Journal of the American Heart Association

ORIGINAL RESEARCH

Truncating Variants in *TTN* are Associated With Primary Atrial Myopathy

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BACKGROUND: Truncating TTN variants (TTNtv) are the main genetic cause of dilated cardiomyopathy (DCM) and are independently associated with atrial fibrillation (AF). In DCM, AF usually arises from left atrial (LA) remodeling attributable to left ventricular systolic dysfunction. Whether TTNtv are linked to primary LA dysfunction independent of left ventricular systolic dysfunction remains unclear.

METHODS: This retrospective, multicenter study evaluated atrial function by strain echocardiography in TTNtv carriers across the left ventricular ejection fraction (LVEF) spectrum and its relationship with AF. Individuals with TTNtv and LVEF ≥50% (TTNtv+/DCM–) were compared with matched healthy controls, and those with LVEF <50% (TTNtv+/DCM+) were compared with matched patients with idiopathic, variant-negative DCM (iDCM).

RESULTS: Among 460 participants, 153 carried a TTNtv (87 with LVEF ≥50%, 66 with LVEF <50%). All LA strain parameters were significantly lower in TTNtv+/DCM– than in controls (P<0.001). In TTNtv+/DCM+, only LA contractile strain was reduced compared with iDCM (P<0.001). LA contractile strain correlated with LVEF only when LVEF was <50% (TTNtv+/DCM+, r=0.50, P<0.001; iDCM, r=0.47, P<0.001). In TTNtv+/DCM–, all LA strain parameters except contractile strain correlated with LV strain. AF incidence was higher in TTNtv+/DCM+ (3.15/100 person-years) than in TTNtv+/DCM– (1.48) and iDCM (2.27), though cumulative incidence was not significantly different (P=0.200).

CONCLUSIONS: LA myopathy, detected by strain imaging, appears early in TTNtv+/DCM– individuals and may represent an early phenotypic marker independent of left ventricular systolic dysfunction. When LVEF declines below 50%, atrial dysfunction worsens in parallel. AF was more frequent in TTNtv carriers, supporting further research on LA strain for AF risk stratification within this population.

Key Words: atrial fibrillation ■ cardiomyopathy ■ echocardiography ■ remodeling ■ titin

Individuals with early-onset atrial fibrillation (AF) show a disproportionately high prevalence of pathogenic variants in genes associated with inherited cardiomyopathies.[1–3] Among these, *TTN* truncating variants (*TTN*tv), which affect the titin protein, are frequently identified in this population.[4,5] Although *TTN*tv are a recognized cause of dilated cardiomyopathy (DCM), recent evidence suggests they may also contribute to atrial remodeling independently of ventricular dysfunction.[6]

The evaluation of left atrial (LA) function has emerged as a cornerstone in understanding cardiovascular pathophysiology, offering profound insights into both early disease detection and prognostic assessment.[7] The LA, plays a crucial role in left ventricular (LV) filling, operating through 3 distinct functional

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This manuscript was sent to Sakima A. Smith, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.047740

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- *TTN* truncating variants are associated with a primary atrial cardiomyopathy.
- Abnormalities of left atrial strain, precede left atrium enlargement and left ventricular dysfunction, and may be a useful early phenotypic marker.

What Are the Clinical implications?

- This study identifies primary atrial dysfunction as a novel phenotypic feature of *TTN* truncating variant-related cardiomyopathy and highlights its value as an early marker of disease progression to guide closer follow-up and timely detection of atrial fibrillation and/or left ventricular dysfunction.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
iDCM	dilated cardiomyopathy (idiopathic)
LAds	left atrial conduit strain
LAcs	left atrial contractile strain
LAEF	left atrial emptying fraction
LArs	left atrial reservoir strain
LAVI	left atrial volume index
LV-GLS	left ventricular global longitudinal strain
TTNtv	TTN truncating variants
TTNtv+/DCM+	TTN truncating variant and left ventricular ejection fraction <50%
TTNtv+/DCM–	TTN truncating variant and left ventricular ejection fraction ≥50%

phases: reservoir, conduit, and contractile.[7] These phases are integral to the maintenance of hemodynamic stability and cardiac performance, as they directly influence LV preload and overall cardiac output.[7] Notably, recent advances in imaging techniques, such as 2-dimensional and 3-dimensional echocardiography and cardiac magnetic resonance strain analysis, have highlighted the utility of LA strain as a sensitive biomarker for early atrial dysfunction, often preceding structural alterations in atrial volume.[7–9]

Evidence suggests that impaired LA strain is closely associated with adverse cardiovascular outcomes, including heart failure (HF), AF, and ischemic stroke, underscoring its prognostic value.[8–10] For instance, studies on patients with DCM have identified LA strain as a stronger predictor of outcomes than conventional metrics such as LV ejection fraction (LVEF) and LA volume index.[8,10]

The clinical implications of LA strain extend beyond its diagnostic and prognostic capabilities, highlighting its potential role in risk stratification and therapeutic decision-making.[9] In inherited cardiomyopathies, primary atrial dysfunction, reflected by reduced strain values, has been observed even in the absence of left ventricular systolic dysfunction.[10,11] In *LMNA* (lamin A/C)-related cardiomyopathy, primary atrial myopathy has been identified as an early marker of cardiac dysfunction, with reduced LA contractile strain on echo serving as a significant predictor of AF, even in the absence of left ventricular systolic dysfunction or atrial dilation.[11] Similarly, in patients with *TTN*tv-related DCM, decreased LA strain on cardiac magnetic resonance—particularly reservoir and booster (contractile) phases—has been observed, reflecting both primary atrial dysfunction and its close interdependence with left ventricular performance.[12]

This study aimed to evaluate atrial function in individuals carrying a *TTN*tv, across a spectrum of normal and abnormal LVEF values, to characterize the effects of *TTN*tv on LA structure and function, and to explore the relationship of atrial dysfunction with AF risk.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Population and Study Design

This is a multicenter, retrospective study including individuals with confirmed *TTN*tv and available digitalized transthoracic echocardiography from 3 international referral centers: Brigham and Women's Hospital (Boston, USA), Hospital Universitario Puerta de Hierro Majadahonda (Madrid, Spain) and Stanford Center for Inherited Cardiac Disease, (Palo Alto, USA). Genetic testing results were reviewed to confirm the pathogenicity of all included *TTN*tv. All *TTN*tv included had a percentage spliced in value >0.9. Subjects were included irrespective of LVEF. Institutional Review Board approval was obtained from each participating center. The study followed the Declaration of Helsinki, and informed consent was obtained per local Institutional Review Board policies.

Exclusion criteria included: pathogenic variants in other cardiovascular disease genes; genetic testing before 2016; no echocardiogram at initial evaluation (or within 3 months of the first medical visit); poor image quality; AF, atrial or ventricular pacing at or before

the first echocardiogram; suspected environmental causes (alcohol, chemotherapy, pregnancy)[13]; significant coronary disease; uncorrected cardiac shunt; any mitral/aortic stenosis or severe regurgitation.

Healthy and DCM Controls

Subjects with a *TTN*tv and LVEF ≥50% (*TTN*tv+/DCM-) were compared with age- and sex-matched healthy subjects selected from a local database of community volunteers and genotype-negative family relatives with normal LVEF.

Subjects with a *TTN*tv and LVEF <50% (*TTN*tv+/DCM+) were compared with age-, sex-, and LVEF-matched patients with non-ischemic idiopathic DCM (iDCM), who had no pathogenic variants identified by panel based genetic testing, selected from inherited cardiomyopathy databases at our institutions.

Matching was performed using a structured, rule-based approach conceptually aligned with propensity score matching. Subjects were paired through sequential filtering, sorting, and application of standardized inclusion criteria across age, sex, and LVEF. Two strategies were applied: one based on age and sex, and another incorporating LVEF. Tolerances were set at ±2 years for age and ±5% for LVEF, with exact matching for categorical variables. A semi-manual approach was employed: initial filtering and pair selection were guided by predefined thresholds, followed by manual review to ensure clinical comparability. The process followed standardized protocols and was independently reviewed to ensure consistency and minimize selection bias. Covariate balance was confirmed using standardized mean differences (with a threshold of <0.1 indicating acceptable balance) and visual inspection.

Data Collection

Clinical data were collected at each center, de-identified, and entered into a dedicated database. Baseline information included demographics, clinical history, treatments, and electrocardiographic data at the initial clinical evaluation. Follow-up information was collected up to the most recent clinical contact, with data reviewed through February 2023. Heart rhythm was evaluated by electrocardiography and periodic ambulatory monitoring based on the clinician's discretion. AF episodes were defined as those lasting over 30 seconds on documented recordings.[14]

Echocardiography Parameters

Echocardiographic studies from the initial evaluation (or within 3 months of the first visit) were re-analyzed by the same local investigator, blinded to clinical and genetic data. A level-3 trained cardiologist performed the reanalysis following American Society of Echocardiography guidelines.[15] Resting transthoracic echocardiograms, part of routine care, were acquired using Philips (Philips Medical Systems) and GE (GE Medical Systems) scanners by credentialed sonographers. Digital data in DICOM format were interpreted with IntelliSpace Cardiovascular 3.2. LVEF was calculated using the Simpson's biplane method in apical 4- and 2-chamber views. LA volumes were measured at end-systole (LA maximal volume) and end-diastole (LA minimal volume) in the apical 4-chamber view, with maximal volumes indexed to body surface area (left atrial volume index [LAVI]). Diastolic parameters and valvulopathies, including E/A and E/e′ ratios, were assessed using pulsed and tissue Doppler. Tricuspid annular plane systolic excursion was measured with M-mode. Mitral and tricuspid regurgitation were significant if vena contracta ≥3 mm and effective regurgitant orifice area ≥20 mm^2.

Myocardial strain was measured using chamber and phase specific tracings for LV and LA. Among the recorded cardiac cycles, the one with the best image quality and optimal speckle-tracking performance was selected for strain analysis. The average LV global longitudinal strain (LV-GLS) was calculated from the 4-chamber, 2-chamber, and 3-chamber apical views using LV AutoStrain software (TOMTEC-Arena, Germany). LA strain analysis was performed from the apical 4-chamber view using LA AutoStrain software (TOMTEC-Arena, Germany), which combines 2-dimensional speckle-tracking echocardiography with electrocardiographic synchronization. The software defines reservoir, conduit, and contractile phases of left atrial function based on ECG (R-R interval gating technique) and valve timing, allowing precise quantification of phase-specific strain: LA reservoir (LArs), LA conduit (LAds), and LA contractile (LAcs) strain. For ease of interpretation, negative (LAds, LAcs and LV-GLS) and positive (LArs) percentages are reported as absolute values. The LA emptying fraction (LAEF) was calculated with the following formula: (LA maximum volume–LA minimum volume)/LA maximum volume×100. LAVI, LArs, LAds and LAcs were repeated by the initial operator and one additional investigator on a random sample of 12 patients using the same method, to assess intra- and interobserver variability.

Statistics

All continuous variables were tested for normality (Shapiro–Wilk test, Q–Q plots and histograms) and presented as mean±SD if the distribution was normal or median (Q1–Q3) otherwise. LA function values (LAcs, LAds, LAcs, and LAEF) were plotted using scatter plot diagrams. Missing data were imputed using multiple imputations by chained equations (MICE package in

Table 1. Baseline Genetic Characteristics of Patients With a Truncating Variant in Titin

	*TTN*tv+/DCM– (n=87)*	*TTN*tv+/DCM+ (n=66)†
Variant location		
Band A	69 (79%)	56 (85%)
Band I	14 (16%)	9 (14%)
Z disc	4 (4.6%)	1 (1.5%)
Mechanism		
Truncating	74 (85%)	61 (92.4%)
Splicing	13 (15%)	5 (7.6%)
Compound heterozygous/homozygous	1 (1.1%)	1 (1.5%)
Proband	15 (17%)	46 (70%)
Family members	72 (83%)	20 (30%)

Values are expressed as frequencies (%).
*TTNtv+/DCM–: Truncating Variant in Titin and LVEF ≥50%.
†TTNtv+/DCM+: Truncating Variant in Titin and LVEF <50%.

R). Inter- and intra-observer variability was assessed using intraclass correlation coefficients. Comparisons between groups were performed using chi-square tests for categorical variables and independent samples t-tests for normally distributed continuous variables or the Mann–Whitney U test for non-normally distributed continuous variables. Multivariable logistic regression was used to identify the independent variables associated with belonging to TTNtv groups (TTNtv+DCM– versus Healthy and TTNtv+DCM+ versus iDCM). Separate multivariable logistic regression models were built for each echocardiographic LA function parameter (LArs, LAds, and LAcs, as well as LAEF). Variables included in the multivariable model were selected based on clinical relevance and univariable significance (P<0.2 in the univariable logistic model). Spearman correlation analysis was performed to assess the relationship between LVEF/LV-GLS and LArs, LAds, and LAcs. Correlation values were illustrated using scatter plots.

A univariable Cox proportional hazards model was performed using incident AF as the outcome of interest, and *TTN*tv, LAVI, and hypertension as potential clinical predictors. Multivariable Cox modeling was only performed if variables with P<0.1 were detected in univariable Cox model. The incidence of AF was evaluated using survival analyses. The first clinical encounter, corresponding to the baseline echocardiogram for all patients, was defined as time zero. AF incidence at various time points in the *TTN*tv+/DCM+ cohort was compared with that of the iDCM controls. Kaplan–Meier curves and the log-rank test were used to illustrate and compare AF incidence between groups. Individuals with death or heart transplant during follow up were censored. The proportional hazards assumption was tested using Schoenfeld residuals (phtest). A P value <0.05 was considered statistically significant. Statistical analyses were performed using R software (v.4.3.3).

RESULTS

A total of 460 subjects were recruited, including 153 patients with a *TTN*tv. Of these, 87 (56.9%) had an LVEF ≥50% (*TTN*tv+/DCM–), while 66 (43.1%) had an LVEF <50% (*TTN*tv+/DCM+). The majority of *TTN*tv (81.7%) were in the *TTN* A-band region (Table 1). The proportion of probands was higher in patients with LVEF <50% compared with those with preserved LVEF (70% versus 17%, P=<0.001). The median number of carrier relatives per proband was 0 (range: 0–3). Additionally, 2 patients were found to be either homozygous or compound heterozygous for *TTN*tv variants. Table S1 lists all *TTN*tv identified in the study cohort.

Baseline Characteristics in Individuals With LVEF ≥50%

Compared with healthy controls (n=169), the 87 individuals with *TTN*tv and LVEF ≥50% were 6.40 (±2.30) years younger (P=0.001) and had a higher prevalence of hypertension (14.9% versus 1.2%, P<0.001). Most patients in both groups were asymptomatic. The average body mass index was <30 kg/m^2 in both, although it was slightly but significantly higher in the *TTN*tv cohort (P=0.02). The prevalence of diabetes was similar. *TTN*tv+/DCM– patients had a lower median LVEF and LV-GLS compared with healthy controls (P<0.001). No significant differences were observed in LAVI or diastolic function parameters. All clinical and echocardiographic characteristics at baseline for both cohorts are summarized in Table 2.

Baseline Characteristics in Patients With LVEF <50%

A total of 138 patients with iDCM were age-, sex-, and LVEF-matched to 66 patients with *TTN*tv+/DCM+. Patients in the iDCM had a higher prevalence of hypertension (45% versus 23.5%, P=0.005) and left bundle

Table 2. Baseline Demographic, Clinical and Echocardiographic Characteristics of Patients With a Truncating Variant in Titin and Left Ventricular Ejection Fraction ≥50% (TTNtv+/DCM–) Versus Healthy Controls (Healthy)

	*TTN*tv+/DCM– (n=87)	Healthy (n=169)	*P* value
Age (mean±SD)	36.80±12.30	43.20±14.60	0.001
Sex (men)	33 (37.9%)	58 (34.3%)	0.6
Race			
White	79 (90.8%)	149 (88.2%)	0.004
Black, Asian or unknown	8 (9.2%)	19 (11.2%)	
Hypertension	13 (14.9%)	2 (1.2%)	<0.001
BMI (kg/m^2)	25.00 (22.75–28.40)	23.58 (21.84–26.42)	0.02
NYHA at first visit			
I	81 (93.1%)	169 (100%)	…
II	6 (6.9%)	0	
III	0	0	
IV	0	0	
Follow up days	1298 (730–2092)	…	…
IVSd (mm)	8.00 (7.35–9.00)	7.50 (6.40–8.50)	0.04
LVEDD (mm)	46.00 (42.00–49.60)	47.00 (45.00–50.00)	0.02
LVEDV index (mL/m^2)	48.40 (39.90–59.85)	52.00 (45.00–57.50)	0.4
LVEF (%)	59.60 (55.00–61.25)	61.70 (59.70–64.00)	<0.001
LV-GLS	17.70 (15.48–20.03)	21.35 (19.50–22.93)	<0.001
E/A	1.30 (1.00–1.70)	1.40 (1.10–1.70)	0.2
E/e′	6.30 (5.40–7.35)	6.40 (5.40–7.80)	0.6
LA volume index (mL/m^2)	25.80 (20.25–31.10)	24.70 (19.70–31.00)	0.09
PH on echo	0	0	…
Diastolic dysfunction*			
Yes	0	0	…
No	86 (98.9%)	167 (100%)	
Indeterminate	1 (1.1%)	0	
TAPSE (mm)	26 (23–28)	25 (23–29)	0.6

Values are presented as mean±SD or median (Q1–Q3) and frequencies (%). Strain values are presented as absolute. BMI indicates body mass index (kg/m^2); CRT, cardiac resynchronization therapy; E/e′, mean value of lateral and septal E/e′ ratios; FH, family history; IVSd, interventricular septum in diastole; LA, left atrial; LBBB, left bundle-branch block; LV, left ventricle; LVEDD, left ventricle end diastolic diameter; LVEDV, left ventricle end diastolic volume; LVEF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain; NYHA: New York Heart Association Functional Class; PH, pulmonary hypertension (Echocardiographic Systolic Pulmonary Artery Pressure ≥35 mm Hg; Right atrial pressure was estimated at 5, 10, or 15 mm Hg based on the size and collapsibility of the inferior vena cava); and TAPSE, tricuspid annular plane systolic excursion.

*Diastolic dysfunction was classified according to the 2016 American Society of Echocardiography guidelines.

branch block (32.6% versus 1.5%, *P*<0.001). In contrast, patients with *TTN*tv+/DCM+ more frequently had a family history of cardiomyopathy (82% versus 35%, *P*<0.001). No significant differences were observed in LV global longitudinal strain, diastolic function parameters, LAVI or estimated pulmonary artery systolic pressure. All clinical and echocardiographic data at the time of the first clinical assessment for both cohorts are detailed in Table 3.

Atrial Myopathy in *TTN*tv+/DCM- Patients

LA function was evaluated using LAEF, LArs, LAds, and LAcs. Although no significant differences were found in LAVI or diastolic function parameters, *TTN*tv+/DCM- exhibited lower LArs (*TTN*tv+/DCM–: 39.70 [32.95–49.50] versus healthy controls: 57.70 [50.90–61.40]; *P*<0.001), LAds (28.80 [19.80–36.80] versus 37.10 [29.60–41.00]; *P*<0.001), and LAcs (11.20 [8.45–14.80] versus 23.10 [20.30–27.20]; *P*<0.001) (Figure 1). LAEF (Figure S1) was also lower in the *TTN*tv cohort (61.70 [54.25–70.65] versus 64.90 [58.30–73.00]; *P*=0.007). The intraobserver and interobserver correlation coefficients were >0.75 for LAVI, LArs, LAds and LArs.

In multivariable analysis, LArs, LAds, and LAcs remained independently and significantly lower in *TTN*tv+/DCM– compared with healthy controls (Table 4). In contrast, LAEF did not reach statistical significance. These findings were unchanged when LV-GLS was included in the analysis instead of LVEF (Table S2).

Table 3. Baseline Demographic, Clinical and Echocardiographic Characteristics of Patients With a Truncating Variant in Titin and LVEF <50% (TTNtv+/DCM+) Versus Individuals With Idiopathic, Pathogenic Variant-Negative, DCM (iDCM)

	*TTN*tv+/DCM+ (n=66)	iDCM (n=138)	*P* value
Age (mean±SD)	51.30±14.10	52.00±14.46	0.7
Sex (Male)	46 (70%)	91 (66%)	0.7
Race			
White	58 (87.9%)	107 (78%)	0.9
Black, Asian or unknown	6 (12.1%)	31 (22%)	
Hypertension	15 (23.5%)	62 (45%)	0.005
BMI (kg/m^2)	27.45 (24.38–31.03)	28.45 (24.53–32.70)	0.4
NYHA at first visit			
I	27 (40.9%)	63 (46%)	0.02
II	29 (43.9%)	38 (28%)	
III	10 (15.2%)	26 (19%)	
IV	0	11 (8%)	
LBBB	1 (1.5%)	45 (32.6%)	<0.001
FH at first visit	54 (82%)	48 (35%)	<0.001
CRT	9 (6.5%)	2 (3%)	0.5
Follow up days	2310 (1230–3540)	2400 (1102–3960)	0.6
IVSd (mm)	8.95 (7.43–10.00)	10.00 (8.00–11.00)	0.03
LVEDD (mm)	59.00 (55.00–63.50)	58.00 (53.48–63.45)	0.3
LVEDV index (mL/m^2)	74.95 (63.80–89.05)	78.40 (61.80–96.75)	0.2
LVEF (%)	35.40 (24.40–42.00)	35.00 (26.13–41.88)	0.8
LV-GLS	11.10 (8.40–13.80)	10.50 (7.45–13.30)	0.6
E/A	0.90 (0.72–1.80)	0.93 (0.70–1.40)	0.2
E/e′	10.50 (7.90–14.30)	10.00 (7.60–13.48)	0.9
LA volume index (mL/m^2)	38.15 (26.85–50.68)	34.85 (26.78–46.85)	0.1
PH in echo	18 (27.3%)	28 (20.3%)	0.3
Diastolic dysfunction*			
Grade 1	87 (65.4%)	36 (56.2%)	0.4
Grade 2/3	26 (40.6%)	41 (30.8%)	
Indeterminate	2 (3.1%)	5 (3.8%)	
TAPSE (mm)	22 (18–26)	22 (19–25)	0.9

Values are presented as mean±SD or median (Q1–Q3) and frequencies (%). Strain values are presented as absolute. BMI indicates body mass index (kg/m^2); CRT, cardiac resynchronization therapy; E/e′, mean value of lateral and septal E/e′ ratios; FH, family history; IVSd, interventricular septum in diastole; LA, left atrial; LBBB, left bundle branch block; LV, left ventricle; LVEDD, left ventricle end diastolic diameter; LVEDV, left ventricle end diastolic volume; LVEF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain; NYHA: New York Heart Association Functional Class; PH, pulmonary hypertension (Echocardiographic Systolic Pulmonary Artery Pressure ≥35 mm Hg; Right atrial pressure was estimated at 5, 10, or 15 mm Hg based on the size and collapsibility of the inferior vena cava); and TAPSE, tricuspid annular plane systolic excursion.

*Diastolic dysfunction was classified according to the 2016 American Society of Echocardiography guidelines.

Atrial Myopathy in *TTN*tv+/DCM+ Patients

There was no significant difference in LArs (*TTN*tv+/DCM+: 16.90 [11.03–29.95] versus iDCM controls: 22.80 [14.40–28.78]; *P*=0.319) or LAds (*TTN*tv+/DCM+: 10.30 [6.63–15.65] versus iDCM controls: 11.45 [6.23–15.98]; *P*=0.3) between cohorts. Only LAcs (*TTN*tv+/DCM+: 6.50 [3.25–10.35] versus iDCM controls: 10.85 [6.80–14.70]; *P*<0.001) (Figure 2) and LAEF (*TTN*tv+/DCM+: 44.60 [28.90–52.85] versus iDCM controls: 49.00 [39.68–58.78]; *P*=0.03) were significantly lower in the patients with *TTN*tv+/DCM+ (Figure S1).

In the multivariable analysis, only hypertension [OR=0.44 (0.20–0.91), *P*=0.03] and LAcs [OR=0.88 (0.80–0.95), *P*=0.002] remained significantly and independently lower in the *TTN*tv+/DCM+ group compared with patients with iDCM. LAEF was again not significantly different between cohorts in the multivariable analysis (*P*=0.09).

Correlation Between Echocardiographic LA Strain and LV Function Parameters

To evaluate the relationship between LAcs and LVEF, a correlation analysis was conducted across the 4

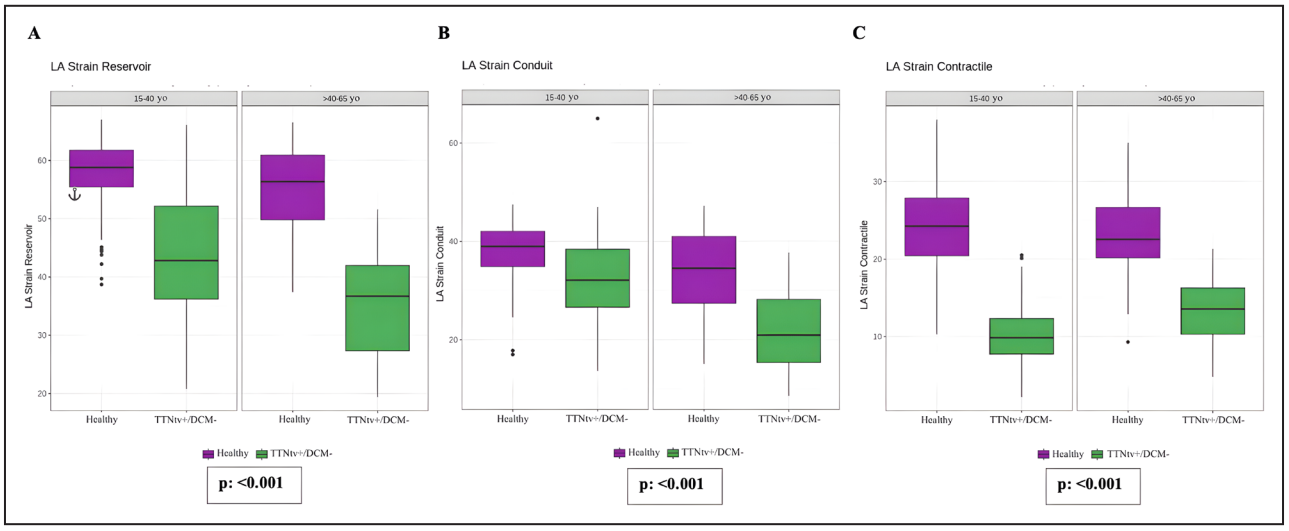


Figure 1. Baseline echocardiographic left atrial strain measurements from: patients with a truncating variant in TTN and LVEF ≥50% (TTNtv+/DCM–), versus healthy controls.
A, LA reservoir strain. **B**, LA conduit strain. **C**, LA contractile strain. Strain values are presented as absolute percentages. The subgroup of patients aged >65 years was excluded from the figure because of the small number of individuals. LA indicates left atrial; and yo, years old.

cohorts. The results showed no significant correlation when LVEF was ≥50% (*TTN*tv+/DCM- and Healthy controls). However, when LVEF was <50% (*TTN*tv+/DCM+ and iDCM controls), a positive correlation was observed between the 2 parameters, indicating that the lower the LVEF, the lower the LAcs (Figure 3).

Similar findings were observed for LArs and LAds. A positive correlation was identified in both cases only when LVEF was <50%. LArs was positively correlated with LVEF (LArs *TTN*tv+/DCM+, r=0.50, *P*<0.001; LArs iDCM, r=0.53, *P*<0.001), as was LAds (LAds *TTN*tv+/DCM+, r=0.42, *P*<0.001; LAds iDCM, r=0.45, *P*<0.001).

We also evaluated the correlation between LA strain and LV-GLS. No significant correlation was observed between LAcs and LV-GLS in patients with *TTN*tv+/DCM– and healthy controls. In contrast, LAcs and LV-GLS were only correlated when LVEF was <50% (Figure 3). LArs and LAds were positively correlated with LV-GLS in patients with *TTN*tv+/DCM– (LArs, r=0.49, *P*<0.001; LAds, r=0.84, *P*<0.001;), *TTN*tv+/DCM+ (LArs, r=0.70, *P*<0.001; LAds, r=0.62, *P*<0.001) and iDCM controls (LArs, r=0.70, *P*<0.001; LAds, r=0.59, *P*<0.001) whereas no correlation was found in healthy controls (LArs, r=0.09, *P*=0.2; LAds, r=0.04, *P*=0.6).

Atrial Fibrillation Incidence and LA Strain

Among the 460 patients included, 43 AF events were recorded during follow-up. In the *TTN*tv+/DCM- cohort, 5 AF events occurred (5.7%/1.48 per 100 person-years). In contrast, 17 AF events (25.8%/3.15 per 100 person-years) were observed in the *TTN*tv+/DCM+ cohort. Additionally, 21 AF events (15.3%/2.27 per 100 person-years) were documented in patients within the iDCM cohort.

A univariable Cox regression analysis was performed to assess whether *TTN*tv, hypertension, and LAVI influenced AF incidence among patients diagnosed with AF. None of these variables were found to be significantly associated with AF incidence during follow-up (*TTN*tv hazard ratio [HR]:0.99 [95% CI: 0.77–2.92], *P*=0.2; Hypertension, HR:1.20 [95% CI: 0.60–2.39], *P*=0.6; LAVI, HR: 0.90 [95% CI: 0.98–1.02], *P*=0.8). The cumulative incidence of AF at different time points in the *TTN*tv+/DCM+ group compared with the iDCM cohort, did not reach statistical significance (Figure 4).

Baseline demographic, genetic, clinical, and echocardiographic characteristics of patients with a *TTN*tv diagnosed with AF during follow-up are presented in Table S3. Patients with AF and a *TTN*tv had a lower LAEF (*P*=0.02) and LVEF (*P*<0.001), as well as a higher LAVI (*P*=0.01) and a greater proportion of women (*P*=0.02). There was a non-significant trend towards lower in LArs, LAds, or LAcs (*P*=0.07, *P*=0.1, and *P*=0.2, respectively) between subjects with and without AF.

DISCUSSION

In this study we evaluated atrial function using echocardiographic LA strain in individuals with *TTN*tv with and without LV systolic dysfunction. We identified that *TTN*tv was associated with a primary atrial myopathy, evidenced by reduced echocardiographic LA strain detectable prior to the onset of LA enlargement or left ventricular systolic dysfunction and reductions in atrial

Table 4. Multivariable Models of Differences Between Patients With a Truncating Variant in TTN and LVEF ≥50% (TTNtv+/DCM–) Versus Healthy Controls

	OR	*P* value
LA reservoir strain model		
BMI	1.00 (0.90–1.10)	0.9
Hypertension	20.10 (3.00–230.60)	0.005†
Age	0.92 (0.89–0.95)	<0.001†
LVEF	0.84 (0.75–0.93)	0.002†
LA volume (mL/m^2)	1.00 (0.95–1.05)	0.9
LA reservoir strain	0.84 (0.79–0.88)	<0.001†
LA conduit strain model		
BMI	1.04 (0.90–1.10)	0.3
Hypertension	27.50 (5.30–218.60)	<0.001†
Age	0.92 (0.89–0.95)	<0.001†
LVEF	0.83 (0.70–0.90)	<0.001†
LA volume (mL/m^2)	1.00 (0.97–1.06)	0.4
LA Conduit strain	0.89 (0.85–0.93)	<0.001†
LA contractile strain model		
BMI	0.87 (0.72–1.02)	0.1
Hypertension	118.80 (5.30–5656.10)	0.006†
Age	0.97 (0.92–1.02)	0.2
LVEF	0.77 (0.60–0.90)	0.001†
LA volume (mL/m^2)	0.90 (0.87–1.01)	0.1
LA contractile strain	0.50 (0.40–0.60)	<0.001†
LAEF model		
BMI	1.05 (0.98–1.13)	0.2
Hypertension	33.30 (6.37–281.20)	<0.001†
Age	0.92 (0.89–0.95)	<0.001†
LVEF	0.83 (0.76–0.90)	<0.001†
LA volume (mL/m^2)	1.02 (0.99–1.07)	0.2
LAEF	0.98 (0.96–1.01)	0.2

Each multivariable logistic regression model included one LA functional parameter—reservoir strain, conduit strain, contractile strain, or LAEF—as the main predictor. All models were adjusted for age, BMI, hypertension, LVEF, and LA volume. The LA parameter under evaluation is shown in the title of each block and was not included again as a covariate. Odds ratios reflect the association with the end point of belonging to the TTNtvt+/DCM– group and are shown per 1-unit increase in each variable: age (years), BMI (kg/m^2), LVEF (%), LA volume (mL/m^2), and LA strain/LAEF (%). BMI indicates body mass index; LA, left atrial; LAEF, left atrial emptying fraction; LVEF, left ventricular ejection fraction; and OR, odds ratio.

†XXX.

contractile function in patients with DCM that was out of proportion to the degree of systolic dysfunction.

Echocardiographic Assessment of *TTN*tv-Related Cardiomyopathy Reveals Early Primary Atrial Myopathy

Previous studies have demonstrated a primary atrial myopathy associated with *TTN*tv-related DCM. Henkens et al.,[12] described this condition based on lower LA strain on cardiac magnetic resonance in patients with *TTN*tv-related DCM, compared with those with idiopathic DCM. Our study is the first to report atrial myopathy in patients with *TTN*tv+/DCM– before the onset of LV systolic dysfunction, as evidenced by decreased echocardiographic LA strain, independent of other variables that may influence LA function and assessed with a more accessible tool than cardiac magnetic resonance. In patients with *TTN*tv+/DCM–, atrial myopathy may be both a harbinger of LV dysfunction and progress concurrently with its decline.

New echocardiographic techniques have emerged as valuable tools for identifying atrial myopathy.[7,9] In this study, we demonstrate the presence of a potential primary atrial myopathy, reflected by reduced echocardiographic LA strain (LArs, LAds, LAcs) in patients with a *TTN*tv. LArs and LAds measure LA function during systolic active filling and early diastolic passive emptying, respectively, and are more sensitive to loading conditions.[7,9] This was evident in our study, as no significant differences were found in these parameters between *TTN*tv+/DCM+ and iDCM, both conditions typically associated with elevated LV pressures. In contrast, LAcs, which reflects atrial contractile function in late diastole and is less dependent on loading conditions,[7,9] was the only parameter significantly reduced in patients with *TTN*tv+/DCM+ compared with iDCM, demonstrating the effect of *TTN*tv on primary atrial function. In vitro data further support the notion that *TTN*tv may contribute to atrial myopathy through structural and functional alterations that are specific to atrial tissue, independently of ventricular dysfunction.[6]

Interrelationship between Echocardiographic LA Strain and LV Function Parameters

We examined the correlation between LVEF and LV-GLS with various LA strain parameters among study participants. Tremblay-Gravel et al[11] reported a positive correlation between LAcs and LVEF in *TTN*tv-related cardiomyopathy when LVEF was <50%, which aligns with our findings. In contrast, no correlation was found between any LA strain parameter and LVEF, in patients with *TTN*tv+/DCM–. Our interpretation of these results suggests that LA function, as assessed by LA strain, is inherently reduced in the presence of a *TTN*tv. However, as LVEF declines and HF-related factors, such as increased atrial pressure develop, a further deterioration in LA function is observed.

We demonstrated that LVEF is associated with all echocardiographic LA strain parameters, when LVEF is <50%. This relationship likely reflects the hemodynamic interdependence between the atrium and ventricle, particularly through increased left atrial afterload in the setting of LV dysfunction. Nevertheless, we found that LAcs was independently and significantly lower in patients with *TTN*tv+/DCM+ compared with an LVEF-,

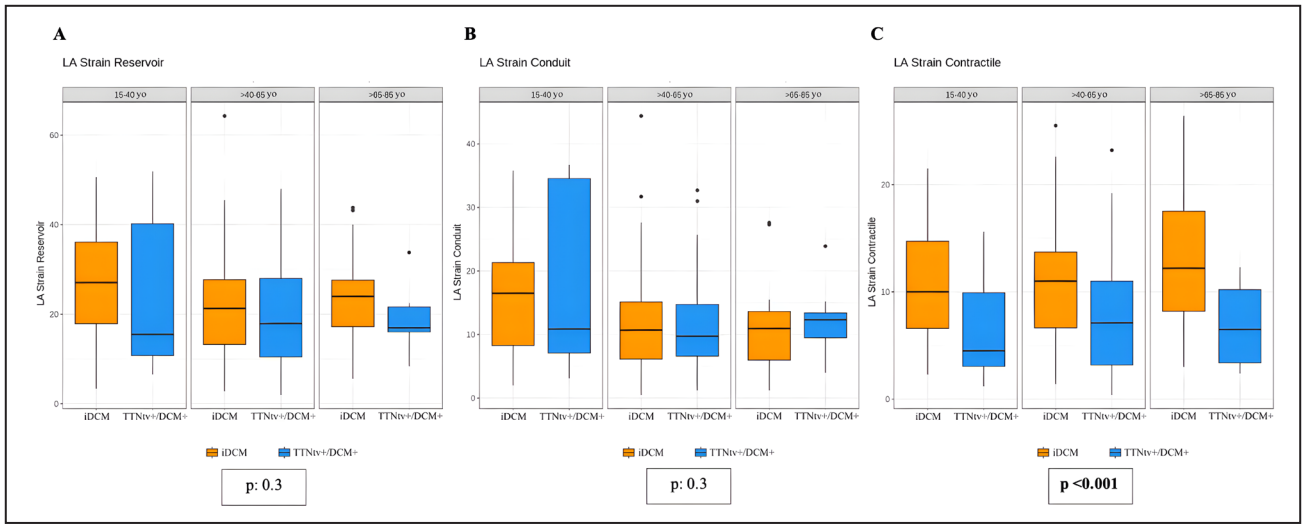
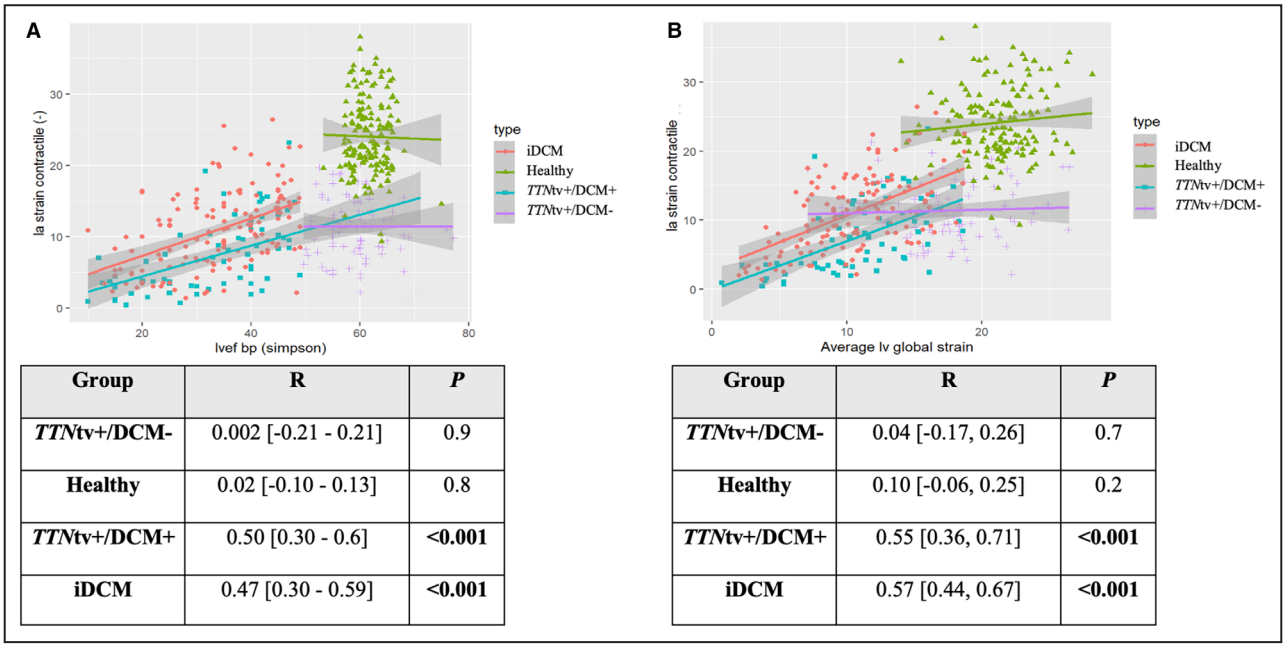


Figure 2. Baseline echocardiographic left atrial function measurement from: patients with a truncating variant in TTN and LVEF <50% (TTNtv+/DCM+) versus individuals with idiopathic, pathogenic variant-negative, DCM (iDCM).
A, LA reservoir strain. **B**, LA conduit strain. **C**, LA contractile strain. Strain values are presented as absolute percentages. iDCM, indicates dilated cardiomyopathy (idiopathic); LA, left atrial; and yo, years old.

age-, and sex-matched population. Previous computational models[16] simulating LV and LA function in patients with DCM, with and without *TTN*tv mutations, demonstrated that LV dysfunction alone was insufficient to explain the more pronounced LA dysfunction observed in *TTN*tv carriers.[12] To align with real-world patient data, the simulation required the inclusion of an additional primary LA dysfunction component. This supports the notion that the presence of *TTN*tv not only affects ventricular mechanics but also directly impairs atrial function, even when LVEF is <50%.

LV-GLS has been described as another early phenotypic marker in patients harboring *TTN*tv.[17] However, we found that this measure of LV contractile function



Group	R	*P*
***TTN*tv+/DCM-**	0.002 [-0.21 - 0.21]	0.9
Healthy	0.02 [-0.10 - 0.13]	0.8
***TTN*tv+/DCM+**	0.50 [0.30 - 0.6]	**<0.001**
iDCM	0.47 [0.30 - 0.59]	**<0.001**

Group	R	*P*
***TTN*tv+/DCM-**	0.04 [-0.17, 0.26]	0.7
Healthy	0.10 [-0.06, 0.25]	0.2
***TTN*tv+/DCM+**	0.55 [0.36, 0.71]	**<0.001**
iDCM	0.57 [0.44, 0.67]	**<0.001**

Figure 3. Interdependence between echocardiographic left atrial contractile strain and left ventricular function, across LVEF values.
A, LVEF. **B**, LV-GLS. Strain values are presented as percentages. Healthy indicates healthy controls; iDCM, indicates dilated cardiomyopathy (idiopathic); LVEF, left ventricular ejection fraction; LV-GLS, left ventricular global longitudinal strain; R, Pearson correlation coefficient; TTNtv+/DCM–, truncating variant in titin and LVEF ≥50%; and TTNtv+/DCM+, truncating variant in titin and LVEF <50%.

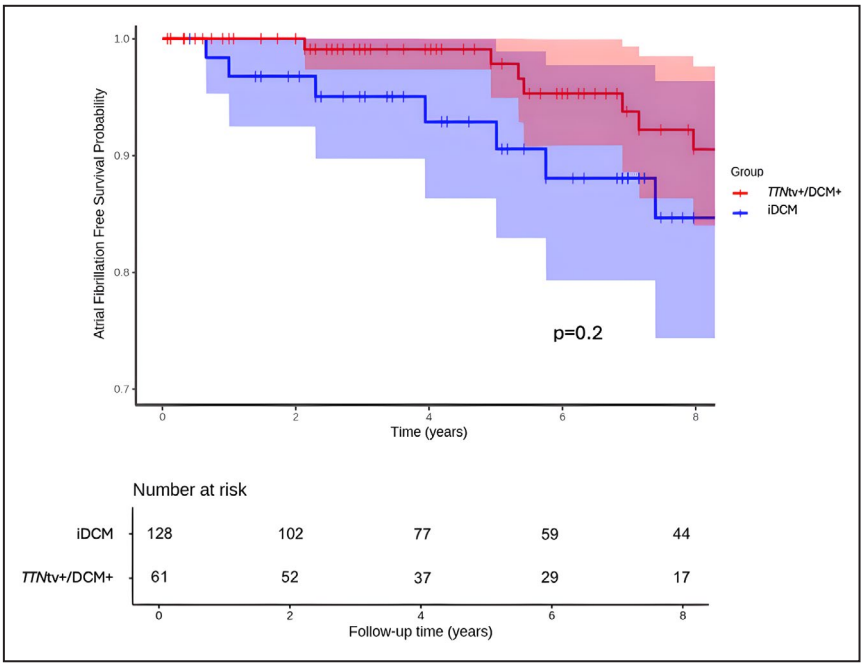


Figure 4. Atrial fibrillation incidence in patients with a truncating variant in titin and left ventricular ejection fraction <50% (TTNtv+/DCM+), compared with individuals with idiopathic, pathogenic variant-negative, DCM (iDCM).
iDCM indicates dilated cardiomyopathy (idiopathic).

did not correlate with atrial function measured by LAcs when LVEF was ≥50%. This shows that LAcs may be reduced even when LV-GLS remains preserved and supports the hypothesis that *TTN*tv has a direct effect on atrial function.

These findings support the potential role of monitoring echocardiographic parameters of LA function as early disease markers, facilitating the detection of subclinical cardiac involvement in asymptomatic individuals carrying *TTN*tv, before changes in other echocardiographic parameters become evident.

Atrial Myopathy and Atrial Fibrillation in *TTN*tv-Related Cardiomyopathy

The mechanisms by which TTNtv contribute to atrial arrhythmias, particularly in the absence of ventricular disease or overt cardiomyopathy, remain unclear. This effect may involve altered sarcomeric function, impaired mechanotransduction, and disrupted intracellular signaling, promoting a substrate for atrial arrhythmogenesis, as described by Huang et al.[6]

*TTN*tv are among the most frequently identified variants in genetic testing of patients with early-onset AF.[4,5] In our study, AF events were more frequent in *TTN*tv+/DCM+ (25.8%) compared with patients with *TTN*tv+/DCM– (5.7%), highlighting the increased risk of atrial tachyarrhythmias associated with LV dysfunction in *TTN*tv cardiomyopathy during follow-up.[18–20] However, the 5.7% rate of AF over 52.12±36.69 months observed in *TTN*tv+/DCM– individuals, underscores the implications of early atrial myopathy in this disease. Although we do not have follow up data for the healthy volunteers in this study, the rate of AF in a comparably matched healthy population is 0.5% in this time frame.[21] However, once overt LV cardiomyopathy develops, the severity of HF as opposed to the presence of a *TTN*tv was associated with AF. Patients with a *TTN*tv who were diagnosed with AF during follow-up had a more dilated LA, along with lower LVEF and LAEF. However, no significant differences were observed in LA strain values.

One interpretation of these findings is that this study may have been underpowered to support the hypothesis that the presence of a *TTN*tv is associated with higher AF risk in patients with LV dysfunction. This may be attributable to a potential underdiagnosis of AF during follow-up. Because AF is not always symptomatic, subclinical cases may have remained undetected. Moreover, periodic ambulatory rhythm monitoring is not routinely performed in patients with *TTN*tv unless symptoms are present, despite evidence that AF in this context is associated with a worse clinical course.[22] As a result, AF incidence in this population may have been underestimated.

Limitations

This study has limitations that should be acknowledged. Its retrospective design introduces potential

biases and limits causal inferences. Although patients with poor acoustic windows were excluded, echocardiographic strain measurements may still have been influenced by subtle image quality limitations. LA strain parameters were assessed using only the apical 4-chamber view, as the left atrium was not consistently well visualized in the 2-chamber view. Another relevant limitation is the inability to accurately estimate the true duration of atrial disease in the studied population. Since atrial dysfunction may develop subclinically over time, the lack of precise temporal information on disease progression prevents a comprehensive understanding of its natural history. Furthermore, given the retrospective design, the study does not assess incident AF in a prospective manner, which limits the ability to establish temporal associations between atrial myopathy and AF development in patients with *TTN*tv+/DCM+. Although previous studies have suggested that the location of *TTN*tv may affect titin protein length and the severity of cardiac dysfunction[23–25] the predominance of A-band variants in our cohort precluded analysis of their association with LV or LA function. Additionally, 35% of the iDCM controls had a family history of cardiomyopathy. We were unable to determine the impact of unknown genetic etiologies in this population on the development of atrial myopathy. Biomarker levels, such as NT-proBNP, were not collected for most patients at baseline. The correlation between NT-proBNP and LA strain needs to be established in future research. Despite these limitations, our results yield valuable insights into the characterization of the primary atrial myopathy associated with *TTN*tv.

Future Directions

Future work will be critical to unmask the prognostic role of early atrial myopathy in patients with *TTN*tv. The detection of atrial dysfunction—through echocardiographic LA strain—prior to LA enlargement or LV impairment supports its potential as an early phenotypic marker. Additional evidence is needed to determine whether atrial myopathy is associated with a faster decline in LVEF and overall disease progression. Some patients in our study were already receiving prognostic HF medications at their first visit to the referral medical center. Future research is needed to assess the impact of these treatments on the progression of atrial myopathy. Research incorporating dedicated rhythm monitoring and longitudinal follow-up in patients with *TTN*tv with atrial myopathy is essential to clarify its relationship with AF development.

CONCLUSIONS

Atrial myopathy, assessed through echocardiographic LA strain, is evident in the early stages of cardiac involvement when a *TTN*tv is present, preceding alterations in other early disease markers, and may serve as a novel early marker of phenotypic expression in this condition. Once LVEF falls below 50%, atrial myopathy continues to worsen in parallel, consistent with a risk of loss of atrial contractility as cardiomyopathy progresses. AF was more frequently observed in patients carrying *TTN*tv. Further research is warranted to evaluate the potential role of atrial strain as a risk stratification tool for AF in patients with *TTN*tv.

ARTICLE INFORMATION

Received November 5, 2025; accepted January 28, 2026.

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Acknowledgments

None.

Sources of Funding

The authors received unrestricted support from the Steggall Family foundation and Fundación Interhospitalaria para la Investigación Cardiovascular (FIC. Madrid, Spain) for this study. The Centro Nacional de Investigaciones Cardiovasculares (CNIC. Madrid, Spain) is supported by the Instituto de Salud Carlos III (ISCIII. Madrid, Spain) Ministerio de Ciencia e Innovación (MCIN. Spain), the Pro-CNIC Foundation (Spain), and the Severo Ochoa Centers of Excellence program (CEX2020-001041-S. Spain). PGP is funded by the Pathfinder Cardiogenomics Programme of the European Innovation Council of the European Union (DCM-NEXT project; project 101 115 416).

Disclosures

Neal Lakdawala has received grant funding from BMS and Pfizer and modest consulting incomes from BMS, Pfizer, Alexion, Cytokinetics, Tenaya, Bayer, Nuevocore, Kardigan and Lexeo.

Supplemental Material

Tables S1–S3
Figure S1
STROBE Checklist

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