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## Transthyretin amyloid cardiomyopathy in France: A cross-sectional multi-centre study (333 patients)

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## ABSTRACT

**Aims:** We designed a two-part epidemiological study, an observatory for amyloid transthyretin amyloidosis (OBSAMYL). The first objective was to identify and count the number of patients diagnosed with ATTR amyloidosis in participating French centres. The second was to evaluate the use and safety profile of tafamidis meglumine in real-world settings.

**Methods:** This was a non-interventional descriptive retrospective multi-centre national study. A census was conducted to estimate the number of patients diagnosed with ATTR amyloidosis who were still alive at the time of the study (defined as 1 June 2017). Patients with ATTR amyloidosis were contacted by French centres from the French Rare Diseases network program. Patients aged  $\geq 18$  years with hereditary transthyretin-mediated amyloidosis (ATTRv) or wild-type transthyretin amyloidosis (ATTRwt) or a pathogenic transthyretin (TTR) mutation were eligible.

**Results:** Of the 38 centres (13 cardiology and 25 neurology) invited to participate, 22 (60.5%) (10 cardiology, 12 neurology) participated. There were 333 patients in cardiology census population. Before diagnosis one-fourth of the patients had cardiac decompensation, and one-fifth had a pacemaker. The 177 ATTRwt-CM patients were older ( $80.1 \pm 7.0$  years versus  $64.2 \pm 14.3$  years;  $P < 0.001$ ), had a higher incidence of hypertension (51.4% versus 35.3%;  $P = 0.003$ ), and a higher incidence of arrhythmia (45.8% versus 28.3%;  $P = 0.001$ ) than 156 ATTRv patients. There were no differences in disease severity according to New York Heart Association classification. The ATTRv-mixed + CM group had more neurological symptoms (paraesthesia or dysesthesia, neuropathic pain, digestive disorders, and orthostatic hypotension) than the ATTRwt-CM group ( $P < 0.001$ ). Biopsies were performed on nearly 90% of patients with most of them being positive. The most common biopsy sites were salivary glands (137 biopsies) and cardiac tissues (77 biopsies). Tafamidis meglumine was administered to 174 cardiology patients, including 96 with ATTRv-mixed, 61 with ATTRwt-CM, and 17 with ATTRv-CM. Tafamidis meglumine was generally well tolerated. 18 adverse events, including 12 severe adverse events were reported in 174 patients as safety-related incidents. Tafamidis meglumine was likely responsible for five adverse events, one of which was severe.

**Conclusion:** This study of real-world clinical ATTR amyloidosis cases in France further elucidated the characteristics of and diagnostic approach to a cardiology patient population census of 333 patients. As of June 1, 2017, 177 ATTRwt-CM, 117 ATTRv-mixed, and 39 ATTRv-CM patients were alive. Our experience with tafamidis meglumine in the cardiology population confirmed its good tolerance.

**Introduction**

Transthyretin amyloidosis (ATTR) is a systemic multiorgan condition defined by the presence of transthyretin (TTR), an extracellular protein that is deposited in several organs and tissues. The “amyloid fibrils” come from a plasma protein, TTR, mainly synthesised in the liver. ATTR amyloidosis has two distinct forms: wild-type ATTR (ATTRwt) amyloidosis and hereditary ATTR amyloidosis (ATTRv, where the ‘v’ stands for variant). Cardiomyopathy (CM) is a common manifestation of ATTR amyloidosis associated with an estimated life expectancy of 3–5 years without treatment [1,2].

ATTRwt, formerly known as senile systemic amyloidosis, occurs predominantly in men over 60 years old, in whom amyloid deposits are derived from wild TTR [3,4]. In relation to cardiomyopathy, ATTRwt is known as ATTRwt-CM.

ATTRv exists in two more frequent forms: hereditary amyloidosis with cardiomyopathy (ATTRv-CM) and hereditary amyloidosis with polyneuropathy (ATTRv-PN). Patients with ATTR amyloidosis diagnosed with both cardiomyopathy and neuropathy are considered to have a mixed phenotype (ATTRv-mixed).

Amyloid infiltration of the myocardium causes progressive restrictive cardiomyopathy leading to cardiac failure. The diagnosis is often suspected on extracardiac manifestations, particularly carpal tunnel syndrome or neurological and peripheral nerve disorders. A diagnosis of ATTR-CM can be made using nuclear scintigraphy (after evidence of cardiac amyloidosis observed via echocardiography or cardiac magnetic resonance) and the exclusion of light-chain cardiac amyloidosis via blood and urine tests [4]. Histological confirmation and typing should be performed in cases of suspected cardiac amyloidosis when the above criteria are not satisfied [4]. If a patient has ATTR-CM, genotyping is recommended to determine whether ATTRwt-CM or ATTRv-CM is involved. There are few data on the prevalence of ATTRv-CM; however, recent data suggest that ATTRv-CM is an overlooked cause of common cardiovascular conditions (including heart failure with preserved ejection fraction, low-flow aortic stenosis, and atrial fibrillation) in older

people. In hereditary ATTR amyloidosis, more than 130 mutations in the *TTR* gene (chromosome 18) have been identified likely to affect natural protein configuration [5].

In the ATTR-ACT study, tafamidis meglumine treatment reduced mortality of 30% in patients with ATTR-CM during a follow-up of 30 months [6].

The number and characteristics of patients with amyloidosis followed up in French hospital settings, and the treatment practices involved remain unknown. Thus, a two-part epidemiological study was designed, an OBServatory for AMYLoId transthyretin amyloidosis (OBSAMYL). The objective was to estimate the number of patients and to describe characteristics of patients with ATTR-CM (v and wt) and ATTRv-mixed. A second objective was to observe the real-world use and safety profile of tafamidis meglumine 20 mg through secondary data collection.

**Methods**

We followed the Strengthening of the Reporting of Observational studies in Epidemiology reporting guidelines to draft this manuscript [7].

**Study design**

This was a non-interventional descriptive retrospective national multi-centre study.

The study had two parts: 1) a census part to estimate, in the participating centres, the number of patients diagnosed with ATTR amyloidosis (ATTRv and ATTRwt), who were alive at the study point date (defined as June 1, 2017) whatever if they received tafamidis or not; 2) the second part mainly focused on the subgroup of patients with cardiomyopathy who had received tafamidis meglumine among the census population as well as any additional patients who had received tafamidis meglumine (after June 1, 2017, or those who had died before June 1, 2017).

The 2 analyses described in this paper focused on cardiomyopathy, excluding asymptomatic, undetermined and ATTRv-PN populations. Another study focus on neurological impairment was submitted for publication in a journal of neurology [8].

In France, tafamidis meglumine 20 mg, stabiliser of the TTR tetramer, have obtained a European marketing authorization in 2011 for the treatment of ATTRv with neuropathy. In November 2018, tafamidis meglumine 20 mg became available with temporary authorisation for amyloidosis with ATTR-CM. This was a safety study performed after market approval was granted in ATTRv-PN to obtain further drug safety information.

## Centre selection

French centres from the French Rare Diseases network program treating ATTR amyloidosis patients were contacted. According to the centres, several tools were used to identify these patients, including tracking files of different networks (Cardiogen network [<https://www.filiere-cardiogen.fr/professionnel/>], Amyloidosis Network [[www.reseau-amylose.org](http://www.reseau-amylose.org)], NNERF and Filnemus [<https://www.filmemus.fr>]). The data were collected between August 21, 2018, and September 6, 2019. The investigators were experts on the disease.

Due to its observational nature, this study did not modify patient-physician relationships or patient care and follow-up. The data sourced in this study included patients' medical records, and investigators filled in an e-case report form (e-CRF). The statistical report (available on reasonable request from [thibaud.damy@aphp.fr](mailto:thibaud.damy@aphp.fr)) was based on data collected at the time of the database lockdown on October 17, 2019.

## Participants

All patients alive on the June 1, 2017 and aged  $\geq 18$  years with a diagnosis of ATTR-CM (ATTRv and ATTRwt) and ATTRv-mixed were included in the census part of the study.

The tafamidis part included patients with at least one documented prescription of tafamidis meglumine outside of a clinical trial since its launch in France through an early access program in 2010.

## Diagnosis of amyloidosis

ATTRv-CM cases had a confirmed pathogenic *TTR* gene mutation, clinical symptoms such as heart failure or heart rhythm disorders (at diagnosis or described as first symptoms), and/or morphological anomalies detected by imaging equipment (such as echocardiography magnetic resonance imaging). Patients underwent bone scintigraphy (using Tc-99 m-3,3-diphosphono-1,2-propanodicarboxylic acid, hydroxymethylene diphosphonate, or others) and/or a positive cardiac biopsy revealing amyloid deposits.

ATTRwt cases had the same criteria as those defining ATTRv-CM, with no pathogenic mutations detected during genotyping.

ATTRv-mixed cases included ATTRv coexisting with polyneuropathy and cardiomyopathy. ATTRv with polyneuropathy cases required a confirmed pathogenic *TTR* gene mutation and clinical symptoms assessed by a neurologist without cardiac symptoms and/or involvement [8]. We classified patients with Val30Met mutation in early and late-onset cases (before and after 50 years of age) according to a previously described classification [9].

Undetermined cases were patients whose data on pathogenic mutations were known but lacked at least one criterion of the different amyloidosis. Members of the scientific committee discussed about these cases while reviewing the data. Some unclear cases were reclassified based on their experience and the available data. The 6 patients who had a Gly6Ser mutation were not considered as affected with hereditary amyloidosis in the analyses as it is a polymorphism.

Data entry rules were communicated to the centres prior to the site

initiation visits in order to avoid duplicate cases. The centre that had followed the patient the most closely, (i.e., number of consultations since the diagnosis) was responsible for data entry on the e-CRF. Alerts were also set up to identify potential duplications at the time of patient inclusion based on a combination of variables (sex, month/year, and mutation type).

The ATTR-ACT study comparing tafamidis meglumine to placebo in patients with ATTR-CM (ATTRv and ATTRwt) was ongoing during that period [10]. Not any medication was yet marketed in the cardiology field at the time of the study, therefore, those patients with cardiac amyloidosis were not eligible for an open prescription.

At the centres, laboratories performed medical investigations. *TTR* gene sequencing was mostly performed by laboratories of the National Reference Centre (Henri Mondor Hospital, Paris). We used an online registry of genes and mutations that included their associated clinical phenotypes for *TTR* gene sequencing in cases of hereditary amyloidosis [11]. Clinicians determined the location for the biopsies, and the biopsy specimens were stained with Congo red. In association with immunostaining using anti-TTR antibodies, polarised light microscopy was used to visualise apple-green birefringence in Congo red-stained specimens [12].

The study was conducted in accordance with legal and regulatory requirements with scientific purpose, value, and rigour. The study followed generally accepted good pharmacoepidemiology practices guidelines [13].

The variables, data sources, study size, quality control, handling of missing values, patient information, and ethical conduct of the study are described in the Supplementary files.

## Statistical analyses

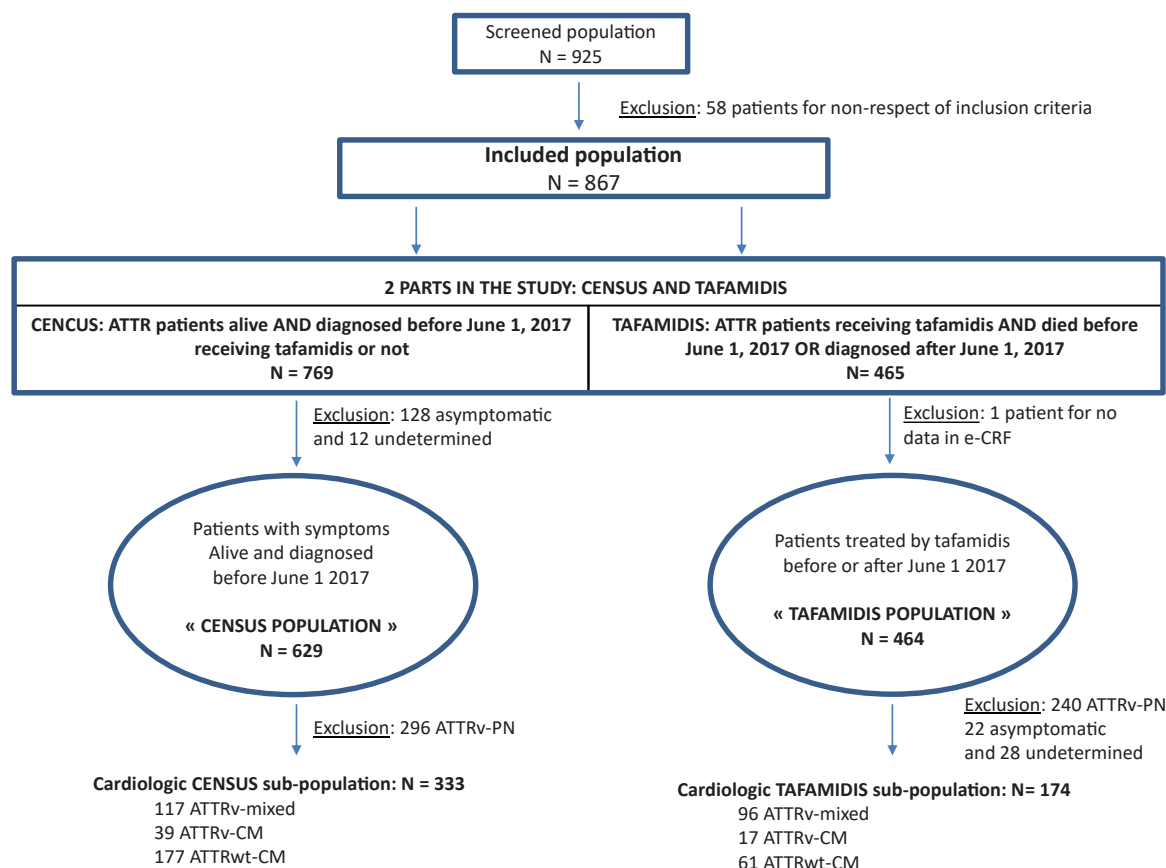
Analyses of the collected data were mainly descriptive. All e-CRF parameters and evaluation criteria are summarised using descriptive statistics. Continuous variables are shown as sample size, mean, standard deviation, minimum, median, and maximum data points, while discrete variables are shown as frequency and percentage for each category and number of missing data.

In all analyses, the date of diagnosis was defined as the date of the first genetic *TTR* test that revealed the pathogenic *TTR* gene mutations in hereditary ATTR amyloidosis. For senile TTR-related amyloidosis, the date of diagnosis was defined as the date of bone scintigraphy revealing the amyloid deposits. The oldest patient information was retained and used if both diagnoses were present.

## Results

Of the 38 centres (13 cardiology and 25 neurology) invited, 22 (60.5%) (10 cardiology, 12 neurology) participated. The main reasons for refusal were the small number of eligible patients and patients being lost to follow-up. The final report was based on data collected when the database was locked on October 17, 2019. A total of 925 patients were screened for study inclusion. Consequently, 867 (93.7%) patients were included, and the overall census population comprised 769 patients. 629 patients were alive in June 1, 2017 and had a confirmed diagnosis of symptomatic ATTR amyloidosis. Patients with an undetermined diagnosis or with an asymptomatic form were excluded from the analysis. A total of 464 patients received tafamidis meglumine at least one time and were considered in the Tafamidis population (Fig. 1). The distribution of patients between the cardiology and neurology centres is shown in Supplementary Table S1. One cardiology centre (Henri Mondor) included 318 patients, and one neurology reference centre (Kremlin-Bicêtre) included 242 patients. Therefore, these two sites accounted for 65% of the study population (560/867). In addition to the reference cardiology centre, nine cardiology sites were included.

Of 629 patients from the total census population (Fig. 1), 333 were cardiology patients: 177 had ATTRwt-CM, 117 had ATTRv-mixed, and



**Fig. 1.** Diagram of amyloid transthyretin amyloidosis patients included in the census and the tafamidis populations. The analysis was based on data collected at time of the database and locked on 17 October 2019.

39 had ATTRv-CM. Of 464 patients from the total tafamidis meglumine population, 174 were cardiology patients: 61 had ATTRwt-CM, 96 had ATTRv-mixed, and 17 had ATTRv-CM ([Supplementary Information Table S1](#)).

#### Patient characteristics of the census cardiology sub-population (n = 333).

For the census population, [Table 1](#) contains all the characteristics of 333 patients, severity of disease, diagnosis examinations, and biopsies. We compared 177 patients with ATTRwt-CM and 156 with ATTRv (mixed and CM). Among this last population, we compared 117 ATTRv patients depending on their phenotype (mixed or CM).

One-fourth of the 333 patients had cardiac decompensation before diagnosis, and one-fifth had a pacemaker. The 177 ATTRwt-CM patients had an older average age than the 156 ATTRv patients ( $80.1 \pm 7.0$  years versus  $64.2 \pm 14.3$  years;  $P < 0.001$ ), a greater incidence of hypertension (51.4% versus 35.3%;  $P = 0.003$ ), and a greater incidence of arrhythmia (45.8% versus 28.3%;  $P = 0.001$ ). There were no differences in disease severity according to New York Heart Association (NYHA) classification. The ATTRv-mixed and CM groups had more neurological symptoms (paraesthesia or dysesthesia, neuropathic pain, digestive disorders, and orthostatic hypotension) than the ATTRwt-CM group ( $P < 0.001$ ). The diagnosis was made more than 3 years after the first symptoms in 37.6% of the ATTRwt-CM patients and 34.3% of the ATTRv-mixed + CM patients. Biopsies were performed on nearly 90% of patients with most of them being positive (59.7% of the 139 ATTRwt-CM patients and 77.4% of the 133 ATTRv-mixed and CM patients;  $P = 0.002$ ). The most common biopsy sites ([Table 1](#)) were salivary glands (137 biopsies) and cardiac tissues (77 biopsies).

The most frequent TTR mutations ([Table 2](#)) were Val122Ile (59

cases), Val30Met (39 patients), and Ser77Tyr (19 patients).

#### Description of the tafamidis cardiology sub-population

We analysed the characteristics and disease severity of 174 cardiology patients who received tafamidis meglumine, including 96 with ATTRv-mixed, 61 with ATTRwt-CM, and 17 with ATTRv-CM ([Table 3](#)). The time of exposure to tafamidis meglumine during the study period varied among the groups, especially considering the late disposal of tafamidis meglumine in cardiology. This time of exposure was  $2.5 \pm 6.9$  months for ATTRwt-CM patients (median, 0 [range, 0–36]),  $6.3 \pm 10.4$  months for ATTRv-CM patients (median, 1 [range, 0–33]), and  $35.5 \pm 28.6$  months for ATTRv-mixed patients (median, 31 [range, 0–99]).

Tafamidis meglumine was generally well tolerated. 18 adverse events including 12 severe adverse events were reported in 174 patients ([Table 4](#)) as safety-related incidents. Tafamidis meglumine was likely responsible for five adverse events one of which was severe.

#### Discussion

This study of real-world clinical ATTR amyloidosis cases in France further elucidated the characteristics and diagnostic approach of a cardiology patient population census of 333 patients. As of June 1, 2017, 177 ATTRwt-CM, 117 ATTRv-mixed, and 39 ATTRv-CM patients were alive and reported in this paper. We reported our experience with tafamidis meglumine in the cardiology population and confirmed its good tolerance among these patients.

#### Change of amyloidosis genotypes and phenotypes in France

Compared to the Transthyretin Amyloidosis Outcomes Survey



**Table 1**  
Patients characteristics depending on genotype in the cardiology census sub-population and depending on phenotype in ATTRv.

	ATTRwt	ATTRv	P	ATTRv		P
	CM	Mixed and CM		Mixed	CM	
N	177	156		117	39	
<b>Patient characteristics</b>						
Age, years	80.1 ± 7.0	64.2 (14.3)	< 0.001 <sup>a</sup>	62.8 (15.1)	68.2 (10.8)	0.044 <sup>a</sup>
Sex, male	154 (87.0%)	112 (71.8%)	< 0.001 <sup>b</sup>	84 (71.8%)	28 (71.8%)	1.000 <sup>b</sup>
Weight, kg	71.2 ± 12.2	71.8 ± 13.3	0.692 <sup>a</sup>	69.9 ± 13.5	76.8 ± 11.7	0.011 <sup>a</sup>
BMI, kg/m <sup>2</sup>	24.9 ± 3.3	24.7 ± 4.3	0.798 <sup>a</sup>	24.0 ± 4.1	26.5 ± 4.5	< 0.004 <sup>a</sup>
Hypertension	91 (51.4%)	55 (35.3%)	0.003 <sup>b</sup>	36 (30.8%)	19 (48.7%)	0.042 <sup>b</sup>
Diabetes	20 (11.3%)	14 (9.0%)	0.484 <sup>b</sup>	10 (8.5%)	4 (10.3%)	0.746 <sup>b</sup>
<b>Time from first symptom(s) to diagnosis</b>						
< 1 year	34 (29.1%)	36 (26.3%)	0.745 <sup>b</sup>	25 (24.8%)	11 (30.6%)	0.796 <sup>b</sup>
1–2 years	39 (33.3%)	54 (39.4%)		39 (38.6%)	15 (41.7%)	
3–5 years	25 (21.4%)	29 (21.2%)		23 (22.8%)	6 (16.7%)	
> 5 years	19 (16.2%)	18 (13.1%)		14 (13.9%)	4 (11.1%)	
Years, mean±SD	2.9 ± 3.9	2.9 ± 4.3	0.945 <sup>a</sup>	3.2 ± 4.6	2.2 ± 3.5	0.230 <sup>a</sup>
median [range]	2.0 [0.0–27.0]	1.0 [0.0–25.0]		1.0 [0.0–25.0]	1.0 [0.0–18.0]	
Q1–Q3	0.0–4.0	0.0–4.0		1.0–4.0	0.0–3.0	
<b>Time from diagnosis to inclusion</b>						
Years	3.4 ± 1.2	5.3 ± 4.3	< 0.001 <sup>a</sup>	6.0 ± 4.8	3.5 ± 1.7	0.003 <sup>a</sup>
<b>Cardiac history and symptoms</b>						
Hospitalisation for cardiac decompensation	42 (25.1%)	30 (21.1%)	0.404 <sup>b</sup>	17 (16.0%)	13 (36.1%)	0.011 <sup>b</sup>
Arrhythmia	76 (45.8%)	41 (28.3%)	0.001 <sup>b</sup>	31 (28.4%)	10 (27.8%)	0.939 <sup>b</sup>
Abnormal cardiac conduction	39(23.5%)	38 (26.0%)	0.605 <sup>b</sup>	30 (27.5%)	8 (21.6%)	0.480 <sup>b</sup>
Pacemaker insertion	36 (21.6%)	30 (20.7%)	0.852 <sup>b</sup>	23 (21.1%)	7 (19.4%)	0.832 <sup>b</sup>
Pulmonary embolism	3 (1.8%)	1 (0.7%)	0.386 <sup>b</sup>	1 (0.9%)	0 (0.0%)	0.564 <sup>b</sup>
<b>Disease severity (NYHA) at diagnosis</b>						
Class I	11 (7.9%)	7 (8.4%)	0.976 <sup>b</sup>	6 (10.3%)	1 (4.0%)	0.338 <sup>b</sup>
Class II	69 (49.3%)	43 (51.8%)		31 (53.4%)	12 (48.0%)	
Class III	47 (33.6%)	26 (31.3%)		18 (31.0%)	8 (32.0%)	
Class IV	13 (9.3%)	7 (8.4%)		3 (5.2%)	4 (16.0%)	
<b>Neurological and carpal tunnel symptoms</b>						
Paraesthesia or dysesthesia	7 (4.3%)	50 (35.5%)	< 0.001 <sup>b</sup>	50 (47.2%)	0 (0.0%)	< 0.001 <sup>b</sup>
Neuropathic pain	13 (7.8%)	41 (29.1%)	< 0.001 <sup>b</sup>	41 (38.7%)	0 (0.0%)	< 0.001 <sup>b</sup>
Diarrhoea, constipation	8 (4.5%)	30 (19.2%)	< 0.001 <sup>b</sup>	30 (25.6%)	0 (0.0%)	< 0.001 <sup>b</sup>
Orthostatic hypotension signs	8 (4.5%)	28 (17.9%)	< 0.001 <sup>b</sup>	28 (23.9%)	0 (0.0%)	< 0.001 <sup>b</sup>
History of carpal tunnel	113 (64.2%)	90 (57.7%)	0.224 <sup>b</sup>	71 (60.7%)	19 (48.7%)	0.190 <sup>b</sup>
Carpal tunnel surgery	95 (54.0%)	66 (42.3%)	0.034 <sup>b</sup>	51 (43.6%)	15 (38.5%)	0.575 <sup>b</sup>
<b>Exams</b>						
ECG/Holter monitoring	166 (96.5%)	136 (90.1%)	0.019 <sup>b</sup>	100 (88.5%)	36 (94.7%)	0.266 <sup>b</sup>
Echocardiography	169 (96.6%)	139 (91.4%)	0.048 <sup>b</sup>	102 (89.5%)	37 (97.4%)	0.132 <sup>b</sup>
Bone scintigraphy	164 (95.3%)	101 (83.5%)	< 0.001 <sup>b</sup>	69 (82.1%)	32 (86.5%)	0.553 <sup>b</sup>
Positive scintigraphy <sup>c</sup>	160 (97.6%)	78 (77.2%)	< 0.001 <sup>b</sup>	49 (71.0%)	29 90.(6%)	0.029 <sup>b</sup>
Cardiac MRI	112 (67.5%)	106 (72.6%)	0.324 <sup>b</sup>	79 (72.5%)	27 (73.0%)	0.953 <sup>b</sup>
<b>Biopsies</b>						
Biopsies/patients	146 / 169 (86.4%)	135 / 147 (91.8%)	0.124 <sup>b</sup>	104 / 111 (93.7%)	31 36 (86.1%)	0.149 <sup>b</sup>
Positive biopsies/patients with biopsies	83 / 139 (59.7%)	103 / 133 (77.4%)	0.002 <sup>b</sup>	85 / 102 (83.3%)	18 / 31 (58.1%)	0.003 <sup>b</sup>
<b>Positive biopsies/biopsies by location</b>						
Salivary gland	39 / 59 (66.1%)	62 / 78 (79.5%)		52 / 66 (78.8%)	10 / 12 (83.3%)	
Cardiac and myocardial	45 / 46 (97.8%)	31 / 31 (100%)		20 / 20 (100%)	11 / 11 (100%)	
Skin	1 / 1 (100%)	20 / 25 (80%)		20 / 25 (80.0%)	0 / 0 (0.0%)	
Nerve	1 / 1 (100%)	13 / 13 (100%)		13 / 13 (100%)	0 / 0 (0.0%)	
Abdominal fat	1 / 2 (50%)	1 / 1 (100%)		1 / 1 (100%)	0 / 0 (0.0%)	
Other/muscular/gastric	3 / 4 (75.0%)	5 / 8 (62.5%)		5 / 8 (62.5%)	0 / 0 (0.0%)	

Data are expressed as median [interquartile range], mean ± standard deviation, or percentage.

ATTR, amyloid transthyretin; CM, cardiomyopathy; BMI, body mass index; MRI, magnetic resonance imaging; NYHA, New York Heart Association; Q, quartile; SD, standard deviation; v, variant; wt, wild-type.

<sup>a</sup>Analysis of variance.

<sup>b</sup>Chi-squared test.

<sup>c</sup>Cardiac fixation on bone scintigraphy.

(THAOS) population, we observed some changes in our cardiological census sample. In the THAOS study on cardiac amyloidosis patients from Western Europe, 94 French patients were included at January 2016 [14]. Three ATTRwt-CM patients were included, and the mutations observed in the ATTRv patients included Val30Met (n = 42, including

27 early-onset and 15 late-onset cases), Ser777Tyr (n = 15), Val122Ile (n=12), Ile107Val (n=5), and all other ≤ 3 genotypes (n=17). Among the 94 patients, 13 had cardiac mutations (12 Val122Ile, one Ile68Leu). No Leu111Met or Thr60Ala mutations were observed. A comparison of the THAOS patients with our population census (patients alive in June 1,

**Table 2**  
Prevalence of TTR gene mutations in the cardiologic census sub-population.

TTR gene mutation	Total n = 333 (%)	ATTRwt- CM n = 177 (%)	ATTRv- mixed n = 117 (%)	ATTRv- CM n = 39 (%)
Val122Ile	59 (17.7)	0 (0)	31 (26.5)	28 (71.8)
Val30Met	39 (11.7)	0 (0)	38 (32.5)	1 (2.6)
Early-onset	15	0	15	0
Late-onset	23	0	22	1
Age unknown	1	0	1	0
Ser77Tyr	19 (5.7)	0 (0)	17 (14.5)	2 (5.1)
Ser77Phe	7 (2.1)	0 (0)	5 (4.3)	2 (5.1)
Lle68Leu	6 (1.8)	0 (0)	3 (2.6)	3 (7.7)
Lle107Val	5 (1.5)	0 (0)	5 (4.3)	0 (0)
Thr49Ala	3 (0.9)	0 (0)	3 (2.6)	0 (0)
Thr49Ile	3 (0.9)	0 (0)	2 (1.7)	1 (2.6)
Pro24Ser	2 (0.6)	0 (0)	2 (1.7)	0 (0)
Val28Met	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Glu61Lys	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Ser50Arg	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Glu61Gly	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Glu62Lys	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Glu54Leu	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Arg21Gln	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Glu89Lys	1 (0.3)	0 (0)	0 (0)	1 (2.6)
Phe33Leu	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Phe44Tyr	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Thr106Asn	1 (0.3)	0 (0)	1 (0.9)	0 (0)
Thr59Arg	1 (0.3)	0 (0)	1 (0.9)	0 (0)

ATTR, amyloid transthyretin; CM, cardiomyopathy, v, variant; wt, wild-type.

2017) showed that we observed more patients with ATTRwt-CM (n=177). This might be because of the improvement of the diagnosis in cardiology with the development of non-invasive methods leading to more ATTR-CM diagnosis and change in the prevalence of the different type of amyloidosis. We also observed a change in the patient's genotypes with more mutations leading to cardiac phenotypes. We observed 7 genetic mutations among 39 ATTRv-CM patients and 21 among 117 ATTRv-mixed patients. Val122Ile was the most frequent mutation observed in the French 2017 population. The high frequency of this mutation can be explained by the origin of our patients coming from West Africa (namely, Togo, Benin, and the Ivory Coast) and the Caribbean islands. Thus, the Val30Met mutation is no longer the most frequent mutation in ATTRv-CM patients in France. We also observed more female patients than in THAOS, reflecting cardiologists improved diagnosis and probably other causes that deserve to be investigated.

#### Diagnostic approach and medical treatment of ATTR-CM patients

ATTRv patients (ATTRv-CM and mixed) had more frequently neurological symptoms than ATTRwt-CM. The time between first symptoms to diagnosis was shorter for the ATTRv-CM (mean duration,  $2.2 \pm 3.5$  years; median duration, 1.0 [range, 0.0–18.0] years) and ATTRwt-CM patients (mean duration,  $2.9 \pm 3.9$  years; median duration, 2.0 [range, 0.0–27.0] years) than for the 296 ATTRv-PN patients (mean duration,  $3.4 \pm 4.2$  years; median duration, 2.1 [range, 0.0–21.9] years) described in the neurology paper [8]. This finding could be because of the non-invasive imaging diagnosis tool, the scintigraphy, used to confirm the diagnosis of ATTRv-CM patients [15,16]. The greater delay in diagnosis for the ATTRwt and mixed patients could reflect clinical inertia for ATTR diagnosis despite the increase of awareness and the number of physicians consultations to arrive to the diagnosis [17,18]. In France, scintigraphy is a common tool for cardiology diagnostics; however, scintigraphy is less often used in neurology and is not systematic. Scintigraphy was performed in approximately 90% of patients in this study, and the results were positive in 90% of patients. If a biopsy was performed, inter-centre heterogeneity was observed [4], as the main centre has set-up a "one stop shop program" [19].

Tafamidis meglumine was well tolerated by the patients in our study. Of 174 patients, we observed one case of urinary tract infection — a finding that is not in accordance with the product characteristics summary stating that this infection is frequent. In the multi-centre study, ATTR-ACT, 264 patients (21 from France) received tafamidis meglumine 80 or 20 mg, and no differences were observed among patients in our real-world study [10] [20]. The mean age of the 264 ATTR-ACT patients was  $74.5 \pm 7.2$  years, and 91.3% of the patients were male; overall, 54.9% (145/264) had hypertension and 7.6% (20/264) had diabetes. Regarding the NYHA classes of the ATTR-ACT patients: 9.1% (24) were class I, 61.4% (162) were class II, and 9.5% (78) were class III. This comparison confirms that the ATTR-ACT results can be generalised to a real-world population [21].

#### Strengths of the French rare diseases network and limitations of the study

The French referral centres followed up amyloidosis patients and provided their data when they had a substantial number of them. Practices were homogeneous among the centres and practitioners. The two main national centres, both in neurology and cardiomyopathy, managed approximately 65% of the patients. The 10 cardiology centres communicated regularly with each other, and nearly all the French practitioners who competently followed ATTR amyloidosis in cardiomyopathy patients participated. This French network was established by the Health Ministry in 2005, focusing on amyloidosis within cardiology. The reference centre (Henri Mondor Hospital, Créteil) provides expertise and referrals in cases of the disease and is equipped to perform pathological and molecular biology testing. The centre has coordinated a national network organisation within a "Rare Disease Plan" framework to better identify and follow up patients at a national level. A drawback of this study is that a family history of hereditary ATTR was not analysed since these parameters were not requested in the e-CRF. Biological parameters (such as brain natriuretic peptide [BNP], N-terminal pro-BNP, and troponin) were not collected for this study.

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#### Declaration of Competing Interest

T.D. has served on the scientific board of, and receiving funding for, Pfizer, Alnylam, Akcea Prothena, and GSK. E.D. has received grants and/or fees from Pfizer, General Electric healthcare, Abbott, AstraZeneca. O. L. has received grants and/or fees from Alnylam, Amicus, Pfizer, Sanofi-Genzyme. J.C.E. has received expenses and honoraria for meetings from Abbott, Actelion, Alnylam, AstraZeneca, Bristol Myers Squibb, Novartis, Pfizer, Vifor. J.N.T. received grants and honoraria from Novartis, grants from Akcea, honoraria from Abbott, AstraZeneca, Boehringer Bayer, Pfizer, ViforPharma, Bristol Myers Squibb. J.I. received fees from Alnylam, Pfizer. GH has received expenses and honoraria for meetings from Abbott, Actelion, Alnylam, AstraZeneca, Novartis, Pfizer. F.R. has received grants and/or fees from Abbott, Air Liquide, Astra Zeneca, Servier, Boehringer, Astra Zeneca, Vifor, Bayer, Pfizer, Novartis, Novonordisk. A.H. has received consulting fees from Alnylam, Pfizer. J. A. has received honoraria for meetings from Pfizer, Shire. V.A. received grants and consulting fees from Alnylam, Pfizer. A.C., M.B., J.R. and L.S. are Pfizer employees. A.G.M. has received consulting fees from Pfizer. J.C.A. has received consulting fees from Pfizer. S.A. reports speaker honoraria and travel support from LFB, Alnylam, Akcea, Pfizer, Sanofi, Pharnext, Inflectis, Biogen, Novartis Hansa, UCB, Argenx, Alexion, Roche. Board member: Sanofi, Pfizer pharnext, Inflectis, Hansa, LFB, Biogen, Alnylam, Argenx, Alexion, Roche. Research funding: LFB, Pfizer, Biogen. P.C. has received consulting fees and/or honoraria from Alnylam, Amicus, Bristol Myers Squibb, Sanofi, Pfizer. L.M. has received consulting fees and/or

**Table 3**  
Baseline characteristics in the 174 patients of the cardiologic tafamidis sub-population.

N	ATTRwt	ATTRv	P	ATTRv	P	
	CM 61	Mixed + CM 113		Mixed 96		CM 17
<b>Patients characteristics</b>						
Age (years)	77.5 ± 7.7	64.6 ± 12.4	< 0.001 <sup>a</sup>	63.5 ± 12.9	71.0 ± 6.4	0.031 <sup>a</sup>
Sex, male	49 (80.3%)	80 (70.8%)	0.171 <sup>b</sup>	68 (70.8%)	12 (70.6%)	0.984 <sup>b</sup>
Weight (kg)	73.4 ± 11.9	69.4 ± 13.3	0.081 <sup>a</sup>	69.0 ± 13.9	71.8 ± 9.0	0.474 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	25.3 ± 2.7	23.8 ± 4.0	0.015 <sup>a</sup>	23.5 ± 4.2	25.2 ± 2.6	0.189 <sup>a</sup>
Hypertension	36 (59.0%)	37 (32.7%)	< 0.001 <sup>b</sup>	29 (30.2%)	8 (47.1%)	0.172 <sup>b</sup>
Diabetes	6 (9.8%)	9 (8.0%)	0.675 <sup>b</sup>	7 (7.3%)	2 (11.8%)	0.530 <sup>b</sup>
<b>Time from first symptom(s) to diagnosis</b>						
< 1 year	11 (25.0%)	18 (19.6%)	0.351 <sup>b</sup>	12 (15.2%)	6 (46.2%)	0.045 <sup>b</sup>
1–2 years	14 (31.8%)	36 (39.1%)		31 (39.2%)	5 (38.5%)	
3–5 years	9 (20.5%)	26 (28.3%)		25 (31.6%)	1 (7.7%)	
> 5 years	10 (22.7%)	12 (13.0%)		11 (13.9%)	1 (7.7%)	
Years, mean±SD	3.3 ± 3.4	3.4 ± 4.7	0.890 <sup>a</sup>	3.6 ± 4.6	2.1 ± 4.9	0.286 <sup>a</sup>
median [range]	2.0 [0.0–11.0]	2.0 [0.0–25.0]		2.0 [0.0–25.0]	1.0 [0.0–18.0]	
Q1–Q3	0.5–5.0	1.0–4.0		1.0–4.0	0.0–1.0	
<b>Time from diagnosis to inclusion</b>						
Years	2.7 ± 1.0	4.8 ± 4.0	< 0.001 <sup>a</sup>	5.3 ± 4.2	2.2 ± 1.1	0.005 <sup>a</sup>
<b>Cardiac history and symptoms</b>						
Hospitalisation for cardiac decompensation	9 (15.5%)	15 (14.6%)	0.870 <sup>b</sup>	12 (13.6%)	3 (20.0%)	0.518 <sup>b</sup>
Arrhythmia	25 (42.4%)	28 (26.7%)	0.039 <sup>b</sup>	24 (26.7%)	4 (26.7%)	1.000 <sup>b</sup>
Abnormal cardiac conduction	12 (20.3%)	26 (24.8%)	0.519 <sup>b</sup>	25 (27.8%)	1 (6.7%)	0.079 <sup>b</sup>
Pacemaker insertion	13 (22.0%)	24 (22.9%)	0.904 <sup>b</sup>	21 (23.3%)	3 (20.0%)	0.776 <sup>b</sup>
Pulmonary embolism	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
<b>Severity of the disease (NYHA) at the diagnosis</b>						
Class I	5 (10.9%)	5 (10.2%)	0.622 <sup>b</sup>	5 (12.2%)	0 (0.0%)	0.105 <sup>b</sup>
Class II	26 (56.5%)	26 (53.1%)		22 (53.7%)	4 (50.0%)	
Class III	12 (26.1%)	17 (34.7%)		14 (34.1%)	3 (37.5%)	
Class IV	3 (6.5%)	1 (2.0%)		0 (0.0%)	1 (12.5%)	
<b>Neurological symptoms</b>						
Paraesthesia or dysesthesia	3 (5.1%)	46 (45.1%)	< 0.001 <sup>b</sup>	46 (52.3%)	0 (0.0%)	< 0.001 <sup>b</sup>
Neuropathic pains	5 (8.3%)	33 (32.4%)	< 0.001 <sup>b</sup>	33 (37.5%)	0 (0.0%)	0.005 <sup>b</sup>
Diarrhoea, constipation	6 (9.8%)	27 (24.1%)	0.022 <sup>b</sup>	27 (28.1%)	0 (0.0%)	0.015 <sup>b</sup>
Orthostatic hypotension signs	5 (8.2%)	28 (24.8%)	0.008 <sup>b</sup>	27 (28.1%)	1 (5.9%)	0.050 <sup>a</sup>
History of carpal tunnel	45 (73.8%)	63 (55.8%)	0.019 <sup>b</sup>	53 (55.2%)	10 (58.8%)	0.782 <sup>b</sup>
History of carpal tunnel surgery	40 (65.6%)	44 (38.9%)	< 0.001 <sup>b</sup>	38 (39.6%)	6 (35.3%)	0.738 <sup>b</sup>
<b>Exams</b>						
ECG/Holter	55 (90.2%)	95 (88.0%)	0.664 <sup>b</sup>	80 (87.0%)	15 (93.8%)	0.441 <sup>b</sup>
Echocardiogram	56 (91.8%)	96 (88.1%)	0.448 <sup>b</sup>	81 (87.1%)	15 (93.8%)	0.448 <sup>b</sup>
Bone scintigraphy	59 (96.7%)	63 (79.7%)	0.003 <sup>b</sup>	49 (77.8%)	14 (87.5%)	0.388 <sup>b</sup>
Positive scintigraphy*	58 (98.3%)	45 (71.4%)	< 0.001 <sup>b</sup>	32 (65.3%)	13 (92.9%)	0.044 <sup>b</sup>
Cardiac MRI	44 (74.6%)	69 (66.3%)	0.274 <sup>b</sup>	59 (66.3%)	10 (66.7%)	0.977 <sup>b</sup>
<b>Biopsies</b>						
Nb biopsies / Nb of patients	46 / 57 (80.7%)	90 / 106 (84.9%)	0.491 <sup>b</sup>	81 / 90 (90.0%)	9 / 16 (56.3%)	< 0.001 <sup>b</sup>
Nb positive biopsies / Nb of patients with biopsies	31 / 45 (68.9%)	74 / 88 (84.1%)	0.042 <sup>b</sup>	69 / 79 (87.3%)	5 / 9 (55.6%)	0.014 <sup>b</sup>
<b>Number of positive biopsies / number of biopsies done according to the location (%)</b>						
Salivary gland	13 / 24 (54.2%)	51 / 61 (83.6%)		49 / 57 (86.0%)	2 / 4 (50.0%)	
Cardiac	20 / 21 (95.2%)	18 / 18 (100%)		14 / 14 (100%)	4 / 4 (100%)	
Skin	1 / 1 (100%)	17 / 20 (85.0%)		17 / 20 (85.0%)	0 / 0 (0.0%)	
Nerve	0 / 0 (0.0%)	10 / 10 (100%)		10 / 10 (100%)	0 / 0 (0.0%)	
Abdominal fat	0 / 0 (0.0%)	1 / 1 (100%)		1 / 1 (100%)	0 / 0 (0.0%)	
Other/Gastric	1 / 1 (100.0%)	2 / 6 (33.3%)		2 / 6 (33.3%)	0 / 0 (0.0%)	

Data are expressed as median [interquartile range], mean ± standard deviation, or percentage.

ATTRwt-CM patients received tafamidis for 2.5 ± 6.9 months, ATTRv-mixed patients received it for 35.5 ± 28.6 months, and ATTRv-CM patients received it for 6.3 ± 10.4 months.

ATTR, amyloid transthyretin; CM, cardiomyopathy; BMI, body mass index; MRI, magnetic resonance imaging; NYHA, New York Heart Association; Q, quartile; nb, number. SD, standard deviation; v, variant; wt, wild-type.

<sup>a</sup>Analysis of variance.

<sup>b</sup>Chi-squared test.

<sup>c</sup>Cardiac fixation on bone scintigraphy.



**Table 4**

Description of adverse event occurring in the cardiologic tafamidis sub-population.

	Total	ATTRwt-CM		ATTRv	
				Mixed	CM
N	174	61	96	17	
	n (%)	n (%)	n (%)	n (%)	
AEs (including SAEs)	18 (10.3)	2 (3.3)	13 (13.5)	3 (17.7)	
SAEs	12 (6.9)	2 (3.3)	8 (8.3)	2 (11.8)	
Treatment discontinuation related to an AE (including SAEs)	5 (2.9)	0 (0.0)	5 (5.2)	0 (0.0)	
Treatment discontinuation related to an SAE	1 (0.6)	0 (0.0)	1 (1.0)	0 (0.0)	
AEs likely related to study drug (including SAEs)	5 (2.9)	0 (0.0)	4 (4.2)	1 (5.9)	
SAEs likely related to study drug	1 (0.6)	0 (0.0)	1 (1.0)	0 (0.0)	
<b>Number of adverse events (n)</b>					
Death	11	2	7	2	
Lung disorder	2	0	2	0	
Drug ineffective	1	0	1	0	
Diarrhoea	1	0	1	0	
Bone pain	1	0	1	0	
Disease progression	1	0	1	0	
Infection	1	0	1	0	
Multiple allergies	1	0	1	0	
Urinary tract infection	1	0	0	1	

AE, adverse event; ATTR, amyloid transthyretin; CM, cardiomyopathy; SAEs, serious adverse events; v, variant; wt, wild-type.

or honoraria from Akcea, Alnylam, Pfizer. C.Q. has received honoraria from Alnylam, Akcae and Pfizer. Y.P. has received consulting fees from Akcea, Alnylam, Pfizer. E.L. has received consulting fees from Akcea, Alnylam, Pfizer. G.S. has received grants and honoraria from Alnylam, Pfizer. C.T. reports personal fees and non-financial support from Biogen, Sanofi-Genzyme, Pfizer, Alnylam, Roche, personal fees from Akcea, Argenx, Ultragenyx, non-financial support from Santhera, LFB. S.O. has received honoraria for meetings from Pfizer. P.C. has received consulting fees from Alnylam, Amicus, Bristol Myers Squibb, Pfizer. M. S. has received consulting fees from Alnylam, Pfizer.

The remaining authors have no relevant conflict of interest: M Kharoubi, B Francou, E Cariou, R Juntas Morales, F Morio, M Mallaret, C Labeyrie, P Petiot.

## Data Availability

Data will be made available on request.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.rare.2024.100021](https://doi.org/10.1016/j.rare.2024.100021).

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