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ORIGINAL ARTICLE

Real-world characteristics and treatment of cardiac transthyretin amyloidosis: A multicentre, observational study

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Abstract

Aims Data on the clinical profiles of patients with transthyretin amyloidosis cardiomyopathy (ATTR-CM) in the post-approval era of tafamidis 61 mg are lacking. Study aims were characterization of contemporary ATTR-CM patients, analysis of potential eligibility for the 'Transthyretin Amyloidosis Cardiomyopathy Clinical Trial' (ATTR-ACT) and identification of factors associated with the decision on tafamidis 61 mg treatment.

Methods and results This retrospective study analysed ATTR-CM patients seen at eight University Hospitals in the first year after approval of tafamidis 61 mg for ATTR-CM in Germany (April 2020 to March 2021). The cohort comprised 366 patients (median age 79 [74; 82] years, 84% male), with 47% and 45% of the cohort being in National Amyloidosis Centre ATTR stage $\geq$ II and NYHA class $\geq$ III, respectively. Sixty-four per cent of patients met key eligibility criteria of the pivotal ATTR-ACT. In recently diagnosed patients (58% with diagnosis $\leq$6 months), the rate of variant ATTR was significantly lower than in patients diagnosed more than 6 months ago (9.3% vs. 19.7%). Of the 293 patients without prior ATTR specific treatment, tafamidis 61 mg was newly initiated in 77%. Patients with tafamidis 61 mg treatment were significantly younger, were more often eligible for ATTR-ACT, had lower NYHA class and higher serum albumin levels. These variables explained 16% of the variance of treatment decision. Unadjusted survival was higher in patients with than those without treatment (1-year survival 98.6% vs. 87.3%, $P < 0.001$).

Conclusions Wild-type ATTR was the primary aetiology amongst contemporary ATTR-CM patients and almost two-thirds of patients were in an advanced disease stage. Clinical profiles of 64% of patients in routine care matched those of the ATTR-ACT. Further effort is needed to detect patients at an earlier disease stage and to validate criteria justifying treatment initiation.

Keywords Cardiac amyloidosis; Cardiomyopathy; Heart failure; TTR; Transthyretin; Tafamidis

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Introduction

Transthyretin amyloidosis (ATTR) is a progressive systemic disease characterized by the extracellular accumulation of insoluble transthyretin fibrils in multiple organs.[1] Amyloid infiltration often involves the heart in both forms of genetic variant (vATTR) and wild-type (wtATTR) disease. Patients with ATTR cardiomyopathy (ATTR-CM) frequently develop typical signs and symptoms of heart failure (HF), which then becomes the strongest determinant of an unfavourable prognosis.[2,3] The median survival in untreated patients with ATTR-CM was 2.5 to 3.6 years in earlier reports.[2,4,5]

In 2020, the first disease modifying therapy for ATTR-CM was approved and became commercially available in several European countries based on the findings of the pivotal 'Transthyretin Amyloidosis Cardiomyopathy Clinical Trial' (ATTR-ACT). Treatment with tafamidis meglumine (20 and 80 mg) compared with placebo was associated with improved clinical outcome and attenuation of the longitudinal decline in functional capacity and quality of life.[6] However, the benefit of tafamidis meglumine treatment appeared to depend on early initiation during the disease course.

Our knowledge on characteristics and outcome of patients with ATTR-CM is derived from historical cohorts enrolled 10 to 15 years ago by few reference centers world-wide mostly with high portions of vATTR and neurological involvement.[4,7,8] During the last five years, disease awareness, clinical recognition of 'red flags' for initiation of screening, and diagnostic modalities have improved markedly resulting in a substantial increase in the detection of patients with both vATTR and wtATTR.[9–14] Recent studies provided evidence on certain patient groups at high-risk of ATTR-CM in whom active screening for ATTR-CM might be reasonable.[15–17] It is still unclear how these developments should be applied to the clinical profiles of patients diagnosed nowadays in routine care. Finally, data on the use of tafamidis 61 mg in the clinical post-approval setting are lacking so far and it is of major interest which clinical criteria are used to decide on the eligibility of tafamidis 61 mg treatment.

Hence, the objectives of this study were to 1) characterize contemporary patients with ATTR-CM with respect to demographics, diagnostic modalities, disease stage, co-morbidities, and outcome 2) analyse real-world patient characteristics with respect to eligibility for the ATTR-ACT participation and 3) identify patient characteristics associated with the decision to initiate tafamidis 61 mg.

Methods

Study population

In this retrospective, multicenter, observational registry (ATTRreal-y1), patients with a diagnosis of ATTR-CM, who were seen in the cardiology department of one of the participating tertiary care centers between April 1st, 2020 and March 31st, 2021 (corresponding to the first year after tafamidis 61 mg approval for treatment of ATTR-CM in Germany) were included. Participating centers were University Hospitals of Düsseldorf, Berlin, Essen, Homburg, Köln, Münster, Regensburg, and Würzburg. Diagnosis of ATTR-CM was made locally according to the recommendations of the European Society of Cardiology (ESC) cardiac amyloidosis working group either by endomyocardial biopsy (EMB), extracardiac biopsy and typical cardiac morphology on imaging, or non-invasively via positive bone scintigraphy in the absence of monoclonal gammopathy.[1] Patients could be diagnosed and treated for ATTR-CM before April 1, 2020, but the first assessment at the respective center between April 1, 2020 and March 31, 2021 was regarded as the baseline for this registry. Analyses were made from anonymized data contributed by each center. The study complies with the Declaration of Helsinki and was approved by the local ethics committees of the University of Cologne (22–1090 retro) and Würzburg (2021101101 and 2021101102). Informed consent has been obtained from all patients.

Data collection

Clinical baseline und follow-up parameters with respect to demographics, co-morbidity, laboratory markers, concomitant medication, electrocardiogram (ECG), imaging and other diagnostic results were gathered from routine care procedures at each center. The measurements of interventricular septal thickness at end-diastole (IVSd) as well as systolic and diastolic functional parameters were determined locally according to current recommendations.[18,19] Patients were clinically followed-up at each center as part of routine care so that vital status was assessed from records. Patients who could not be reached by phone at the end of the observation period, and for whom no information could be obtained through their primary care physician, were classified as lost to follow-up.

An advanced disease stage of ATTR-CM was defined by the presence of dyspnea classified as NYHA class III or IV or by National Amyloidosis Centre (NAC) stage II or III.[5,20] Patient characteristics were checked whether they fulfilled key selection criteria applied for ATTR-ACT.[6] This analysis considered the following inclusion criteria of ATTR-ACT: age between 18 and 90 years, N-terminal pro-brain natriuretic peptide (NT-proBNP) level $\geq$ 600 pg/mL, IVSd $>$ 12 mm, and clinical signs of HF (NYHA functional class II or higher, history of cardiac decompensation or use of diuretics). The following exclusion criteria of ATTR-ACT were considered: NYHA class IV, estimated glomerular filtration rate (eGFR) $<$ 25 mL/min/1.73 m^2, mechanical circulatory support system, TTR genotype not tested, and tafamidis meglumine 20 mg treatment. Patients with gene silencer therapy were also excluded since they do not qualify for additional tafamidis 61 mg therapy.

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Data analysis

Data are reported as count (percent), mean (standard deviation, SD) or median (quartiles) as appropriate. In order to consider temporal changes in the diagnostic course and impact on patient characteristics, the study cohort was analysed by the time that had elapsed between the first diagnosis of ATTR-CM and baseline assessment. Patients diagnosed within the last six months prior to baseline assessment were classified as recently diagnosed ATTR-CM and were compared with patients, who already had confirmed ATTR-CM for more than 6 months. In order to examine clinical characteristics potentially impacting the decision on initiation of tafamidis 61 mg therapy, patients with newly initiated tafamidis 61 mg were compared with those who did not receive this treatment. For this analysis, patients receiving gene silencers (i.e., inotersen or patisiran), patients treated with tafamidis meglumine 20 mg approved for polyneuropathy (PNP), and patients treated with tafamidis 61 mg prior to the baseline introduction within a compassionate use programme were excluded. Multivariable logistic regression analysis with tafamidis 61 mg initiation as dependent variable was performed entering all characteristics, which were significantly ($P < 0.05$) associated with tafamidis 61 mg initiation in univariable analysis. Nagelkerke's R^2 was employed to measure the extent to which these variables collectively explained the variance of the model. Secondary analysis was performed on wtATTR patients only, as these differed substantially from vATTR patients by age and associated co-morbidities.

For assessing group difference, the unpaired *t*-test, Mann–Whitney *U* test or chi-square test was employed as appropriate. Testing for normal distribution was done using the Kolmogorov–Smirnov or Shapiro–Wilk tests. Differences in Kaplan–Meier survival curves were tested using the log-rank test. A *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Macintosh version 29.0.0.0. Kaplan–Meier survival plots were created in R (version 4.2.0) using the UpSetR (version 1.4.0) and the survival (version 3.3–1) and survminer (version 0.4.9) packages, respectively. For additional graphical illustrations, Microsoft Excel (version 16.82), Microsoft PowerPoint (version 16.88.1), and BioRender were utilized.

Results

Study population

The study population available for current analysis encompassed 366 patients: their median age was 79 [74; 82] years, 84% were men, and 13.7% of patients had vATTR (*Table 1*). Median time since first diagnosis of ATTR-CM was 4 [0; 18] months. Forty-five per cent of patients were in NYHA class III or IV, and 26% had a history of cardiac decompensation. According to the NAC staging system, 53% of patients were in stage I, 32% in stage II, and 15% in stage III.[5] A total of 63% (192/305) of the study sample were in NAC stage $\geq$ II and/or NYHA class III/IV. Mean IVSd was 18 (±4) mm, mean left ventricular ejection fraction (LVEF) was 52 (±10) % and average global longitudinal strain (GLS) was −10.7 (±3.6) %. Median follow-up time was 14 [11; 20] months. Twenty-six patients were lost to follow-up and were not considered for survival analysis. Overall estimated 1-year survival rate was 96.9% (Figure S1).

Eligibility for ATTR-ACT

The key selection criteria of ATTR-ACT were applied to 310 patients of the study sample due to incomplete data in 56 patients. Of those, 81% (252/310) would have been eligible for ATTR-ACT inclusion. An NT-proBNP level below the inclusion target was observed in 48 and was the most frequent cause for not fulfilling inclusion criteria (*Figure 1*). Of potentially eligible patients fulfilling inclusion criteria, 22% (55/252) fulfilled at least one exclusion criterion, with the main cause being lack of TTR genotype testing (n = 25). Finally, 64% (197/310) of the sample with available data met key criteria for participation in the ATTR-ACT (*Table 1*). In addition to effects of the key inclusion/exclusion criteria, patients with ATTR-ACT eligibility had significantly higher rates of male gender, arterial hypertension, diabetes, coronary artery disease (CAD), atrial fibrillation (AF), lumbar spinal stenosis, beta-blocker use, diuretic use, oral anticoagulation use, advanced disease stage, and any biopsy for diagnosis. They also had significantly higher NAC stage, troponin levels, and systolic pulmonary arterial pressure (sPAP), significantly lower LVEF, GLS and tricuspid annular plane systolic excursion (TAPSE), and significantly lower rates of non-invasive ATTR diagnosis; 87% (172/197) of these patients were finally treated with tafamidis 61 mg. Out of 113 patients who were ineligible for the ATTR-ACT, 33 patients received gene silencers or tafamidis meglumine 20 mg approved for PNP. 66% of the remaining patients (53/80) were treated with tafamidis 61 mg.

Recent versus longer-standing diagnosis of ATTR

Of the total cohort, 42% had been diagnosed with ATTR-CM more than 6 months prior to the study baseline assessment, while the remaining 58% had received their diagnosis more recently (*Table 2*). Recently diagnosed patients were older, had a lower proportion of vATTR-CM, suffered less frequently from PNP, and had been less often treated with tafamidis meglumine 20 mg approved for PNP (*Figure 2*). They were less frequently in advanced NAC stage, had a higher LVEF, and reported less often previous cardiac decompensation. Recently diagnosed patients with wtATTR-CM were signifi-

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Table 1 Baseline characteristics of the entire ATTR-CM cohort, and by ATTR-ACT key selection criteria

		Patients available for the ATTR-ACT analysis (n = 310)		
	ATTR-CM study cohort (n = 366)	Key criteria of the ATTR-ACT fulfilled (n = 197) (63.5%)	Key criteria of the ATTR-ACT not fulfilled (n = 113) (36.5%)	P
Type of ATTR-CM				<0.001
Wild-type, %	77.9	93.9	43.4	
Variant, %	13.7	6.1	31.0	
Not tested, %	8.5	0.0	25.7	
Time since first diagnosis (months), Mdn [Q_1; Q_3]	4 [0; 18]	4 [0; 16]	4 [1; 24]	0.224
Demographic data				
Male patients, %	84.4	89.3	80.5	0.031
Age (years), Mdn [Q_1; Q_3]	79 [74; 82]	80 [76; 83]	76 [66; 82]	<0.001
BMI (kg/m^2), M ± SD	26.9 ± 11.4 (n = 347)	27.2 ± 14.8 (n = 194)	26.6 ± 4.4 (n = 107)	0.473
Modified BMI [(kg/m^2) × (g/L)], M ± SD	1187 ± 591 (n = 224)	1201 ± 770 (n = 126)	1173 ± 213 (n = 74)	0.101
Vital parameters				
SBP (mmHg), M ± SD	133 ± 20 (n = 310)	132 ± 19 (n = 176)	134 ± 22 (n = 92)	0.629
DBP (mmHg), M ± SD	77 ± 12 (n = 309)	77 ± 12 (n = 176)	78 ± 12 (n = 92)	0.362
HR (1/min), M ± SD	73 ± 14 (n = 353)	72 ± 14 (n = 194)	74 ± 14 (n = 111)	0.186
Symptoms				
NYHA class				<0.001
I, %	14.8 (n = 331)	6.6	27.9 (n = 104)	
II, %	40.5 (n = 331)	42.6	39.4 (n = 104)	
III, %	42.6 (n = 331)	50.8	27.9 (n = 104)	
IV, %	2.1 (n = 331)	0.0	4.8 (n = 104)	
History of cardiac decompensation, %	26.0 (n = 246)	28.7 (n = 136)	23.1 (n = 91)	0.348
Co-morbidities				
History of arterial hypertension, %	66.4 (n = 363)	69.0	56.6	0.028
Diabetes mellitus, %	18.5 (n = 362)	21.9 (n = 196)	11.5	0.022
CAD, %	42.7 (n = 356)	46.7	29.7 (n = 111)	0.004
AF, %	57.9 (n = 354)	65.5 (n = 194)	40.5 (n = 111)	<0.001
History of CTS, %	37.5 (n = 355)	39.6	30.6 (n = 111)	0.116
Lumbar spinal stenosis, %	14.4 (n = 355)	17.3	9.0 (n = 111)	0.047
History of SAVR or TAVI, %	4.5 (n = 355)	4.6 (n = 196)	4.5 (n = 111)	0.972
PNP, %	32.6 (n = 356)	30.5	40.5 (n = 111)	0.073
PM, %	16.2 (n = 352)	14.7	14.4 (n = 111)	0.942
Medication				
Diuretics, %	66.5 (n = 352)	77.9 (n = 195)	45.0 (n = 109)	<0.001
ACEi, AT1-I or ARNI, %	56.6 (n = 355)	56.9 (n = 195)	54.1 (n = 111)	0.627
Beta-blocker, %	55.4 (n = 352)	62.4 (n = 194)	37.3 (n = 110)	<0.001
Oral anticoagulation, %	60.8 (n = 357)	68.9 (n = 196)	44.5 (n = 110)	<0.001
Biomarker				
Serum albumin (g/L), M ± SD	43.0 ± 3.9 (n = 239)	42.9 ± 4.2 (n = 129)	42.9 ± 3.8 (n = 79)	0.623
NT-proBNP (pg/mL), Mdn [Q_1; Q_3]	2520 [1229; 4349] (n = 343)	2855 [1841; 4534]	982 [271; 3794] (n = 112)	<0.001
GFR (mL/min), M ± SD	60.8 ± 21.1 (n = 348)	59.7 ± 17.4 (n = 197)	65.1 ± 27.5 (n = 109)	0.095
Troponin T (ng/mL), M ± SD	0.055 ± 0.043 (n = 226)	0.055 ± 0.030 (n = 120)	0.055 ± 0.062 (n = 76)	0.019
Hb (g/L), M ± SD	13.5 ± 2.9 (n = 345)	13.7 ± 3.6 (n = 194)	13.4 ± 1.5 (n = 107)	0.608
NAC stage				0.004
I, %	52.5 (n = 337)	47.7	65.1 (n = 109)	
II, %	32.3 (n = 337)	38.1	20.2 (n = 109)	
III, %	15.1 (n = 337)	14.2	14.7 (n = 109)	
Advanced disease stage, %	63.0 (n = 305)	71.6	49.5 (n = 105)	<0.001
Imaging				
LVEF (%), M ± SD	51.9 ± 10.2 (n = 362)	50.5 ± 9.8	55.1 ± 9.8	<0.001
IVSd (mm), M ± SD	18.3 ± 3.9 (n = 362)	19.0 ± 3.3	16.7 ± 4.5	<0.001
E/e', M ± SD	18.1 ± 8.8 (n = 271)	17.4 ± 8.2 (n = 153)	16.6 ± 8.6 (n = 72)	0.228

(*Continues*)

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Table 1 (continued)

		Patients available for the ATTR-ACT analysis (n = 310)		
	ATTR-CM study cohort (n = 366)	Key criteria of the ATTR-ACT fulfilled (n = 197) (63.5%)	Key criteria of the ATTR-ACT not fulfilled (n = 113) (36.5%)	P
GLS (%), M ± SD	−10.7 ± 3.6 (n = 246)	−10.2 ± 3.4 (n = 115)	−12.0 ± 3.9 (n = 91)	<0.001
sPAP (mmHg), M ± SD	36.7 ± 11.7 (n = 239)	37.8 ± 10.0 (n = 145)	33.4 ± 13.0 (n = 60)	0.004
TAPSE (mm), M ± SD	17.3 ± 5.7 (n = 350)	16.5 ± 4.8 (n = 188)	19.6 ± 5.8 (n = 110)	<0.001
Pericardial effusion, %	21.6 (n = 361)	21.8	17.0 (n = 112)	0.305
Diagnostic modalities				
EMB, %	51.6 (n = 364)	57.7 (n = 196)	45.1	0.034
Extracardial biopsy, %	13.7 (n = 364)	13.3 (n = 196)	14.2	0.825
Any biopsy, %	60.7 (n = 364)	66.8 (n = 196)	54.0	0.025
Bone scintigraphy, %	65.2 (n = 362)	64.6 (n = 195)	66.4	0.755
Non-invasive only, %	39.3 (n = 364)	33.2 (n = 196)	46.0	0.025
CMR, %	58.6 (n = 302)	59.4 (n = 165)	62.7 (n = 102)	0.586
ATTR specific medication				
Tafamidis 61 mg, %	78.4	87.3	66.4	<0.001
Pre-treated, %	22.4	20.8	21.2	0.927
Newly prescribed, %	56.0	66.5	45.2	<0.001
Inotersen or patisiran, %	4.1	0.0	12.4	<0.001
Tafamidis dose				
Tafamidis, %	78.4	87.3	66.4	<0.001
meglumine 20 mg, %	6.5	0.0	18.6	<0.001
61 mg, %	71.9	87.3	47.8	<0.001

The 'n' within the columns indicates the number of patients for whom the respective variable was available.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARNI, angiotensin receptor neprilysin inhibitor; AT1-I, angiotensin 1 inhibitor; ATTR, transthyretin amyloidosis; ATTR-ACT, Transthyretin Amyloidosis Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloidosis cardiomyopathy; BMI, body mass index; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; CTS, carpal tunnel syndrome; DBP, diastolic blood pressure; EMB, endomyocardial biopsy; GFR, glomerular filtration rate; GLS, global longitudinal strain; Hb, haemoglobin; HR, heart rate; IVSd, interventricular septal thickness at end-diastole; LVEF, left ventricular ejection fraction; M, mean; Mdn, median; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; PNP, polyneuropathy; Q, quartile; SAVR, surgical aortic valve replacement; SBP, systolic blood pressure; SD, standard deviation; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TAVI, transcatheter aortic valve implantation.

cantly less likely to be in 'advanced disease stages' compared with those with longer-standing diagnosis (*Table* S1).

The use of bone scintigraphy within the diagnostic course was higher in recently diagnosed patients, while extracardiac biopsy was notably less frequent. Fully non-invasive diagnosis of ATTR was numerically slightly more often made in recently diagnosed patients (41.0% vs 36.8%, P = 0.419). Estimated 1-year survival rate of patients with longer-standing and recently diagnosed ATTR-CM did not differ in unadjusted analysis (97.6% vs. 96.4%, respectively; P = 0.530, Figure S2A). Corresponding data on wtATTR-CM are presented in Figure S2B.

New tafamidis 61 mg treatment for ATTR-CM

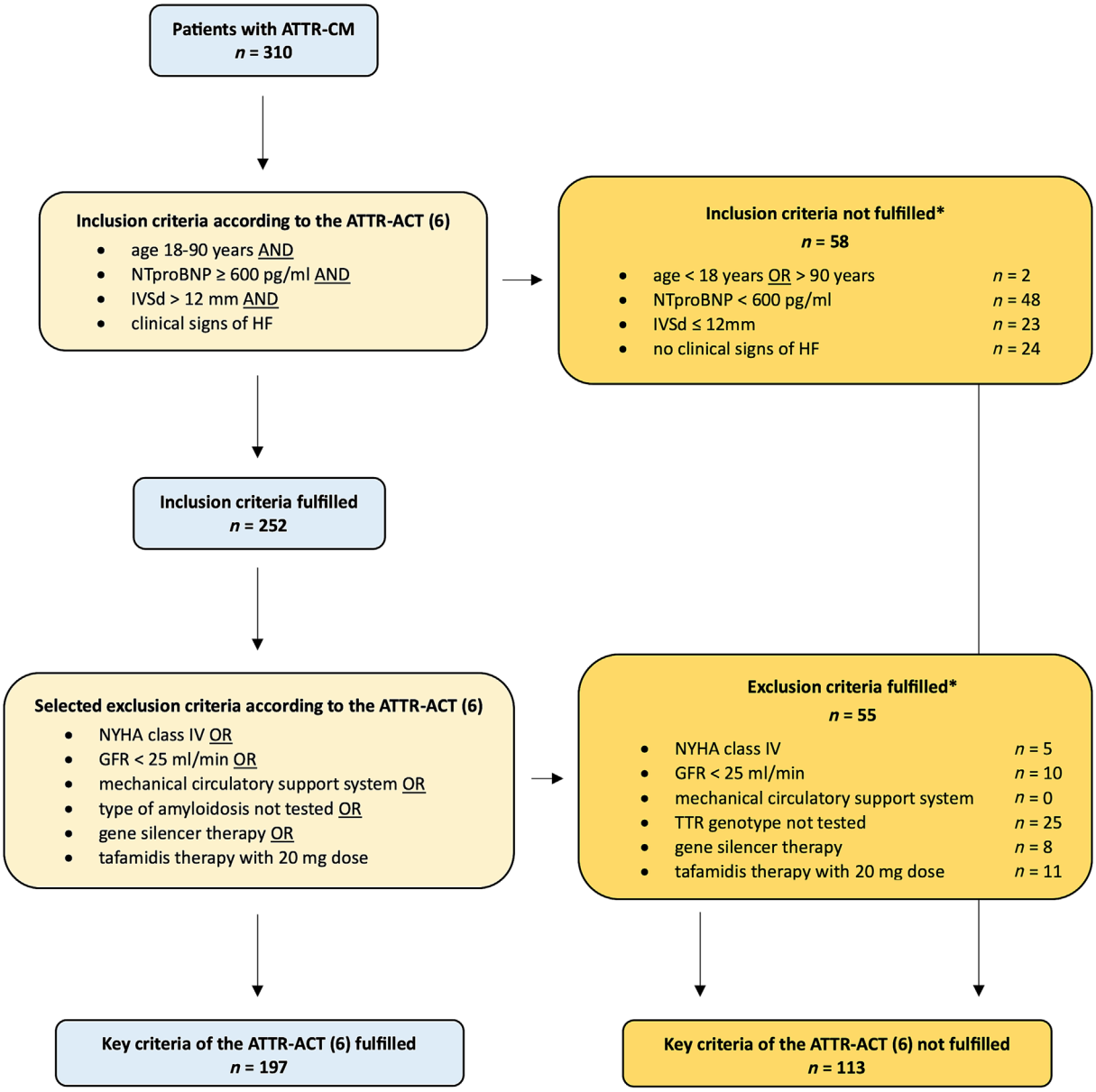
After excluding patients who received gene silencers (n = 15), tafamidis 61 mg within a compassionate use programme (n = 36), or tafamidis meglumine 20 mg (n = 22), the study sample comprised 293 patients. In 77% of these patients, tafamidis 61 mg was initiated (*Table 3*). In 46 of 67 untreated patients, physicians reported one of three prespecified reasons why tafamidis 61 mg was not initiated, with the most common reasons being advanced HF (24%) and severely impaired general patient condition (15%).

Patients with newly commenced tafamidis 61 mg treatment were significantly younger. While there were no significant differences between both groups in terms of co-morbidities and concomitant medications, patients not receiving tafamidis 61 mg were in higher NYHA class and had lower serum albumin levels. Untreated patients less frequently fulfilled the key selection criteria of ATTR-ACT. A logistic regression model incorporating these variables yielded a R^2 of 0.156 (P = 0.001). Survival in patients treated with tafamidis 61 mg was significantly higher compared with those without treatment in unadjusted analysis: 98.6% versus 87.3%, $P < 0.001$; *Figure 3*.

When only wtATTR-CM patients were considered, the findings mirrored those of the entire cohort in terms of age, serum albumin levels and ATTR-ACT eligibility. Patients receiving tafamidis 61 mg less frequently had a history of aortic valve replacement and demonstrated a significantly higher eGFR (Table S2). A logistic regression model incorporating these sig-

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Figure 1 Flowchart depicting frequency of criteria defining a potential participation in the ATTR-ACT trial.[6] *More than one criterion possible.



nificant variables showed a R^2 of 0.233 ($P < 0.001$). The higher survival rate in patients treated with tafamidis 61 mg was also observed in wtATTR-CM patients ($P < 0.001$; Figure S3).

Discussion

The main findings from this analysis of a large contemporary real-world ATT-CM cohort were as follows: (i) almost two-thirds of patients presented with advanced disease stage at baseline, as indicated by NYHA class and NAC stage; (ii) 64% of studied patients complied with the selection criteria of ATTR-ACT, with low NT-proBNP levels, lack of HF symptoms, and only mild left ventricular hypertrophy as most frequent reasons for non-eligibility; (iii) the vast majority of patients had wtATTR, and there was a trend for this share to increase over time amounting to 89% in recently diagnosed patients; (iv) tafamidis at a dose of 61 mg daily was initiated in 77% of patients, particularly in those with less morbidity.

The time delay in diagnosis of ATTR-CM patients is an important reason, why many patients frequently exhibit an advanced disease stage at diagnosis.[21] This contradicts the fact that the current therapy had greatest benefit in the early dis-

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Table 2 Baseline characteristics by time since first diagnosis

	Time since ATTR-CM diagnosis n = 366		
	>6 months n = 152 (41.5%)	≤6 months n = 214 (58.5%)	P
Type of ATTR-CM			<0.001
Wild-type, %	77	78.5	
Variant, %	19.7	9.3	
Not tested, %	3.3	12.1	
Time since first diagnosis (months), Mdn [Q_1; Q_3]	21 [13; 35]	1 [0; 2]	<0.001
Demographic data			
Male patients, %	86.8	82.7	0.283
Age (years), Mdn [Q_1; Q_3]	78 [71; 82]	80 [75; 82]	0.016
BMI (kg/m^2), M ± SD	26.4 ± 3.6 (n = 142)	27.2 ± 14.5 (n = 205)	0.726
Modified BMI [(kg/m^2) × (g/L)], M ± SD	1160 ± 186 (n = 92)	1207 ± 754 (n = 132)	0.6
Vital parameters			
SBP (mmHg), M ± SD	131 ± 22 (n = 121)	134 ± 19 (n = 189)	0.16
DBP (mmHg), M ± SD	78 ± 13 (n = 120)	77 ± 11 (n = 189)	0.433
HR (1/min), M ± SD	73 ± 14 (n = 145)	73 ± 14 (n = 208)	0.953
Symptoms			
NYHA class			0.488
I, %	18.0 (n = 133)	12.6 (n = 198)	
II, %	37.6 (n = 133)	42.4 (n = 198)	
III, %	42.9 (n = 133)	42.4 (n = 198)	
IV, %	1.5 (n = 133)	2.5 (n = 198)	
History of cardiac decompensation, %	33.3 (n = 93)	21.6 (n = 153)	0.041
Co-morbidities			
History of arterial hypertension, %	64.2 (n = 151)	67.9 (n = 212)	0.464
Diabetes mellitus, %	17.2 (n = 151)	19.4 (n = 211)	0.593
CAD, %	40.4 (n = 146)	44.3 (n = 210)	0.467
AF, %	58.5 (n = 147)	57.5 (n = 207)	0.849
History of CTS, %	37.0 (n = 146)	37.8 (n = 209)	0.876
Lumbar spinal stenosis, %	12.3 (n = 146)	15.8 (n = 209)	0.36
History of SAVR or TAVI, %	3.4 (n = 145)	5.2 (n = 210)	0.424
PNP, %	43.2 (n = 146)	25.2 (n = 210)	<0.001
PM, %	19.3 (n = 145)	14.0 (n = 207)	0.184
Medication			
Diuretics, %	69.4 (n = 144)	64.4 (n = 208)	0.326
ACEi, AT1-I or ARNI, %	50.7 (n = 146)	60.8 (n = 209)	0.059
Beta-blocker, %	54.9 (n = 144)	55.8 (n = 208)	0.866
Oral anticoagulation, %	55.1 (n = 147)	64.8 (n = 210)	0.066
Biomarker			
Serum albumin (g/L), M ± SD	43.3 ± 4.5 (n = 101)	42.7 ± 3.4 (n = 138)	0.349
NT-proBNP (pg/mL), Mdn [Q_1; Q_3]	2959 [1002; 5004] (n = 142)	2219 [1308; 4124] (n = 201)	0.386
GFR (mL/min), M ± SD	59.9 ± 23.1 (n = 143)	61.3 ± 19.6 (n = 205)	0.292
Troponin T (ng/mL), M ± SD	0.059 ± 0.056 (n = 96)	0.052 ± 0.029 (n = 130)	0.816
Hb (g/L), M ± SD	13.6 ± 1.5 (n = 142)	13.5 ± 3.5 (n = 203)	0.053
NAC stage			0.016
I, %	43.2 (n = 139)	59.1 (n = 198)	
II, %	38.8 (n = 139)	27.8 (n = 198)	
III, %	18.0 (n = 139)	13.1 (n = 198)	
Advanced disease stage, %	69.4 (n = 121)	58.7 (n = 184)	0.058
Imaging			
LVEF (%), M ± SD	50.1 ± 10.9 (n = 151)	53.2 ± 9.5 (n = 211)	0.014
IVSd (mm), M ± SD	18.4 ± 4.4 (n = 151)	18.3 ± 3.4 (n = 211)	0.384
E/e', M ± SD	18.7 ± 9.0 (n = 117)	17.6 ± 8.6 (n = 154)	0.285
GLS (%), M ± SD	−10.7 ± 3.8 (n = 104)	−10.7 ± 3.5 (n = 142)	0.906
sPAP (mmHg), M ± SD	36.4 ± 12.8 (n = 102)	36.9 ± 10.8 (n = 137)	0.713
TAPSE (mm), M ± SD	17.4 ± 6.6 (n = 146)	17.3 ± 4.9 (n = 204)	0.459
Pericardial effusion, %	23.3 (n = 150)	20.4 (n = 211)	0.502
Diagnostic modalities			
EMB, %	48.7	53.8 (n = 212)	0.338
Extracardial biopsy, %	19.7	9.4 (n = 212)	0.005
Any biopsy, %	63.2	59.0 (n = 212)	0.419
Bone scintigraphy, %	59.3 (n = 150)	69.3 (n = 212)	0.049
Non-invasive only, %	36.8	41.0 (n = 212)	0.419
CMR, %	61.2 (n = 116)	57.0 (n = 186)	0.469

(*Continues*)

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Table 2 (continued)

	Time since ATTR-CM diagnosis n = 366		
	>6 months n = 152 (41.5%)	≤6 months n = 214 (58.5%)	P
ATTR specific medication			
Tafamidis 61 mg, %	81.6	76.2	0.215
Pre-treated, %	54	0	<0.001
Newly prescribed, %	27.6	76.2	<0.001
Inotersen or patisiran, %	6.6	2.3	0.046
Tafamidis dose			
Tafamidis, %	81.6	76.2	0.215
meglumine 20 mg, %	13.2	1.9	<0.001
61 mg; %	68.4	74.3	0.218

The 'n' within the columns indicates the number of patients for whom the respective variable was available.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARNI, angiotensin receptor neprilysin inhibitor; AT1-I, angiotensin 1 inhibitor; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis cardiomyopathy; BMI, body mass index; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; CTS, carpal tunnel syndrome; DBP, diastolic blood pressure; EMB, endomyocardial biopsy; GFR, glomerular filtration rate; GLS, global longitudinal strain; Hb, haemoglobin; HR, heart rate; IVSd, interventricular septal thickness at end-diastole; LVEF, left ventricular ejection fraction; M, mean; Mdn, median; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; PNP, polyneuropathy; Q, quartile; SAVR, surgical aortic valve replacement; SBP, systolic blood pressure; SD, standard deviation; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TAVI, transcatheter aortic valve implantation.

ease stages.[22] In our cohort, NYHA classes III/IV were present in 45% of patients, and advanced NAC stage in 47%. Similar rates of advanced NAC stage have been observed in cohorts enrolling 5 to 20 years ago.[3,5,9,23,24] A temporal shift towards earlier diagnosis of ATTR-CM has been reported in the THAOS registry and the UK-NAC.[23,24] Amongst the most recently diagnosed patients at the UK-NAC, 56% were in NAC stage I and 82% were in NYHA class I or II.[24] The THAOS registry also reported that more than 60% of patients diagnosed in 2019 were in lower NYHA classes.[23] Our findings from several tertiary care centres in Germany, with almost two-thirds of patients being in an advanced disease stage, question the generalizability of above findings which were derived from highly selected centres with longer-standing amyloidosis programmes and potential preselection of patients. Our results underscore the need for additional efforts of early detection via targeted screening of patients at risk of cardiac amyloidosis as proposed by the ESC.[1,25] Important to note, despite the need of early diagnosis of ATTR-CM was already well known during the enrollment time of our study patients, the ESC position statement on diagnosis of ATTR-CM and cumulating clinical evidence on the advocacy of 'red flags' for distinct subspecialities succeeded after enrollment.[1,9] Hence, characteristics of patients might be dynamic in response to clinical developments and patients diagnosed during the last 3 years might be at an earlier disease stage compared to our patients.

Non-invasive, imaging-based diagnosis of ATTR-CM can be achieved in 70%–75% of patients.[23,26] Bone scintigraphy was used in 65% of our patients, which is comparable with results of patients enrolled in the THAOS registry or in routine care data from the United States.[23] However, the overall biopsy rate was still 61%, and only 39% of the patients were diagnosed relying on non-invasively obtained information. Of note, there are no standardized referral pathways for amyloidosis patients in Germany so far, and some steps of the diagnostic algorithm can be performed before patients are transferred to a tertiary care centre.

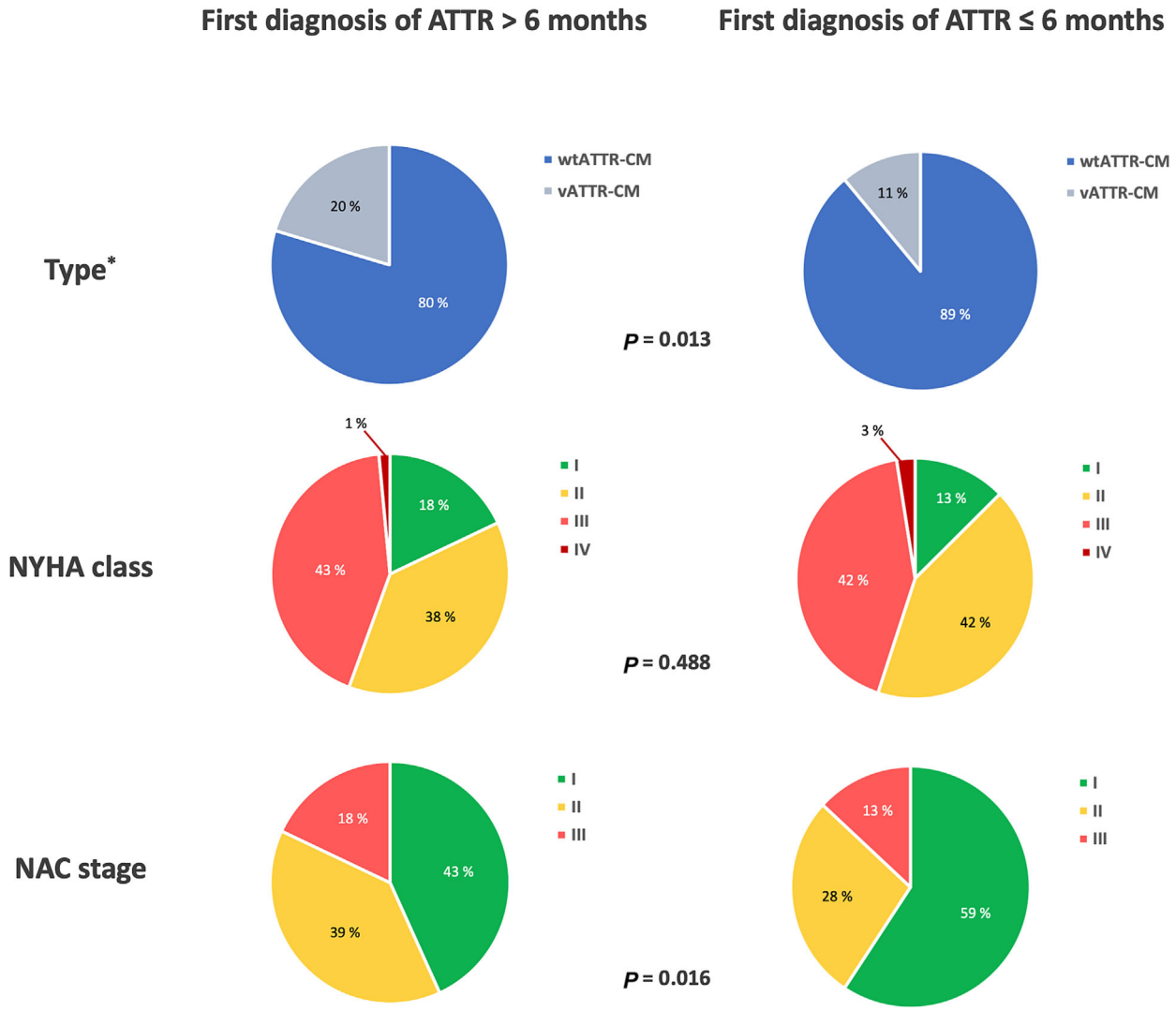
Eligibility for ATTR-ACT

In the context of the cost intensive therapy of ATTR-CM, generalizing and applying results obtained in a strictly controlled trial to the world of routine care remains a challenge. Sixty-four per cent of our patients fulfilled criteria for participation in ATTR-ACT,[6] with 19% not meeting the inclusion criteria, particularly because of low NT-proBNP levels, low degree of left ventricular hypertrophy, and clinical signs of HF not altered enough. In contrast to the trial inclusion criteria, tafamidis 61 mg is approved and recommended for treatment of ATTR-CM at the 'earliest detectable disease stage' including NYHA class I.[1,11,17,27,28] Importantly, there is no generally accepted definition of ATTR-CM, but usually an unexplained septum thickness of at least 12 mm is a key requirement in addition to the proof of transthyretin amyloid deposits.[1,11] With respect to prespecified key exclusion criteria, lack of genetic testing was the most prevalent in our cohort, which would not be an exclusion for treatment in routine care outside the trial.[6] Only about 6% of patients with fulfilled inclusion criteria might have been excluded for medical reasons such as advanced NYHA class or renal dysfunction indicating that the majority of real-world patients seen in tertiary care centres might be eligible for treatment based on the approval trial and treatment recommendations.

Compared with the baseline characteristics of the ATTR-ACT population, patients who met key selection criteria in our study had a higher prevalence of wtATTR-CM (94% vs. 76%), were approximately 5 years older, more symptomatic (NYHA

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Figure 2 Distribution of wt-/v-ATTR, NYHA class and NAC stage by time since diagnosis. *Only patients with available genotype considered.



class ≥ III: 51% vs. 30%), and had a thicker IVSd (19.0 mm vs. 16.7 mm).[6] Despite this cohort being older and more symptomatic, NT-proBNP levels were similar in both cohorts. Considering that NYHA classification is subjective and volatile, and shows poor correlation with objectively measured markers of functional capacity,[29] our real-world patients with ATTR-ACT eligibility are clinically very similar to the trial population with the exception of a slightly higher wild-type fraction.

Recently diagnosed patients

The high proportion (89%) of wtATTR-CM amongst recently diagnosed patients is a naturally extension of the steep proportional surge of patients diagnosed with wtATTR, that is, from 0% to 66% over the last 20 years at the UK-NAC and up to 86% in the THAOS registry.[23,24] This shift from vATTR-CM to wtATTR-CM is consistent with population based, administrative data revealing a continuous temporal increase in the frequency of patients diagnosed with cardiac amyloidosis.[10] This was particularly pronounced in elderly and very elderly male patients, which again is indicative of wtATTR.[10,30,31] The substantial relative and absolute increase in patients with wtATTR, which primarily manifests as cardiomyopathy, highlight the need to cope with the increased demand of diagnostic and therapeutic capacities by implementation of larger networks integrating both referral centres and primary care cardiologists. This is especially important because even recently diagnosed patients still had high rates of advanced ATTR-CM.

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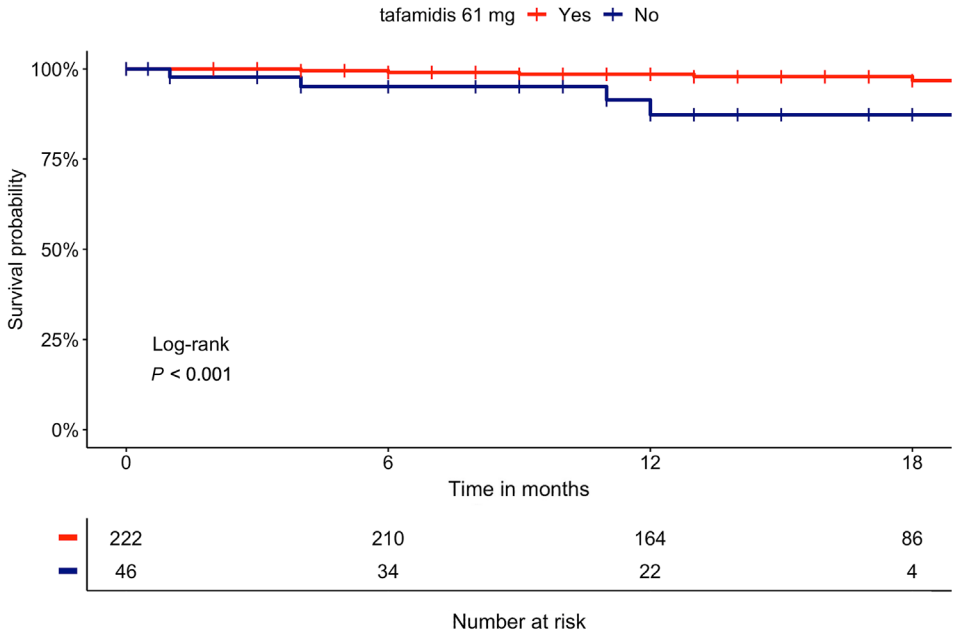
Table 3 Baseline characteristics by initiation of tafamidis at a 61 mg dose

	Tafamidis treatment at a 61 mg dose $n = 293$		
	Newly started $n = 226$ (77.1%)	Not treated $n = 67$ (22.9%)	*P*
Type of ATTR-CM			0.174
Wild-type, %	84.1	74.6	
Variant, %	6.2	11.9	
Not tested, %	9.7	13.4	
Time since first diagnosis (months), Mdn [Q_1; Q_3]	2 [0; 8]	2 [0; 14]	0.855
Time since diagnosis ≤ 6 months, %	70.4	68.7	0.79
Key criteria for ATTR-ACT participation fulfilled, %	74.9[a]	48.1[a]	<0.001
Demographic data			
Male patients, %	87.2	79.1	0.101
Age (years), Mdn [Q_1; Q_3]	79 [76; 82]	81 [76; 84]	0.044
BMI (kg/m^2), M ± SD	27.3 ± 14.0 ($n = 220$)	26.6 ± 4.0 ($n = 61$)	0.992
Modified BMI [(kg/m^2)x(g/L)], M ± SD	1215 ± 741 ($n = 136$)	1129 ± 206 ($n = 47$)	0.256
Vital parameters			
SBP (mmHg), M ± SD	134 ± 18 ($n = 198$)	132 ± 21 ($n = 53$)	0.491
DBP (mmHg), M ± SD	77 ± 11 ($n = 198$)	79 ± 14 ($n = 53$)	0.653
HR (1/min), M ± SD	73 ± 13 ($n = 219$)	74 ± 14 ($n = 65$)	0.802
Symptoms			
NYHA class			0.004
I, %	11.6 ($n = 207$)	16.9 ($n = 59$)	
II, %	44.0 ($n = 207$)	28.8 ($n = 59$)	
III, %	43.5 ($n = 207$)	45.8 ($n = 59$)	
IV, %	1.0 ($n = 207$)	8.5 ($n = 59$)	
History of cardiac decompensation, %	27.6 ($n = 156$)	22.4 ($n = 49$)	0.478
Co-morbidities			
Arterial hypertension, %	67.4 ($n = 224$)	74.6	0.262
Diabetes mellitus, %	20.2 ($n = 223$)	17.9	0.682
CAD, %	46.6 ($n = 221$)	42.4 ($n = 66$)	0.549
AF, %	60.3 ($n = 219$)	58.5 ($n = 66$)	0.793
CTS, %	40.7 ($n = 221$)	32.3 ($n = 65$)	0.221
Lumbar spinal stenosis, %	15.4 ($n = 221$)	7.7 ($n = 65$)	0.112
History of SAVR or TAVI, %	3.6 ($n = 221$)	7.6 ($n = 66$)	0.175
PNP, %	28.5 ($n = 221$)	18.2 ($n = 66$)	0.094
PM, %	15.1 ($n = 219$)	18.8 ($n = 64$)	0.479
Medication			
Diuretics, %	67.7 ($n = 220$)	66.7 ($n = 66$)	0.872
ACEi, AT1-I or ARNI, %	63.6 ($n = 220$)	57.6 ($n = 66$)	0.373
Beta-blocker, %	58.4 ($n = 219$)	62.1 ($n = 66$)	0.594
Oral anticoagulation, %	62.4 ($n = 221$)	66.7 ($n = 66$)	0.532
Biomarker			
Serum albumin (g/L), M ± SD	43.3 ± 4.0 ($n = 141$)	41.6 ± 3.7 ($n = 52$)	0.005
NT-proBNP (pg/mL), Mdn [Q_1; Q_3]	2529 [1342; 4329] ($n = 219$)	2835 [744; 6272] ($n = 56$)	0.68
GFR (mL/min), M ± SD	60.2 ± 18.2 ($n = 218$)	57.1 ± 24.3 ($n = 62$)	0.054
Troponin T (ng/mL), M ± SD	0.054 ± 0.035 ($n = 133$)	0.061 ± 0.052 ($n = 44$)	0.745
Hb (g/L), M ± SD	13.3 ± 1.6 ($n = 217$)	14.1 ± 6.0 ($n = 61$)	0.491
NAC stage			0.056
I, %	54.9 ($n = 215$)	46.4 ($n = 56$)	
II, %	31.6 ($n = 215$)	26.8 ($n = 56$)	
III, %	13.5 ($n = 215$)	26.8 ($n = 56$)	
Advanced disease stage, %	62.6 ($n = 198$)	67.3 ($n = 49$)	0.539
Imaging			
LVEF (%), M ± SD	52.0 ± 9.9 ($n = 225$)	51.1 ± 11.4 ($n = 65$)	0.549
IVSd (mm), M ± SD	18.4 ± 3.3 ($n = 225$)	18.0 ± 4.3 ($n = 65$)	0.532
E/e′, M ± SD	17.7 ± 8.9 ($n = 179$)	20.3 ± 10.1 ($n = 37$)	0.086
GLS (%), M ± SD	−10.8 ± 3.4 ($n = 139$)	−10.2 ± 4.4 ($n = 55$)	0.271
sPAP (mmHg), M ± SD	37.3 ± 11.3 ($n = 160$)	36.0 ± 11.2 ($n = 30$)	0.57
TAPSE (mm), M ± SD	17.3 ± 5.1 ($n = 213$)	17.1 ± 6.3 ($n = 65$)	0.614
Pericardial effusion, %	20.1 ($n = 224$)	21.5 ($n = 65$)	0.799
Reason for withholding tafamidis			
Advanced HF, %	n.a.	23.9 ($n = 46$)	n.a.
Patient wish, %	n.a.	10.9 ($n = 46$)	n.a.
General condition, %	n.a.	15.2 ($n = 46$)	n.a.
Others, %	n.a.	50.0 ($n = 46$)	n.a.

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The 'n' within the columns indicates the number of patients for whom the respective variable was available.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARNI, angiotensin receptor neprilysin inhibitor; AT1-I, angiotensin 1 inhibitor; ATTR-ACT, Transthyretin Amyloidosis Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloidosis cardiomyopathy; BMI, body mass index; CAD, coronary artery disease; CTS, carpal tunnel syndrome; DBP, diastolic blood pressure; GFR, glomerular filtration rate; GLS, global longitudinal strain; Hb, haemoglobin; HF, heart failure; HR, heart rate; IVSd, interventricular septal thickness at end-diastole; LVEF, left ventricular ejection fraction; M, mean; Mdn, median; n.a., not available; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; PNP, polyneuropathy; Q, quartile; SAVR, surgical aortic valve replacement; SBP, systolic blood pressure; SD, standard deviation; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TAVI, transcatheter aortic valve implantation.
[a]% referring to patients with available data.

Figure 3 Unadjusted Kaplan–Meier survival estimates by new administration of tafamidis 61 mg.



Tafamidis 61 mg treatment and overall survival

The existing studies on the use of tafamidis outside of ATTR-ACT need to be interpreted with caution. Studies were single-centred with small samples,[32–34] enrolled patients entirely or partly before commercial availability of tafamidis 61 mg,[3,32,34] used tafamidis doses other than 61 mg,[3,34] or included patients from trials or compassionate use programmes.[32–34] Other studies rely on secondary data from healthcare company databases.[35,36] Our registry provides one of the largest real-world primary data sets entirely enrolled after the approval and commercial availability of tafamidis 61 mg for treatment of ATTR-CM. Treatment with tafamidis 61 mg was initiated in 77% of patients. The findings must be interpreted in the time context of the availability of the primary analysis of ATTR-ACT but predating subsequent detailed post hoc analyses by baseline NYHA class and formal guideline recommendations on the treatment of ATTR-CM.[1,6,11,17,22] Patients in whom tafamidis 61 mg was initiated in real-world more closely resembled the patient group selected for ATTR-ACT suggesting that the treatment decision was guided by the trial.[6] In other real-world studies, the proportions of patients treated with tafamidis 61 mg were lower, at 41% and 66%, but further comparative analysis are precluded by the above limitations of these studies.[34,35]

Most clinical patient characteristics such as co-morbidities, imaging parameters reflecting disease severity, and concomitant medications showed no significant difference between treated and non-treated patients. The decision for tafamidis 61 mg treatment was significantly associated with a younger patient age, higher serum albumin levels and distinct markers of symptoms or morbidity. In addition to age, other studies have found associations between tafamidis 61 mg treatment and biomarkers such as troponin, NT-proBNP and creatinine.[34,35] In our study, only a trend towards a lower NAC stage in treated patients was observed. The combination of significantly different variables statistically explained only about 16 to 23% of the variance of the decision for or against tafamidis 61 mg treatment. Albeit those markers might reflect overall prognosis in ATTR-CM patients, it is unlikely that the

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decision of physicians on treatment was deliberately based on serum albumin or eGFR.[9,37] These findings highlight the need for validated and objectively measurable clinical parameters or scores to ensure comprehensible decision-making.

In a longitudinal comparison of patients enrolled in the THAOS registry, 1-year survival rate was initially below 80%, and patient survival improved even before the era of specific ATTR-CM therapies.[24,38] The 1-year survival rate in our entire cohort was 97%, which is slightly higher than in the overall ATTR-ACT cohort (89%) and the wtATTR-CM patients included in ATTR-ACT (93%).[6,39] A similar survival rate was reported in patients seen in the UK-NAC within the last 10 years.[24] However, a potential preselection of the UK-NAC population might impact these results. Of note, patients treated with tafamidis 61 mg showed a significantly better 1-year survival than patients not-treated. Similar results were reported in a French cohort enrolled in the years 2008 to 2018 and a Japanese single-centre study.[3,34] Considering that the treatment benefit of tafamidis 61 mg with respect to mortality is actually not seen before 18 months, the different survival in our treated patients is most likely not alone attributable to tafamidis 61 mg but rather to different baseline risk profiles due to preselection.[6]

Limitations

Inherent to a retrospective study, some variables were not complete or could not be assessed at all. ATTR genotype was missing in 9% of patients. However, based on the age distribution of patients, the proportion of vATTR would be estimated at about 5%, thus unlikely altering our results.[40] We could only assess the reason for the decision against tafamidis 61 mg use retrospectively by crude categories such as 'advanced heart failure' or 'severely impaired general condition'. Clinical decisions on treatment were reached by experts of respective amyloidosis centres, taking into account both trial data and best clinical care. Important though, despite no detailed functional patient characteristics were available, the difference in serum albumin between treated and non-treated patients suggests that markers of nutrition, or maybe geriatric syndromes in general, might have impacted physician's decision. Finally, follow-up was relatively short, event rates were low, and only all-cause mortality was available as outcome. Although this information is useful for comparisons with other study populations, no conclusion can be drawn on the treatment effect of tafamidis 61 mg on hard clinical endpoints.

Conclusions

wtATTR is the predominant cause of ATTR-CM in contemporary real-world patients seen in tertiary care centres in Germany. As indicated by NYHA class and NAC stage these patients are still at an advanced stage of amyloidosis, underscoring the necessity of screening efforts for early detection. Almost two-thirds of the patients matched the profile of ATTR-ACT with comparable levels of risk-stratifying biomarkers, indicating reasonable generalizability of the trial results to routine care. Acknowledging the very early phase of our study after approval of tafamidis 61 mg, there remains a need to validate clinical parameters for decision-making regarding treatment.

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Conflict of interest

AZ, BU, FK, IK, KH, LM, MP, PL, RP, SSp, SSt, and TR report personal fees from Pfizer. Additionally, KH, RP, and SSp received grants, while RN and VC declare travel support from Pfizer. BU, FK, IK, KH, LM, RP, SSp, SSt, and VC disclose personal fees from Alnylam. Furthermore, VC also reports travel support from Alnylam. Personal fees from AstraZeneca are documented from FK, IK, KH, LM, SSp, and TR. IK, LM, TR, and YB received personal fees from Bayer. Furthermore, IK, LM, and TR declare personal fees from Bristol Myers Squibb. IK, TR, and YB report personal fees from Novartis, and BU, IK and KH received personal fees from Sobi. Personal fees from Daiichi Sankyo are disclosed by IK and TR. IK and YB declare personal fees, and VC reports grants and travel support from Boehringer Ingelheim. Personal fees from Akcea Therapeutics Germany are reported by IK and KH. Additionally, IK documents personal fees from Vifor Pharma Deutschland, Servier Deutschland, AIM, Delab and Diplan. KH declares personal fees from Amicus, GSK, Hormosan, ViiV and the German Society of Neurology. Personal fees from Roche and Berlin Chemie are declared by YB. VC reports grants and travel support from Lili. TR received grants and personal fees from Edwards. FK documents personal fees from BridgeBio, and LM discloses personal fees from IFFM e.V.. SSt reports personal fees from IONIS. AY performed consultant activities for Pfizer, Alnylam, AstraZeneca, GE, BridgeBio, NovoNordisk and Alexion. All of the above-mentioned conflicts of interest were outside the submitted work.

KH and SSp also received grants and personal fees from Alnylam during the conduct of the study. Additionally, KH discloses grants from Berlin Institute of Health within the study period. AY reports an ongoing research cooperation with Philips and Circle Cardiovascular Imaging at their institution. The other authors have no conflicts of interest to declare.

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Funding

No funding was received for conducting this study.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of the entire wtATTR-CM cohort, and categorized based on the time since first diagnosis.

Table S2. Baseline characteristics of wtATTR-CM patients categorized based on the initiation of tafamidis approved for ATTR-CM treatment.

Figure S1. Kaplan–Meier survival estimates for the entire ATTR-CM cohort.

Figure S2. A. Kaplan–Meier survival estimates for ATTR-CM patients, categorized based on the time since first diagnosis. B. Kaplan–Meier survival estimates for wtATTR-CM patients, categorized based on the time since first diagnosis.

Figure S3. Kaplan–Meier survival estimates for wtATTR-CM patients, categorized based on the administration or non-administration of tafamidis 61 mg.

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