

# Treatment With Tafamidis Slows Disease Progression in Early-Stage Transthyretin Cardiomyopathy

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## ABSTRACT

**BACKGROUND:** Transthyretin cardiomyopathy (TTR-CM) is a progressive, fatal disease caused by the accumulation of misfolded transthyretin (TTR) amyloid fibrils in the heart. Tafamidis is a kinetic stabilizer of TTR that inhibits misfolding and amyloid formation.

**METHODS:** In this post hoc analysis, data from an observational study (Transthyretin Amyloidosis Cardiac Study;  $n=29$ ) were compared with an open-label study of tafamidis in patients with TTR-CM (Fx1B-201;  $n=35$ ). To ensure comparable baseline disease severity, patients with New York Heart Association (NYHA) functional classification  $\geq$ III were excluded in this time-to-mortality analysis.

**RESULTS:** Patients with either wild-type or Val122Ile genotypes treated with tafamidis have a significantly longer time to death compared with untreated patients ( $P=.0004$ ). Similar results were obtained when limiting the analysis to wild-type patients only, without restricting NYHA functional classification ( $P=.0262$ ).

**CONCLUSIONS:** These results support earlier conclusions suggesting that tafamidis slows disease progression compared with no treatment outside of standard of care and warrant further investigation.

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**KEYWORDS:** Transthyretin, cardiac amyloidosis, heart failure, tafamidis

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## Introduction

Transthyretin cardiomyopathy (TTR-CM) is a rare, underdiagnosed condition that leads to progressive heart failure.<sup>1</sup> TTR-CM, a type of cardiac amyloidosis, is caused by destabilization of TTR, a homotetrameric transport protein. Impairment of myocardial function occurs when the unstable tetramers dissociate, resulting in misfolded proteins that aggregate into amyloid fibrils and deposit in the heart, which over time can lead to dysrhythmias and heart failure.<sup>1</sup>

Diagnosis of TTR-CM is often late in the course of the disease, and patients have a prognosis of 3- to 5-year survival from diagnosis.<sup>2,3</sup> TTR-CM can either be inherited or occur spontaneously; more than 90% of the patients have spontaneous or wild-type TTR-CM, which is not inherited and usually affects men older than 60 years of age.<sup>4</sup> The inherited form of TTR-CM usually occurs in people in their 50s and 60s.<sup>1</sup> There are more than 100 identified TTR gene variants.<sup>5</sup> The most common variant in the United States, substitution of isoleucine for valine at position 122 (Val122Ile), is present in 3% to 4% of African Americans or people of African descent.<sup>1,6–8</sup>

Traditional therapies for heart failure, such as diuretics, provide symptomatic treatment but do not address the underlying disease, and in heart failure patients with TTR cardiac amyloidosis, certain calcium-channel blockers are contraindicated.<sup>1,9</sup> Tafamidis is a novel, selective stabilizer of TTR that inhibits the misfolding of unstable TTR and subsequent amyloid

formation.<sup>10</sup> An open-label study of tafamidis in patients with TTR-CM found that tafamidis effectively stabilized TTR and was well tolerated.<sup>11</sup>

Preliminary data on survival in patients diagnosed with TTR-CM showed that treatment with tafamidis significantly increased survival time.<sup>12</sup> Survival in patients with wild-type or Val122Ile who were either untreated or treated with 20 mg tafamidis daily was evaluated in a post hoc analysis by comparing data from the Transthyretin Amyloidosis Cardiac Study (TRACS), a natural history study, with data from an open-label trial of tafamidis (Fx1B-201).<sup>12</sup> This analysis showed that fewer patients treated with tafamidis died or had cardiovascular-related hospitalizations. One limitation was that at baseline, these patient populations had differing disease severity.<sup>12</sup> Approximately 24% of the patients in TRACS had New York Heart Association (NYHA) functional classification of  $\geq$ III, whereas only 5.7% of the Fx1B-201 patients had the same classification. The current analysis aims to compare patient populations with similar disease severity to understand the effect of tafamidis treatment on survival at an earlier disease stage (NYHA functional classification I/II).

## Methods

This post hoc analysis compared data from 2 separate studies in patients with TTR-CM. Details of these studies have been published and are summarized here.<sup>2,11</sup>



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**Table 1.** Demographic and baseline characteristics.

	TRACS (N=29)		FX1B-201 (N=35)	
	Wild-type (n=18)	Val122Ile (n=11)	Wild-type (n=31)	Val122Ile (n=4)
Age, years	75.5 (5.6)	71.1 (5.0)	76.9 (4.6)	72.8 (3.4)
Sex, % male	100.0	81.8	93.5	75.0
Race, % African American	0.0	100.0	0.0	75.0
NYHA functional classification $\geq$ III, n (%)	4 (22.2)	3 (27.3)	1 (3.2)	1 (25.0)
Duration of TTR-CM-related symptoms, months	35.4 (33.6)	21.6 (17.8)	94.8 (97.5)	74.5 (34.2)
Age at TTR-CM symptom onset, years	72.7 (5.4)	69.5 (5.6)	73.6 (5.3)	69.3 (2.5)
Age at TTR-CM diagnosis, years	74.8 (5.7)	70.3 (5.6)	75.0 (4.9)	71.5 (3.1)
NT-pro-BNP, pg/mL	4524 (2958) n=11	4762 (4117) n=10	4910 (4465)	5318 (343) n=2
Left ventricular posterior wall thickness, mm	19.3 (3.3)	18.0 (2.6)	20.3 (3.5) n=30	19.5 (3.1)
Left ventricular ejection fraction, %	59.0 (11.5)	50.4 (12.3)	47.8 (13.9) n=30	39.0 (15.0)

Abbreviations: NT-pro-BNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; TRACS, Transthyretin Amyloidosis Cardiac Study; TTR-CM, transthyretin cardiomyopathy; Val122Ile, valine to isoleucine substitution at position 122.

All values are shown as mean (SD) unless otherwise noted. Sample sizes are provided where patient data are missing.

Transthyretin Amyloidosis Cardiac Study is a prospective, longitudinal, natural history study to assess the morbidity and mortality of TTR-CM.<sup>2</sup> Patients with wild-type (n=18) or Val122Ile (n=11) TTR-CM were included and were followed for 2 years. The study provided baseline data on a variety of cardiac functions in this patient population and also reported changes in these functions over time. Survival was measured from the date of diagnosis. These patients were not treated outside of standard of care and served as a control group for the current analysis.

A phase II, multicenter, open-label, single-treatment study (Fx1B-201; ClinicalTrials.gov: NCT00694161) assessed the effects of tafamidis on TTR stabilization, its safety and tolerability, and effects on clinical outcomes in patients with wild-type (n=31) or Val122Ile (n=4) TTR-CM.<sup>11</sup> Patients in this trial were treated with once daily 20mg tafamidis for 12 months. Survival in this study was measured from the date of diagnosis. These patients served as the treatment group for the current analysis.

In the current analysis, survival of patients from the TRACS study was compared with that of patients in the Fx1B-201 study and was restricted to include only NYHA classification I/II patients to provide a more comparable cohort of patients across the 2 studies. In a separate survival analysis, only patients with wild-type TTR (removing variant Val122Ile but without any restriction on NYHA functional classification due to sample size limitations) were included. Time-to-mortality analysis was conducted to provide Kaplan–Meier estimates of survival from time of diagnosis. The study with tafamidis also assessed safety of the treatment.

## Results

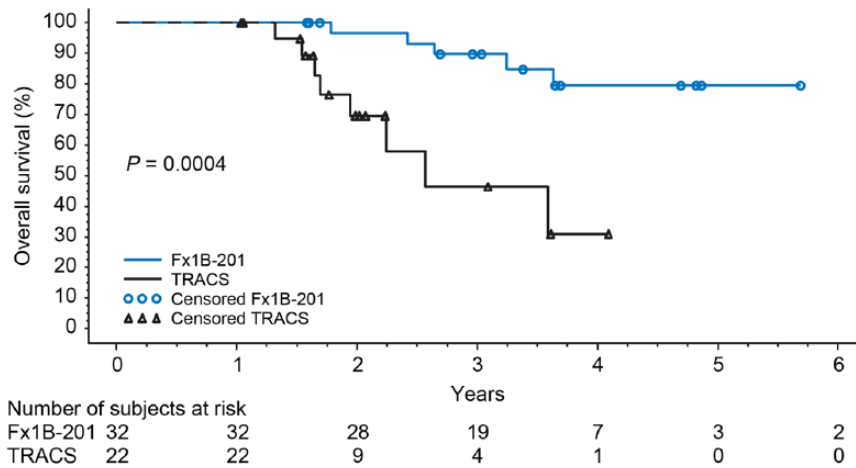
### Patients

Patient population details can be found in full within the published articles.<sup>2,11</sup> Of the 29 patients in the TRACS study, 18

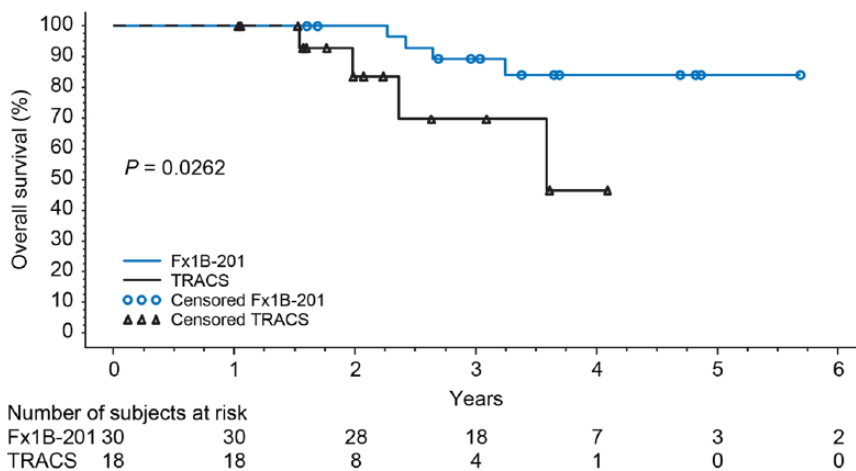
had wild-type TTR and 11 had the Val122Ile variant. In the Fx1B-201 study, 31 patients had wild-type TTR and 4 had the Val122Ile variant (Table 1). Seven patients (Val122Ile: n=1; wild-type: n=6) from the TRACS study enrolled in the Fx1B-201 treatment study. Most of the patients with the Val122Ile TTR variant were men and African American with a comparable mean age (Table 1). Within each study, mean duration of TTR-CM symptoms, mean age at symptom onset and diagnosis, and cardiac-related clinical characteristics were similar between the 2 cohorts (Table 1). During the TRACS study, there were 12 patient deaths (Val122Ile: n=8; wild-type: n=4). Causes of death included heart failure (n=3), sudden death (n=3), sepsis (n=3), unclassified (n=2), and heart transplant (n=1).<sup>2</sup> In the Fx1B-201 study, 2 patients (both wild-type) died: 1 from complications due to immunoglobulin light chain (AL) amyloidosis and 1 due to hemorrhagic stroke after a fall.<sup>11</sup>

### Time-to-mortality analysis

There were 7 patients in TRACS and 2 patients in Fx1B-201 who had NYHA functional classification  $\geq$ III and were excluded from the time-to-mortality analysis. One patient was found to be misdiagnosed and was removed from the analysis (re-biopsy demonstrated amyloid deposits that were positive for immunoglobulin light chain with no evidence of TTR deposition). In the time-to-mortality analysis restricted to patients with NYHA functional classification I/II, there was a significant difference in survival for patients treated with tafamidis compared with untreated patients over the long-term follow-up ( $P=.0004$ ; Figure 1). Similarly, in the time-to-mortality analysis for only wild-type patients, those treated with tafamidis showed significant survival benefit compared with untreated patients ( $P=.0262$ ; Figure 2).



**Figure 1.** Time to mortality from diagnosis date for patients with NYHA functional classification I or II. NYHA, New York Heart Association; TRACS, Transthyretin Amyloidosis Cardiac Study.



**Figure 2.** Time to mortality from diagnosis date for patients with wild-type transthyretin. TRACS, Transthyretin Amyloidosis Cardiac Study.

### Safety

The safety of tafamidis treatment in patients with TTR-CM was assessed in the open-label study and showed that tafamidis-related adverse events were comparable with those common in elderly patients with cardiac disease. Detailed safety data from this study have been published.<sup>11</sup>

### Discussion

These post hoc analyses were conducted to understand the effect of tafamidis on survival in patients with more comparable earlier stage TTR-CM (NYHA functional classification I/II) and separately in patients with wild-type TTR-CM only. These new analyses support earlier conclusions<sup>12</sup> and suggest that tafamidis slows disease progression compared with untreated patients among those at an earlier disease stage as well as in patients with wild-type TTR-CM. These analyses are hypothesis-generating in a field in which there are few clinical studies on treatment of TTR-CM, especially in patients with wild-type TTR-CM.

Early diagnosis and treatment of cardiac amyloidosis is thought to be essential in treating the disease before irreversible

organ damage.<sup>1</sup> This analysis suggests that patients at an early disease stage may benefit from tafamidis treatment, similar to what has been demonstrated in patients with TTR familial amyloid polyneuropathy.<sup>13</sup>

A longitudinal study found that patients with wild-type TTR-CM have a 100% 2-year survival rate from the time of diagnosis, and therefore, the benefit of treatment may not be evident at earlier time points.<sup>14</sup> The results of our analysis show that patients with wild-type TTR-CM who were treated with tafamidis exhibited a significant difference in survival compared with those who were untreated (Figure 2). A recent retrospective analysis found that median overall survival for patients with wild-type TTR-CM was about 3.6 years,<sup>15</sup> which is similar to our results (Figure 2).

There are limitations to this analysis. The sample sizes for the analyses are small. In addition, the analyses represent the comparison of data from 2 open-label, noncontemporaneous studies. For the analysis conducted in wild-type patients, all patients were included regardless of NYHA functional classification, which could affect the comparability between the treatment and control groups in terms of baseline disease severity.

Although broad conclusions cannot be drawn from these results, the current analysis supports previous results and strengthens the rationale for the use of tafamidis to treat TTR-CM. Emerging data point to a potential survival benefit with tafamidis and support evaluating tafamidis treatment in a larger scale study.

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### Author Contributions

All authors were involved in the analysis and/or interpretation of the data and the development of the manuscript; all authors approved the final version.

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