the first approved transthyretin stabilizer, has demonstrated benefit in clinical trials,[5] yet its real-world use and impact under these constraints have not been fully described. In this letter, we report the diagnostic characteristics and twelve-month clinical outcomes of patients with ATTR-CM in the Black Sea region of Türkiye, comparing those treated with tafamidis with untreated patients in routine clinical practice.

We prospectively followed 120 consecutive adults with ATTR-CM diagnosed and managed at two tertiary centers in the Black Sea region between 2023 and 2025. Diagnosis was based on a guideline-aligned non-invasive algorithm, which included echocardiography with strain analysis, serum and urine immunofixation with free light chain assays to exclude light chain amyloidosis, and technetium-labeled bone scintigraphy. Genetic testing was performed to distinguish wild-type from hereditary transthyretin disease.[6] All patients were discussed in a multidisciplinary team. Tafamidis eligibility and reimbursement followed national Social Security Institution criteria for ATTR-CM, which require patients to have NT-proBNP levels > 600 pg/mL, New York Heart Association functional class I–III with a six-minute walk distance > 100 m, left ventricular wall thickness ≥ 12 mm, no prior heart or liver transplantation, preserved renal function (estimated glomerular filtration rate ≥ 30 mL/min/1.73 m²), and a modified body mass index (BMI) (BMI × serum albumin) > 600.

Among the cohort, 57 patients received tafamidis, while 63 remained untreated despite confirmed ATTR-CM diagnosis. Baseline clinical characteristics were largely comparable between the two groups, including age, sex distribution, functional status, comorbidities, and echocardiographic findings, although untreated patients tended to have higher natriuretic peptide concentrations (Table 1). Several diagnostic "red flag" features were frequently observed, such as atypical HFpEF presentations, discordance between electrocardiographic voltage and left ventricular wall thickness, and intolerance to commonly used rate-limiting agents. A geographical pattern was also evident: patients residing farther from tertiary centers generally experienced longer delays in diagnosis, highlighting the impact of regional accessibility on timely disease recognition.

The primary outcome was the composite of cardiovascular death or heart failure hospitalization over twelve months. Tafamidis use was associated with a lower risk of this composite endpoint compared with no tafamidis (log-rank $p = 0.021$; hazard ratio, 0.66; 95% confidence interval: 0.46–0.95), as illustrated in the Kaplan–Meier curve in Figure 1. Secondary outcomes, including heart failure hospitalization and intensification of outpatient diuretic therapy, also favored the tafamidis group. These associations remained consistent in prespecified adjusted analyses using inverse probability of treatment weighting and in sensitivity analyses that accounted for competing risks and restricted mean survival time at twelve months. Over 12 months of follow-up, the composite endpoint occurred in 28.6% of untreated patients and 14.0% of those receiving tafamidis, corresponding to an absolute risk reduction of 14.5% and a number needed to treat of 7 to prevent one additional composite event.

These findings align with emerging international real-world data from European, Japanese, and Hellenic cohorts, which consistently demonstrate that tafamidis treatment is associated with fewer clinical events and more stable functional status in patients with ATTR-CM.[7-10] At the same time, our results highlight several context-specific challenges in Türkiye. First, the positive correlation between distance to the hospital and time to diagnosis suggests that patients in rural areas reach specialist care later, despite presenting with characteristic

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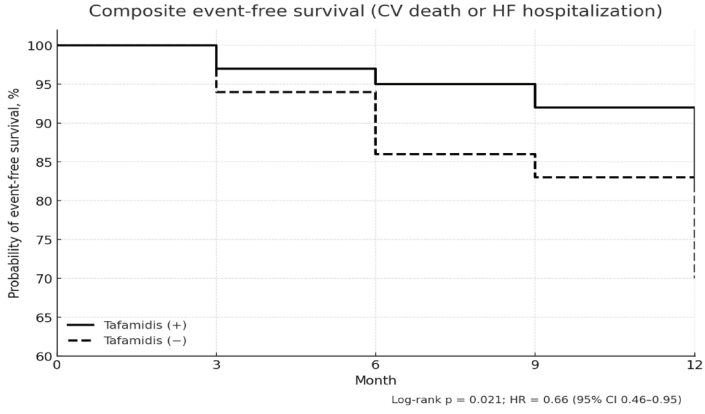
TABLE 1. Baseline Clinical and Echocardiographic Characteristics of Patients with ATTR-CM.

Parameters	All patients (n = 120)	Tafamidis (-) (n = 63)	Tafamidis (+) (n = 57)	*p* value
Age, years	77.1 ± 7.7	78.7 ± 7.5	76.8 ± 8.1	0.051
Gender; male, n (%)	77 (65)	40 (63)	37 (64)	0.614
Residence: urban, n (%)	85 (70)	46 (73)	39 (69)	0.208
HFpEF, n (%)	99 (83)	51 (81)	48 (85)	0.201
wt-ATTR, n (%)	114 (95)	59 (94)	55 (96)	0.472
hATTR, n (%)	6 (5)	2 (3)	4 (7)	0.067
Body mass index, kg/m^2	26.1 (24.8–28.1)	25.9 (24.1–29.3)	26.2 (23.8–28.1)	0.318
NYHA class, n (%)				
I-II	89 (74)	46 (73)	43 (75)	0.336
III	29 (24)	15 (24)	14 (25)	0.659
IV	2 (1)	2 (3)	0	0.101
Six-Minute Walk test, mt	189 (149-221)	192 (152-252)	187 (137-231)	0.061
Ischemic heart disease, n (%)	31 (26)	17(27)	14 (25)	0.517
Hypertension, n (%)	75 (62)	40 (64)	35 (61)	0.258
Diabetes mellitus, n (%)	19 (16)	10 (16)	9 (15)	0.604
Hyperlipidemia, n (%)	33 (28)	16 (25)	17 (30)	0.172
Stroke, n (%)	35 (29)	20 (31)	15 (26)	0.084
Malignancy, n (%)	5 (4)	3 (4)	2 (3)	0.378
Carpal tunnel syndrome, n (%)	42 (35)	20 (31)	22 (38)	0.103
Lumbar canal stenosis, n (%)	9 (7)	5 (8)	4 (7)	0.303
Peripheral neuropathy, n (%)	10 (8)	5(8)	5 (9)	0.541
Rhythm, n (%)				
Sinus rhythm	42 (35)	24 (38)	18 (32)	0.083
Atrial fibrillation	72 (60)	39 (62)	33 (57)	0.152
Pacemaker	13 (11)	8 (12)	5 (9)	0.138
QRS duration, ms	130 ± 12	132 ± 17	128 ± 16	0.205
Laboratory parameters				
Hemoglobin, gr/dL	13.3 (12.5–14.3)	13.1 (11.9–14.2)	13.2 (12.1–14.4)	0.092
NT-pro-BNP, pg/mL	3502 (1194–4891)	3854 (3059–5003)	3280 (1202–4483)	0.003
High-sensitivity troponin T, ng/L	59 (31–79)	61 (45–108)	58 (40–77)	0.059
eGFR, mL/min/1.73 m^2	46 (33–57)	43 (31–52)	47 (36–55)	0.061
Serum albumin	3.83 ± 0.61	3.95 ± 0.46	3.74 ± 0.61	0.059
Echocardiography				
LV end-diastolic diameter, mm	45 (39–51)	46 (41–53)	43 (39–48)	0.528
Interventricular septum thickness, mm	15 (13–18)	16 (14–20)	15(14–19)	0.269
Ejection fraction, %	50 (44–57)	50 (41–58)	51 (45–57)	0.674
Absolute global longitudinal strain (%)	11.6 (9.0–14.0)	10.9 (7.6–11.7)	11.9 (9.4–14.4)	0.107
Pulmonary artery pressure, mm/hg	31 (22–36)	33 (26–39)	30 (21–35)	0.058
Aortic stenosis	16 (13)	9 (14)	7 (12)	0.136

TABLE 1. Continued.

Parameters	All patients (n = 120)	Tafamidis (-) (n = 63)	Tafamidis (+) (n = 57)	*p* value
Medication, n (%)				
RAAS blockers	41 (34)	20 (32)	21 (36)	0.162
Beta-blocker	18 (15)	9 (14)	9 (16)	0.783
Calcium channel blocker	39 (33)	21 (34)	18 (31)	0.479
Diuretics	110 (91)	58 (92)	52 (91)	0.375
SGLT-2 inhibitors	88 (73)	47 (74)	41 (72)	0.571
Antiplatelet	39 (32)	20 (32)	19 (33)	0.394
Oral anticoagulant	84 (70)	44 (69)	40 (70)	0.475
Indicators of clinical worsening during follow-up				
Inability to continue tafamidis therapy, n (%)	20 (17)	14 (22)	6 (10)	0.003
Hospitalization for cardiovascular causes, n (%)	9 (7)	6 (9)	3 (5)	0.025
All-cause mortality, n (%)	19 (16)	14 (22)	5 (8)	0.001
Composite endpoint (CV death or HF hospitalization), n (%)	19 (16)	13 (20)	6 (9)	0.030
Clinical outcomes during 12-month follow-up				
Inability to continue tafamidis therapy, n (%)	5 (4)	-	5 (9)	NA
Hospitalization for cardiovascular causes, n (%)	13 (11)	9 (14)	4 (7)	0.003
All-cause mortality, n (%)	15 (13)	10 (16)	5 (9)	0.005
Composite endpoint (CV death or HF hospitalization), n (%)	26 (22)	18 (28)	8 (14)	0.001

Data are presented as mean ± standard deviation (SD), median with interquartile range (IQR), or number (percentage), as appropriate. Comparisons between groups were performed using the χ^2 test. The composite endpoint includes cardiovascular death or hospitalization for heart failure. ATTR-CM, transthyretin cardiac amyloidosis; hATTR, hereditary ATTR; wt-ATTR, wild-type ATTR; HFpEF, heart failure with preserved ejection fraction; eGFR, estimated glomerular filtration rate; NA, not applicable; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; RAAS, renin–angiotensin–aldosterone system; LV, left ventricle; CV, cardiovascular death.



Months					
Numbers at risk	0	3	6	9	12
Tafamidis (+)	57	54	52	51	50
Tafamidis (−)	63	59	56	53	48

FIG. 1. Kaplan–Meier curves for composite event-free survival (cardiovascular death or heart failure hospitalization) in patients with and without tafamidis.

CV, cardiovascular death; HF, heart failure; HR, hazard ratio; CI, confidance interval.

diagnostic red flags.[4,11,12] Second, a substantial proportion of patients who fulfilled diagnostic criteria could not initiate tafamidis because they did not meet strict reimbursement thresholds based on natriuretic peptide levels and disease stage, or because they had advanced heart failure, active malignancy, or preferred not to start long-term therapy.[13] Taken together, these observations indicate that both system-level and patient-level factors may restrict timely initiation of disease-modifying treatment, even when clinical suspicion and diagnostic pathways are appropriately established.

This letter has several limitations. The findings are based on two tertiary centers in a single region, with a modest sample size and a twelve-month follow-up. Treatment allocation was non-randomized and partly influenced by reimbursement criteria; thus, residual confounding may persist. Therefore, the observed associations should not be interpreted as evidence of causal benefit.

Nonetheless, this regional experience provides a concise snapshot of how ATTR-CM is diagnosed and managed in routine practice in Türkiye. Tafamidis treatment was associated with fewer early composite clinical events over twelve months in patients who could initiate therapy, whereas many others were denied access due to strict biomarker thresholds or late presentation. These findings underscore a nationwide need to reduce diagnostic delays, expand access to non-invasive diagnostic tools, and revise reimbursement criteria to align treatment availability with guideline-based recommendations. Simultaneously, ongoing clinician education and structured collaboration between tertiary centers and peripheral hospitals will be crucial to ensure that advances in amyloidosis care translate into equitable outcomes across the country.

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