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Clinical Research

Impact of RNAi therapeutics on cardiac parameters in patients with hereditary transthyretin amyloidosis initially treated with stabilizers: A French real-world study

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ABSTRACT

Background: Cardiomyopathy in hereditary transthyretin amyloidosis (ATTRv) is increasingly reported due to improved diagnostic techniques and increased clinician awareness. Optimal therapeutic strategies for mixed phenotypes remain challenging.

Aims: To describe the changes in cardiac parameters among patients with ATTRv and cardiac involvement who had switched from stabilizer monotherapy to ribonucleic acid interference (RNAi) therapeutics or added RNAi to stabilizer monotherapy (switching/adding RNAi).

Methods: Data from patients with ATTRv and confirmed cardiomyopathy who had started tafamidis monotherapy between 2010 and 2022 and switched to/added RNAi therapeutics (patisiran or vutrisiran) between 2018 and 2023 were retrospectively collected from October 2023 to May 2024. Functional, laboratory and imaging parameters were collected, and progression assessed according to the 2021 expert consensus on transthyretin amyloidosis with cardiomyopathy monitoring.

Results: Fifty patients (median [interquartile range] age 63 [58–70] years; 66% male) from 10 French centres were included. Mean ± standard deviation follow-up durations on treatment were 3.8 ± 2.7 years for tafamidis monotherapy and 2.5 ± 1.9 years for RNAi (±tafamidis). Switching/adding RNAi was mainly for neurological progression (n = 40; 80%). Under tafamidis monotherapy, 24% of patients worsened with simultaneous declines in clinical, laboratory and imaging parameters, while 76% were stable. After switching/adding RNAi, 90% of patients were stable, none worsened and 10% improved.

Conclusion: This real-world French study is the first switch/add-on study in mixed phenotypes of ATTRv. It highlights the potential benefits of early switching/adding of RNAi in patients with insufficient cardiac response under tafamidis.

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Abbreviations

ATTR transthyretin amyloidosis
ATTRv hereditary transthyretin amyloidosis
ATTR-CM transthyretin amyloidosis with cardiomyopathy
BNP B-type natriuretic peptide
CI confidence interval
FAP familial amyloid polyneuropathy
GLS global longitudinal strain
LVEF left ventricular ejection fraction
LVWT left ventricular wall thickness
NT-proBNP N-terminal pro-B-type natriuretic peptide
NYHA New York Heart Association
RNA ribonucleic acid
RNAi ribonucleic acid interference
TTE transthoracic echocardiography

1. Introduction

Hereditary transthyretin amyloidosis (ATTRv) is an autosomal-dominant, adult-onset, progressive, systemic disease caused by mutations in the *transthyretin* gene that leads to the formation of unstable, monomeric transthyretin protein fibrils. These fibrils aggregate and cause damage to tissues and organs, mainly affecting peripheral nerves and cardiac tissue in ATTRv [1–3].

Traditionally, neurologists have been the primary consulting physicians for individuals presenting with ATTRv due to the predominately polyneuropathic presentation of the disease. Patients with cardiac involvement often present with non-specific symptoms such as fatigue or oedema, which can lead to misdiagnosis or delayed diagnosis [4]. However, due to advances in diagnostic modalities and increased physician awareness, the diagnosed prevalence of cardiac or mixed (cardiac and neurological) phenotype is rising [4–6]. Advanced imaging techniques, such as transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging, are essential for early detection and assessment of the extent of cardiac involvement. Furthermore, bone scintigraphy using ^{99m}Tc-pyrophosphate scans has shown high sensitivity and specificity for detecting transthyretin amyloidosis (ATTR) and is being used in place of tissue biopsies for confirmation of disease [7,8].

Different drugs are available to control disease progression in patients with ATTRv. Among them, tafamidis (a transthyretin stabilizer) and patisiran and vutrisiran (two ribonucleic acid [RNA] interference [RNAi] therapies), are approved in the European Union to delay peripheral neurological impairment (tafamidis 20 mg) or to treat ATTRv with polyneuropathy (patisiran and vutrisiran) [9]. By stabilizing the transthyretin protein, preventing its misfolding and the deposition of amyloid fibrils (tafamidis) or by degrading its messenger RNA and interfering with its production (patisiran or vutrisiran), these treatments aim to prevent amyloid deposition, modifying the fatal course of the disease. Tafamidis has also been shown to significantly slow down cardiological aspects of the disease course, leading to the approval of the highest dosage studied (61 mg) in the treatment of ATTR cardiomyopathy (ATTR-CM) in 2020 by the European Medicines Agency. In France, tafamidis 61 mg is the only approved treatment for ATTR-CM [10]. Since May 2024 [11], patisiran – which is recommended for ATTRv with neuropathy – can also be used for the treatment of adult patients with ATTR-CM, under compassionate use among patients whose disease progresses despite tafamidis treatment or who are intolerant to tafamidis. In September 2020, when recommending tafamidis 61 mg as first-line treatment for ATTR-CM [10] the French Health Authority stated that it had not ruled on the strategy of using tafamidis, in conjunction or sequentially, with other existing treatments (such as RNAi) or using tafamidis at a different dosage in patients with ATTRv mixed phenotype. However, pivotal studies of RNAi (patisiran and vutrisiran) and recent case studies among patients with mixed ATTRv have reported that cardiomyopathy may stabilize or improve when RNAi therapeutics are introduced [12–20].

At the time of our study, to the best of our knowledge, no scientific data supported or refuted the possibility that ATTR mixed patients with cardiac progression under tafamidis could respond upon switching to, or adding on, RNAi treatment [3]. Our study therefore aimed to describe changes in cardiac parameters among patients with ATTRv with mixed phenotype, who were initially treated with tafamidis and then switched to, or added on, treatment with RNAi therapeutics (switching/adding) in a real-world setting. Considering that an increasing number of patients are being identified with cardiac or mixed ATTRv phenotypes, there is a need to consider the most appropriate management strategy for these patients as early as possible to prevent irreversible damage [4–6].

2. Methods

2.1. Study design and setting

This observational study was a collaborative effort among 10 expert centres affiliated with national rare disease networks dedicated to cardiac amyloidosis. The study was conducted in compliance with the principles outlined in the Declaration of Helsinki and relevant national regulations. According to French regulations, the study did not require prior approval from an ethics committee as it was retrospective in nature and involved the analysis of previously collected and anonymized data. No formal sample size calculation was performed given the retrospective and exploratory nature of the study; all eligible patients available during the study period were included. Data were retrospectively collected from hospital registries using a predefined standardized form shared across centres to harmonise variables and definitions.

2.2. Participants

Adult patients were identified from hospital records. Included patients had to present with the following characteristics: adult, confirmed ATTRv, cardiac involvement and initial treatment with tafamidis followed by RNAi treatment (patisiran or vutrisiran) for at least 1 year. Cardiac involvement could be present before the initial treatment with tafamidis or develop subsequently.

The hereditary nature of the ATTR was determined by genetic sequencing. Cardiac involvement was assessed using the New York Heart Association (NYHA) classification of heart failure and confirmed through TTE, bone scintigraphy (Perugini grade ≥ 2) and the absence of clonal dyscrasias according to international guidelines [7]. Included patients had to be classified as NYHA class II or III, or class I with N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 500 pg/mL or B-type natriuretic peptide (BNP) > 100 pg/mL.

The potential candidates for study participation were informed about the study and its purpose. In line with French regulations for retrospective studies, data were included on a non-opposition basis: patients were informed that their demographic and clinical data could be collected and analysed unless they explicitly objected, and they could opt out at any time. All data were anonymized in compliance with the European Union General Data Privacy Regulation (GDPR EU 2016/679 of 27 April 2016) and French data privacy regulations.

2.3. Data collection

Between October 2023 and May 2024, data were retrospectively collected from patients who started tafamidis monotherapy between 2010 and 2022 and switched to, or added, RNAi treatment between 2018 and 2023 (Fig. 1). Patient demographic, clinical (patient history, physical examination, NYHA class), laboratory (NT-proBNP, troponin) and radiological (TTE) data were collected at the visit closest to tafamidis initiation (baseline), the visit closest to RNAi initiation (i.e. when swit-

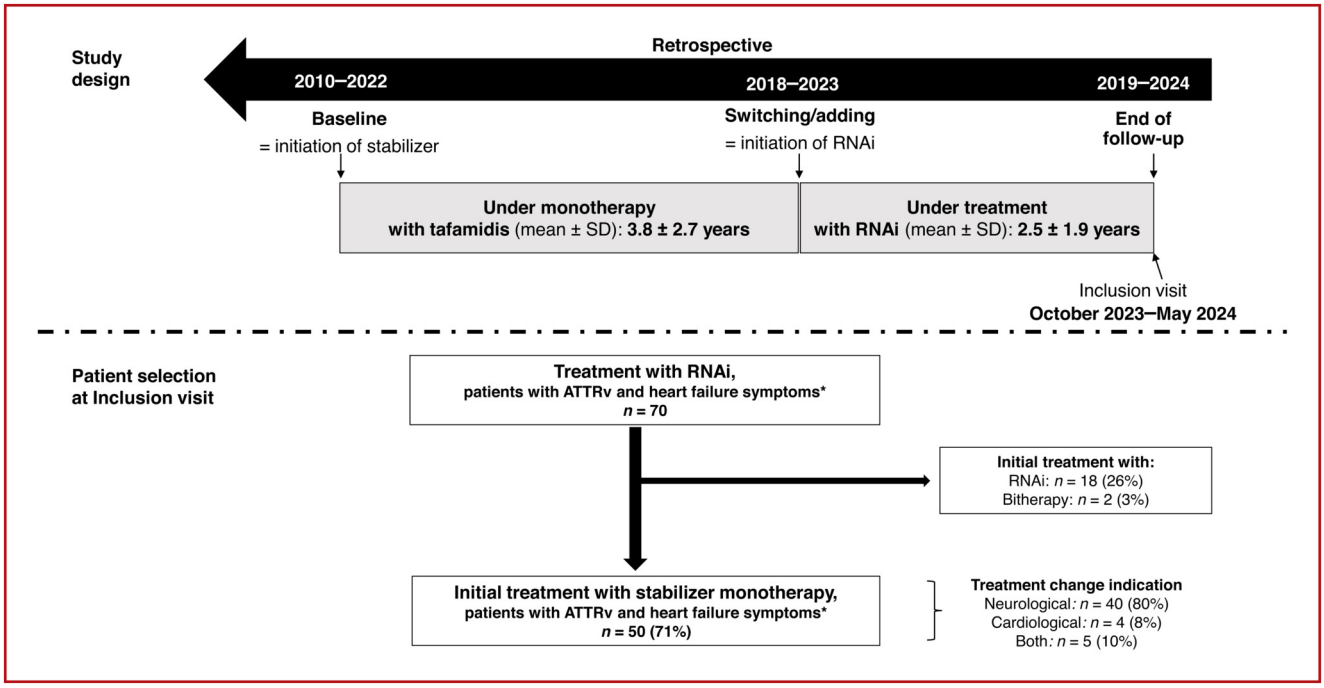


Fig. 1. Study flowchart of patients with ATTRv. *: heart failure symptoms = NYHA class II or III or class I with NT-proBNP > 500 pg/mL or BNP > 100 pg/mL. Cardiac symptoms could be present at baseline or may develop subsequently. They were confirmed through TTE, bone scintigraphy (Perugini grade ≥ 2) and absence of clonal dyscrasias according to international guidelines. ATTRv: hereditary transthyretin amyloidosis; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; RNAi: ribonucleic acid interference; SD: standard deviation; TTE: transthoracic echocardiography.

ching to, or adding, RNAi (after tafamidis monotherapy) and the end of follow-up (after RNAi initiation).

TTE was used to assess left ventricular wall thickness (LVWT) and left ventricular chamber remodelling according to standard American Society of Echocardiography criteria. Left ventricular systolic function was assessed through left ventricular ejection fraction (LVEF) using the biplane Simpson's equation and global longitudinal strain (GLS) calculations. Radionuclide bone scintigraphy was performed with ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid or ^{99m}Tc-pyrophosphate. Experts in each centre rated cardiac radiotracer retention according to the visual grading scale from Perugini et al. [7]: grade 0, absent cardiac uptake; grade 1, mild uptake less than bone; grade 2, moderate uptake equal to bone; and grade 3, high uptake greater than bone. One centre used an alternative quantification involving early phase and heart-to-mediastinum ratio on the anterior view [21].

Neurological involvement was measured using the Familial Amyloid Polyneuropathy (FAP) score, developed by the Reference Centre for Rare Peripheral Neuropathies using a methodology proposed by the French Health Authority. FAP staging classifies walking ability on a three-point scale based on the degree of assistance needed [22].

2.4. Outcomes

The primary outcome was the global response following RNAi initiation. According to an expert consensus published in 2021 [23], cardiac progression in patients with ATTR is defined as worsening in at least one marker from each of the following three domains: clinical and functional endpoints, disease severity by biomarkers and laboratory markers, and disease severity by imaging and electrocardiographic parameters. To minimize subjectivity, we prospectively applied predefined thresholds in each domain. Patients were classified as worsened following the expert consensus criteria. Improved was defined using the exact opposite thresholds of worsening to maintain symmetry with the expert consensus definition, or stable if neither worsening nor improving. For clinical and functional response, worsened or improved was defined by a change in NYHA stage. For laboratory response, worsened or improved required a change of ≥ 30% in BNP/NT-proBNP. For cardiac imaging, worsened or improved was defined as a change of ≥ 2 mm in LVWT, ≥ 5% in LVEF, ≥ 1% in GLS or one grade in diastolic dysfunction. Global response required concordant changes across domains, in line with the 2021 consensus, and all outcomes were adjudicated independently by two blinded experts, with consensus in case of disagreement.

The secondary outcome was subclinical response, defined using only laboratory and imaging endpoints (to mitigate the potential subjectivity of the NYHA classification), applying the same thresholds as for global response. In addition, clinical, laboratory and imaging responses were also analysed separately for each parameter [24].

2.5. Statistical analysis

Descriptive statistics were used to summarise the data. For comparisons between two independent time points, Student's *t* or Wilcoxon tests were applied for continuous variables, and Chi^2 or Fisher's exact tests for categorical variables. To evaluate longitudinal trends across repeated measures within patients, linear mixed-effects models with random intercepts were used to account for intra-patient correlation and missing data. For non-normally distributed repeated measures, Friedman tests were used as sensitivity analyses. No data imputation was performed; analyses were based on available observations only.

All analyses were performed using R software (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria). The Shapiro-Wilk test was applied to assess normality of distributions. Post-hoc pairwise comparisons were Bonferroni adjusted, and the significance threshold was set at $P < 0.05$.

3. Results

3.1. Demographic, clinical and diagnostic characteristics

Among 70 patients with ATTRv and cardiac involvement who had received RNAi therapeutics across the 10 participating centres, 50 ful-

Table 1
Demographic and clinical characteristics including the neurological and cardiological status of the population at baseline[a].

	All patients (n = 50)
Age at diagnosis (years)	63 (58–70)
Male	33 (66)
Transthyretin mutations	
Val30Met	24 (48)
Ser77Tyr	5 (10)
IL107Val	5 (10)
Val122Ile	2 (4)
Others	14 (28)
Perugini grade (from bone scintigraphy)	(n = 29)
0	3 (10)
1	2 (7)
2	11 (38)
3	13 (45)
FAP score	(n = 28)
0	1 (4)
1	24 (86)
2	2 (7)
3	1 (4)
NYHA heart failure classification	(n = 47)
I	21 (45)
II	25 (53)
III	1 (2)
Laboratory markers	
NT-proBNP (ng/L) (n = 36)	317 (176–786)
Troponin (ng/L) (n = 26)	21 (14–37)
ECG parameters	
Ventricular conduction abnormalities (L/RBBB) (n = 33)	6 (18)
Atrial fibrillation (n = 47)	6 (13)
Pacemaker (n = 50)	2 (4)
TTE parameters	
LVWT (mm) (n = 47)	14 (12–16)
sPAP (mmHg) (n = 24)	33 (30–40)
GLS (%) (n = 36)	15 (11–17)
LVEF (%) (n = 47)	63 (59–70)

Data are expressed as median (interquartile range) or number (%). ECG: electrocardiogram; FAP: familial amyloid polyneuropathy; GLS: global longitudinal strain; L/RBBB: left or right bundle branch block; LVEF: left ventricular ejection fraction; LVWT: left ventricular wall thickness; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; TTE: transthoracic echocardiography; sPAP: systolic pulmonary artery pressure.

[a] Baseline = initiation of monotherapy with tafamidis.

filled the prespecified inclusion criteria (tafamidis monotherapy prior to RNAi initiation, ≥ 1 year of RNAi treatment and availability of essential endpoint data) and were included in the analysis set (Fig. 1). The remaining 20 patients were excluded due to not meeting these criteria.

Thirty-three (66%) were male and the median (interquartile range) age at diagnosis was 63 (58–70) years (Table 1). Nearly half of the patients (48%) had a Val30Met transthyretin variant. Most patients with bone scintigraphy presented positive Perugini classification 2 or 3 (24/29; 83%). Among those with a reported FAP score (n = 28), the symptoms were mainly mild, with 24 patients (86%) having a FAP score of 1.

Patients exhibited heterogenous cardiac symptoms, imaging parameters and circulating biomarkers at baseline (Table 1). Regarding cardiac function, 53% of patients had moderate heart failure with NYHA class II, and the median (interquartile range) NT-proBNP value was 317 (176–786) pg/mL. TTE revealed generally preserved LVEF (median [interquartile range]: 63% [59–70]), with reduced GLS (15% [11–17]) and left ventricular hypertrophy (LVWT 14 [12–16] mm).

3.2. Medical management

Patients were initiated on tafamidis between 2010 and 2022, with 34% starting treatment with tafamidis from 2018 onwards, following its availability through compassionate access for the treatment of ATTR-CM in France. RNAi switch or add-on occurred between 2018 and 2023. The decision to switch to, or add, RNAi therapeutics was made by the multidisciplinary treating teams according to real-world practice and French regulatory pathways, most often in response to neurological progression (n = 40; 80%), and less frequently due to cardiological progression or both (Fig. 1). Sequencing could also be influenced by whether the prescriber was a neurologist or a cardiologist. Thirty-three patients (66%) discontinued tafamidis and were switched to RNAi monotherapy. For the remainder (34%), tafamidis was continued concomitantly with the RNAi. Overall, patients had received tafamidis monotherapy for a mean of almost 4 years before the initiation of RNAi. At the end of follow-up, on average, RNAi treatment (with tafamidis in case of add-on or without tafamidis in case of switch) lasted 2.5 years (Fig. 1).

3.3. Changes in cardiac parameters under tafamidis monotherapy and subsequent treatment with RNAi therapeutics

Globally, an integrative evaluation of each cardiac monitoring parameter was performed in patients who had data available in all three domains identified in the expert consensus (i.e. a “full dataset”). This revealed that on tafamidis monotherapy (full dataset in the three domains: n = 34), in terms of global response, 24% of patients worsened, 76% were stable and none improved (Fig. 2). Under RNAi therapeutics (complete dataset in the three domains: n = 29), no patients worsened, 10% improved and 90% were stabilized. Regarding NYHA class, 31% of patients worsened, 58% were stable and 11% improved under monotherapy with tafamidis (n = 45) while 12% worsened, 62% stabilized and 26% improved after switching to, or adding, an RNAi (n = 42).

The subclinical response to treatment was also evaluated, considering only laboratory and imaging endpoints. More patients improved subclinically (simultaneous improvement on biomarkers and imaging) while receiving an RNAi compared to tafamidis monotherapy (17% vs. 3%) and fewer worsened (simultaneous progression on biomarkers and imaging) (13% vs. 50%) (Fig. 2). Similar results were observed when analysing clinical, laboratory and imaging criteria separately.

Linear mixed-effects models were performed to evaluate longitudinal changes in cardiac biomarkers and echocardiographic parameters across the stabilizer (tafamidis) period and RNAi therapeutic period (Table 2). Overall, time had a significant effect on troponin ($F(2.43) = 5.33$; $P = 0.009$) and LVEF ($F(2.81) = 6.62$; $P = 0.002$), while trends for NT-proBNP, LVWT, systolic pulmonary artery pressure and GLS did not reach statistical significance. Post-hoc analyses showed that troponin levels increased significantly during the stabilizer period (mean difference = +7.0 pg/mL; 95% confidence interval [CI] 1.9 to 12.1; $P = 0.031$) but subsequently decreased under RNAi therapeutics (−6.4 pg/mL; 95% CI −11.4 to −1.5; $P = 0.043$). Similarly, LVEF significantly decreased during the stabilizer period (−4.1%; 95% CI −6.9 to −1.4; $P = 0.012$) but stabilized after initiation of RNAi therapeutics, leading to an overall decrease at the end of the evaluation versus baseline (−4.6%; 95% CI −7.5 to −1.8; $P = 0.005$). Changes in NT-proBNP and LVEF showed similar temporal patterns, with an initial deterioration during the tafamidis period followed by stabilization after RNAi initiation. This was reflected by a marked attenuation in NT-proBNP progression, with levels increasing by 51% during the tafamidis period compared with only a 4% increase during the RNAi period. In contrast, GLS exhibited a progressive decline across time points, while LVWT showed a mild but continuous increase. None of these trends reached statistical significance, likely reflecting limited sample size and inter-patient variability (Fig. 3).

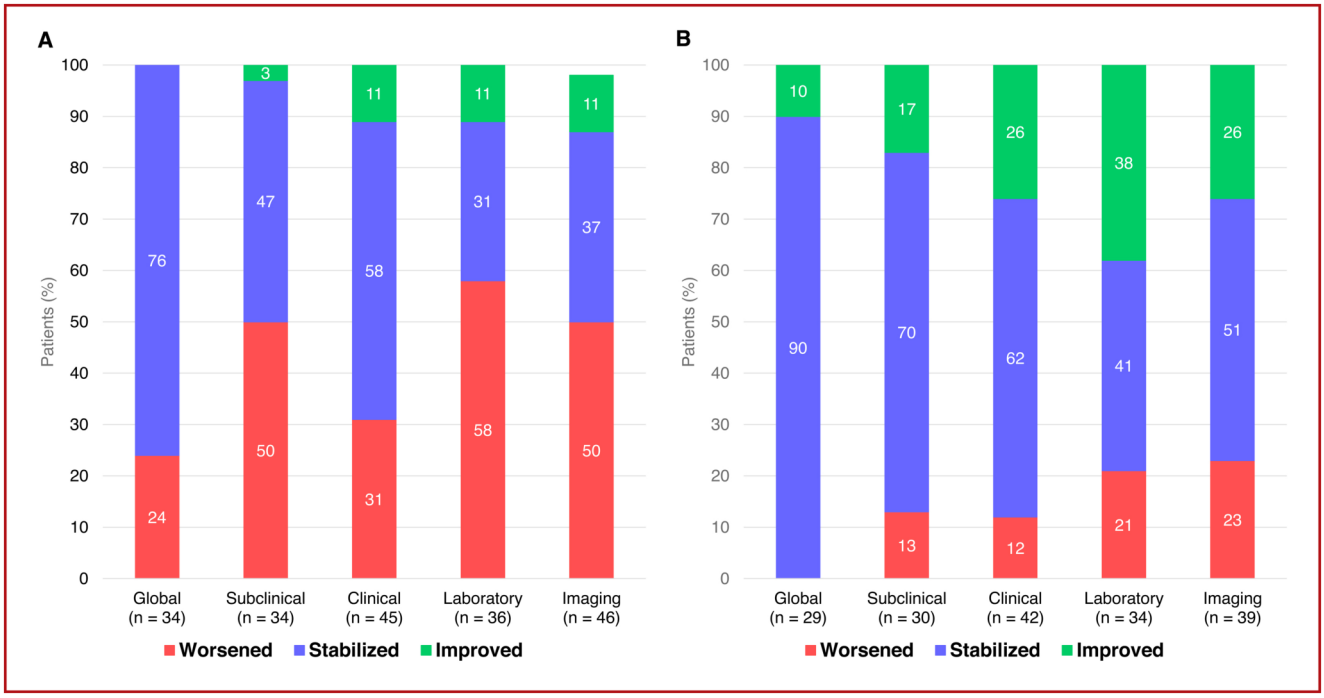


Fig. 2. Responses to A. monotherapy with tafamidis and B. to subsequent treatment with an RNAi. Patients were classified as worsened or improved based on NYHA class for clinical response, a change of ≥ 30% in BNP/NT-proBNP or troponin for laboratory response, and a change of ≥ 2 mm in LVWT, ≥ 5% in LVEF, ≥ 1% in global GLS, or one stage in diastolic dysfunction grade for cardiac response. For the global response, worsening was defined as a worsening in at least one marker from each domain (i.e. clinical, laboratory and imaging), improving was the opposite of the definition of worsening, and stable was defined as neither worsening nor improving. Subclinical response mimics global response considering laboratory and imaging responses only. BNP: B-type natriuretic peptide; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; LVWT: left ventricular wall thickness; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; RNAi: ribonucleic acid interference.

Table 2
Mixed-effects model analysis of cardiac parameters before and after transition to RNAi therapeutics.

	Fixed effect of time (Omnibus test)	Random intercept (subject)	Post-hoc comparisons for time, mean difference (95% CI); *P*		
	F (df1, df2); *P*	Variance; *P*	Stabilizer period	End of RNAi period vs. baseline	RNAi period
NT-proBNP (pg/mL)	1.97 (2, 64); 0.15	167,936; < 0.001			
Troponin (pg/mL)	5.33 (2, 43); 0.009	549; < 0.001	7.0 (1.9,12.1); 0.031	0.6 (−5.4, 6.6); 1.00	−6.4 (−11.4, −1.5); 0.043
LVWT (mm)	1.22 (2, 82); 0.30	5.39; < 0.001	–	–	–
sPAP (mmHg)	0.16 (2, 41); 0.85	1.06×10^{-5}; < 0.001	–	–	–
GLS (%)	0.91 (2, 63); 0.41	1.68×10^{-5}; < 0.001	–	–	–
LVEF (%)	6.62 (2, 81); 0.002	55.8; < 0.001	−4.1 (−6.9, −1.4); 0.012	−4.6 (−7.5, −1.8); 0.005	−0.5 (−3.4, 2.4); 1.00

CI: confidence interval; df1: numerator degrees of freedom; df2: denominator degrees of freedom; F: F-statistic; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; LVWT: left ventricular wall thickness; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RNAi: ribonucleic acid interference; sPAP: systolic pulmonary artery pressure.

At the individual level, patients with a higher baseline cardiomyopathy burden showed a greater likelihood of cardiac progression under tafamidis monotherapy, particularly among those with three baseline criteria. In patients with two baseline criteria, most remained stable and a minority worsened. Following initiation of RNAi therapeutics, 11% of patients with ≥ 2 baseline criteria improved, 89% achieved stabilization and none exhibited further deterioration (Fig. 4).

4. Discussion

This multicentre, retrospective, real-life study describes the changes in cardiac parameters among 50 patients who were switched from tafamidis to RNAi or had an RNAi added to tafamidis. To our knowledge, this is the first study to evaluate long-term (≥ 1 year) cardiac parameter changes in patients with ATTRv – primarily with neurological progression despite years of tafamidis monotherapy – following either a switch to RNAi therapeutics or its addition to ongoing tafamidis. These findings provide critical insights into the cardiac effects of modifying treatment in this clinically challenging population. These data preceded the results of a pivotal randomized controlled study showing the benefit of RNAi on morbi-mortality in patients with ATTR-CM [20].

4.1. Baseline and progression profile of a mixed ATTRv population

At baseline (i.e. tafamidis initiation), most patients presented with a mild neurological phenotype and around half of them exhibited

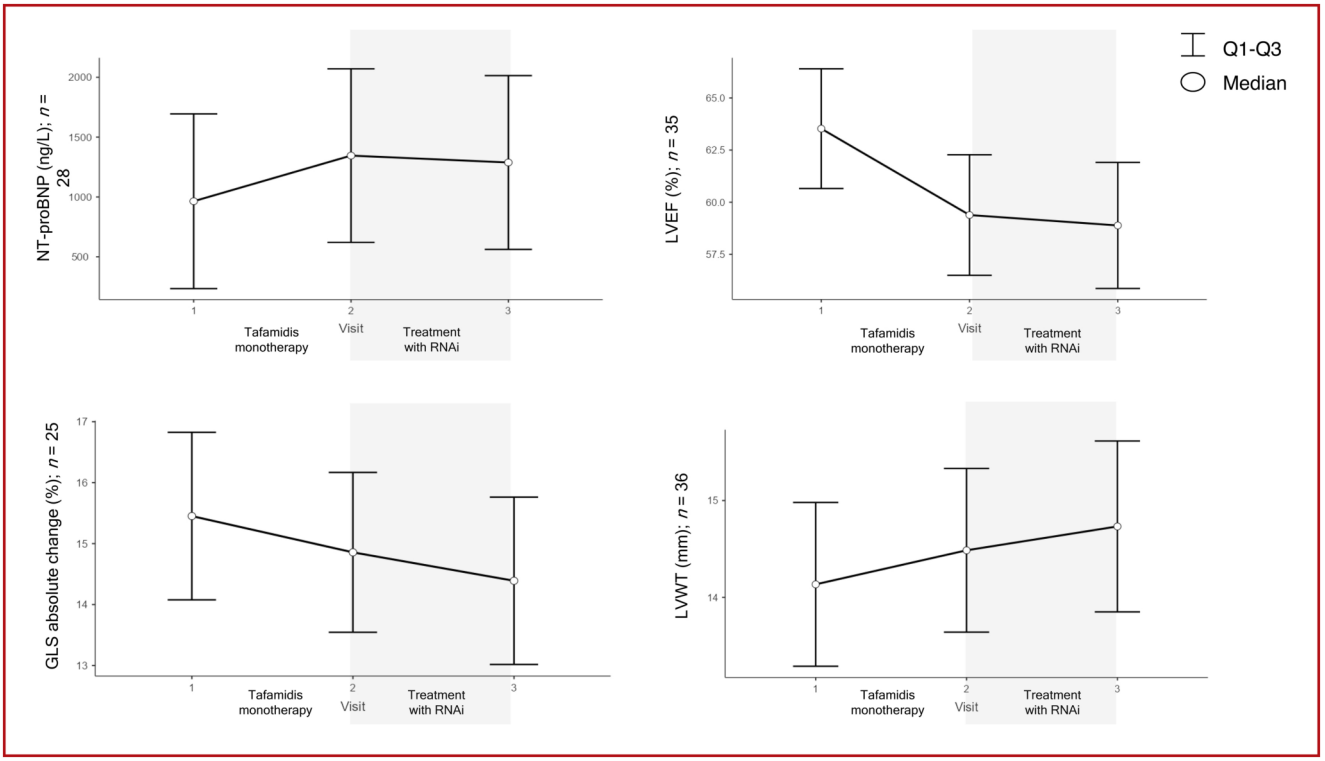


Fig. 3. Evolution of individual cardiac laboratory and imaging parameters among patients with ATTRv at data at each time point. Only laboratory and imaging parameters with complete data for at least 25 patients are presented. ATTRv: hereditary transthyretin amyloidosis; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; LVWT: left ventricular wall thickness; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RNAi: ribonucleic acid interference; Q: quartile.

moderate heart failure symptoms (NYHA class II) and the median (interquartile range) NT-proBNP level was 317 (176–786) pg/mL. This multisystemic impairment underscores the importance of multidisciplinary care for patients with ATTRv. Moreover, as some mutations can lead to false negative bone scintigraphy results, there is a need for expertise to detect false negative cases [25].

Additionally, while most investigators cited neurological progression as the primary reason for switching to, or adding on, an RNAi in patients receiving tafamidis therapy, the recorded cardiac parameters before the treatment change clearly indicated cardiac progression on tafamidis therapy as well. The use of RNAi upon neurological progression likely reflects the current limitation of RNAi indications to neurological impairment in patients with mixed phenotype ATTRv.

4.2. ATTR-CM cardiac monitoring

In our study, we observed a heterogeneous progression pattern. The progression of ATTR with cardiac involvement is currently monitored according to a consensus that is not evidence based, using a composite of three distinct types of heart failure parameters: functional evaluation, laboratory markers and imaging results [23]. In addition, evidence of cardiac progression should prompt physicians to perform comprehensive neurological assessments in patients with ATTRv, including electromyography and Sudoscan® (Impeto Medical, Paris, France) to detect or confirm the presence of neurological progression [26,27]. Such findings would support the consideration of RNAi therapeutics. For cardiologists, the selection of optimal parameters for assessing cardiac progression in ATTRv with cardiac involvement remains a topic of debate. Threshold values and decision algorithms lack robust evidence, and the three categories of parameters provide unequal measures of heart failure severity.

Moreover, following RNAi switch or add-on, fewer patients exhibited worsening cardiac symptoms and changes in laboratory or imaging parameters, aligning with the endpoint data from the APOLLO-B and HELIOS-B studies [20,28]. The increase in troponin and decline in LVEF observed during tafamidis monotherapy are consistent with ongoing subclinical myocardial injury and progressive systolic dysfunction, despite transthyretin stabilization. Conversely, the subsequent stabilization or improvement in both parameters under RNAi likely reflects a true disease-modifying effect, mediated by the reduction in circulating transthyretin and amyloidogenic precursors. These findings align with exploratory data from the APOLLO and HELIOS studies, which also reported improvement or stabilization of cardiac parameters in patients with ATTRv treated with RNAi agents [20,28]. Notably, NT-proBNP levels, a strong prognostic factor in ATTR-CM [29], had varying degrees of worsening over time, with a 51% increase during the tafamidis period versus a 4% increase during the RNAi period. This study provides important insights into the cardiac response to RNAi in patients with ATTRv in real life, reinforcing the pivotal studies of RNAi [15,20,30,31].

The expert consensus criteria used to define response in this study set forth definitions for worsening on various parameters. For each response parameter, we chose to evaluate improvement as the opposite of worsening as defined in the consensus criteria, using the same cut-off values. Revising these criteria to enable cardiologists to classify therapeutic responses, not only in terms of worsening (where improving is the opposite of worsening and stable is defined as neither improved nor worsened) would provide valuable guidance for clinical decision-making regarding switching to, or supplementing treatment with, RNAi therapeutics in patients receiving tafamidis. This study also highlights the limitations of the current expert consensus in requiring a simultaneous worsening in three domains to identify progression, which may lead to late identification and management of the patient with potential irreversible damage.

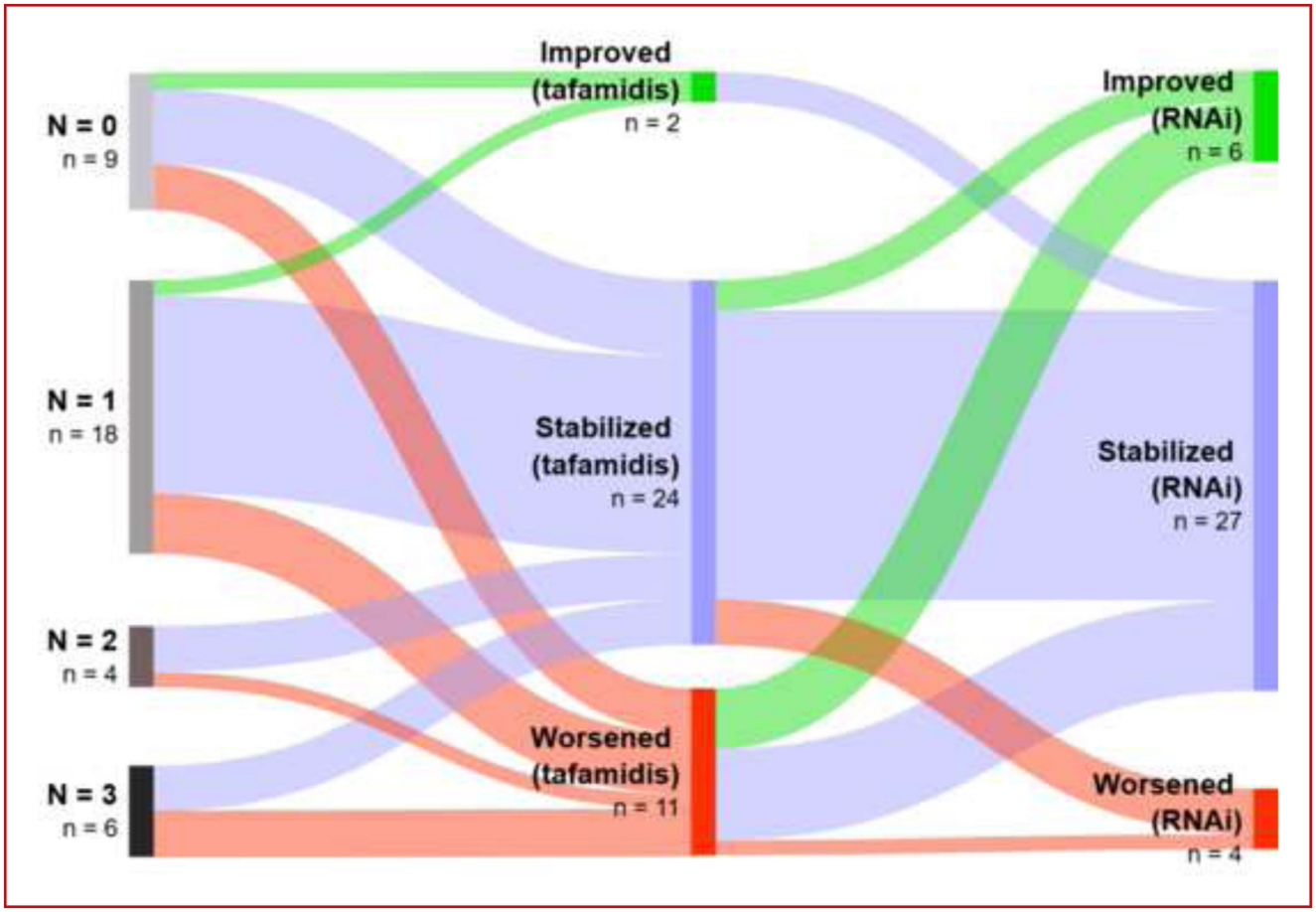


Fig. 4. Sankey diagram illustrating individual cardiac progression on cardiac imaging (worsening, stabilization or improvement) according to initial cardiomyopathy impairment. The criteria taken into account were NYHA classification of heart failure > I, NT-proBNP > 500 pg/mL and LVWT ≥ 12 mm. Only data from the 37 patients with evaluations at all time points are presented. LVWT: left ventricular wall thickness; *n*: number of patients; *N*: number of baseline criteria for cardiomyopathy (range 0–3); NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association.

4.3. Clinical implications for surveillance of disease progression

In France, the initiation of vutrisiran therapy is currently restricted to neurologists and tafamidis 61 mg is reserved for cardiologists [32]. Also in France, patisiran can be initiated by a neurologist and, more recently, cardiologists have also been authorized to initiate this treatment under compassionate use provisions. This division of therapeutic authorities currently complicates medical management and limits treatment options when isolated cardiac progression occurs. The regression of cardiac signs and symptoms observed in this study may be attributed to the RNAi mechanism of action. These agents directly knock down transthyretin production in the liver, whereas stabilizers act by preventing transthyretin monomer formation [13].

In addition to the need to enhance cardiac progression monitoring, several uncertainties remain, particularly concerning the timing and approach to treatment (such as monotherapy versus combination therapy) and the criteria for adjusting therapy in response to neurological or cardiac progression.

The data from our study highlight the need for collaborative and multidisciplinary approaches for the management of ATTRv. According to European Society of Cardiology expert consensus, both RNAi therapies and stabilizers may have roles as first-line therapies in ATTRv mixed phenotypes [31]. Moreover, the recent positive results from the HELIOS-B phase 3 study of vutrisiran in patients with ATTRv and cardiac involvement underscore the urgent need to implement cardiac monitoring, not only in expert centres but also in secondary cardiac referral centres to identify patients who may benefit from new therapies [20].

4.4. Strengths and limitations

The large sample size of our study represents a major strength. In March 2014, 500 diagnosed and symptomatic cases of ATTRv were identified in France. By including 50 patients, our study encompassed nearly 10% of the national ATTRv patient population [33]. Another strength of our study is that it reflects real-life clinical practice in ATTRv. Our findings demonstrate that locoregional collaboration with a national network can identify the profiles of patients who may benefit from earlier treatment changes and refine disease progression criteria as well as modalities for monitoring progression. TTE was performed in centres with a high level of expertise and a common protocol.

This study has several limitations. First, it was retrospective, non-randomized and involved a relatively small patient population, which reflects the rarity of ATTRv with cardiac impairment. Nonetheless, the retrospective design allowed collection of long-term follow-up data (> 1 year after therapy modification), providing valuable real-world insight into disease evolution after switching to, or adding, RNAi therapeutics.

As the study relied on existing clinical records from multiple expert centres without centralized data monitoring or inter-centre audits, variability in data completeness and quality cannot be excluded. No data imputation was performed; analyses were based on available observations only. Missing data, especially for neurological and cardiac biomarkers, partly reflects heterogeneity in clinical practice rather than omission. This variability is inherent to real-world multicentre studies and highlights the challenges of uniform cardiac monitoring in patients with ATTRv.

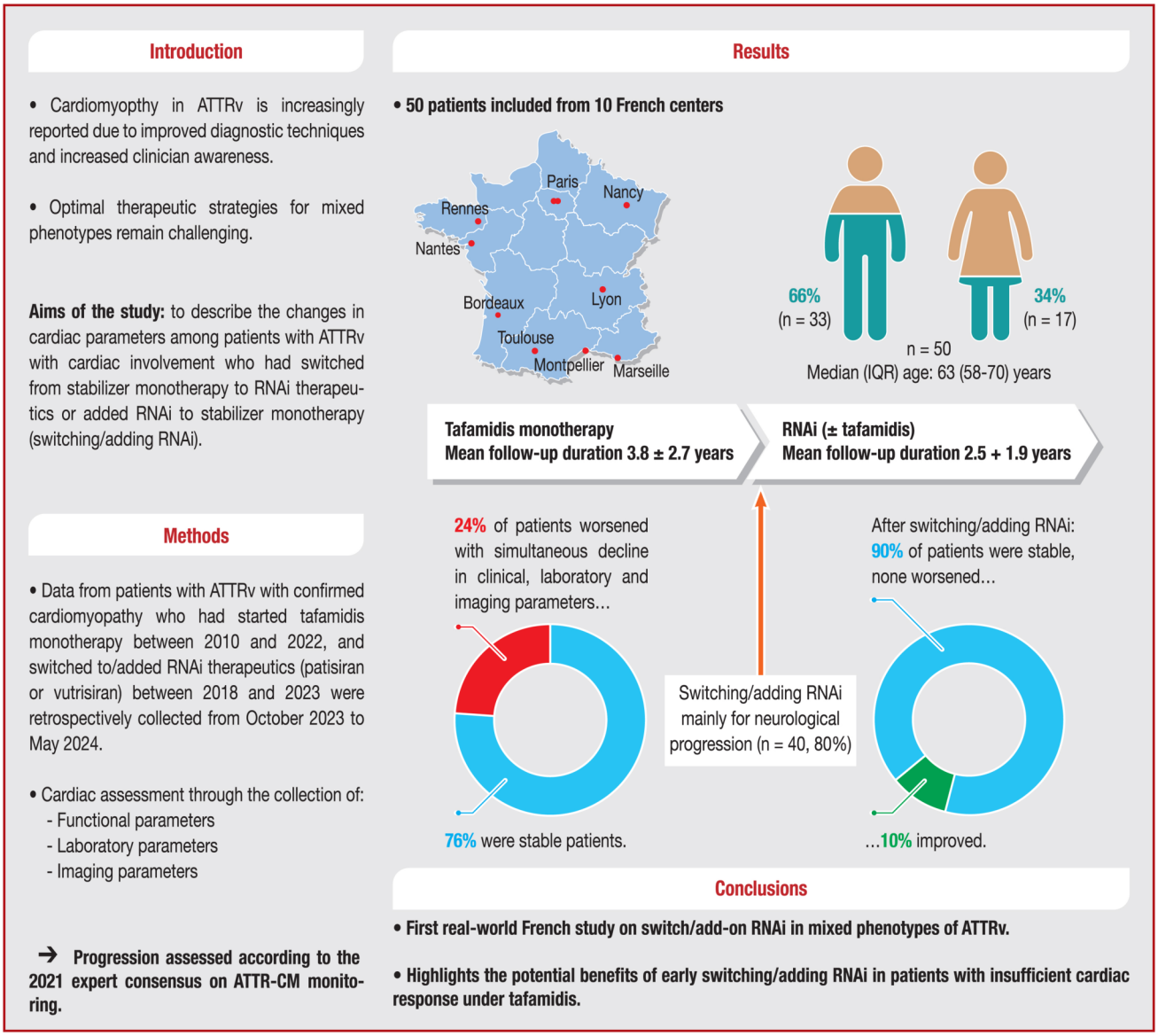
Furthermore, no *a priori* sample size estimation was performed; therefore, non-significant findings should be interpreted with caution, as they may reflect limited statistical power rather than the absence of a true clinical effect.

Finally, differences in local practices and availability of specific assessments (e.g. diastolic function grading, 6-minute walk test or quality-of-life questionnaires) may have led to incomplete or inconsistent evaluations over time. Such heterogeneity might have resulted in the underestimation of progression in some patients classified as stable.

Despite these limitations, this large multicentre study reflects the real-world management of patients with ATTRv and provides valuable information for refining monitoring strategies and therapeutic decision-making.

5. Conclusions

For patients whose cardiac parameters deteriorated under initial stabilizer monotherapy, these findings support the early consideration of RNAi therapeutics in patients with mixed-phenotype ATTRv showing suboptimal cardiac response to a stabilizer. Additionally, our study offers valuable insights into the clinical presentation and progression of the disease in a real-world setting. Its findings also support the pivotal trials of RNAi therapeutics, demonstrating that they are promising therapeutic alternatives for cardiac management in patients with ATTR. Finally, despite its limitations, which restrict the generalizability of its findings, our study underscores the necessity for simplified monitoring using evidence-based algorithms that integrate a multimodal approach. Enhancing collaboration between neurologists and cardiologists appears to be a priority for optimal ATTRv management (Central Illustration).



Central illustration. Impact of RNAi therapy (switching or adding) on cardiac parameters in patients with ATTRv initially treated with stabilizers: a French real-world study. ATTR-CM: transthyretin amyloidosis with cardiomyopathy; ATTRv: hereditary transthyretin amyloidosis; IQR: interquartile range; RNAi: ribonucleic acid interference.

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Data availability statement

Data are available upon reasonable request. Please contact Dr Olivier Huttin (e-mail: drhuttinolivier@gmail.com).

Disclosure of interest

A.F. declares being a consultant for Pfizer and Amgen. V.A. declares being a consultant for Alnylam, AstraZeneca, Bayer; Research grants from Alnylam and Pfizer. O.L. declares being a consultant for Alnylam, AstraZeneca, Amicus, Pfizer, BMS. N.P. declares being consultant for Alnylam and Pfizer. M.M. declares receiving support from Alnylam and Pfizer. G.H. declares being a consultant for Alnylam, AstraZeneca, Pfizer. F.R. declares being a consultant for air liquid, Abbott, Alnylam, Bayer, BMS, MSD, Newcard, Novartis, Novonordisk, Pfizer, Servier, Viford. A.J.D. declares being a consultant for Alnylam. E.D. declares being a consultant for GE healthcare, Abbott structural, Alnylam, Pfizer, AstraZeneca. T.D. declares being a consultant for Amicus, Alnylam, AstraZeneca, Pfizer. P.R. declares being a consultant for Pfizer, Alnylam, Amicus, Sanofi, BMS, Cytokinetics. O.H. declares being consultant for BMS, Alnylam, Pfizer. The other authors declare that they have no competing interest. All authors declare no conflicts of interest.

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