

Baseline Characteristics and Secondary Medication Adherence Patterns Among Patients Receiving Tafamidis Prescriptions: A Retrospective Analysis Using a National Specialty Pharmacy Dispensing Database

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Introduction: Transthyretin amyloid cardiomyopathy (ATTR-CM) is a serious, underrecognized condition, which leads to heart failure and early mortality if left untreated. Until recently, heart transplantation was the only treatment for ATTR-CM. Regulatory approval of tafamidis transformed treatment for patients. In the phase 3 Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), which established the safety and efficacy of tafamidis, medication adherence was high with 97.2% of patients taking $\geq 80\%$ of scheduled doses. Evidence of real-world adherence to cardiology drugs demonstrates low adherence and suboptimal outcomes; however, real-world adherence to tafamidis has not been investigated. The main objective of this study was to describe adherence patterns of patients filling tafamidis in the Symphony Health database.

Methods: This retrospective analysis of the Symphony Health Solutions claims database used secondary adherence measures, including modified medication possession ratio (MPRm), days between fills adherence rate, and compliance rate, to assess adherence patterns of 2020 patients filling tafamidis free acid 61-mg capsules or tafamidis meglumine 4x20-mg capsules from June 1, 2019 to August 31, 2020.

Results: Patients receiving a tafamidis formulation had characteristics consistent with the expected patient population; 71.6% were aged 75–84 years, 83.2% were male, and the highest proportion resided in the Northeast region (30.5%) of the United States. Adherence for tafamidis was high, as 75% to 100% of the patients across subgroups met or exceeded the commonly defined adherence threshold of 80%. Median number of refills ordered and received was six refills per patient. Most patients received refills with no gap ($n=1633$) or a gap <30 days ($n=1267/1317$ patients). Adherence was high across follow-up time, sex, and age subgroups. Adherence varied by geographic region, with the Northeast being significantly higher than the Midwest (mean MPRm 94.41% vs 88.21%, $p=0.0007$).

Conclusion: These results provide evidence that real-world adherence to tafamidis in patients with ATTR-CM is high.

Keywords: claims analysis, amyloidosis, cardiomyopathy, transthyretin amyloid, adherence

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a life-threatening, yet manageable cause of heart failure whose prevalence is difficult to estimate as it is underdiagnosed and undertreated.^{1–3} The underlying etiology of ATTR-CM is the deposition of misfolded aggregates of transthyretin in tissues including the myocardial interstitial space.⁴ Formation of transthyretin amyloid fibrils may occur as a result of a destabilizing gene mutation (hereditary) or spontaneous age-linked

process (wild type).⁵ Left untreated, patients progress to severe disease and experience rapid reductions in quality of life and increased healthcare resource utilization, including hospitalization.⁴ Ultimately, the disease proves fatal (median survival 2 to 6 years).⁶ Prior to 2019, no proven pharmacotherapies were available for patients with ATTR-CM, and the only treatment was heart transplant.^{4,7–10} The discovery and subsequent regulatory approval of tafamidis was transformative to the treatment paradigm.^{5,11}

Vyndaqel® (tafamidis meglumine 4x20-mg capsules once daily) and Vyndamax™ (tafamidis free acid 61-mg capsule once daily), which are collectively referred to as tafamidis from here on in, are first-in-class therapies approved in the United States (US) by the Food and Drug Administration (FDA) as treatment for wild-type or hereditary ATTR-CM in adults.¹² The mechanism of action for tafamidis is to prevent the amyloidogenic cascade by stabilizing transthyretin at the thyroxine binding sites.^{13,14} Its safety and efficacy were established in the pivotal phase 3 Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), in which tafamidis treatment was associated with significantly reduced mortality and cardiovascular-related healthcare utilization, as well as reductions in functional decline and better maintained quality of life versus placebo.¹⁵

The World Health Organization (WHO) has reported that for long-term treatment of chronic illnesses, average adherence rates in developed countries are approximately 50%.¹⁶ Across chronic diseases, and particularly in cardiovascular conditions, medication adherence is essential to successful treatment and are associated with better disease and economic outcomes.^{17–19} Nonadherence to medications used for cardiac conditions increases cardiac event risk, healthcare resource utilization, and mortality.²⁰ In ATTR-ACT, adherence was high with 97.2% of patients taking at least 80% of their scheduled doses.^{15,21} Studies evaluating real-world data often utilize secondary adherence, which measures whether patients receive refills as prescribed during a defined observation period.¹⁹ To ensure consistency throughout, the term adherence was used in place of secondary adherence from here on in. Evidence suggests that real-world adherence rates are generally lower than in clinical trials, and this discrepancy may lead to disparities between clinical efficacy and effectiveness.¹⁹ Thus, investigation into the adherence of tafamidis is needed to account for the real-world behaviors of patients and provide a comparative perspective to the findings of ATTR-ACT.

Given the relative recency of the FDA approval for tafamidis, to our knowledge there is no published real-world evidence describing both treatment patterns and adherence rates in the US. Moreover, the patient population receiving tafamidis has yet to be characterized.

Study Objectives

The primary objective of the study was to describe adherence patterns of patients filling tafamidis in the Symphony Health dataset population. The secondary objective was to evaluate the use of concomitant medications in the same patient population.

Materials and Methods

Overview

This non-interventional, observational, retrospective cohort study of patients who have been prescribed tafamidis in the US utilized de-identified individual patient data (point-of-sale prescription data, non-retail invoice data, and demographic data) from Symphony Health's specialty pharmacy dispensing database. The Symphony database includes commercial as well as Managed Medicaid and Medicare Advantage pharmacy claims data of over 280 million patients across the US and approximately 65% of the US specialty market.^{22–24}

Study Population

Adult patients (≥ 18 years) with at least one prescription claim and a days' supply greater than zero across all claims for tafamidis in the Symphony Health Solutions (SHS) administrative claims database between June 1, 2019 and August 31, 2020 were included. The earliest accepted tafamidis prescription date was used as the index date and patients were subsequently followed until their last (most recent) tafamidis prescription. These data were used to inform the patient demographic and clinical characteristics of patients with evidence of tafamidis prescription fills.

Further inclusion and exclusion criteria were used to determine the patient cohort for the tafamidis adherence analysis. For inclusion in the tafamidis adherence analysis, patients must have had at least two fully adjudicated prescription claims for tafamidis and a 3-month minimum follow-up period; thus, the last month of treatment initiation/enrollment was May 2020 (with 3-month follow-up going through August 2020) (Figure 1). Patients who had a single claim, claims on a single day, <3 months follow-up, and whose first and last claims were the same were excluded.

The study was considered to be exempt from the requirements for “human subjects research” in the US as it only used commercially available de-identified secondary data sources, under DHHS regulations 45 CFR 46.104. Thus, review and informed consent from the institutional review board/independent ethics committee was not necessary. Analyses performed for this study were not required to undergo an approval process by Pfizer board members. The study was conducted in accordance with legal and regulatory requirements and followed the generally accepted research practices described in Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).^{25–27}

Measures of Medication Day Gaps and Adherence

Follow-up intervals were calculated based on the first prescription claim of tafamidis treatment until August 2020 (end of data availability) or once prescription activity was no longer seen within the study period. Follow-up was defined as the time (in months) between the first accepted claim and the last claim of any status (accepted, reversed, or rejected). Patient follow-up periods differed based on their individual prescription fill dates. Uptake over time was defined as the number of first-time fills in each month of the study period. Additionally, days’ supply was provided by the Symphony database across both accepted and reversed claims. Prescribed daily doses were not provided by the Symphony database.

Refill gaps were measured using the following metrics: Day Gaps Between Prescription Refills and Days Between Fills Adherence Rate (DBR).²⁸ Day Gaps Between Prescription Refills were calculated as the days between prescription refills minus the days’ supply of the prescription. When the time between fills exceeded the days’ supply of the previous fill, there was considered to be a gap in fills. Gaps were reported as specific categories (0 days, 1 to 30 days, 31 to 60 days, 61 to 90 days, and >90 days).

$$\text{Day Gaps Between Prescription Refills} = \text{Days between prescription refills} - \text{days' supply}$$

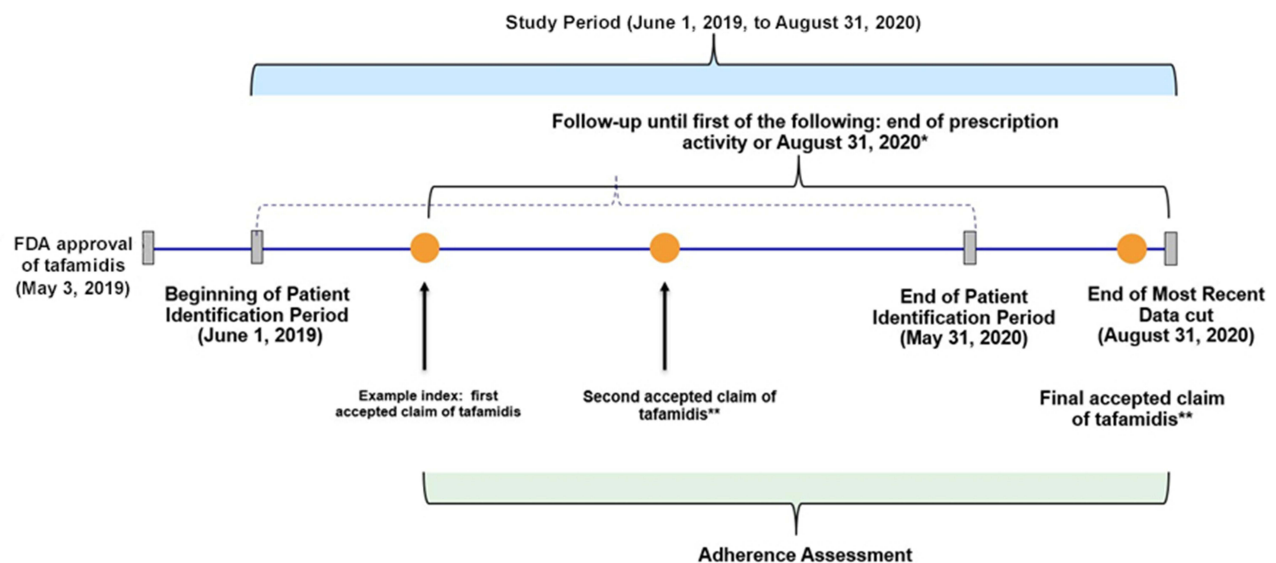


Figure 1 Study design with key timepoints and an example index eligible for adherence analysis.

Notes: *Minimum follow-up of 3 months was required; **A second accepted claim for tafamidis will be required as an additional attrition step for patients to be included in the adherence analysis; date of treatment initiation = index date.

DBR was calculated as the days in the follow-up period minus total days' supply divided by the days in the follow-up period and was reported as a percentage. There is a potential for adherence values to exceed 100%, as the calculation does not take into account the possibility of patients picking up their medication refill before the previous supply is exhausted, creating a total days' supply that is greater than the follow-up period.

$$DBR = \left(1 - \frac{\text{Follow-up period} - \text{total days' supply}}{\text{Days in the follow-up period}} \right) \times 100$$

As this was an exploratory study, multiple measures including modified Medication Possession Ratio (MPRm) and Compliance Rate (CR) were used to evaluate adherence to tafamidis. MPRm was calculated as the days' supply of tafamidis dispensed throughout the observation period from first to last dispensing, divided by the number of days between first and last dispensing plus the days' supply of the last dispensing, multiplied by 100 and reported as a percentage.²⁹ MPRm was chosen as the MPR variation used in this study because it included the days' supply dispensed with last dispensing in the denominator.²⁹ CR was utilized as it provides an adherence rate that includes all days' supplied with treatment up until the last day of refill.²⁹ CR was calculated as total days' supply minus last accepted days' supply for each patient, divided by the number of days in the follow-up period. CR was multiplied by 100 and reported as a percentage.

$$MPRm = \frac{(\text{Sum of days supplied for all refills from first to last dispensing})}{(\text{Days between first dispensing to last dispensing plus days supplied in last dispensing})} \times 100$$

$$CR = \left(\frac{\text{Total days' supplied} - \text{last days' supply}}{\text{Days in the follow-up period}} \right) \times 100$$

Both adherence measures were calculated for the overall cohort and in sub-cohorts based on the length of follow-up between first and last prescription claim: >0 months to 3 months, >3 months to ≤6 months, >6 months to ≤12 months, and >12 months. Additionally, adherence was reported in subgroups defined by baseline characteristics, including age, gender, region, and payment plan type. Patients were categorized as adherent (Yes/No) based on a calculated MPRm ≥70%, 75%, and 80% threshold. Eighty percent is a commonly employed adherence threshold³⁰ and was the defined adherence cut-off in the ATTR-ACT trial. However, given the recency of therapy approval, various thresholds were assessed.

Statistical Methods and Data Analyses

Data were handled and analyzed using Athena Engine software, v2 or later Copyright © -2021, Amazon Web Services, Inc. Patient characteristics, prescription characteristics, and adherence were reported using descriptive statistics. Categorical variables were summarized by the number of available observations, frequency, percentage, and 95% confidence limits. Continuous variables were summarized by the number of available observations, mean, standard deviation, 95% confidence limits, median, quartiles, minimum, and maximum, where appropriate. Missing categorical data were included as a separate "missing" category. Missing continuous data were not included in the summaries and analyses and no imputations were performed. This study did not have any hypotheses specified a priori. All statistical analyses were descriptive and exploratory. An $\alpha=0.05$ was utilized to determine statistical significance; statistical tests included chi-square test, one-way ANOVA, post-hoc Tukey's test, and Mann-Whitney *U*-test.

Results

Study cohort attrition is presented in Table 1. Among the 2020 patients who had >0 days' supply across all accepted/reversed claims, 1365 patients were included in the MPRm and CR adherence analyses and 1366 patients were included in the DBR adherence analyses. These patients met the inclusion criteria for adherence analyses as they had at least two fully adjudicated prescription claims for tafamidis and a 3-month minimum follow-up period. A total of 1317 patients were found to have at least one gap in fill and were therefore included in the gaps in fills analyses.

Table 1 Study Cohort Attrition

Category	No.
Total no. of patients in dataset	3567
Patients with at least one accepted claim	2124
Patients with >0 days' supply across all accepted/reversed claims	2020 ^a
Patients qualifying for DBR calculation	1366 ^a
Patients qualifying for MPRm and CR calculation	1365 ^a
Patients with a gap in fills	1317 ^a

Note: ^aThe subsequent analyses were conducted using these cohorts.

Abbreviations: CR, compliance rate; DBR, days between fills adherence rate; MPRm, modified medication possession ratio.

Patient Characteristics

Baseline patient characteristics included sex, age groups, payment plan types, and US geographic region (Table 2). Overall, there was a significantly higher proportion of males (83.2% vs 16.8%, $p < 0.0001$) and mean age was 75 years. Most patients had coverage that included Medicare (70.4%) or pharmacy benefit management organizations (PBMs) (14%). The proportion of patients receiving tafamidis varied significantly by geography; the Northeast had the highest proportion of patients receiving tafamidis, whereas the Midwest and West had fewer patients. Prescription characteristics included duration of follow-up, tafamidis uptake over time, refills ordered and received, days' supply, prescribing physician specialties, and tafamidis meglumine and tafamidis free acid patient count. Across cohorts, the patient count was evenly distributed. The mean duration of follow-up was 6 months. Most patients with 0 months of follow-up were observed initiating treatment with tafamidis in the last month of the study period, accounting for the lack of follow-up for these patients (Figure 2).

Preliminary Prescription Information

The highest rates of tafamidis uptake were observed in July and October of 2019, with even distribution throughout the remaining months (Figure 3). Among all claims and accepted claims, the most frequent prescriber specialties reported were cardiology and interventional cardiology; however, specialty information was not reported for the majority of providers. For patients with fully adjudicated claims, more received tafamidis meglumine than tafamidis free acid ($n=995$ vs 529, respectively) and approximately 10% switched between products during the study period.

There was a mean of seven refills ordered per patient and six refills received per patient. The median refills received and ordered were six refills per patient. Most tafamidis prescriptions were dispensed as a 30-day supply. The mean total days' supply per patient was approximately 198 days (~6.6 months; range: 1 month to 22 months). Total days' supply across the study period aligned with the corresponding duration of follow-up.

Prescription Characteristics Over Follow-Up

Distribution of Gaps in Fills

The vast majority of patients had either no gaps or one gap in fill (equating to a 1- to 30-day supply gap). The proportion of patients with more than one gap in fill was low. Of the 1317 patients who had at least one gap in fill, 96% had a <30-day gap. The average number of gaps in fill for these patients was two gaps, with a mean gap of 10 days (Table 3).

Adherence to Tafamidis

DBR was calculated for a sub-cohort of 1366 patients; one patient was excluded from MPRm and CR analyses because the patient's first and last accepted claim were the same.

Adherence to tafamidis was high, as evidenced by mean MPRm of 92%. Among those with at least 9 months and 12 months of follow up, adherence rates were similar, and the proportion of patients with MPRm $\geq 80\%$ was 79% and 81%,

Table 2 Baseline Patient Characteristics

Segment	N=2020	%
Sex*		
Male	1681	83.2
Female	339	16.8
Age group (at index date, derived from year of birth) ^a		
0–44	6	0.3
45–54	18	0.9
55–64	113	5.6
65–74	436	21.6
75–84	1447	71.6
≥85	0	0.0
Mean, SD, 95% CI age	75, 6.05, +/- 0.26	
Min, max, median age	39, 80, 79	
25th, 75th quartile	73.75, 79	
Geographic region ^a		
Northeast	616	30.5
South	596	29.5
Midwest	438	21.7
West	307	15.2
Unknown	63	3.1
Months of follow-up	Patient count	
0	281	—
>0–3	369	
>3–6	492	
>6–9	310	
>9–12	326	
12–15	242	
Duration of treatment (days)		
Mean, SD, 95% CI	178, 132.57, +/- 5.78	—
Min, max, median	0, 448, 161	
25th, 75th quartile	62.75, 294	

Notes: *Denotes $p < 0.0001$ assessed by Chi square test. ^aIndex date is defined as date of first accepted claim.

Abbreviations: CI, confidence interval; SD, standard deviation.

respectively. Adherence rates were similar in males and females and across age groups; no statistically significant differences were observed. Among patients aged 55 to 84 years, the highest proportion of adherence (87%) was seen in the 55–64 age group. Adherence varied across geographic regions, though all regions demonstrated high rates of

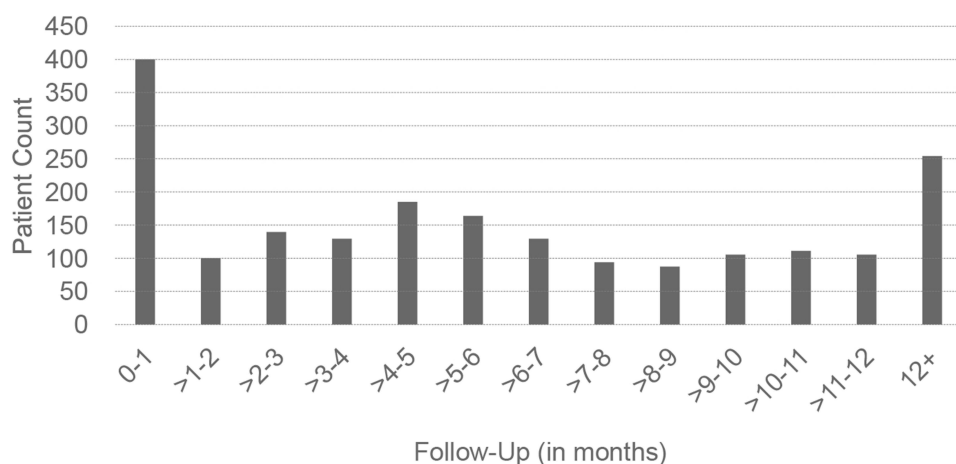


Figure 2 Patient count across specified follow-up periods.

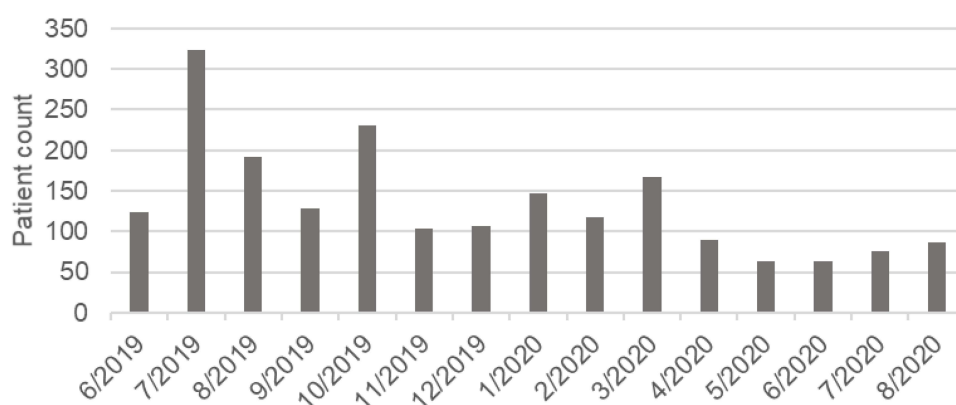


Figure 3 Patient uptake of tafamidis over time.

adherence, generally. Statistically significant differences were observed between the Northeast and Midwest with MPRm (94.41% vs 88.21%, $p=0.0007$). Median MPRm was similar among patients who took tafamidis meglumine or tafamidis free acid for the duration of the study period (98.9% and 94.0%, respectively); approximately 10% of the patients switched therapies. DBR, MPRm, and CR results by subgroup are presented in Table 4.

Most concomitant medications in this patient population were indicated for use in heart failure, thrombosis, hypertension, hypothyroidism, neuralgia, seizures, restless leg syndrome (RLS) and gastroesophageal reflux disease. Polypharmacy among patients was common, with the most frequently prescribed medications including furosemide, apixaban, torsemide, spironolactone, atorvastatin calcium, metoprolol succinate, tamsulosin, allopurinol, levothyroxine sodium, and gabapentin (Table 5).

Discussion

According to a WHO report, average adherence rates for long-term therapy of chronic illnesses in developed countries are roughly 50%.¹⁶ Poor adherence over the course of a long-term treatment regimen severely diminishes its effectiveness and leads to poor outcomes, decreased quality of life, increased healthcare costs, and is a significant concern, particularly with respect to cardiovascular therapies. Without treatment, patients with ATTR-CM experience severe and progressive disease that correlates to frequent hospitalizations and poor survival.⁶ Patients with an accumulation of variant (ATTRv) transthyretin amyloid fibrils also experience a more rapid disease progression and diminished quality of life.⁶ Based on its mechanism of stabilization of transthyretin to prevent the formation and the accumulation of amyloid plaques, timely diagnosis and treatment, including with tafamidis, is paramount to limiting disease progression,

Table 3 Gap Periods and Number of Gaps

Distinct Patients with a Gap		N=1317
Patient count by No. of gaps		
Patient count		No. of gaps
408		1
333		2
208		3
167		4
115		5
58		6
21		7
3		8
4		9
Gaps in fills (days)		
Mean, SD, 95% CI		10, 19.68, +/- 1.06
Min, max, median		1, 324, 5
25th, 75th quartile		2, 10
Patient count by gap period		
Gap (days)		Patient count
0		1633
1–30		1267
31–60		134
61–90		50
>90		38

Note: This analysis was done on accepted claims only.

Abbreviations: CI, confidence interval; SD, standard deviation.

cardiovascular-related hospitalizations, and mortality.^{13–15,17–20} The current analysis demonstrates high rates of adherence among patients taking tafamidis in the real world (75% to 100% of the patients having adherence $\geq 80\%$), especially by real-world standards and within the cardiology setting.^{31,32} Although the proportion of patients with $\geq 80\%$ adherence across subgroups were generally lower than adherence levels reported in the ATTR-ACT trial (97.2% of the patients having adherence $\geq 80\%$), this was to be expected.¹⁵ The level of scrutiny that controlled trials undergo to ensure patients administer their medications consistently and appropriately is not usually present in real-world non-interventional studies.

This study included a sample that is representative of the ATTR-CM population expected to be users of tafamidis. The majority of patients were over 65 years of age and had prescription coverage provided by Medicare. In this analysis 83% of the patients were male, a proportion that is less skewed than published reports with male to female ratio estimates ranging from 10:1 to 20:1,^{33–38} but in-line with the level of male predominance reported in two recent systematic

Table 4 MPRm, DBR, and CR by Subgroup

Category	No.	MPRm ^a					DBR ^b		CR ^a	
Follow-Up (Months)		Mean % (SD) ^c	Median (min, max)	MPRm ≥70% No. (%)	MPRm ≥75% No. (%)	MPRm ≥80% No. (%)	Mean % (SD) ^c	Median (min, max)	Mean % (SD) ^c	Median (min, max)
>3–6	488	93.45 (21.68)	100.67 (14.02, 155.17)	424 (87)	409 (84)	399 (82)	117.12 (34.17)	112.22 (16.95, 230.77)	91.99 (21.00)	100.84 (0.00, 138.01)
>6–9	309	91.16 (22.17)	98.90 (11.45, 135.89)	266 (86)	258 (83)	244 (79)	–	–	91.69 (28.07)	98.76 (–48.39, 166.67)
	310	–	–	–	–	–	105.14 (29.72)	108.25 (11.54, 197.97)	–	–
>9–12	326	90.47 (22.46)	98.21 (6.80, 133.16)	271 (83)	264 (81)	256 (79)	99.79 (26.62)	122.09 (8.55, 153.58)	89.66 (26.41)	98.04 (0.00, 152.28)
>12	242	92.49 (19.32)	97.71 (6.85, 135.44)	220 (91)	209 (86)	197 (81)	100.95 (22.50)	105.69 (7.35, 158.27)	89.37 (25.13)	97.53 (–17.09, 135.98)
Age (years)										
35–44	2	99.42 (8.02)	99.42 (93.75, 105.10)	2 (100)	2 (100)	2 (100)	110.42 (8.16)	110.42 (104.65, 116.20)	99.33 (8.92)	99.33 (93.02, 105.63)
45–54	13	89.88 (21.45)	95.24 (45.45, 114.13)	11 (85)	11 (85)	11 (85)	104.72 (28.52)	104.22 (49.53, 137.61)	88.94 (23.85)	93.33 (38.46, 116.88)
55–64	76	96.22 (19.76)	100.84 (8.43, 137.14)	70 (92)	68 (89)	66 (87)	110.11 (25.07)	114.58 (9.20, 165.52)	95.77 (22.92)	100.96 (0.00, 144.83)
65–74	301	91.34 (20.89)	98.36 (12.50, 130.18)	261 (87)	251 (83)	244 (81)	105.72 (29.29)	110.57 (9.87, 212.90)	89.73 (25.29)	98.13 (0.00, 136.69)
75–84	973	91.95 (21.96)	99.29 (6.80, 155.17)	837 (86)	808 (83)	773 (79)	–	–	90.65 (26.28)	99.17 (–48.39, 166.67)
	974	–	–	–	–	–	107.74 (31.32)	111.51 (7.35, 230.77)	–	–

(Continued)

Table 4 (Continued).

Category	No.	MPRm ^a					DBR ^b		CR ^a	
Follow-Up (Months)		Mean % (SD) ^c	Median (min, max)	MPRm ≥70% No. (%)	MPRm ≥75% No. (%)	MPRm ≥80% No. (%)	Mean % (SD) ^c	Median (min, max)	Mean % (SD) ^c	Median (min, max)
Sex										
Male	1154	92.44 (21.60)	99.54 (6.80, 155.17)	1004 (87)	969 (84)	931 (81)	–	–	91.20 (25.88)	99.51 (–48.39, 166.67)
	1155	–	–	–	–	–	107.81 (30.50)	111.75 (7.35, 230.77)	–	–
Female	211	89.88 (21.50)	95.45 (8.43, 132.35)	177 (84)	171 (81)	165 (78)	105.17 (30.50)	109.38 (9.20, 200.00)	88.14 (25.65)	94.49 (0.00, 148.35)
Geographic region										
Midwest	310	88.21 ^d (24.01)	97.16 (11.45, 133.16)	252 (81)	245 (79)	233 (75)	102.62 ^d (32.97)	109.71 (9.87, 198.53)	85.98 ^d (29.03)	96.90 (–48.39, 137.06)
Northeast	419	94.41 ^d (19.18)	100.28 (6.80, 132.35)	378 (90)	363 (87)	355 (85)	–	–	93.53 ^d (22.88)	100.30 (–17.09, 148.35)
	420	–	–	–	–	–	111.17 ^d (28.11)	115.38 (8.55, 201.92)	–	–
South	391	91.64 (20.70)	98.59 (13.54, 137.14)	340 (87)	323 (83%)	307 (79)	106.70 (29.07)	111.80 (14.53, 214.29)	90.18 (25.11)	98.36 (0.00, 152.28)
West	209	91.89 (23.80)	98.36 (6.85, 135.44)	177 (85)	176 (84%)	168 (80)	106.39 (33.74)	109.89 (7.35, 230.77)	90.96 (27.66)	98.21 (0.00, 138.01)
Unknown	36	102.95 (15.21)	105.05 (63.38, 155.17)	34 (94)	33 (92%)	33 (92)	118.00 (23.80)	118.17 (55.90, 187.50)	103.62 (17.98)	105.76 (53.57, 166.67)

Notes: ^aDenotes statistical significance according to one-way ANOVA, geographic region: mean MPRm, $p<0.001$; mean DBR, $p=0.0008$; and mean CR, $p<0.001$. ^bExcludes patients with only one claim, only claims on the same day, patients which have their first claim equal to their last accepted claim, and/or patients with < 3 months follow-up. ^cExcludes patients with < 3 months follow-up. ^dPatients with < 9 months of follow-up were excluded from the statistical analysis (ANOVA or post-hoc Tukey's test). ^eSignificant according to Tukey's test (post-hoc) following ANOVA, Midwest vs Northeast: MPRm difference=6.20, 95% CI 1.82 to 10.59, $p=0.0011$; DBR difference=8.54, 95% CI 2.34 to 14.75, $p=0.0017$; CR difference=7.55, 95% CI 2.30 to 12.80, $p=0.0009$.

Abbreviations: CR, compliance rate; DBR, days between fills adherence rate; MPRm, modified medication possession ratio; SD, standard deviation.

Table 5 Concomitant Therapy Use

Ranking by Patient Count ^a	Patient Count	Therapy
1	702	Furosemide
2	656	Apixaban
3	528	Torsemide
4	514	Spironolactone
5	511	Atorvastatin calcium
6	442	Metoprolol succinate
7	427	Potassium chloride
8	300	Tamsulosin
9	253	Allopurinol
10	235	Levothyroxine sodium
11	234	Gabapentin
12	231	Amiodarone hydrochloride
13	223	Prednisone
14	223	Pantoprazole sodium
15	199	Omeprazole
16	199	Cephalexin
17	197	Carvedilol
18	197	Amoxicillin
19	194	Metolazone
20	190	Lisinopril

Note: ^aTop 20 most common medications received by patients on and post-tafamidis initiation.

literature (83% and 86%).^{39,40} Among healthcare practitioners whose specialty was specified, cardiologists were the primary prescribers of tafamidis.

The ratio of refills ordered to refills received was 1. Moreover, most patients receiving tafamidis during the study period did not have gaps between refills and those patients with a gap in therapy were likely to have one for <30 days, suggesting the majority of patients are adherent. The observed MPR_m (92%; 95% CI 90.89 to 93.19) is well over the commonly defined adherence threshold reported in most clinical trials of 80%.³⁰ Polypharmacy was common among patients treated with tafamidis; however, medications were generally consistent with both the age and diagnosis of the patient population and included medications used for hypertension, thrombosis, heart failure, hypothyroidism, neuralgia, seizures, restless legs syndrome, and gastroesophageal reflux disease. Medication lists were used as a proxy for patient comorbidity data as they were not captured in the Symphony specialty pharmacy claims database. Comorbidity data is instead captured through medical claims data. Overall, these results provide evidence that not only is tafamidis being used by the expected population, but that among patients who initiate tafamidis, adherence is high. The proportion of patients taking only tafamidis meglumine (n=995) was higher than those only taking tafamidis free acid (n=529). Though the single-pill dosage of tafamidis free acid offers convenience to patients that might contribute to adherence, mean MPR_m for both formulations were over 90% and only 10% of

the patients switched. The similar adherence rates may be attributed to both being administered once daily (tafamidis free acid 61-mg capsule once daily or tafamidis meglumine 4×20-mg capsules once daily). Further, results were generally consistent across the various measures used to assess adherence as well as when stratified by patient characteristics.

Overall, adherence measures were similar for differing follow-up durations, age groups, and sexes. In general, high adherence was noted across all measures regardless of the region, with at least 75% of the population being designated “adherent” at the commonly employed 80% threshold. However, some geographic variations were noted. Adherence across all measures was significantly higher in the Northeast than the Midwest; of note, the Midwest had lower number of patients receiving tafamidis, whereas the Northeast region had the highest. This finding is in line with an analysis by Gilstrap et al, in which the highest incidence and prevalence of ATTR-CM was seen in the Northeast; the authors attributed this observation to better detection of ATTR-CM and presence of amyloidosis centers of excellence in the region.⁴¹ A center of excellence may offer specialists with a higher level of expertise and enhanced patient support for the specific disease state; it is plausible that these characteristics may also contribute, at least in part, to the observed higher adherence in the Northeast. Conversely, lower uptake in the Midwest and lower adherence in the region might be linked. Future studies may provide better understanding of contributing factors and identify opportunities for educational interventions to further improve adherence in patients in the Midwest. Due to the rarity of ATTR-CM in claims data, other patient characteristics such as race/ethnicity were not able to be assessed. These variables are likely confounders in any associations between treatment and adherence.⁴² They also constitute key privacy concerns for datasets of patients with rare diseases. Due to the low prevalence of patients with ATTR-CM receiving tafamidis in the specialty pharmacy database, race did not pass the expert determination Privacy Review process.

The concepts of implementation and adherence presented in this study align with other standardized taxonomies including the taxonomy provided by the Ascertaining Barriers to Compliance (ABC) project team, as well as adherence reporting guidelines that utilize ABC taxonomy such as the ESPACOMP Medication Adherence Reporting Guideline (EMERGE).^{43,44} We operationalized the concepts using the terminology defined by ISPOR, which places an enhanced focus on refill data.⁴⁴ This was deemed to be appropriate, as metrics included for adherence analysis in this study required multiple fills of tafamidis prescriptions.

Limitations

There are limitations to pharmacy claims studies for assessing adherence; the limitations of this analysis are consistent with other studies. Fully adjudicated claims data were employed to mitigate errors in data entry and potential biases that may arise due to the inability to provide quality control or consistency for data collection. While the Symphony database has been used successfully in adherence research to demonstrate both relatively high and low levels of adherence,^{22,23} its use is subject to limitations common to all retrospective claims-based analyses, including incorrect data entry, the inability to recognize partial adherence, failure to record prescriptions filled outside of the database, and lack of documented reasoning for refill adherence behavior of patients.⁴⁵

An increased amount of screening and awareness of ATTR-CM is needed to provide a complete and accurate perspective of the population with ATTR-CM diagnoses.^{1,3} Until this occurs, tafamidis as a treatment of ATTR-CM may be underutilized, resulting in patient selection biases, and thus may affect available real-world data.

Our results can only be considered as a proxy to real-world adherence of tafamidis, as adherence measures provide an overview of prescription fills. It is not known whether filled tafamidis is taken as prescribed. Claims databases are not equipped to provide further insights on these types of barriers to adherence. In addition, because patients may fill their medication before they have exhausted their previous supply, there is a potential to have adherence values over 100% as calculated by MPRm, DBR, and CR. While some studies cap the MPR at one, in this study, such capping was not done. Instead, median values were calculated and relied upon to observe central tendencies.

As the majority of tafamidis prescriptions were dispensed as a 30-day supply, we are unable to report whether there was a difference between patients that received a 30-day supply or 90-day supply. Recently, in a study utilizing the Symphony database, patients who were prescribed a 90-day supply of medications had significantly higher adherence

rates in comparison to those who were prescribed a 30-day supply within 1 year post-discharge.²³ Subsequent studies may explore the influence that days' supply has on patient adherence to tafamidis. Additionally, the manner in which refills were ordered was not available in the Symphony database. Considering the average age of patients receiving tafamidis, the logistics of refill ordering and pickup may influence adherence.

It should be noted that in this analysis, discontinuation was not assessed. Medication discontinuation in electronic database studies can only be assessed within the context of a pre-specified operational definition for the required number of days without medication available (maximum permissible gap). However, in this study, we did not have a known or agreed-upon maximum permissible gap. Given the very recent approval of tafamidis and resulting lack of any baseline understanding of prescription-taking behavior, studying or inferring discontinuation from this data was not deemed appropriate. These data may allow for future research on gaps and medication taking behavior.

Patterns of nonadherence vary and may also include non-initiation, incorrect implementation, and early discontinuation.⁴⁶ Non-initiation was not possible to examine based on the study design. There are many factors that influence adherence. Cost and adverse events are often assumed reasons for discontinuation and/or nonadherence; however, because fully adjudicated claims were used for this study, cost of treatment and its impact on adherence was not considered. Currently in the US, the cost of tafamidis treatment is covered through various methods, including financial assistance programs that patients may qualify for.⁴⁷ Future studies may investigate the impact that varying modes of coverage for tafamidis costs and adverse events associated with tafamidis have on adherence to the medication.

The large numbers of patients receiving tafamidis in the Symphony Health dataset, including both Medicare and non-Medicare prescriptions, allowed assessment of adherence across age groups, including those in the <65 years of age population. These patients represented a small but not insignificant proportion of patients (~7%). The consistency of multiple adherence measures across age groups, sex, and regions provides strong evidence that adherence is high for patients on tafamidis, regardless of their individual follow-up periods. Other studies have utilized the Symphony health database to demonstrate high adherence rates in their respective pharmacotherapies of interest.^{23,48,49} These studies were also able to utilize similar subgroups such as follow-up time, age groups, and gaps in fills to characterize the patient population they evaluated.^{23,48,49}

As the first study examining adherence among tafamidis users in a real-world setting, this study provides key insights and will lay the foundation for future research to further elucidate patient and physician behavior. The limitations of this study will provide an opportunity for future studies to collect or incorporate additional data elements to help move beyond descriptive analyses to causal relationships. Potential topics for exploration will aim to provide insight into adherence at all stages, including initiation and persistence. Deeper understanding of adherence in vulnerable minority populations and factors contributing to nonadherence in different segments of patient populations, will help to minimize any potential health disparities and further optimize treatment outcomes through various education programs. Additional research could extend to determining the impact this level of adherence has on patient outcomes and its value to payers.

Conclusion

This is the first study reporting real-world adherence of tafamidis in patients with ATTR-CM in the US. Based on our analysis, the characteristics of patients receiving tafamidis are consistent with the expected patient population being older, predominantly male, and with the highest proportion of patients in the Northeast US. Patients were generally prescribed tafamidis by their cardiologist and received concomitant medications primarily indicated for heart failure, thrombosis, and hypertension. Adherence to tafamidis was high across patients of various age groups as well as in males and females. While adherence was generally high across all regions, there is room for improvement in the Midwest. In addition, patients filled as many prescriptions as they were prescribed by their physician. Gaps in refills were minimal; moreover, on average, patients with gaps had one to two gaps of 1 to 30 days. These findings suggest that overall, this patient population exhibits strong real-world adherence behaviors, which may contribute to the effectiveness of tafamidis in ATTR-CM.

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Darrin Benjumea is an employee of Genesis Research who has been contracted by Pfizer, Inc. for involvement in this study. Andrew Peterson is an employee of University of the Sciences who has been contracted by Pfizer, Inc. for involvement in this study. Sapna Prasad and Alex O'Brien are employees of Clarify Health Solutions and were contracted by Pfizer, Inc. for involvement in this study. Anuja Roy, Nick Marchant, Jose Alvir, Rahul Bhambri, Jason Lynn, Yong Chen, Jason Kemner, and Bhash Parasuraman are employees of Pfizer and own stock and/or stock options. The authors report no other conflicts of interest in this work.

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