Natural history and impact of treatment with tafamidis on major cardiovascular outcome-free survival time in a cohort of patients with transthyretin amyloidosis

Mélanie Bézard, Mounira Kharoubi, Arnault Galat, Elsa Poullot, Soulef Guendouz, Pascale Fanen, Benoit Funalot, Anissa Moktefi, Jean-pascal Lefaucheur, Mukedaisi Abulizi, et al.

ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 264–274
doi:10.1002/ejhf.2028

RESEARCH ARTICLE

Natural history and impact of treatment with tafamidis on major cardiovascular outcome-free survival time in a cohort of patients with transthyretin amyloidosis

Mélanie Bézard[1,2,3,4]*, Mounira Kharoubi[1,2,3,4], Arnault Galat[1,2,3,4], Elsa Poullot[2,5], Soulef Guendouz[1,2,3,4], Pascale Fanen[2,6], Benoit Funalot[2,6], Anissa Moktefi[2,5], Jean-Pascal Lefaucheur[7,8], Mukedaisi Abulizi[9], Jean-François Deux[2,3,4,10], Thierry Gendre[2,3,11], Vincent Audard[2,3,12,13], Khalil el Karoui[12,13], Florence Canoui-Poitrine[14], Amira Zaroui[1,2,15], Emmanuel Itti[2,3,9,13], Emmanuel Teiger[1,2,3,4], Violaine Planté-Bordeneuve[2,3,11], Silvia Oghina[1,2,3]†, and Thibaud Damy[1,2,3,4,16]†

[1]AP-HP (Assistance Publique-Hôpitaux de Paris), Cardiology Department, DHU-ATVB, Henri Mondor University Hospital, Créteil, France; [2]AP-HP (Assistance Publique-Hôpitaux de Paris), French Referral Centre for Cardiac Amyloidosis, Cardiogen Network, Henri Mondor University Hospital, Créteil, France; [3]AP-HP (Assistance Publique-Hôpitaux de Paris), GRC Amyloid Research Institute, Henri Mondor University Hospital, Créteil, France; [4]Inserm U955, Université Paris-Est Créteil (UPEC), Créteil, France; [5]AP-HP (Assistance Publique-Hôpitaux de Paris), Henri Mondor University Hospital, Pathology Department, Créteil, France; [6]AP-HP (Assistance Publique-Hôpitaux de Paris), Genetics Department, Henri Mondor University Hospital, Créteil, France; [7]EA4391, ENT, Université Paris Est Créteil 8 rue du General Sarrail, Créteil, France; [8]AP-HP (Assistance Publique-Hôpitaux de Paris), Clinical Neurophysiology Unit, Henri Mondor University Hospital, Créteil, France; [9]AP-HP (Assistance Publique-Hôpitaux de Paris), Nuclear Medicine Department, Henri Mondor University Hospital, Créteil, France; [10]AP-HP (Assistance Publique-Hôpitaux de Paris), Radiology Department, Henri Mondor University Hospital, Créteil, France; [11]AP-HP (Assistance Publique-Hôpitaux de Paris), Neurology Department, Henri Mondor University Hospital, Créteil, France; [12]AP-HP (Assistance Publique-Hôpitaux de Paris), Nephrology and Renal Transplantation Department, Henri Mondor University Hospital, Créteil, France; [13]Univsité Paris Est Créteil, Institut National de la Santé et de la Recherche Médicale (INSERM) U955, Institut Mondor de Recherche Biomédicale (IMRB), Créteil, France; [14]AP-HP (Assistance Publique-Hôpitaux de Paris), Public Health Departement, Henri Mondor University Hospital, Créteil, France; [15]CHU la Rabta, Cardiology Department, Jebbari Tunis, Tunisia; and [16]AP-HP (Assistance Publique-Hôpitaux de Paris), Clinical Investigation Center 1430, Henri Mondor University Hospital, Créteil, France

Received 22 June 2020; revised 9 October 2020; accepted 18 October 2020; online publish-ahead-of-print 9 November 2020

Aims

Hereditary (ATTRv) and wild-type (ATTRwt) transthyretin amyloidosis are severe and fatal systemic diseases, characterised by amyloid fibrillar accumulation principally in the heart or peripheral nerves (or both). Since 2012, tafamidis has been used in France to treat patients with ATTRv with neuropathy (alone or combined with cardiomyopathy). Recently, the Phase III ATTR-ACT trial showed that tafamidis decreased the relative risk of mortality in ATTR amyloidosis with cardiomyopathy. The aims of this study were to assess the clinical characteristics of ATTR amyloidosis in a real-life population in comparison to the population included in the ATTR-ACT trial and to assess the impact of tafamidis treatment on major cardiovascular outcome (MCO)-free survival time without cardiac decompensation, heart transplant, or death.

Methods and results

From June 2008 to November 2018, 648 patients with ATTR amyloidosis (423 ATTRwt and 225 ATTRv) consecutively referred to the French Referral Center for cardiac amyloidosis were included. A total of 467 (72%) patients matched the inclusion criteria of the ATTR-ACT trial. For the 631 patients with cardiomyopathy, tafamidis treatment was

*Corresponding author. Henri Mondor University Hospital, 51 Avenue Marechal de Lattre de Tassigny, 94000 Créteil, France. Tel: +33 1 49812253, Fax: +33 1 49812253, Email: bezard.melanie@yahoo.com

†These authors contributed equally.

associated with a longer median MCO-free survival time ($n = 98$): 1565 (1010–2400) days vs. 771 (686–895) days without treatment (log-rank $P < 0.001$). This association was confirmed after considering confounding factors (age at inclusion, N-terminal pro-B-type natriuretic peptide and amyloidosis type) with a propensity score (hazard ratio 0.546; $P = 0.0132$).

Conclusion In a large cohort of ATTRwt and ATTRv patients, representative of the inclusion criteria of the ATTR-ACT trial, the present results show an association between tafamidis treatment and a lower occurrence of cardiovascular outcomes in a real-life population.

Keywords Tafamidis • Transthyretin cardiac amyloidosis • ATTR-ACT trial • Real life

Introduction

Amyloidosis is a severe, progressive and fatal systemic disease, characterised by an accumulation of insoluble fibrillar proteins in the extracellular matrix of various organs including the heart and peripheral nerves.[1] Cardiac involvement may occur in the three main types of amyloidosis; namely amyloidosis associated with immunoglobulin light chains (AL), wild-type (also known as 'senile') transthyretin (TTR) amyloidosis (ATTRwt) and hereditary TTR amyloidosis caused by *TTR* gene variants (ATTRv).[2–4] Cardiac TTR amyloidosis is characterised by increased ventricular wall thickness and myocardial rigidity resulting in TTR deposition. This causes an increase in ventricular pressure with a minimal increase in volume[3] and leads to diastolic dysfunction, progressing to heart failure.[5]

ATTRwt is associated with aging. In contrast, ATTRv is a heterogeneous disorder characterised by three different phenotypes (neuropathic, cardiomyopathic, or mixed)[3], depending on the *TTR* gene mutation.

The prognosis of ATTR amyloidosis varies according to the mutation type, the phenotype and the diagnostic delay. In ATTRwt and ATTRv with cardiac involvement, associated or not with neurological symptoms, the disease evolves progressively,[6] leading to cardiac failure and death within 10 years of onset,[7] whereas survival time is longer in ATTRv with pure neuropathic profile. The median survival time in untreated cardiomyopathic or mixed cardio-neuropathic forms is 2.5 years for ATTRv (mainly ATTRV122I) and 3.6 years for ATTRwt.[8,9]

Several disease-modifying drugs such as tafamidis have been approved for the treatment of neurological ATTRv. Tafamidis binds to TTR at the thyroxine-binding site and inhibits dissociation of the TTR tetramer, which is the rate-limiting step in amyloidogenesis.[9] It has been approved for the treatment of ATTRv with neuropathy since 2012 in France, but its impact on survival time remains to be determined.[8] ATTRv patients with cardiac involvement can only be treated if they present mixed cardiologic and neurologic impairment.

In ATTR cardiac amyloidosis, an open-label Phase II trial with 31 patients showed that tafamidis (20 mg daily) stabilised TTR and presented an acceptable safety profile.[10] In a retrospective study of 29 patients with ATTR cardiac amyloidosis treated with TTR stabilisers (tafamidis or diflunisal), survival time was longer in these patients compared to 91 untreated patients.[5] Treatment with these drugs was associated with a lower risk of occurrence of a combined endpoint of poor outcome (heart transplant or death).[5] Long-term use of tafamidis was associated with a favourable safety and tolerability profile, without any unexpected adverse events.[11] The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) was designed to determine the efficacy and safety of tafamidis in ATTR amyloidosis. Overall, 441 patients with ATTRv and ATTRwt were included, of whom 266 were treated with tafamidis.[8] The ATTR-ACT trial demonstrated that tafamidis reduced the relative risk of mortality by 30% and the recurrence of rehospitalisation for acute heart failure by 32%. Following evaluation by the French National Agency for Medicines and Health Products Safety (ANSM), tafamidis has become available in France since November 2018 through an early access programme (RTU; temporary recommendation for use) for treatment of ATTR-associated cardiac amyloidosis [New York Heart Association (NYHA) class I to III].[12]

The aims of the present study are (i) to assess the clinical characteristics of ATTR amyloidosis in a real-life population compared to the selected population included in the Phase III ATTR-ACT trial, and (ii) to assess the impact of tafamidis treatment on major cardiovascular outcome (MCO)-free survival time, without cardiac decompensation, heart transplant, or death.

Methods

The study was approved by the institutional ethics committee (authorisation number #1431858), and informed consent for participation in this research was obtained from all patients. Data were recorded electronically in the Henri Mondor Amyloidosis Network registry as authorised by the French CNIL (Commission National de l'Informatique et des Libertés).

Study population

This cohort study was conducted in France from June 2008 to November 2018. All consecutive patients with a confirmed diagnosis of ATTRv or ATTRwt referred to the Henri Mondor Amyloidosis Network, France, were included prospectively. Diagnosis of ATTR amyloidosis was made as previously described.[2] *TTR* gene sequencing was performed to differentiate ATTRwt from ATTRv. Cardiac amyloidosis was considered in patients with amyloidosis when there was an increase in ventricular wall thickness (>12 mm) measured at echocardiography in the absence of other known causes of cardiac hypertrophy.[13]

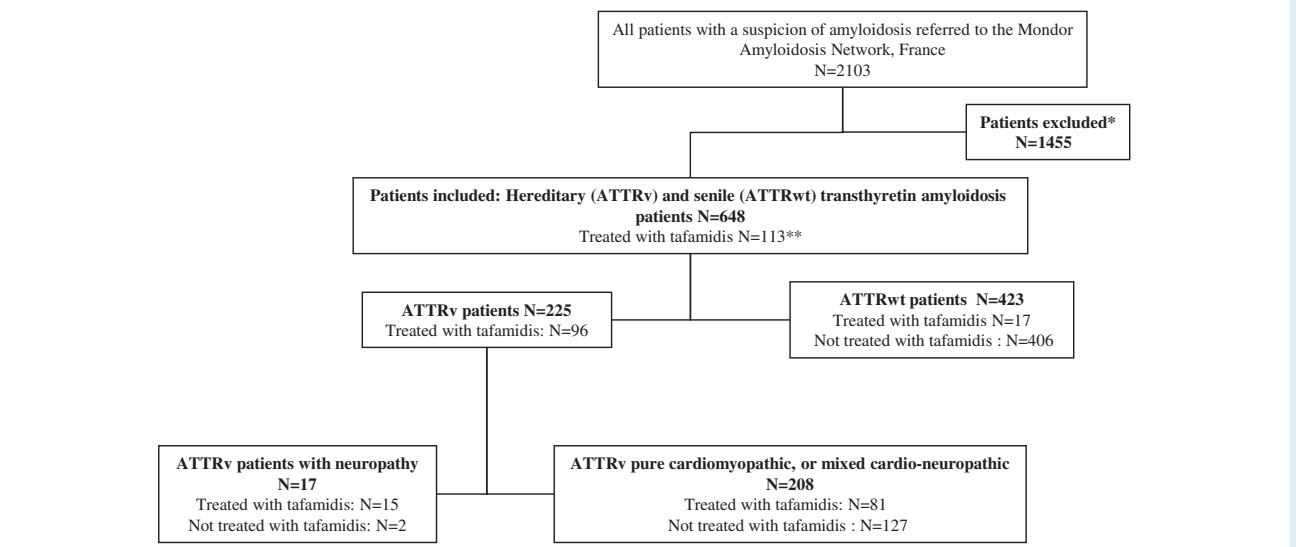

Figure 1 Population flow-chart for study subgroups. *Patients with immunoglobulin light chains amyloidosis (AL) (n = 347), patients with other diagnoses (n = 1005), patients with transthyretin amyloidosis (ATTR) who had received a liver transplant before inclusion (n = 29), patients with asymptomatic ATTR amyloidosis (n = 59), patients treated with patisiran without being treated first by tafamidis (n = 2), patients treated with diflunisal (n = 4), patients with ATTR amyloidosis waiting for genotyping (n = 9). **Follow-up of patients was censured at the date of different events: liver transplantation (n = 12), treatment with tafamidis after November 2018 (n = 41), treatment with tafamidis and patisiran, inotersen or diflunisal (n = 23).

Patients with a diagnosis of cardiac amyloidosis other than ATTRv or ATTRwt, who had ATTR amyloidosis but no clinical symptoms or identified genotypic marker, or who had been received a liver transplant or been treated with patisiran or diflunisal before inclusion were excluded (*Figure 1*). Patients in whom tafamidis treatment was initiated after November 2018 were not included.

Selection of patient subgroups

Patients were distributed into subgroups by genotype (ATTRwt or ATTRv), phenotype (pure neuropathic profile, pure cardiomyopathic, or mixed cardio-neuropathic profile), tafamidis treatment (treated or untreated) and ATTR-ACT status categories.

Four ATTR-ACT status categories were defined, based on matching the eligibility criteria of the ATTR-ACT trial with respect to N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels ≥600 pg/mL, NYHA class and interventricular septum thickness (IVST) as follows: (i) NT-proBNP ≤600 pg/mL and an IVST considered as 'too mild' for inclusion in ATTR-ACT; (ii) NYHA class IV: considered as 'too severe' for inclusion; (iii) NT-proBNP ≥600 pg/mL and NYHA class I–III considered as eligible for inclusion in ATTR-ACT and indeed included in the trial; and (iv) NT-proBNP ≥600 pg/mL and NYHA class I–III considered as eligible for inclusion in ATTR-ACT but not included.

Data collection

Data were collected during routine clinical practice at the discretion of the investigator and included information on clinical, cardiovascular, biological and echocardiographic characteristics, disease history, cardiovascular risk factors, cardiac decompensation (hospitalisation for the setting up of an intravenous diuretic treatment), heart transplantation, death, and treatment.

Patients who underwent liver transplantation or were switched to patisiran (0.3 mg/kg body weight), inotersen (300 mg), or diflunisal during follow-up were censored at the date of the event.

Statistical analyses

Analyses were performed using Statistical Analysis Software version 9.4 (SAS Institute, Inc., Cary, NC, USA). Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range) if highly skewed, and categorical variables were summarised as counts (percentages). Normality was tested using the Shapiro–Wilk test. Analysis of variance, the Wilcoxon rank-sum test, or the Kruskal–Wallis test (whether data were normally distributed or not) was used to compare continuous variables, and the Chi-square or Fisher exact test was used to compare categorical variables between the different subgroups described above. P-values <0.05 were considered statistically significant. Median follow-up time was calculated using the Kaplan–Meier reverse method.[14] Kaplan–Meier survival analysis using the log-rank test was performed to compare patient subgroups for the following outcomes: cardiac decompensation, heart transplantation, or death. A Cox proportional hazards model was also performed to assess the effect of treatment in populations matched for potential confounding factors. Propensity scores were constructed using logistic regression modelling with observed treatment groups as the outcome.[15] The propensity score included age at inclusion, NT-proBNP level and amyloidosis type (ATTRwt vs. ATTRv). In the matched analysis using this propensity score, we included 48 cases, each matched with two controls (48 cases vs. 96 controls), and 23 cases, each matched

with one control (23 cases vs. 23 controls). Estimated glomerular filtration rate (eGFR) was calculated according to the following formula:

$$186 * \left(\left(Creatinine_{\mu mol/_L} * 0.0113 \right)^{-1.154} \right) * \left(Age\ at\ Inclusion^{-0.203} \right) * (1.21\ if\ African\ person *) * (0.742\ if\ woman)$$

Ethnic groups were classified as 'African' for people with sub-Saharan African or Afro-Caribbean origin, or 'non-African' for people with North-African, South-American, Asian, or Caucasian (including Portuguese) origin.

Results

From June 2008 to November 2018, 648 patients with ATTR amyloidosis were enrolled, including 423 patients (65%) with ATTRwt and 225 (35%) with ATTRv. In the ATTRv group, 47 patients carried the ATTRV30M mutation, 117 carried the ATTRV122I mutation and 61 harboured another mutation (online supplementary *Table S1*). This patient cohort was predominantly male (81%) with a mean ± SD age of 76 ± 11 years and NYHA class I or II in 57% of cases (online supplementary *Table S2*).

Baseline genotype and phenotype characteristics

Online supplementary *Table S2* presents the baseline characteristics of the overall population and compares patients with ATTRwt to those with ATTRv and patients with pure neuropathic ATTRv to those with pure cardiomyopathic or mixed cardio-neuropathic ATTRv. Patient age, age at symptom onset, gender, cardiovascular risk factors and clinical laboratory variables differed significantly between these patient subgroups (online supplementary *Table S2*). There were significantly ($P < 0.0001$) more men in the ATTRwt group ($n = 370$; 87%) than in the ATTRv group ($n = 154$; 68%). Mean age at inclusion, body mass index, risk factors, median NT-proBNP and the proportion of patients with NT-proBNP ≥600 pg/mL and high-sensitivity cardiac troponin were all significantly higher in the ATTRwt group than in the ATTRv group ($P < 0.05$). eGFR was significantly higher ($P < 0.0001$) in the ATTRv group (70.85 ± 32.13 mL/min/1.73 m^2) than in the ATTRwt group (59.09 ± 19.95 mL/min/1.73 m^2).

The clinical phenotype of ATTRv patients was more frequently pure cardiopathic or mixed cardio-neuropathic (92%) than pure neuropathic (8%). Neuropathic ATTRv patients were younger than cardiomyopathic or cardio-neuropathic ATTRv patients ($P < 0.001$) and had a lower NYHA class (93% vs. 56% of NYHA class I–II; $P < 0.0053$) (online supplementary *Table S2*). Baseline NYHA characteristics in patient subgroups are reported in online supplementary *Table S3*. With respect to disease history, pure cardiomyopathic and mixed cardio-neuropathic ATTRv patients more frequently presented symptoms of carpal tunnel syndrome than neuropathic ATTRv patients ($P = 0.0021$).

Median major cardiovascular outcome-free survival time by genotype category

Median MCO-free survival time (cardiac decompensation, heart transplantation, or death) was assessed for all 648 patients, although the extent of follow-up varied between patient subgroups. Median follow-up in the entire cohort was 629 days (Q1–Q3: 187–1357). Median MCO-free survival time was 799 days (722–1025) in ATTRwt and 949 days (632–1215) in ATTRv with pure cardiomyopathic or mixed cardio-neuropathic profile. Patients with ATTRwt had a lower median MCO-free survival time than patients with ATTRv, whatever their clinical presentation (cardiomyopathic, mixed cardio-neuropathic, or neuropathic for all three outcomes) (log-rank $P < 0.0030$) (*Figure 2*). As expected, median MCO-free survival time decreased with increasing NYHA class (log-rank $P < 0.001$; online supplementary *Figure S1*).

Baseline characteristics stratified by ATTR-ACT criteria

Table 1 compares baseline characteristics of patients with respect to the ATTR-ACT inclusion criteria and baseline characteristics in ATTR-ACT trial participants. Of the 648 included patients with cardiac amyloidosis, 467 (72%) fulfilled the inclusion criteria for the ATTR-ACT trial (*Table 1* and *graphical abstract*) and 23 of them had actually been included in ATTR-ACT. Of these 23 patients, one patient received tafamidis 20 mg, 17 received tafamidis 80 mg, 4 received placebo, and one was screened and randomised but refused finally to participate in the trial for personal reasons.

A total of 45 patients had NYHA class IV to be included in ATTR-ACT, whereas 70 patients presented too low NYHA class and NT-proBNP levels to be included.

Median major cardiovascular outcome-free survival time categorised by ATTR-ACT inclusion criteria

The median time to occurrence of a MCO followed a gradient across ATTR-ACT eligibility categories, which was inversely correlated to disease severity (log-rank $P < 0.001$) (online supplementary *Figure S2*). In patients who had too severe disease for inclusion in ATTR-ACT, the median survival time was 544 days, in patients meeting the inclusion criteria it was 772 days, and in those who had too mild disease for inclusion it was 2513 days (online supplementary *Figure S2*).

Baseline characteristics stratified by tafamidis treatment

Table 2 compares the baseline characteristics of patients receiving or not tafamidis treatment according to ATTR phenotype. Overall, 113 (17%) patients were treated with tafamidis, of whom 17 had ATTRwt and 96 ATTRv (15 neuropathic and 81 cardiomyopathic or mixed cardio-neuropathic). All treated patients received tafamidis

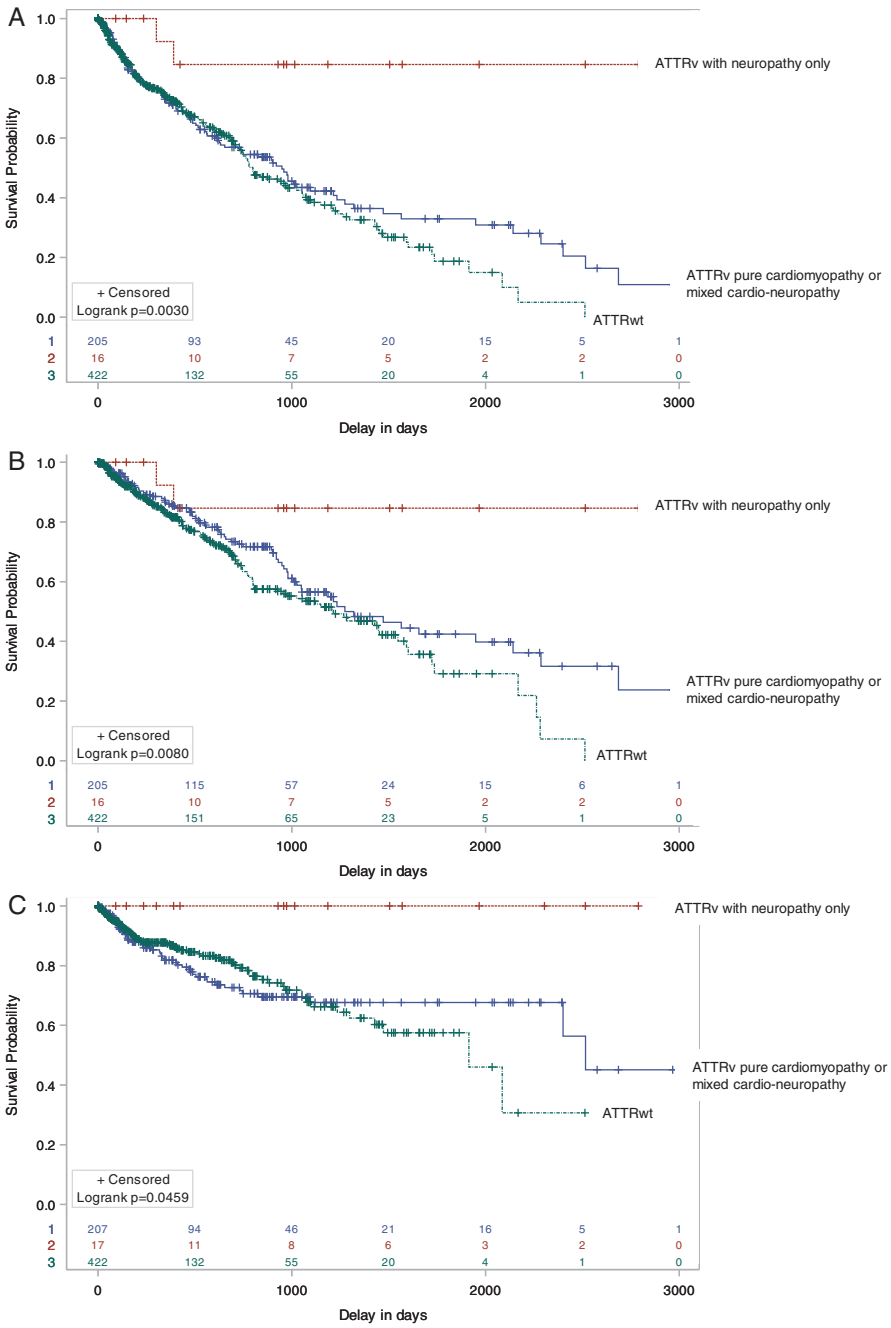

Figure 2 Kaplan–Meier time-to-event analysis in 648 patients with transthyretin amyloidosis. (*A*) Time to death, heart transplant or cardiac decompensation; (*B*) time to death or heart transplant; (*C*) time to cardiac decompensation. Patients are stratified by genotype [hereditary transthyretin amyloidosis (ATTRv) with neuropathy, ATTRv pure cardiomyopathic, or mixed cardio-neuropathic, and wild-type transthyretin amyloidosis (ATTRwt)]. Observations with invalid time, censoring, or missing strata assignment were deleted.

at the dose of 20 mg daily, except 17 patients who were included in the ATTR-ACT trial and received an 80 mg dose.

In patients with ATTR cardiac amyloidosis treated with tafamidis, most were ATTRv (83%). Patients with ATTR cardiac amyloidosis treated with tafamidis (n = 98) were younger (69 ± 10 vs. 78 ± 9 years) and were more frequently carriers of the ATTRV30M mutation (35% vs. 3.2%) than untreated patients (n = 532). Hypertension was significantly more frequent in ATTR cardiac amyloidosis patients not receiving tafamidis (P = 0.0002). Compared with untreated patients, those treated with tafamidis also had lower NT-proBNP and troponin levels and higher eGFR at baseline and more implantable cardioverter-defibrillator implants (35%).

Table 1 Baseline characteristics of the study population and comparison with the subjects enrolled in the ATTR-ACT trial based on inclusion criteria for ATTR-ACT

	Missing data ($n = 66$)	ATTR-ACT (treated group)[9] ($n = 264$)	ATTR included in ATTR-ACT[a] ($n = 23$)	ATTR matching inclusion criteria for ATTR-ACT $n = 444$)	ATTR too severe for inclusion in ATTR-ACT ($n = 45$)	ATTR too mild for inclusion in ATTR-ACT ($n = 70$)	*P*-value[b]
Clinical characteristics							
Age at inclusion, years	0	74 ± 7	77 ± 4	78 ± 8	81 ± 7	63 ± 15	**<0.0001**
Age at first symptoms, years	93	NA	73 ± 7	74 ± 9	77 ± 8	62 ± 13	**<0.0001**
Age at diagnosis, years	3		77 ± 5	78 ± 8	81 ± 7	61 ± 17	**<0.0001**
Male sex	0	241 (91)	20 (87)	361 (81)	38 (84)	54 (77)	0.6661
BMI, kg/m^2	47	NA	25 ± 4	25 ± 4	25 ± 3	25 ± 3	0.9959
ATTRV30M (% of ATTRv)	0		0	8 (5.8)	1 (7.1)	30 (59)	**<0.0001**
ATTRV122I (% of ATTRv)	0	106 (24) (overall randomised population) (ATTRV122I + ATTRT60A + ATTRI68L)	6 (86)	87 (67)	11 (79)	7 (14)	0.1486
ATTRv	0	63 (24)	7 (30)	130 (29)	14 (30)	51 (73)	
ATTRwt		201(76)	16 (70)	314 (71)	31 (69)	19 (27)	**<0.0001**
Type of ATTRv							
ATTRv pure cardiomyopathic, or mixed cardio-neuropathic	329	NA	7 (100)	129 (99)	14 (100)	38 (74)	
ATTRv with neuropathy		NA	0	1 (0.7)	0	13 (25)	**<0.0001**
CV characteristics							
NYHA class							
I	39	24 (9.1)	0	49 (11)	0	28 (42)	**<0.0001**
II		162 (61)	7 (32)	198 (48)	0	23 (35)	
III		78 (29)	12 (54)	163 (40)	0	15 (23)	
IV		NA	3 (14)	0	45 (100)	0	
Heart rate, bpm	5	71 ± 12	72. ±11	77 ± 14	82 ± 16	75 ± 14	**0.0213**
Systolic blood pressure, mmHg	26	127 ± 21	127 ± 21	121 ± 18	130 ± 19	119 ± 18	0.0560
Diastolic blood pressure, mmHg	26	70 ± 10	71 ± 11	75 ± 12	76 ± 11	77 ± 10	0.1560
Atrial fibrillation	62	NA	7 (33)	148 (37)	23 (55)	5 (8.9)	**<0.0001**
Pacemaker	0	13 (4.9)	12 (52)	152 (34)	18 (40)	21 (30)	0.2248
ICD	0	16 (6.1)	11 (48)	94 (21)	12 (27)	7 (10)	**0.0013**
History							
Carpal tunnel surgery or symptoms	0	NA	17 (74)	304 (68)	30 (67)	42 (60)	0.4879
Canal lumbar stenosis surgery	81	NA	1 (5.00)	33 (8.6)	3 (7.3)	5 (8.5)	0.9407
Deafness	26	NA	11 (48)	192 (45)	18 (42)	23 (35)	0.4332
CV risk factors							
Diabetes	0	20 (7.6)	4 (17)	76 (17)	7 (16)	7 (10)	0.5126
Dyslipidaemia	0	NA	10 (43)	148 (33)	16 (36)	15 (21)	0.1381
Hypertension	0	145 (55)	15 (65)	257 (58)	24 (53)	21 (30)	**0.0002**
Biology							
NT-proBNP, pg/mL	41	2996 (1751–4861)	4278 (2192–9925)	3251 (1853–6420)	6292 (2763–14 970)	216 (68–404)	**<0.0001**
NT-proBNP ≥600, pg/mL[c]	41	NA	19 (100)	410 (99)	41 (100)	2 (2.9)	**<0.0001**
NT-proBNP–eGFR staging[d]							
Stage I	147	NA	3 (21)	151 (45)	8 (31)	61 (97)	**<0.0001**
Stage II		NA	5 (36)	115 (35)	11 (42)	2 (3.2)	
Stage III		NA	6 (43)	66 (20)	7 (27)	0	
Hs troponin T, ng/mL	107	0.14 (0.09–0.20)	105 (67–131)	70 (47–104)	101 (75–158)	19 (6–40)	**<0.0001**
Haemoglobin, g/dL	43	NA	13.22 ± 2.04	13.01 ± 1.72	13.12 ± 1.44	13.84 ± 1.42	**0.0036**
Creatinine, µmol/L	10	58.8 ± 17.9	151.19 ± 87.68	124.28 ± 57.39	145.18 ± 48.91	83.43 ± 23.32	**<0.0001**
eGFR, mL/min/1.73 m^2	119	NA	50.61 ± 19.94	60.81 ± 22.98	48.61 ± 13.60	90.57 ± 31.24	**<0.0001**
Echocardiography characteristics							
LVEF, %	24	48 ± 10	42 ± 12	47 ± 12	43 ± 13	60 ± 9	**<0.0001**
IVST, mm	11	17 ± 4	20 ± 4	18 ± 3	19 ± 4	13 ± 4	**<0.0001**
GLS, %	45	9 ± 3	8 ± 2	10 ± 3	8 ± 3	16 ± 4	**<0.0001**
Tafamidis treatment	0	264 (100)	19 (83)	38 (8.6)	6 (13)	40 (57)	**<0.0001**

Values are given as *n* (%), mean ± standard deviation, or median (interquartile range).

ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amiloidosis; ATTRwt, wild-type transthyretin amiloidosis; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; Hs, high-sensitivity; ICD, implantable cardioverter-defibrillator; IVST, interventricular septum thickness; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[a]ATTR patients included both in the cohort study and ATTR-ACT.

[b]Comparison test between ATTR with inclusion criteria for ATTR-ACT, ATTR too severe for inclusion in ATTR-ACT and ATTR too mild for inclusion in ATTR-ACT.

[c]ATTR-ACT trial cut-off value for inclusion.

[d]Following Gillmore *et al.*.[7], Stage I was defined as NT-proBNP <3000 ng/L and eGFR >45 mL/min, Stage III was defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min, and the remainder were Stage II.

Table 2 Baseline characteristics of patients treated or not with tafamidis

	Missing data	ATTRv with neuropathy treated with tafamidis ($n = 15$)	ATTR cardiac amyloidosis treated with tafamidis (ATTRwt + ATTRv pure cardiomyopathic, or mixed cardio-neuropathic) ($n = 98$)	ATTR cardiac amyloidosis not treated with tafamidis (ATTRwt + ATTRv pure cardiomyopathic, or mixed cardio-neuropathic) ($n = 533$)	*P*-value (ATTR cardiac amyloidosis vs. not treated)
Clinical characteristics					
Age at inclusion, years	0	44 ± 14	69 ± 10	78 ± 9	**<0.0001**
Age at first symptoms, years	119	45 ± 10	66 ± 10	75 ± 8	**<0.0001**
Age at diagnosis, years	8	40 ± 15	67 ± 12	78 ± 9	**<0.0001**
Male sex	0	7 (47)	73 (74)	443 (83)	**0.0380**
BMI, kg/m^2	64	23 ± 3	24 ± 4	25 ± 4	**0.0108**
ATTRV30M (% of ATTRv)	0	14 (93.33)	28 (35)	4 (3.2)	**<0.0001**
ATTRV122I (% of ATTRv)	0	0	15 (18)	102 (80)	0.4110
ATTRv	0	15 (100)	81 (83)	127 (24)	
ATTRwt		0	17 (17)	406 (76)	**<0.0001**
CV characteristics					
NYHA class					
I–II	54	12 (92)	52 (56)	271 (56)	0.8929
III–IV		1 (7.7)	40 (43)	215 (44)	
NYHA class I vs.	54	11 (85)	18 (20)	53 (11)	
II vs.		1 (7.7)	34 (37)	218 (45)	0.1187
III vs.		1 (7.7)	32 (35)	175 (36)	
IV		0	8 (8.7)	40 (8.2)	
Heart rate, bpm	14	78 ± 17	73 ± 13	77 ± 14	**0.0172**
Systolic blood pressure, mmHg	38	122 ± 16	127 ± 22	126 ± 21	0.8990
Diastolic blood pressure, mmHg	38	77 ± 10	75 ± 13	75 ± 12	0.7651
Atrial fibrillation	78	0	18 (23)	180 (38)	**0.0102**
Pacemaker	0	6 (40)	39 (40)	172 (32)	0.1502
ICD	0	0	34 (35)	94 (18)	**0.0001**
History					
Carpal tunnel surgery or symptoms	0	5 (33)	70 (71)	350 (66)	0.2765
Canal lumbar stenosis surgery	102	0	5 (6.1)	41 (9.1)	0.3691
Deafness	37	2 (13)	35 (36)	231 (46)	0.0707
CV risk factors					
Diabetes	0	0	11 (11)	97 (18)	0.0907
Dyslipidaemia	0	1 (6.7)	24 (24)	187 (35)	**0.0399**
Hypertension	0	0	37 (38)	311 (58)	**0.0002**
Biology					
NT-proBNP, pg/mL	68	43(25–190)	1961 (411–4041)	3207 (1739–6883)	**<0.0001**
NT-proBNP ≥600 pg/mL[a]	68	1 (8.33)	56 (66.67)	451 (93.76)	**<0.0001**
NT-proBNP–eGFR staging[b]					
Stage I	185	12 (100)	46 (57)	177 (48)	0.0631
Stage II		0	26 (32)	113 (31)	
Stage III		0	8 (10)	78 (21)	
Hs troponin T, ng/mL	136	4.5 (3–5)	49 (19–79)	70 (47–110)	**<0.0001**
Haemoglobin, g/dL	58	13 ± 2	13 ± 1	13 ± 2	**0.0371**
Creatinine, µmol/L	20	77 ± 16	111 ± 60	125 ± 56	**0.0247**
eGFR, mL/min/1.73 m^2	143	91 ± 21	74 ± 35	61 ± 23	**<0.0001**
Echocardiography characteristics					
LVEF, %	48	91 ± 21	51 ± 13	48 ± 13	**0.0288**
IVST, mm	34	11 ± 3	17 ± 4	18 ± 3	**0.0288**
GLS, %	69	17 ± 3	12 ± 5	10 ± 4	**0.0011**

Values are given as *n* (%), mean ± standard deviation, or median (interquartile range).
ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amiloidosis; ATTRwt, wild-type transthyretin amiloidosis; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; Hs, high-sensitivity; ICD, implantable cardioverter-defibrillator; IVST, interventricular septum thickness; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
[a]ATTR-ACT trial cut-off value for inclusion.
[b]Following Gillmore *et al.*[7]: Stage I was defined as NT-proBNP <3000 ng/L and eGFR >45 mL/min, Stage III was defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min, and the remainder were Stage II.

Association between tafamidis treatment and median major cardiovascular outcome-free survival time

In patients with ATTR cardiac amyloidosis, median MCO-free survival time was significantly shorter (log-rank $P < 0.001$) in patients not treated with tafamidis [771 (686–895) days] compared to treated patients [1565 (1010–2400) days] (*Figure 3* and *graphical abstract*). Kaplan–Meier analyses were also performed excluding the ATTRv neuropathic population with similar significant results.

Results of propensity scores are consistent with findings in the full multivariable model and suggest a positive impact of tafamidis

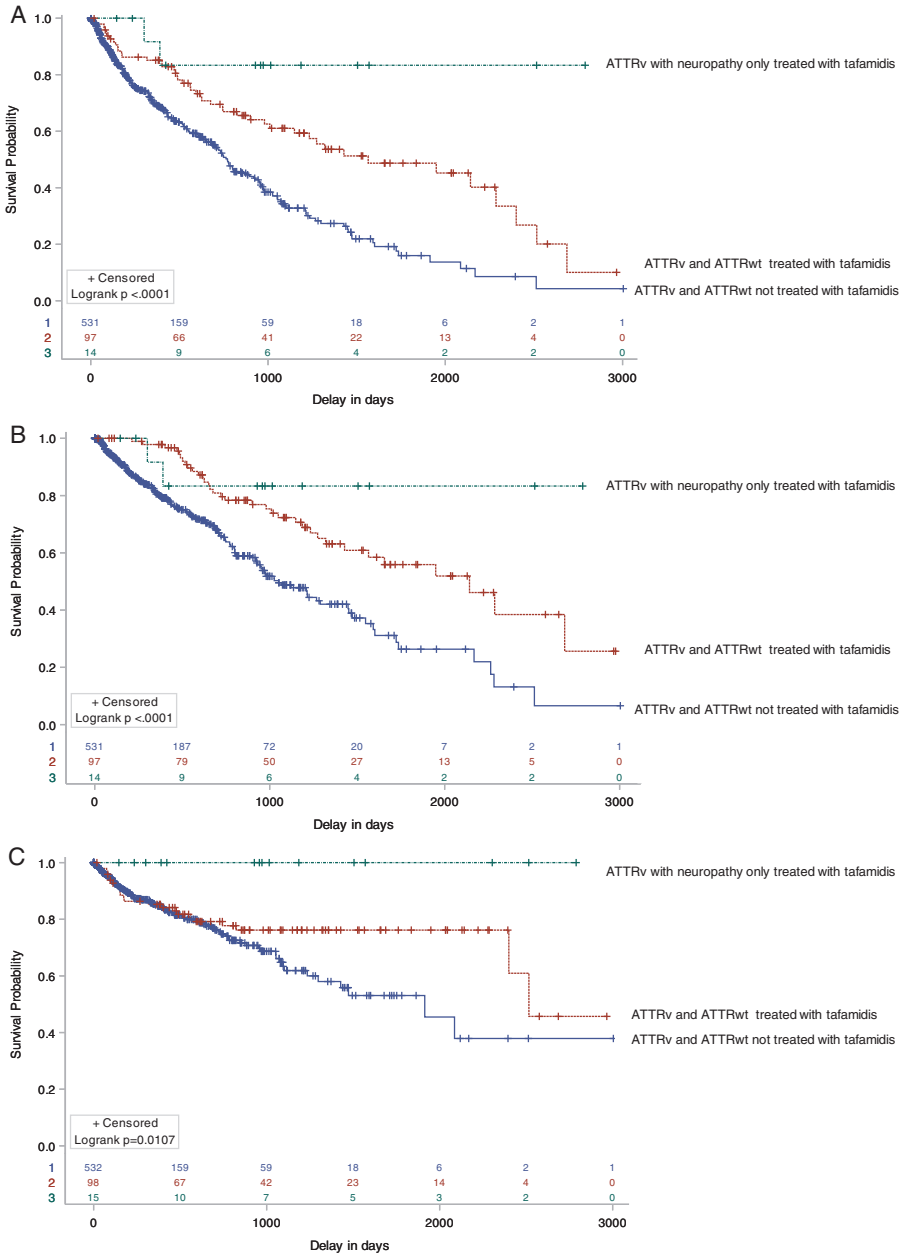

Figure 3 Kaplan–Meier time-to-event analysis in 648 patients with transthyretin amyloidosis. (*A*) Time to death, heart transplant or cardiac decompensation; (*B*) time to death or heart transplant; (*C*) time to cardiac decompensation. Patients are stratified by use of tafamidis. Observations with invalid time, censoring, or missing strata assignment were deleted. ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis.

treatment on MCO (hazard ratio 0.546; $P = 0.0132$) (online supplementary *Figure S3*).

Discussion

Tafamidis treatment has become available in France since 2012 for patients with pure neuropathic forms of ATTRv and since November 2018 for all types of ATTR after the publication of the Phase III ATTR-ACT trial results. Our study focuses on patients treated with tafamidis before October 2018. Patients who received tafamidis were mainly ATTRv and were younger than untreated patients, who were predominantly ATTRwt. Tafamidis treatment was associated with a longer median survival without MCO in patients with ATTR cardiac amyloidosis, confirmed by a calculated propensity score which estimated the treatment effect. Our study confirms the beneficial effects of

tafamidis in a cohort that combines different genotypes and phenotypes of ATTR amyloidosis. In this real-life cohort study, more than two thirds of patients fulfilled the inclusion criteria of the ATTR-ACT trial.

Representativity of the French referral cohort compared to previous international cohorts

As shown in online supplementary *Table S2*, our cohort was comparable to previously reported cohorts from England[7] or Italy,[16] as well as to the large TRACS cohort designed to assess the natural history of cardiac ATTR amyloidosis progression.[17] Baseline characteristics were similar in terms of patient age, sex ratio, eGFR, and NT-proBNP levels.

Compared to the THAOS cohort,[3] our study population showed a much higher ratio of ATTRwt compared to ATTRv (423/225 vs. 125/1286) and, therefore, was older with a higher proportion of male patients. This peculiarity is due to the fact that the THAOS investigators are mostly neurologists.[3] However, our cohort was close to the THAOS cohort studied by Maurer *et al.* in US patients,[18] in which over half of the patients were ATTRwt, with most being men (85%) and having a mean age of 70 years.[6,19] As previously reported by Givens *et al.*,[20] ATTRwt patients are older than ATTRv patients. In our cohort, the two main mutations causing ATTRv were Val30Met and Val122Il (the latter found in patients of African origin).

The ATTR-ACT trial was a multicentre, international, double-blind, placebo-controlled, Phase III trial[8] in which 441 patients with ATTR were randomly allocated in a 2:1:2 ratio to receive tafamidis 80 mg, tafamidis 20 mg, or placebo for 30 months. In this trial, tafamidis was demonstrated to reduce all-cause mortality and cardiovascular-related hospitalisations in patients with ATTR amyloidosis, and to slow the decline in functional capacity and quality of life compared to placebo.[8] In our study, patients matching the inclusion criteria of ATTR-ACT (based on NT-proBNP level and NYHA class) represented 72% ($n = 467$) of the ATTR population, which supports the representativeness of the ATTR-ACT cohort in a real-life setting (*graphical abstract*). This is in line with the results published by Canepa *et al.*,[21] who presented a real-life Italian cohort that closely resembles that enrolled in ATTR-ACT.

The major difference between our cohort and that of ATTR-ACT was the higher proportion of cardiomyopathic or mixed cardio-neuropathic ATTRv patients here compared to the proportion of ATTRv presented in the ATTR-ACT trial.

Impact of transthyretin amyloidosis genotype and phenotype

Transthyretin amyloidosis is a severe systemic disease with a high mortality rate.[22] The impact of ATTR amyloidosis genotype and phenotype on median MCO-free survival time was in line with the data from the THAOS registry based on 1411 ATTR amyloidosis patients.[3] Patients with ATTRwt had a shorter median MCO-free survival time than ATTRv patients (*Figure 2*). ATTRv patients with pure cardiomyopathic or mixed cardio-neuropathic phenotype presented a shorter median MCO-free survival time than did patients with pure neuropathic profile (*Figure 2*). Survival time was also affected by NYHA class.

Association between tafamidis treatment and median major cardiovascular outcome-free survival time

Transthyretin cardiac amyloidosis is a progressive disorder, often undiagnosed until symptoms of heart failure become apparent, leading to ventricular wall thickening and advanced diastolic dysfunction.[5] In the largest and most recent databases of ATTR cardiac amyloidosis, median survival time from diagnosis usually ranges between 25 and 41 months, with longer survival in patients with ATTRwt.[20,23,24] In the present prospective cohort study, median survival time for this outcome in ATTR cardiac amyloidosis patients treated with tafamidis was 1565 days (approximately 52 months) vs. 771 days (approximately 26 months) for those not treated with tafamidis (log-rank $P < 0.0001$) (*graphical abstract*). These results are consistent with those reported by Rosenblum *et al.*[5] in a retrospective study of 120 patients with ATTR amyloidosis, of whom 29 received tafamidis treatment and 91 did not. In this previous study, median survival time in patients taking TTR stabilisers was 65 vs. 26 months in patients not taking such drugs. The primary survival outcome in this study was a combined outcome of all-cause mortality or orthotopic heart transplant, which was considered as a 'death equivalent' since patients who underwent transplantation would otherwise have died.[5]

Our study confirms the positive impact of tafamidis treatment that was observed in the ATTR-ACT trial. Tafamidis treatment was associated with a longer median survival time without a MCO, notably in ATTRv patients (*graphical abstract*). Moreover, despite the minimal proportion of ATTRwt patients treated with tafamidis ($n = 17$), we suggested here that this benefit can also be observed also for patients with ATTRv cardiac amyloidosis with and without neuropathy whatever the origin.

Study limitations

This study has several limitations. Firstly, this is an observational study and not a randomised controlled trial, so that cause and effect relationships between tafamidis treatment and outcome cannot be inferred. Secondly, patients were treated with tafamidis if they corresponded to the approved indication at the time of inclusion, and this accounts for the differences in baseline characteristics between patients who received tafamidis and those who did not. Before the temporary recommendation for use, ATTRv patients with a neuropathic profile were more likely to receive treatment than those with a cardiomyopathic profile (including ATTRwt patients). For this reason, the treated population was younger than the untreated population. However, the propensity score used to estimate the treatment effect, which adjusted to

take into account possible confounding by amyloidosis type and age, limits this bias. The sample size of the population receiving tafamidis treatment limited the number of variables included in propensity score analysis and its accuracy. To our knowledge, this is to date the largest real-life cohort of patients with cardiac amyloidosis treated with tafamidis. Another limit of our study is the non-exhaustive neurological data recording in our database of patients treated with tafamidis considering its indication before November 2018. Therefore, we were not able to provide a neurologic consultation to all ATTR patients due to the number of patients referred to our cardiology referral centre, and for this reason we were not able to compare patients treated with tafamidis with untreated patients regarding neurological examination.

Conclusion

This study of a large real-life cohort of patients with ATTR amyloidosis seems to support the beneficial clinical impact of tafamidis shown in the ATTR-ACT trial and its representativeness. Future studies or registries will continue to document the impact of tafamidis in real life.

Supplementary Information

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

Acknowledgements

The authors thank Qualees which performed statistical analyses and helped with the manuscript writing process.

Funding

This work was supported via independent study grants programme supported by Pfizer within unconditional financial support.

Conflict of interest: B.F. reports financial support (consulting honoraria) from Pfizer. V.A. reports personal fees from Addmedica, outside of the submitted work. T.D. reports financial grants (honoraria and speaker fees) from Alnylam, Akcea, Prothena, Janssen and Pfizer. All other authors have nothing to disclose.

References

1. Damy T, Maurer MS, Rapezzi C, Planté-Bordeneuve V, Karayal ON, Mundayat R, Suhr OB, Kristen AV. Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy. *Open Heart* 2016;**3**:e000289.
2. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016;**133**:2404–2412.
3. Damy T, Kristen AV, Suhr OB, Maurer MS, Planté-Bordeneuve V, Yu CR, Ong ML, Coelho T, Rapezzi C; THAOS Investigators. Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS). *Eur Heart J* 2019 Apr 1. https://doi.org/10.1093/eurheartj/ehz173 [Epub ahead of print].
4. Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Virot P, Jaccard A. Cardiac amyloidosis: updates in diagnosis and management. *Arch Cardiovasc Dis* 2013;**106**:528–540.
5. Rosenblum H, Castano A, Alvarez J, Goldsmith J, Helmke S, Maurer MS. TTR (transthyretin) stabilizers are associated with improved survival in patients with TTR cardiac amyloidosis. *Circ Heart Fail* 2018;**11**:e004769.
6. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, Klarich KW, Miller WL, Maleszewski JJ, Dispenzieri A. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol* 2016;**68**:1014–1020.
7. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, Quarta CC, Rezk T, Whelan CJ, Gonzalez-Lopez E, Lane T, Gilbertson JA, Rowczenio D, Petrie A, Hawkins PN. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018;**39**:2799–2806.
8. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016.
9. Maurer MS, Elliott P, Merlini G, Shah SJ, Cruz MW, Flynn A, Gundapaneni B, Hahn C, Riley S, Schwartz J, Sultan MB, Rapezzi C. Design and rationale of the Phase 3 ATTR-ACT clinical trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). *Circ Heart Fail* 2017;**10**:e003815.
10. Maurer MS, Grogan DR, Judge DP, Mundayat R, Packman J, Lombardo I, Quyyumi AA, Aarts J, Falk RH. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stabilization and clinical outcomes. *Circ Heart Fail* 2015;**8**:519–526.
11. Barroso FA, Judge DP, Ebede B, Li H, Stewart M, Amass L, Sultan MB. Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years. *Amyloid* 2017;**24**:194–204.
12. Collège de la Haute Autorité de Santé. Recommandation relative a la prise en charge a titre derogatoire du tafamidis dans le cadre d'une recommandation temporaire d'utilisation. HAS; 2018. https://www.has-sante.fr/upload/docs/application/pdf/2019-01/cteval421_reco_rtu_annexe_vyndaqel_cd_2018_12_19_v1.pdf (26 October 2020).
13. Béquignon E, Guellich A, Barthier S, Raynal M, Prulière-Escabasse V, Canouï-Poitrine F, Coste A, Damy T. How your ears can tell what is hidden in your heart: wild-type transthyretin amyloidosis as potential cause of sensorineural hearing loss inelderly-AmyloDEAFNESS pilot study. *Amyloid* 2017;**24**:96–100.
14. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996;**17**:343–346.
15. Parsons LS. Performing a 1:N case-control match on propensity score. SUGI 29 Proceedings: SAS Users Group International Conference. Cary, NC: SAS Institute Inc.; 2004. No. 165-29.
16. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, Salvi F, Ciliberti P, Pastorelli F, Biagini E, Coccolo F, Cooke RM, Bacchi-Reggiani L, Sangiorgi D, Ferlini A, Cavo M, Zamagni E, Fonte ML, Palladini G, Salinaro F, Musca F, Obici L, Branzi A, Perlini S. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation* 2009;**120**:1203–1212.
17. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, Falk RH, Cheung KN, Patel AR, Pano A, Packman J, Grogan DR. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J* 2012;**164**:222–228.e1.
18. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, Judge DP, Lenihan DJ, Gottlieb SS, Shah SJ, Steidley DE, Ventura H, Murali S, Silver MA, Jacoby D, Fedson S, Hummel SL, Kristen AV, Damy T, Planté-Bordeneuve V, Coelho T, Mundayat R, Suhr OB, Cruz MW, Rapezzi C. Genotype and phenotype of transthyretin cardiac amyloidosis in the United States: the Transthyretin Amyloid Outcome Survey (THAOS). *J Am Coll Cardiol* 2016;**68**:161–172.
19. Connors LH, Doros G, Sam F, Badiee A, Seldin DC, Skinner M. Clinical features and survival in senile systemic amyloidosis: comparison to familial transthyretin cardiomyopathy. *Amyloid* 2011;**18** Suppl 1:157–159.
20. Givens RC, Russo C, Green P, Maurer MS. Comparison of cardiac amyloidosis due to wild-type and V122I transthyretin in older adults referred to an academic medical center. *Aging Health* 2013;**9**:229–235.
21. Canepa M, Tini G, Musumeci B, Cappelli F, Milandri A, Mussinelli R, Autore C, Perfetto F, Rapezzi C, Perlini S. Real-world versus trial patients with transthyretin amyloid cardiomyopathy. *Eur J Heart Fail* 2019;**21**:1479–1481.

22. Hamon D. Outcome and incidence of appropriate implantable cardioverter-defibrillator therapy in patients with cardiac amyloidosis. *Int J Cardiol* 2016;**222**:562–568.
23. Pinney JH, Whelan CJ, Petrie A, Dungu J, Banypersad SM, Sattianayagam P, Wechalekar A, Gibbs SDJ, Venner CP, Wassef N, McCarthy CA, Gilbertson JA, Rowczenio D, Hawkins PN, Gillmore JD, Lachmann HJ. Senile systemic amyloidosis: clinical features at presentation and outcome. *J Am Heart Assoc* 2013;**2**:e000098.
24. Connors LH, Prokaeva T, Lim A, Théberge R, Falk RH, Doros G, Berg A, Costello CE, O'Hara C, Seldin DC, Skinner M. Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. *Am Heart J* 2009;**158**:607–614.