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ORIGINAL RESEARCH ARTICLE

Contemporary Oral Medication Use and Frequency in Patients with Transthyretin Amyloid Cardiomyopathy

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Abstract

Introduction Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly recognized cause of heart failure (HF), with a higher prevalence in older patients with comorbidities requiring concomitant medical therapy. Acoramidis is a next-generation transthyretin stabilizer with near-complete protein stabilization (≥ 90%) administered orally twice daily (BID) for treatment of ATTR-CM. We report on oral medication use in patients with ATTR-CM using two complementary sources: the ATTRibute-CM trial and real-world claims data.

Methods In the ATTRibute-CM study, participants with ATTR-CM were randomly assigned 2:1 to receive 800 mg of acoramidis hydrochloride or matching placebo BID for 30 months. Participants from acoramidis and placebo groups were pooled for this analysis. Baseline oral medication use was collected upon enrollment in the study. Real-world data were obtained from patients with ATTR-CM in Optum's deidentified Clinformatics Data Mart Database (Optum CDM) who met the stability criteria. Patients meeting the stability criteria had: (1) ≥ 2 years of continuous enrollment with ≥ 3-months look-back and a 12-month look-forward from index diagnosis, during the study period of 2018–2021 and (2) ≥ 28 days of continuous treatment for a given dosing frequency within the 12-month look-forward period.

Results The ATTRibute-CM study randomly assigned 632 participants with ATTR-CM (mean [± SD] age: 77.3 [6.6] years). At entry to the study, 407 (64.4%) participants were using a medication that was administered BID, three times daily (TID), or four times daily (QID), and 392 (62.0%) participants were using at least one medication administered BID. The most frequent BID medications were apixaban, furosemide, metformin, metoprolol, and carvedilol. In ATTRibute-CM, accountability to acoramidis was high (97.1%).

From a pool of 2.46 million patients with HF and cardiomyopathy identified in the Optum CDM, 12,116 patients (mean [± SD] age: 76.3 [9.4] years) met the criteria for ATTR-CM, and 5601 patients met the stability criteria. Analysis from this real-world database demonstrated that 4351 (92.1%) patients were prescribed a medication that was administered BID, TID, or QID and 4166 (88.2%) patients were prescribed at least one BID medication. The most frequent medications regardless of dosing frequency included furosemide, atorvastatin, metoprolol, apixaban, and carvedilol. The most frequent BID medications were apixaban, carvedilol, furosemide, metoprolol, and potassium chloride.

Conclusions Patients with ATTR-CM take oral medications administered multiple times a day for the treatment of HF and other comorbidities. As a BID medication, acoramidis does not appear to deviate from non-ATTR-CM pharmacotherapy

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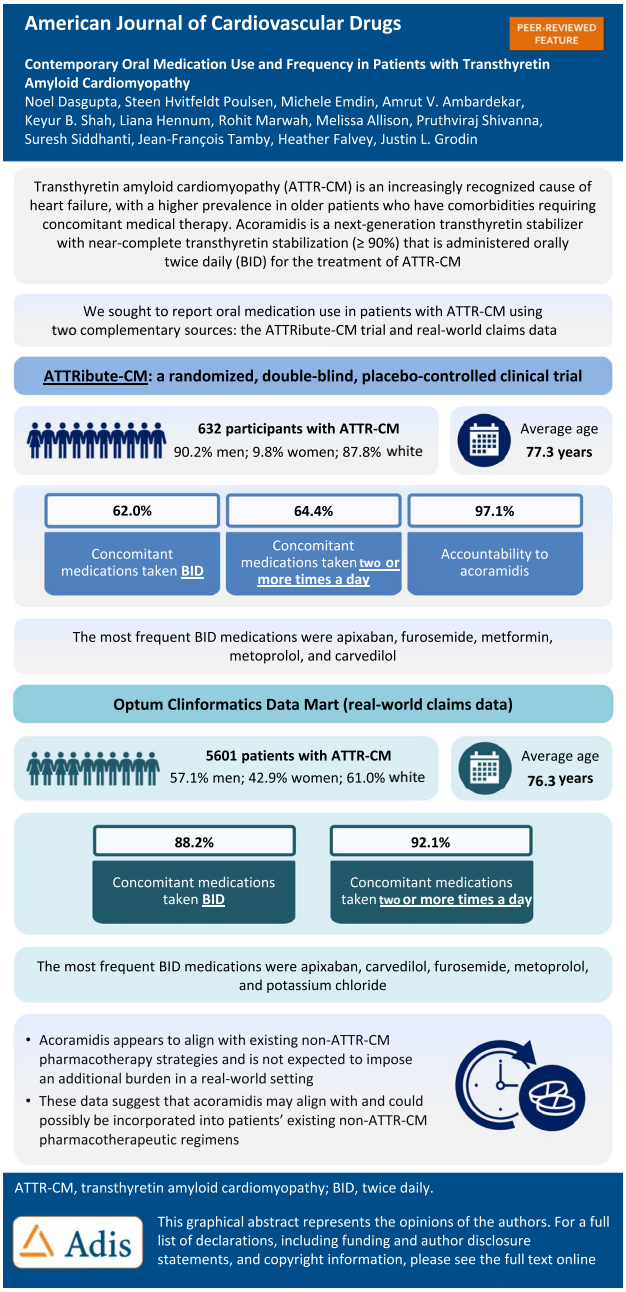
strategies, and is therefore not expected to impose additional burden in a real-world setting. These data suggest that acoramidis may align with and could possibly be incorporated into patients' existing non-ATTR-CM pharmacotherapeutic regimens.
Clinical Trial Registration NCT03860935.

Graphical Abstract



Key Points

Patients with ATTR-CM use oral medications that are taken multiple times a day for the treatment of ATTR-CM and comorbidities.

As an oral medication taken twice a day, acoramidis does not appear to deviate from non-ATTR-CM pharmacotherapy strategies and is not expected to impose additional burden in a real-world setting.

Our findings suggest that administration of acoramidis may align with and could possibly be incorporated into patients' existing non-ATTR-CM and general heart failure pharmacotherapeutic regimens.

1 Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease caused by the destabilization and deposition of misfolded amyloid fibrils in the myocardium [1, 2]. ATTR-CM can be categorized into two types: hereditary, where a pathogenic variant of the *TTR* gene is present, and wild-type ATTR, an age-related disorder with no identified pathogenic *TTR* variant [1, 2]. ATTR-CM in more advanced stages presents with a restrictive cardiomyopathy (CM) and is increasingly recognized as a cause of heart failure (HF). ATTR-CM is also seen as a cause of HF with a high prevalence in older patients (aged > 60 years), who often experience comorbidities requiring concomitant medical therapy [1–4]. Without treatment, patients with HF caused by ATTR have a median survival of approximately 5 years [5]. Common comorbidities in these patients include cardiovascular (atrial fibrillation, ischemic heart disease, and aortic stenosis), musculoskeletal (carpal tunnel syndrome, spinal stenosis, osteoporosis), and metabolic (diabetes) conditions [6]. The combination of treatments for these comorbidities, which include diuretics (e.g., furosemide), anticoagulants (e.g., apixaban), and antidiabetics (e.g., metformin), leads to polypharmacy and may introduce complexity in the treatment regimen.

Acoramidis is a near-complete transthyretin stabilizer (≥ 90%) approved by the US Food and Drug Administration, European Commission, Japanese Ministry of Health, Labour and Welfare, and the UK Medicines and Healthcare products Regulatory Agency for the treatment of ATTR-CM in adults and is administered orally twice daily (BID) [7–11]. In the phase 3 ATTRibute-CM study, acoramidis demonstrated a significant improvement when compared with placebo in the four-step hierarchical primary endpoint consisting of all-cause mortality (ACM), cumulative frequency of cardiovascular-related hospitalization (CVH), change from baseline in N-terminal pro-B-type natriuretic peptide level, and change from baseline in 6-min walk distance [7]. Through 30 months, acoramidis was associated with a 36% decrease in risk for the time to ACM or first CVH and a 50% risk reduction in the annualized frequency of CVH [7, 12]. Acoramidis was generally well tolerated when compared with the placebo arm in this study [7]. Although medication use has been reported in clinical trials, there is limited real-world evidence examining the pattern of oral medication use in patients with ATTR-CM. Given the potentially variable and complex nature of medication regimens for patients with ATTR-CM, it is unknown whether acoramidis would synchronize with current non-ATTR-CM pharmacotherapeutic regimens.

The aims of the study were twofold: to report medication usage among participants with ATTR-CM in the ATTRibute-CM study, and to more broadly describe patient characteristics and medication usage patterns within an ATTR-CM cohort using real-world claims data. These findings may inform whether acoramidis aligns with and could be implemented into patients' current non-ATTR-CM pharmacotherapeutic regimens.

2 Methods

The study design of ATTRibute-CM (NCT03860935) has been described previously. Participants with ATTR-CM were randomly assigned 2:1 to receive 800 mg of acoramidis hydrochloride or matching placebo BID for 30 months [7]. Participants from acoramidis and placebo groups were pooled for this analysis. Baseline oral medication use was collected upon enrollment in ATTRibute-CM. Accountability to acoramidis was defined as the proportion of acoramidis tablets taken of the expected number.

$$\text{Proportion of acoramidis tablets taken of the expected number} = \frac{\text{Number of acoramidis tablets dispensed} - \text{number of acoramidis tablets returned}}{4 \times \text{number of days of exposure}}$$

Oral medication use in patients with ATTR-CM was identified in Optum's deidentified Clinformatics Data Mart Database (Optum CDM) on the basis of the presence of either HF (ICD-10 codes: I50.3, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.83, I50.89, I50.9) and/or CM (ICD-10 codes: I42, I42.0, I42.1, I42.2, I42.5, I42.8, I42.9, I43) from 2018 to 2021 and occurring within 2 years of an amyloidosis diagnosis (excluding light-chain amyloidosis) (ICD-10 codes: E85, E85.0, E85.1, E85.2, E85.4, E85.8, E85.82, E85.89, E85.9), followed for a minimum of 12 months after the first HF/CM diagnosis. This time

frame overlapped with the duration and time period of the ATTRibute-CM study. Retrospective data were obtained from patients meeting stability criteria. Patients who met the stability criteria were those who had: (1) at least 2 years of continuous enrollment with a minimum of 3 months look-back and a 12-month look-forward from index diagnosis, during the study period from 2018 to 2021 and (2) at least 28 days of continuous treatment for a given dosing frequency within the 12-month look-forward period.

Medication classes were based on the World Health Organization Anatomical Therapeutic Chemical level 2 drug classification. Baseline characteristics, oral medication use and frequency, and accountability were reported using descriptive statistics. Continuous variables were summarized by mean and standard deviation. Categorical variables were summarized by counts and percentages. Unknown or not reported categorical data were included as a separate "unknown" or "not reported" category. The findings of this study are reported in compliance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13].

3 Results

3.1 Demographics in ATTRibute-CM and Real-World Patients

Noncomparative demographic data from the ATTRibute-CM study and Optum CDM are co-reported in Table 1. Baseline data from 632 participants with ATTR-CM enrolled in the ATTRibute-CM study were analyzed. Reported baseline demographics included age, sex, and race or ethnicity. Participants had a mean age of approximately 77 years, a higher proportion of men (90.2%), and primarily included white patients (87.8%).

Across 5601 patients in the Optum CDM analysis, the mean age was 76 years, more than half of patients were men (57.1%), and patients were primarily white (61.0%).

3.2 Oral Medication Use and Frequency in ATTRibute-CM

Oral medication usage and frequency in the ATTRibute-CM study are shown in Fig. 1 and Table 2. Nearly all participants reported using an oral medication at baseline in the ATTRibute-CM study ($n = 612$, 96.8%). The most common ATC level 2 drug classifications were antithrombotic agents, diuretics, and beta-blocking agents. In the study, 392 (62.0%) patients were using at least one BID medication, and 407 (64.4%) patients were using a medication that was administered BID, TID, or QID. The most frequent BID medications were apixaban, furosemide, metformin, metoprolol, and carvedilol.

3.3 Accountability to Acoramidis in the ATTRibute-CM Study

Among the study participants, the reported mean proportion of acoramidis tablets taken of the expected number was high (97.1%).

3.4 Patient Attrition in the Optum CDM

Study cohort attrition from the Optum CDM is presented in Fig. 2. From a pool of 2.46 million patients with HF and CM identified in the Optum CDM, 12,116 patients (mean [± SD] age: 76.0 [9.4] years) met the criteria for ATTR-CM, and 5601 patients met the stability criteria (≥ 2 years of continuous enrollment and ≥ 28 days of continuous treatment). A total of 4725 patients had chronic prescription medication use, defined as at least 28 days of supply, of any dosing frequency during 1-year follow-up after index diagnosis.

3.5 Oral Medication Use and Frequency in Real-World Patients

Oral medication usage and frequency in the Optum CDM is shown in Fig. 3 and Table 3. Nearly all patients from the Optum CDM ($n = 4690$, 99.3%) had used an oral medication. The most common ATC level 2 drug classifications were lipid-modifying agents, beta-blocking agents, and diuretics. In the Optum CDM, 4166 (88.2%) patients were using at least one BID medication, and 4351 (92.1%) patients were using a medication that was administered BID, TID, or QID. The most frequent medications regardless of dosing frequency included furosemide, atorvastatin, metoprolol, apixaban, and carvedilol. Rosuvastatin use was also reported in a large proportion of patients (12.4%). The most frequent BID medications were apixaban, carvedilol, furosemide, metoprolol, and potassium chloride.

Patients in the Optum CDM had an average (± SD) of 8.9 (4.1) unique medications per patient (minimum = 1 medication, maximum = 28 medications) and 7.3 (2.9) medication classes per patient (minimum = 1 medication class, maximum = 17 medication classes) (Table 4).

4 Discussion

This study reports on the characteristics and medication usage patterns in patients with ATTR-CM from two different sources: the ATTRibute-CM study and Optum CDM claims

Table 1 Demographics of patients in the ATTRibute-CM study at baseline and the Optum CDM

	Overall safety population in ATTRibute-CM study $N = 632$
Age, years, mean (± SD)	77.3 (6.6)
Sex, *n* (%)	
Male	570 (90.2)
Female	62 (9.8)
Race or ethnic group, *n* (%)	
American Indian or Alaska Native	1 (0.2)
Asian	13 (2.1)
Black or African American	30 (4.7)
Native Hawaiian or Other Pacific Islander	1 (0.2)
White	555 (87.8)
Other	6 (0.9)
Multiple races	2 (0.3)
Not reported	24 (3.9)
	Optum CDM analysis $N = 5601$
Age, years, mean (± SD)	76.3 (9.4)
Sex, *n* (%)	
Male	3198 (57.1)
Female	2403 (42.9)
Race, *n* (%)	
Asian	107 (1.9)
Black	1200 (21.4)
White	3400 (61.0)
Unknown	159 (2.8)
None	735 (13.1)
Ethnicity, *n* (%)	
Hispanic	407 (7.3)
Non-Hispanic	4362 (77.9)
Unknown	107 (1.9)
None	725 (12.9)
Comorbidities reported for patients with ATTR-CM during a 12-month look-back from index diagnosis	$n = 4698$
Comorbidities (CCI), *n* (%)	
Congestive heart failure	3373 (71.8)
Renal disease	2180 (46.4)
Diabetes without chronic complications	2050 (43.6)
Peripheral vascular disease	1737 (37.0)
Chronic pulmonary disease	1710 (36.4)
Cerebrovascular disease	1610 (34.3)
Diabetes with chronic complications	1560 (33.2)
Myocardial infarction	981 (20.9)
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of the skin	774 (16.5)
Dementia	587 (12.5)

ATTR-CM transthyretin amyloid cardiomyopathy, *CCI* Charlson Comorbidity Index, *CDM* Clinformatics Data Mart, *SD* standard deviation

data. Of note, different methodologies were employed for reporting baseline medication use in ATTRibute-CM versus assessing chronic (≥ 28 days) medication use over a 1-year follow-up period. The different methods used may explain some of the differences in medication usage patterns seen from the two different sources.

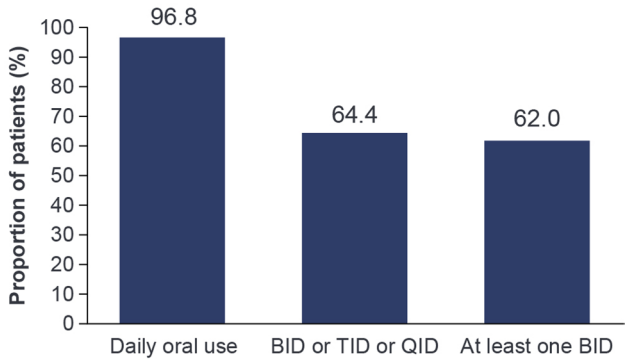


Fig. 1 Oral medication use in the ATTRibute-CM study ($N = 632$) at baseline. *BID* twice daily, *QID* four times daily, *TID* three times daily

Table 2 Oral medication frequency in the ATTRibute-CM study at baseline[a]

	Overall safety population $N = 632$
Most frequent drug class[b] administered BID,[a] number of participants, *n* (%)	
Antithrombotic agents	208 (32.9)
Diuretics	120 (19.0)
Beta-blocking agents	88 (13.9)
Agents acting on the renin-angiotensin system	39 (6.2)
Drugs used in diabetes mellitus	37 (5.9)

BID twice daily

[a]Only medications started before the first dose of study drug and continued on/after the day of the first dose of study drug are included in the analysis

[b]Medication class is based on the World Health Organization Anatomical Therapeutic Chemical level 2 drug classification

More than 95% of patients in the ATTRibute-CM study and from the Optum CDM used an oral medication. Most patients with ATTR-CM were administered multiple oral medications for treatment of HF and other comorbidities, with as many as 92.1% of patients in the Optum CDM prescribed at least one BID, TID, or QID medication. This suggests that a BID, disease-modifying therapy, such as acoramidis, may be seamlessly integrated into the existing ATTR-CM treatment regimen.

On average, patients included in both the ATTRibute-CM study and the Optum CDM were over 75 years of age. While the majority of patients in each setting were male, the proportion of female patients with ATTR-CM was notably higher in the Optum CDM compared with the ATTRibute-CM study (42.9% versus 9.8%). A recent systematic literature review found that prevalent cases of patients with ATTR-CM in the HF population were usually in their late 70s [14]. Between 56 and 94% of the general ATTR-CM population were male [14]. ATTR-CM is underrecognized in women, and at the time of ATTRibute-CM study enrollment, this proportion of male and female patients was reflective of the current demographics. It is possible that with increased awareness of ATTR-CM since the initiation of ATTRibute-CM, diagnosis in female patients is on the rise as reflected by the proportion of female patients in our analysis, but further effort is needed to understand the true prevalence of ATTR-CM in women. However, despite the variation in the proportion of male and female patients with ATTR-CM, in a population with greater sex diversity, a substantial portion of patients still take medications multiple times a day. The patient population of the ATTRibute-CM study and those from the Optum CDM were predominantly white, with other races and ethnicities being underrepresented.

The most common ATC level 2 drug classifications for both settings were antithrombotic agents, diuretics, and beta-blocking agents, which are often prescribed to patients with HF. In the ATTRibute-CM study, the most frequent BID medications were apixaban, furosemide, metformin, metoprolol, and carvedilol. Patient accountability for acoramidis (expressed as the mean proportion of tablets taken of the expected number) in the ATTRibute-CM study was high (approximately 97.1%). While not indicative of real-world adherence, these data demonstrate high accountability to the BID dosing schedule in the ATTRibute-CM study. For the Optum CDM, the most frequent medications regardless of dosing frequency were furosemide, atorvastatin, metoprolol, apixaban, and carvedilol. It is important to note that traditional HF therapies, such as beta-blockers, may not be well tolerated in patients with ATTR-CM [15, 16], and yet beta-blockers were commonly prescribed in the ATTRibute-CM study and the Optum CDM. It is possible that this represents a subset of patients with ATTR-CM who may tolerate these agents, or a subset who do not tolerate them but have yet to be discontinued. In a retrospective study of 2371 patients diagnosed with ATTR-CM at the UK National Amyloidosis Centre who were prescribed conventional HF medications, 1313 (55.4%) patients were treated with beta-blockers [15]. Of those treated with beta-blockers, 829 received low-dose beta-blockers, 285 discontinued beta-blocker treatment, and 117 had their beta-blocker dosing reduced [15]. Although a considerable proportion of patients had their dose of beta-blockers reduced or discontinued, low-dose beta-blockers were associated with reduced risk of mortality in patients with a left ventricular ejection fraction $\leq 40\%$ [15].

Also of note, patients included in this analysis may have been prescribed antidiabetic medications such as sodium-glucose co-transporter 2 (SGLT2) inhibitors (e.g., canagliflozin, dapagliflozin, and empagliflozin). These medications may have been indicated to reduce the risk of cardiovascular

Inclusion/exclusion step	Excluded patient count	Remaining patients in cohort
Patients diagnosed with ATTR and/or treated with tafamidis between 2016 and 2022	20,750	
Exclude patients without HF/CM diagnosis within 2 years of ATTR	873	19,877
Exclude patients without at least one HF/CM diagnosis between 2018 and 2021	7761	12,116
Exclude patients with AL/MM before index diagnosis or within 18 months following index diagnosis	2708	9408
Exclude patients undergoing treatment on AL chemotherapy drugs anytime during 2016 and 2022	87	9321
Exclude patients with heart, liver, or kidney transplants on or before index diagnosis or within 12 months following index diagnosis	239	9082
Exclude patients with heart device implants on or before index diagnosis or within 12 months following index diagnosis	113	8969
Exclude patients who do not meet stability criteria	3368	5601
Final ATTR-CM patient cohort	5601	
Patients with chronic prescription medication of any dosing frequency during 1-year follow-up after index diagnosis	4739	
Patients with chronic prescription medication of any dosing frequency during 1-year follow-up after index diagnosis with days of supply ≥ 28 days within dosing frequency for a brand	4725	
Patients with chronic BID prescription medications during 1-year follow-up after index diagnosis	4166	

Fig. 2 Optum CDM patient attrition. *AL* amyloid light-chain, *ATTR-CM* transthyretin amyloid cardiomyopathy, *BID* twice daily, *CDM* Clinformatics Data Mart, *CM* cardiomyopathy, *HF* heart failure, *MM* multiple myeloma

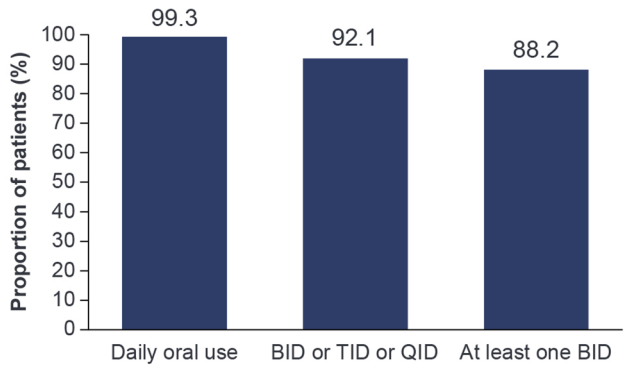


Fig. 3 Chronic (≥ 28 continuous days) oral medication use in patients with ATTR-CM from the Optum CDM ($N = 4725$). *ATTR-CM* transthyretin amyloid cardiomyopathy, *BID* twice daily, *CDM* Clinformatics Data Mart, *QID* four times daily, *TID* three times daily

death and hospitalization for HF [17–19]. An observational study of patients with ATTR-CM who were treated with SGLT2 inhibitors reported that SGLT2 inhibitors were associated with reduced risk of HF hospitalization as well as cardiovascular and ACM [20]. These recent data suggest a possible expanded role for these medications in patients with ATTR-CM.

There was a considerable proportion of patients with ATTR-CM who received medications BID, even with the exclusion of diuretics. Diuretics are often prescribed BID but are administered at different times from other medications because of their potential adverse effects. There are numerous factors that may affect the consistent timing of dosing of specific medications during the day. For example, patients taking BID diuretics often avoid taking diuretics at bedtime. This can potentially lead to a dosing period that is missed for each concomitant medication scheduled at that time. Given that acoramidis has BID dosing frequency and is generally well tolerated [7], these data support the view that the addition of acoramidis could align with the current non-ATTR-CM pharmacotherapeutic dosing schedules of patients with ATTR-CM. This may allow for the seamless implementation of acoramidis administration when added to a patient's medication regimen.

Owing to the relative rarity of ATTR-CM and the subsequent limited distribution of treatment for the disease, it is expected that patients with ATTR-CM who are prescribed

Table 3 Chronic (≥ 28 continuous days) oral medication frequency in patients with ATTR-CM from the Optum CDM

	Overall population $N = 4725$
Most frequent drug class administered,[a,b] number of patients, *n* (%)	
Lipid-modifying agents	3414 (72.3)
Beta-blocking agents	3386 (71.7)
Diuretics	3356 (71.0)
Agents acting on the renin-angiotensin system	2719 (57.5)
Antithrombotic agents	2494 (52.8)
Most frequent medications administered,[a,b] number of patients, *n* (%)	
Furosemide	2128 (45.0)
Atorvastatin calcium	2094 (44.3)
Metoprolol succinate	1402 (29.7)
Apixaban	1270 (26.9)
Carvedilol	1227 (26.0)
Amlodipine besylate	1225 (25.9)
Potassium chloride	1200 (25.4)
Spironolactone	1136 (24.0)
Lisinopril	997 (21.1)
Gabapentin	982 (20.8)
Most frequent drug class administered BID,[a,b] number of patients, *n* (%)	
Beta-blocking agents	2051 (49.2)
Antithrombotic agents	1474 (35.4)
Diuretics	1325 (31.8)
Agents acting on the renin-angiotensin system	700 (16.8)
Drugs used in diabetes mellitus	606 (14.5)

ATTR-CM transthyretin amyloid cardiomyopathy, *BID* twice daily, *CDM* Clinformatics Data Mart, *NDC* National Drug Code

[a]Top five drug classes with the most medication use (based on proportion of patients) are listed here

[b]Medication class is based on the World Health Organization Anatomical Therapeutic Chemical level 2 classification, mapped by NDC using mapping maintained by Definitive Healthcare

Table 4 Unique medications per patient (any dosing frequency) with ATTR-CM from the Optum CDM

Unique medications per patient	
Minimum	1
Maximum	28
Mean (± SD)	8.9 (4.1)
Median	9
Unique medication classes per patient[a]	
Minimum	1
Maximum	17
Mean (± SD)	7.3 (2.9)
Median	7

ATTR-CM transthyretin amyloid cardiomyopathy, *CDM* Clinformatics Data Mart, *NDC* National Drug Code, *SD* standard deviation

[a]Medication class is based on the World Health Organization Anatomical Therapeutic Chemical level 2 classification, mapped by NDC using mapping maintained by Definitive Healthcare

treatment for the disease will have these medications filled by a specialty pharmacy. As shown both in this analysis and in previous studies, patients with HF are prone to polypharmacy [1]. As such, most patients with ATTR-CM are expected to be prescribed medications commonly used for cardiovascular conditions that may lead to adverse effects, including fatigue and hypotension [1]. Given that the ATTR-CM population tends to be older (aged > 60 years), it is important that patients receive additional support and education for their treatment [1]. A multidisciplinary approach to care would aid in the management of current medication regimens and the potential implementation of new therapies [1].

4.1 Limitations

Although the Optum CDM is a high-quality resource for obtaining real-world data, claims databases for study of medication usage are subject to some limitations. These include but are not limited to the exclusion of uninsured patients and patients with Medicare Fee-For-Service or commercial coverage outside of those captured in the Optum CDM, and incomplete data in circumstances where patients obtain medications through means outside of commercial insurance and ascertainment bias.

Findings were reported descriptively, thus medication use could not be used to compare data from these two settings nor be assessed for correlations to specified outcomes or surrogate endpoints. Medication use at baseline was captured in the clinical study report during the ATTRibute-CM trial. Because oral medication use at baseline is a snapshot of a patient's medication history, the proportion of participants who used a BID medication in the ATTRibute-CM study population may not fully reflect the number of patients who were taking a BID medication during the course of the study.

Although patients in the Optum CDM had a diagnosis code for ATTR and either CM or HF, diagnoses for ATTR-CM were not cross-referenced or confirmed due to the limitations of claims databases. This is especially challenging, as there are no uniform coding practices specifically for ATTR-CM. It is possible that a proportion of patients with ATTR-CM were not captured, and that some patients without ATTR-CM were inappropriately included. For example, the discrepancy between the proportion of female patients in the ATTRibute-CM study and the Optum CDM may be due to challenges with the identification of patients with ATTR-CM based on database findings. When analyzing real-world claims, it can also be challenging to extract a complete profile of patients. In this analysis, comorbidities were assessed and the Charlson Comorbidity Index was calculated to address this challenge. Like most claims databases, the challenge in the Optum CDM is that it contains limited biomarker data and diagnostic tests with inconsistency in ICD-10 coding; therefore, ATTR-CM diagnosis could not be verified. Indeed, we cannot exclude misclassification bias due to the nature of the Optum CDM database. Patient characteristics and comorbidities in those who carry the ATTR-CM diagnoses are aligned with the existing literature [21]. Data for patient adherence to acoramidis as well as polypharmacy risks and dosing complexities in the real world were unavailable via the Optum CDM, because acoramidis was not yet approved when this study was conducted.

5 Conclusions

On the basis of its oral dosing schedule, acoramidis, a novel treatment for ATTR-CM recently approved for the treatment of wild-type and variant ATTR-CM, does not appear to deviate from non-ATTR-CM or general HF pharmacotherapy dosing strategies. The findings of this study suggest that treatment with acoramidis may align with and could possibly be incorporated into the current non-ATTR-CM pharmacotherapeutic regimens of patients with ATTR-CM.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40256-025-00752-x.

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Declarations

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Conflict of interest N.D. is a consultant and advisor for Alexion and AstraZeneca; and a speaker for Alnylam. S.H.P. is a consultant and has received fees from BridgeBio, Pfizer, and AstraZeneca; and research support from Novo Nordisk. M.E. and A.V.A. have no relevant financial relationships to disclose. K.B.S. is a consultant, advisor, and speaker for Pfizer. L.H., S.S., J.F.T., and H.F. are employees and stakeholders of BridgeBio Pharma, Inc., San Francisco, CA, USA. R.M., M.A., and P.S. are employees of Definitive Healthcare. J.L.G. is a researcher for Texas Health Resources Clinical Scholarship, Eidos/BridgeBio, Pfizer, and NHLBI R01HL160892; and a consultant and advisor for Pfizer, Eidos/BridgeBio, AstraZeneca, Intellia, Tenax Therapeutics, Alnylam, Novo Nordisk, Lumanity, Ultromics, and Alexion.

Data availability Qualified academic investigators may submit requests for access to aggregated/summary data that support the findings of this study via MedInfo@BridgeBio.com. Requests for access to study data will be evaluated by BridgeBio Pharma, Inc., and access will be provided contingent upon the approval of a research/study proposal and the execution of a data sharing agreement. BridgeBio Pharma will consider requests for access to participant-level data if partici-

pant privacy is assured through methods such as data deidentification, pseudonymization, or anonymization (as required by applicable law), and if such disclosures were included in the relevant study's informed consent form or study protocol.

Ethics approval The ATTRibute-CM (NCT03860935) trial was conducted in accordance with the International Council for Harmonization, Good Clinical Practice, and the Declaration of Helsinki. The trial was approved by an ethics committee at each participating site.

Consent to participate All participants provided written informed consent to participate in the ATTRibute-CM study.

Consent for publication Not applicable.

Author contributions N.D. contributed to investigation, writing—original draft, and writing—review and editing. S.H.P. contributed to writing—original draft and writing—review and editing. M.E. contributed to writing—original draft and writing—review and editing. A.V.A. contributed to investigation, writing—original draft, and writing—review and editing. K.B.S. contributed to writing—original draft and writing—review and editing. L.H. and H.F. contributed to the methodology, writing—original draft, and writing—review and editing. S.S. contributed to investigation, writing—original draft, and writing—review and editing. J.F.T. contributed to investigation, writing—original draft, and writing—review and editing. R.M. contributed to writing—original draft and writing—review and editing. M.A. contributed to investigation, writing—original draft, and writing—review and editing. P.S. contributed to writing—original draft and writing—review and editing. J.L.G. contributed to investigation, writing—original draft, and writing—review and editing.

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