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RESEARCH ARTICLE

Deep phenotyping of p.(V142I)-associated variant transthyretin amyloid cardiomyopathy: Distinct from wild-type transthyretin amyloidosis?

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Aims Transthyretin amyloid cardiomyopathy (ATTR-CM) is an increasingly recognized cause of heart failure. A total of 3–4% of individuals of African descent carry a TTR gene mutation encoding the p.(V142I) variant, a powerful risk factor for development of variant ATTR-CM (ATTRv-CM); this equates to 1.6 million carriers in the United States. We undertook deep phenotyping of p.(V142I)-ATTRv-CM and comparison with wild-type ATTR-CM (ATTRwt-CM).

Methods and results A retrospective study of 413 patients with p.(V142I) ATTRv-CM who attended the UK National Amyloidosis Centre (NAC) was conducted. Patients underwent evaluation at time of diagnosis, including clinical, echocardiography, and biomarker analysis; a subgroup had cardiac magnetic resonance (CMR) imaging. A total of 413 patients with ATTRwt-CM, matched for independent predictors of prognosis (age, NAC Stage, decade of first presentation), were used as a comparator group. At time of diagnosis, patients with ATTRv-CM had significant functional impairment by New York Heart Association classification (NHYA class ≥ III; 38%) and 6-min walk test distance (median 276 m). Median 5-year survival in ATTRv-CM patients was 31 versus 59 months in matched patients with ATTRwt-CM ($p < 0.001$). Patients with ATTRv-CM had significant impairment of functional parameters by echocardiography including biventricular impairment, high burden of regurgitant valvular disease and low cardiac output. Multivariable analysis revealed the prognostic importance of right ventricular dysfunction. CMR and histological analysis revealed myocyte atrophy and widespread myocardial infiltration in ATTRv-CM.

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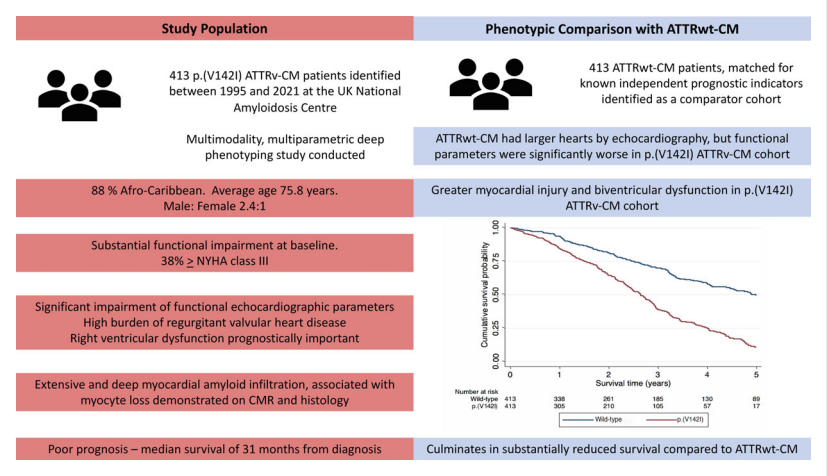
Conclusion p.(V142I)-ATTRv-CM has an aggressive phenotype characterized by myocyte loss and widespread myocardial infiltration which may account for frequent biventricular failure and poor prognosis in this ATTR-CM genotypic subgroup.

Graphical Abstract



Deep phenotyping of p.(V142I) ATTRv-CM revealed a biologically aggressive phenotype characterised by myocyte loss and deep myocardial amyloid infiltration which may account for frequent biventricular failure, significant functional impairment and poor prognosis in this ATTR-CM genotype subgroup. Poor prognosis in this group is likely related to the fact this is a biologically aggressive phenotype, as opposed solely to socioeconomic differences and racial inequalities in healthcare access.

Keywords Amyloid • V122I • Transthyretin • TTR • Cardiomyopathy

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM), now the most commonly diagnosed type of cardiac amyloidosis,[1] is characterized by extracellular deposition in the myocardium of amyloid fibrils composed of misfolded transthyretin protein (TTR) which disrupt cardiac function.[1,2] In the absence of amyloid-specific treatment, relentless accumulation of myocardial amyloid deposits results in an inevitable decline in cardiac function and culminates in death.

Transthyretin (ATTR) amyloidosis can be hereditary, associated with TTR gene variants (ATTRv), or acquired, known as wild type (ATTRwt). Over 130 pathogenic *TTR* mutations are known to cause ATTRv amyloidosis which is inherited in an autosomal dominant fashion.[2] The p.(V142I) variant is most often seen in patients of African ancestry, with a large scale genomic study undertaken in over 9000 African American individuals from the United States demonstrating a p.(V142I) carrier rate of 3.2%.[3,4] The exact disease penetrance of the mutation is unknown, but based on a carrier rate of 3.2% in tandem with estimates of the United States population, there are approximately 1.6 million African Americans that carry the p.(V142I) variant.[5]

A large scale natural history study in patients with ATTR-CM demonstrated that patients with p.(V142I)-ATTRv-CM had greater functional impairment and worse markers of cardiac disease at the time of diagnosis coupled with a more rapid decline in quality of life and shorter survival when compared to other genotypes associated with ATTR-CM, suggesting the possibility of a more biologically aggressive form of disease.[2] Until recently p.(V142I)-ATTRv-CM was little studied in the United States, likely in part due to an under-representation of patients of African ancestry attending specialist amyloid referral centres.[6]

In recent years, there have been significant advances in diagnosis of ATTR-CM, accompanied by development of novel disease-modifying therapeutics.[7–9] Developments in cardiac imaging including cardiac magnetic resonance (CMR), echocardiography and repurposed bone scintigraphy have all led to an upsurge in diagnosis of cardiac amyloidosis and permitted the majority of patients with ATTR-CM to be diagnosed without endomyocardial biopsies (EMB).[2,10] Novel therapeutic agents include the RNA-interference therapeutics (patisiran, vutrisiran), and antisense oligonucleotides (inotersen), which act to reduce TTR production, and tafamidis, a small-molecule compound that stabilises the TTR tetramer.[7–9]

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These agents have all demonstrated efficacy in patients with ATTR amyloidosis, and are now available in a number of healthcare systems. It is well recognized that racial and socioeconomic factors contribute to inequality in health care, particularly in privatized healthcare systems in which financial cost may be a significant barrier to accessing healthcare.[11] This is relevant in the context of novel therapies for ATTR amyloidosis for which the annual cost per patient ranges from $225 000 to $450 000.[4] It is thus difficult to exclude a contribution to poor outcomes in p.(V142I)-ATTRv-CM from inequitable access to health care.[3,4]

We hypothesized that p.(V142I)-associated ATTRv-CM has a biologically aggressive clinical phenotype and undertook a deep phenotyping study utilizing multiple modalities including, but not limited to, echocardiography, cardiac magnetic resonance (CMR), blood biomarkers and histology in the largest known cohort of patients with p.(V142I)-ATTRv-CM. A matched ATTRwt-CM comparator group was utilized to elicit any phenotypic differences between the two groups. A deep multimodality, multiparametric phenotyping study of this design, with an appropriately matched comparator group, has not yet been published in the literature; a comprehensive understanding of this emerging cause of heart failure in a potentially under-represented ethnic group therefore represents an unmet need.

Methods

Patients

All patients referred to and diagnosed with p.(V142I)-ATTRv-CM at the UK National Amyloidosis Centre (NAC) between 1 January 1995 and the censor date of 3 November 2021 were included in the study. Diagnosis was established either via the validated non-biopsy algorithm or by histology.[10]

Patients were followed annually at the NAC after diagnosis and mortality data were obtained via central UK National Health Service records. Patients who commenced any disease-modifying therapy or who were enrolled into interventional clinical trials for ATTR-CM were censored at time of doing so.

A cohort of ATTRwt-CM patients who were matched for recognized predictors of prognosis at the time of diagnosis (NAC Stage, age, and decade of diagnosis) were used for comparison in selected analyses.

All patients were managed in accordance with the Declaration of Helsinki and provided written informed consent for analysis and publication of their data. Study approval was from the Royal Free Hospital ethics committee (ref: 06/Q0501/42).

Echocardiography

Echocardiography was performed by accredited and experienced sonographers using GE-Vivid machines and EchoPac software as previously described.[12] Right atrial pressure (RAP) was assessed based on inferior vena cava (IVC) diameter and collapsibility during inspiration. RAP was reported as 5 mmHg if the IVC was of normal diameters and had greater than 50% collapse during inspiration. If either the IVC was dilated or did not collapse more than 50% during inspiration, it was reported as 10 mmHg and if it was dilated with no inspiratory collapse, it was reported as 15 mmHg.[12]

Tc-DPD scintigraphy

Technetium-3,3-diphosphono-1,2-propanodicarboxlyic acid (Tc-DPD) scans were performed 3 h post intravenous administration of 700 MBq of ^{99m}Tc-DPD using a General Electric Infinia Hawkeye 4 or Discovery 670 gamma camera. Whole body planar and cardiac single-photon emission computed tomography images were acquired using established protocols.[13] Images were interpreted by consultant nuclear medicine radiologists according to the modified Perugini grading system, as previously reported.[14]

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed with a Siemens 1.5 T scanner (Siemens Healthcare, Erlangen, Germany). A standardized CMR protocol, including parametric mapping and post-gadolinium contrast images was used. Long-axis two-, three- and four-chamber and short-axis cine images were acquired and used for volumetric assessments. Native T1 (MOLLI) and T2 maps were produced, and extracellular volume maps were reconstructed following the administration of gadolinium contrast. Myocyte cell volume was calculated using the published formula of left ventricular myocardial volume × (1 − ECV) where ECV is extracellular volume.[15] CMR scans were analysed and reported with Osirix MD software by CMR-accredited consultant cardiologists.

Histology

Formalin-fixed, paraffin-embedded histology samples were stained with Congo red and apple-green birefringence was sought under cross polarized light as previously reported.[16] To confirm the amyloid fibril type, immunohistochemistry was performed using antibodies reactive against serum amyloid A, TTR and kappa and lambda immunoglobulin light chains.[10] Samples in which immunohistochemistry failed to identify the amyloid fibril protein were laser microdissected and analysed by mass spectrometry.

To further assess the degree of myocardial alteration due to amyloid deposits right ventricular septal EMBs were also stained with antibodies against von Willebrand factor, CD31 (for vascular alteration), CD45 and CD68 (for inflammation), as previously described.[17]

Socioeconomic data

Patient post-codes in tandem with geographic disposable income estimates available from the UK Office of National Statistics were used to estimate patient income. Healthcare service usage episodes, defined as National Health Service (NHS) funded hospital service usage in England, 3 years pre-diagnosis, were available for a subset of patients at a population level. These data were sourced from NHS Digital.

Statistical analysis

Statistical analysis was performed on IBM SPSS version 29 software, apart from Kaplan–Meier curves, which were generated using Stata (StataCorp 2021, software release 17). The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to determine normally distributed variables. Normally distributed variables were expressed as mean (standard deviation) and non-normally distributed variables are expressed as median (interquartile range [IQR]). Significant differences in means between cohorts were assessed using an independent samples *t*-test. Differences in categorical data were assessed using the

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Chi^2 test, and medians were compared using the independent samples median test.

Kaplan–Meier curves were used to compare survival between p.(V142) ATTRv-CM and ATTRwt-CM patients across all disease stages. A log rank (Mantel–Cox) test was applied to determine whether the curves differed significantly. Cox proportional hazards regression analysis was used to evaluate survival and provided estimated hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazards assumption was checked and satisfied for all models. Harrell's-c statistic was calculated to confirm validity of the multivariable Cox regression model. Unless stated otherwise, a significance level of 0.05 was used for all hypothesis tests.

Results

Patient demographics

The study comprised 413 patients with p.(V142I)-ATTRv-CM. Baseline patient demographics and disease characteristics are detailed in *Table 1*. A total of 88% of p.(V142I)-ATTRv-CM patients were of Afro-Caribbean descent and males outnumbered females 2.35 to 1. Median age at diagnosis was 76 (IQR 9) years. Differences between this cohort and the matched ATTRwt-CM cohort are highlighted in *Table 1*.

Clinical and functional characteristics

Patients with p.(V142I)-ATTRv-CM had a significant degree of functional impairment by the time of diagnosis. A total of 155 patients (38%) were New York Heart Association functional class ≥III. The median 6-min walk distance achieved was 276 m.

Haemodynamics were generally preserved at diagnosis; median supine blood pressure was 122/74 mmHg in patients with p.(V142I)-ATTRv-CM. There was a significant arrhythmic burden in patients with p.(V142I)-ATTRv-CM, with 52% of patients with evaluable electrocardiograms having some form of documented arrhythmia by the time of diagnosis (18% bradyarrhythmia, 28% atrial fibrillation/flutter, 6% paced rhythms); 48% of patients were in normal sinus rhythm.

Echocardiography

The echocardiographic phenotype of patients diagnosed with p.(V142I)-ATTRv-CM was one characterized by significant biventricular impairment (mean left ventricular ejection fraction 43%, global longitudinal strain −9.7%, tricuspid annular plane systolic excursion [TAPSE] 14.5 mm), impaired diastology (mean E/e' 17.5 cm/s) and a high burden of regurgitant valvular heart disease with 97 (23.4%) patients having significant mitral regurgitation and 131 (31.7%) having significant tricuspid regurgitation. Significant aortic valve disease was far less common with only five patients having significant aortic stenosis and nine having significant aortic regurgitation at diagnosis.

Morphologically both ventricular wall thickness and left ventricular mass were increased with an average interventricular septal thickness at end-diastole (IVSd) of 16.8 mm and left ventricular mass of 296 g. Atrial dimensions did not show substantial dilatation with a mean left and right atrial area of 25.9 and 24.5 mm^2.

Cardiac output was substantially reduced with a mean stroke volume of only 30.8 ml. In terms of right-sided cardiac dysfunction, measures of pulmonary pressures (mean pulmonary artery systolic pressure 43.1 mmHg, mean RAP 11.0 mmHg, mean tricuspid regurgitation gradient 31.7 mmHg and mean right ventricular S wave 9.7 cm/s) were also markedly abnormal in patients with p.(V142I)-ATTRv-CM.

Biochemical parameters

At diagnosis there was significant derangement of cardiac biomarkers among patients with p.(V142I)-ATTRv-CM with a median N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T of 3150 ng/L and 78 ng/L, respectively. Median estimated glomerular filtration rate (eGFR) adjusted for ethnicity was 54 ml/min. Anaemia (defined as a serum haemoglobin of <135 g/dl in men or <110 g/dl in women) was common; 179 (43%) p.(V142I)-ATTRv-CM were anaemic, with a median serum haemoglobin of 129 g/dl. Liver function was also often deranged, with the pattern of derangement suggesting a high prevalence of congestive hepatopathy likely related to underlying amyloid heart failure; median gamma glutamyl transferase (GT) and aspartate aminotransferase were 110 and 32 μ/L, respectively. Whilst it has been reported that Afro-Caribbeans may have higher baseline gamma GT levels, these findings remain of interest, particularly in the context of greater right-sided cardiac impairment, high right-sided pulmonary pressures and a significant burden of tricuspid regurgitation.[18]

Cardiac magnetic resonance imaging

A subgroup of 90 p.(V142I)-ATTRv-CM patients had CMR scans performed at diagnosis (*Figure 1*). There was a high burden of amyloid as evaluated by native T1 values and ECV mapping (mean T1 by MOLLI 1152 ms, mean ECV 58%). The mean native T2 was 49 ms (normal range <55 ms).

Histological findings

Endomyocardial biopsies were available from 6 p.(V142I)-ATTRv-CM patients. Histologically, there was a nodular pattern of amyloid deposition with extensive interstitial architectural disruption and myocyte vacuolization and atrophy, a marker of endothelial dysfunction and ischaemic injury,[19] accompanied by capillary rarefaction. Vascular amyloid infiltration was identified in two of six EMBs.

Patient survival

Median follow-up was 25 months (IQR 24.3 months) in p.(V142I)-ATTRv-CM with 273 deaths at censor time. Median survival from diagnosis in p.(V142I)-ATTRv-CM was poor at 31.2 months; survival in each NAC Stage was 39.4, 29.2 and 21.0 months in Stage I, II and III, respectively. Disease-modifying therapy was commenced

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Table 1 Baseline demographic, clinical, functional, biochemical, and echocardiographic characteristics in patients with p.(V142I)-associated variant transthyretin cardiomyopathy and a matched wild-type transthyretin cardiomyopathy cohort

Variable	p.V142I ($n = 413$)	Wild- type ($n = 413$)	p-value*
Demographics			
Age (years), mean (SD)	75.8 (9.1)	75.8 (9.1)	
Sex (male:female)	292:121	392:21	
Ethnicity, *n* (%)			
Black	365 (88.3)	9 (2.2)	
Caucasian	26 (6.3)	366 (88.6)	
Other	18 (4.4)	10 (2.4)	
Not declared	4 (1.0)	28 (6.8)	
NAC ATTR disease stage, *n* (%)			
I	184 (44.5)	184 (44.5)	
II	159 (38.5)	159 (38.5)	
III	70 (17.0)	70 (17.0)	
Decade of presentation, *n* (%)			
1990–1999	5 (1.2)	0 (0)	
2000–2009	48 (11.6)	44 (10.7)	
2010–2019	321 (77.7)	324 (78.5)	
2020 onwards	39 (9.4)	45 (10.9)	
Socioeconomic variables			
Estimated annual household income (GBP), mean (SD)	28 418 (5580)	30 191 (5387)	<0.001
Healthcare provider visits (median)	17	16	
Clinical, functional and biochemical parameters			
NYHA functional class, *n* (%)			
I	10 (2.4)	53 (12.8)	<0.001
II	248 (62.5)	280 (67.8)	<0.001
III	143 (34.6)	78 (18.9)	<0.001
IV	12 (2.9)	2 (0.48)	<0.001
Electrocardiography, *n* (%)			
Sinus rhythm	193 (46.7)	122 (29.5)	<0.001
Bradyarrhythmia	73 (17.6)	49 (11.9)	<0.001
Atrial fibrillation/flutter	116 (28.1)	188 (45.5)	<0.001
Paced rhythm	23 (5.6)	33 (8.0)	<0.001
Not available	8 (1.9)	21 (5.1)	
Clinical and biochemical parameters, median (IQR)			
Systolic BP (mmHg)	122 (27)	122 (24)	0.851
Diastolic BP (mmHg)	74 (15)	74 (12)	0.567
Pulse (bpm)	74 (19)	68 (18)	<0.001
6MWD (m)	276 (205)	368 (161)	<0.001
Urea (mmol/L)	8.3 (4.8)	10 (5.2)	0.027
Creatinine (mmol/L)	113 (43)	115 (35)	0.064
eGFR (ml/min)	53.8 (17)	59.7 (17)	<0.001
Haemoglobin (g/dl)	129 (16.6)	139 (22)	<0.001
NT-proBNP (ng/L)	3150 (4299)	3036 (3810)	0.648
High-sensitivity troponin T (ng/L)	78 (57)	62 (47)	<0.001
CRP (mg/L)	3 (6)	2 (4)	0.072
Bilirubin (μmol/L)	14 (13)	14 (10)	0.306
Albumin	42 (5)	44 (5)	<0.001
ALP (U/L)	100 (65)	95.5 (59.5)	0.326
GGT (U/L)	110 (156.8)	84.5 (126.8)	0.003
AST (U/L)	32 (16)	29 (12)	<0.001
ALT (U/L)	26 (16)	26 (12)	0.571
Echocardiographic parameters, mean (SD)			
IVSd (mm)	16.8 (2.26)	17.2 (2.36)	0.021
PWTd (mm)	16.4 (2.33)	16.8 (2.47)	0.022

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Table 1 (Continued)

Variable	p.V142I ($n = 413$)	Wild- type ($n = 413$)	*p*-value*
MWT (mm)	16.6 (1.34)	17.1 (1.37)	0.020
RWT	0.80 (0.17)	0.77 (0.16)	0.007
LVEDD (mm)	41.9 (6.06)	44.1 (5.69)	<0.001
LVESD (mm)	32.7 (6.47)	33.5 (6.06)	0.026
LVEDV (ml)	73.5 (28.8)	82.7 (26.7)	<0.001
LVESV (ml)	42.5 (22.2)	43.4 (18.8)	0.272
SV (ml)	30.8 (11.4)	38.7 (15.1)	<0.001
LVEF (%)	43.8 (11.4)	48.2 (11.0)	<0.001
GLS (%)	-9.7 (3.31)	−10.8 (3.66)	<0.001
LAD (mm)	43.6 (5.72)	45.3 (5.41)	<0.001
LAA (mm)	25.9 (5.35)	26.6 (5.71)	0.038
Indexed LAA (mm^2)	14.1 (3.10)	13.7 (2.97)	0.044
RAA (mm)	24.5 (6.64)	24.7 (6.48)	0.361
Indexed RAA (mm^2)	13.3 (3.52)	12.7 (3.21)	0.009
LV mass (g)	296.1 (76.6)	343.6 (92.7)	<0.001
Indexed LV mass (g)	159.8 (37.1)	176.3 (43.8)	<0.001
E wave (mm/s)	83.0 (19.8)	83.8 (19.5)	0.290
A wave (mm/s)	40.6 (19.4)	49.8 (27.8)	<0.001
DT (ms)	162.1 (47.4)	183.0 (56.3)	<0.001
E/A ratio	2.4 (1.05)	2.1 (1.11)	<0.001
E lateral (cm/s)	5.9 (1.94)	6.5 (2.10)	<0.001
E septal (cm/s)	4.2 (1.35)	4.6 (1.61)	<0.001
E/E' average (cm/s)	17.5 (5.76)	16.1 (5.12)	<0.001
MAPSE (mm)	7.4 (2.37)	8.3 (2.62)	<0.001
TAPSE (mm)	14.5 (4.69)	15.1 (4.81)	0.034
S wave (cm/s)	9.7 (2.85)	10.3 (3.17)	0.008
TR gradient (mmHg)	31.7 (11.2)	28.4 (9.41)	<0.001
RAP (mmHg)	11.0 (4.16)	9.9 (4.27)	<0.001
PASP (mmHg)	43.1 (11.4)	38.9 (9.75)	<0.001
Valvular heart disease, *n* (%)			
Significant MR	97 (23.4)	11 (2.7)	<0.001
Significant AS	5 (1.2)	5 (1.2)	0.619
Significant AR	9 (2.2)	8 (1.9)	0.897
Significant TR	131 (31.7)	14 (3.4)	<0.001
Cardiac magnetic resonance, mean (SD)			
T1 (ms)	1152 (47.5)	1147 (50.8)	0.218
T2 (ms)	49 (3.2)	51 (3.8)	0.003
ECV (%)	58 (7.6)	56 (3.3)	0.027
Myocyte cell volume (ml/m^2)	53 (14.9)	59 (14.4)	0.002

6MWD, 6-min walk distance; ALT, alanine transaminase; AR, aortic regurgitation; AS, aortic stenosis; ASP, alkaline phosphatase; AST, aspartate transaminase; ATTR, transthyretin amyloidosis; BP, blood pressure; CRP, C-reactive protein; DT, deceleration time; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyl transferase; GLS, global longitudinal strain; IQR, interquartile range; IVSd, interventricular septal thickness at end-diastole; LAA, left atrial area; LAD, left atrial diameter; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MAPSE, mitral annular plane systolic excursion; LVEDD, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic volume; MWT, mean wall thickness; MR, mitral regurgitation; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; PWTd, posterior wall thickness at end-diastole; RAA, right atrial area; RAP, right atrial pressure; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion; SD, standard deviation; SV, stroke volume; TR, tricuspid regurgitation.

*The reported *p*-value denotes whether the differences between groups are statistically significant.

in 17 (4%) of patients (5 patisiran, 1 inotersen, 11 tafamidis) at a median of 9 months (IQR 25 months) post-diagnosis.

Univariable Cox regression analysis of a range of variables associated with mortality in the p.(V142I)-ATTRv-CM cohort is shown in *Table 2*. Known prognostic echocardiographic variables[12] were included along with age and NAC Stage in a multivariable Cox regression analysis (*Table 3*) This showed indexed right atrial area, TAPSE, average E/e', age and NAC Stage to be independently associated with mortality.

When genotype was added to the multivariable model with the same explanatory variables as those in model for the p.(V142I)-ATTRv-CM cohort but using the combined cohort

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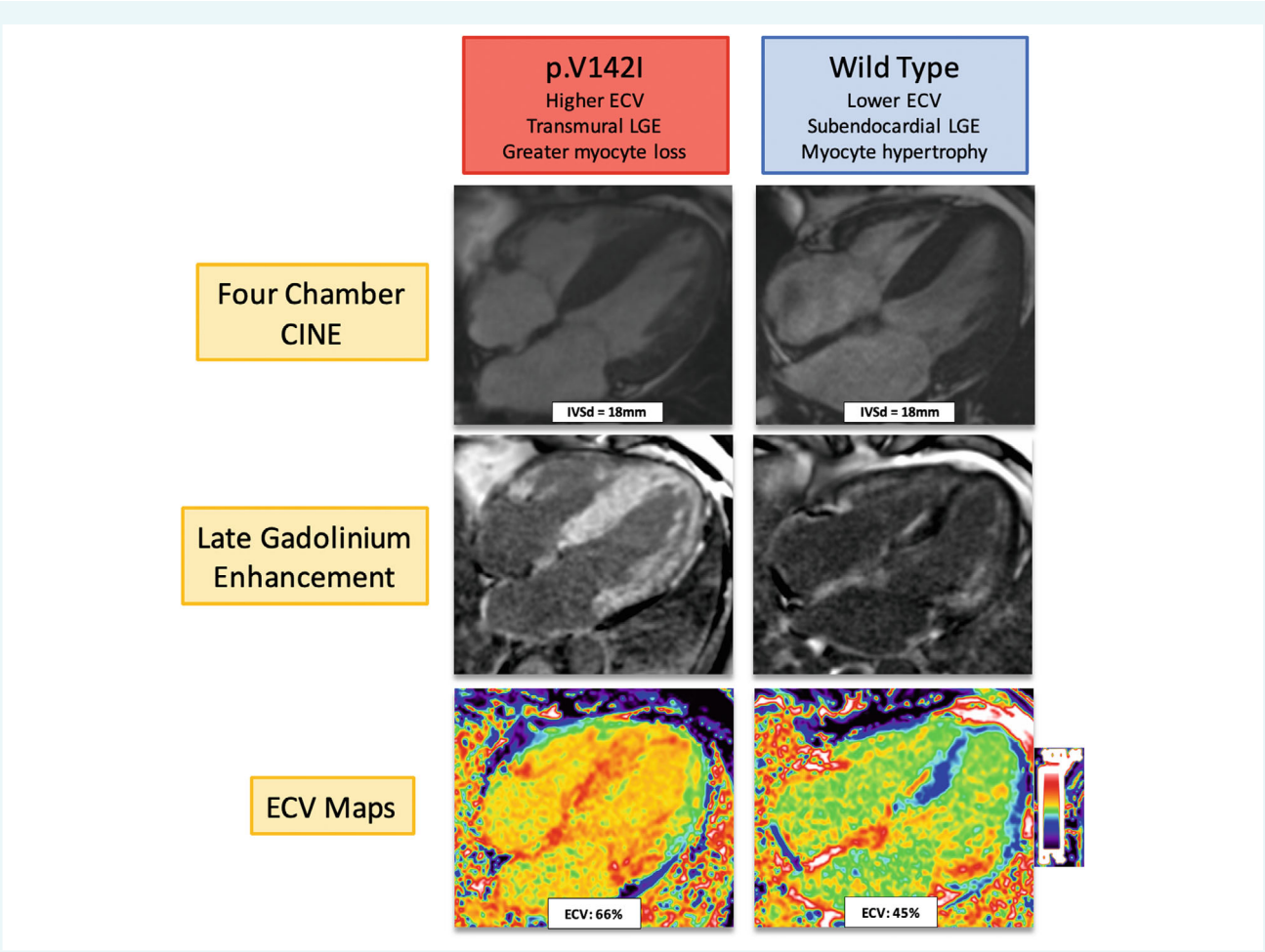

Figure 1 Cardiac magnetic resonance findings in a p.(V142I) ATTRv-CM and a ATTRwt-CM patient. These two patients were both male, aged 70, in National Amyloidosis Centre (NAC) Stage I and had similar reported left ventricular septal thicknesses of 18 mm (shown on cine images). Comprehensive tissue characterization elucidates a markedly more aggressive myocardial infiltrative process in the p.(V142I) patient, with a higher amyloid burden as measured on extracellular volume (ECV) maps coupled with deeper, more transmural late gadolinium enhancement (LGE) despite matched left ventricular wall thicknesses. ATTR-CM, transthyretin cardiomyopathy; IVSd, interventricular septal thickness at end-diastole.

of p.(V142I)-ATTRv-CM and ATTRwt-CM patients, this indicated that the presence of the p.(V142I) variant was the single most powerful predictor of mortality (HR 2.47, 95% CI 1.88–3.24, $p < 0.001$).

Given relatively high serum troponin T values at diagnosis among those with p.(V142I)-ATTRv-CM, its relevance as a marker of myocardial injury was explored by inclusion into the multivariable model shown in *Table 3*. Troponin T was a powerful independent predictor of survival (HR 1.007, 95% CI 1.004–1.009, $p < 0.001$) and whilst TAPSE, age and average E/e' remained independently prognostic after addition of troponin T, the other independently prognostic variables dropped out.

TTR variant zygosity

A total of 23 p.(V142I)-ATTRv-CM patients were homozygous for the pathogenic mutation, with the remaining 390 being identified as heterozygous. ATTRv-CM manifested and was diagnosed at a significantly younger age among homozygotes than heterozygotes (mean age at diagnosis 66 vs. 76 years, $p < 0.001$). However, patient survival from diagnosis was not significantly different between heterozygotes and homozygotes (median survival from diagnosis 2.6 and 3.2 years, respectively) although these findings did translate into a younger median age of death among homozygous p.(V142I)-ATTRv-CM patients of 69 years compared to 79 years in heterozygotes ($p < 0.001$). A Kaplan–Meier curve demonstrating survival is shown in *Figure 2*.

Socioeconomic factors

Estimated mean disposable household income in p.(V142I)-ATTRv-CM patients was £28 141, which was lower than the estimated national average across England and Wales of £31 000. A lower household income was not predictive of mortality in

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Table 2 Univariable Cox regression analysis of risk factors for mortality in patients with p.(V142I)-associated transthyretin cardiomyopathy.

Variable	Hazard ratio (95% CI)	p-value
Clinical/demographics		
NAC ATTR disease stage		
II vs. I	1.825 (1.394–2.389)	<0.001
III vs. I	3.389 (2.414–4.758)	<0.001
NYHA class		
II vs. I	1.806 (0.447–7.296)	0.407
III vs. I	2.451 (0.605–9.937)	0.209
IV vs. I	9.619 (2.104–43.977)	0.004
Age (years)	1.02 (1.003–1.038)	0.02
Estimated disposable annual income (GBP), <median vs. >median	0.924 (0.727–1.176)	0.522
Decade of presentation 1990–2000 vs. 2010–2020	1.524 (1.120–2.073)	0.01
Systolic BP (mmHg)	0.984 (0.976–0.991)	<0.001
Diastolic BP (mmHg)	0.988 (0.977–0.999)	0.027
Pulse (bpm)	1.007 (0.998–1.016)	0.145
6MWD (m)	0.998 (0.997–0.999)	0.003
Presence of arrhythmia	1.083 (1.000–1.173)	0.05
Biochemistry		
Urea (mmol/L)	1.107 (1.087–1.128)	<0.001
Creatinine (mmol/L)	1.006 (1.004–1.008)	<0.001
eGFR (ml/min)	0.978 (0.970–0.986)	<0.001
Haemoglobin (g/dl)	0.990 (0.982–0.997)	0.008
NT-proBNP (ng/L)	3.283 (2.403–4.484)	<0.001
High-sensitivity troponin (ng/L)	1.008 (1.006–1.010)	<0.001
CRP (mg/L)	1.009 (1.004–1.015)	0.001
Prothrombin time (s)	1.006 (0.993–1.020)	0.361
Activated partial thromboplastin time (s)	0.996 (0.979–1.013)	0.647
International normalized ratio	1.030 (0.877–1.208)	0.721
Bilirubin (μmol/L)	1.022 (1.014–1.031)	<0.001
Albumin (g/L)	0.945 (0.917–0.974)	<0.001
ALP (U/L)	1.005 (1.004–1.007)	<0.001
GGT (U/L)	1.002 (1.001–1.002)	<0.001
AST (U/L)	1.006 (1.001–1.010)	0.008
ALT (U/L)	0.998 (0.992–1.004)	0.426
Echocardiographic parameters		
IVSd (mm)	1.055 (1.001–1.111)	0.045
PWTd (mm)	1.042 (0.988–1.099)	0.128
LVEDD (mm)	0.990 (0.969–1.011)	0.990
LVESD (mm)	1.005 (0.986–1.025)	0.587
MWT (mm)	1.053 (0.994–1.115)	0.078
RWT	1.690 (0.843–3.389)	0.139
LVEDV (ml)	1.000 (0.995–1.005)	0.952
LVESV (ml)	1.005 (1.000–1.011)	0.05
SV (ml)	0.976 (0.963–0.989)	<0.001
LVEF (%)	0.972 (0.961–0.983)	<0.001
LAD (mm)	1.018 (0.997–1.040)	0.093
LAA (mm^2)	1.007 (0.984–1.031)	0.548
Indexed LAA (mm^2)	1.012 (0.972–1.053)	0.567
RAA (mm^2)	1.048 (1.029–1.068)	<0.001
Indexed RAA (mm^2)	1.089 (1.052–1.127)	<0.001
LV mass (g)	1.001 (0.999–1.002)	0.509
Indexed LV mass (g)	1.002 (0.998–1.005)	0.348
E wave (mm/s)	0.993 (0.087–0.999)	0.020
A wave (mm/s)	0.988 (0.980–0.996)	0.003
DT time (ms)	0.998 (0.995–1.000)	0.061
E/A ratio	1.083 (0.952–1.232)	0.223
E' lateral (cm/s)	0.947 (0.880–1.019)	0.148
E' septal (cm/s)	0.821 (0.742–0.907)	<0.001
E/E' average (cm/s)	1.024 (1.001–1.048)	0.045
E/E' lateral (cm/s)	1.010 (0.987–1.033)	0.407
MAPSE (mm)	0.901 (0.852–0.953)	<0.001
TAPSE (mm)	0.911 (0.883–0.939)	<0.001
S wave (cm/s)	0.901 (0.859–0.946)	<0.001
TR gradient (mmHg)	0.982 (0.970–0.994)	0.005
RAP (mmHg)	1.061 (1.030–1.094)	<0.001
PASP (mmHg)	0.991 (0.980–1.003)	0.155
MR	1.453 (1.104–1.912)	0.008
AS	1.390 (0.516–3.744)	0.515
AR	1.047 (0.861–1.272)	0.651
TR	1.874 (1.458–2.408)	<0.001
GLS (%)	1.098 (1.055–1.144)	<0.001

6MWD, 6-min walk distance; ALP, alkaline phosphatase; ALT, alanine transaminase; AR, aortic regurgitation; AS, aortic stenosis; AST, aspartate transaminase; ATTR, transthyretin amyloidosis; BP, blood pressure; CI, confidence interval; CRP, C-reactive protein; DT, deceleration time; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyl transferase; GLS, global longitudinal strain; IVSd, interventricular septal thickness at end-diastole; LAA, left atrial area; LAD, left atrial diameter; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MAPSE, mitral annular plane systolic excursion; MR, mitral regurgitation; NAC, National Amyloidosis Centre; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PWTd, posterior wall thickness at end-diastole; RAA, right atrial area; RAP, right atrial pressure; RWT, relative wall thickness; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Table 3 Multivariable Cox regression analysis of risk factors for mortality in patients with p.(V142I)-associated transthyretin cardiomyopathy

Variable	Hazard ratio (95% CI)	p-value
NAC ATTR disease stage		
I vs. II	1.266 (0.919–1.744)	0.149
I vs. III	2.157 (1.416–3.285)	<0.001
Stroke volume (indexed) (ml)	0.992 (0.962–1.023)	0.613
Left atrial area (indexed) (mm^2)	0.972 (0.919–1.028)	0.321
Right atrial area (indexed) (mm^2)	1.056 (1.001–1.113)	0.046
IVSd (mm)	1.009 (0.932–1.091)	0.832
Significant mitral regurgitation	1.075 (0.780–1.481)	0.659
Significant tricuspid regurgitation	1.355 (0.964–1.904)	0.080
E/e' average (cm/s)	1.028 (1.004–1.054)	0.025
RWT	1.108 (0.406–3.027)	0.842
GLS (%)	1.010 (0.958–1.065)	0.710
TAPSE (mm)	0.939 (0.899–0.982)	0.006
Age (years)	1.023 (1.002–1.046)	0.034
Harrell's C-index	0.675 (0.635–0.715)	<0.001

ATTR, transthyretin amyloidosis; CI, confidence interval; GLS, global longitudinal strain; IVSd, interventricular septal thickness at end-diastole; NAC, National Amyloidosis Centre; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion.

this cohort. Population level healthcare service episode statistics data were available for 161 p.(V142I)-ATTRv-CM. Patients with p.(V142I)-ATTRv-CM attended a healthcare provider a median of 17 times in the 3 years prior to diagnosis.

Comparison with matched wild-type transthyretin cardiomyopathy cohort

There were notable differences in baseline characteristics that elucidate a potentially mechanistically different form of ATTR-CM in p.(V142I) patients compared to the matched ATTRwt-CM cohort

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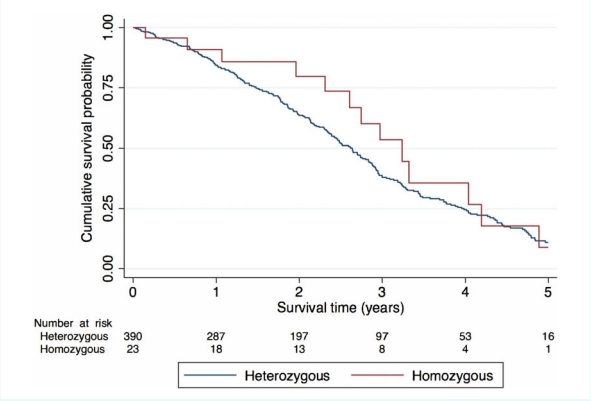

Figure 2 Five-year Kaplan–Meier survival curve stratified for heterozygous and homozygous p.(V142I) ATTRv-CM patients. Whilst homozygous patients are first diagnosed almost 10 years younger than heterozygous patients, survival duration from baseline is not significantly different between the two groups.

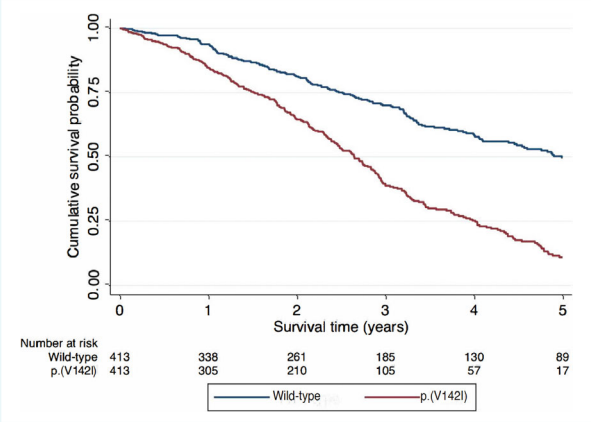

Figure 3 Five-year Kaplan–Meier survival curve stratified for p.(V142I) and wild-type transthyretin genotypes across the overall transthyretin cardiomyopathy (ATTR-CM) cohort. Survival is poor in patients with p.V142I ATTRv-CM patients and is substantially reduced when compared to matched wild-type ATTR-CM patients. Median 5-year survival in the overall cohort of p.V142I ATTR-CM patients was 31%, compared to 54% for ATTRwt-CM patients. All survival differences were statistically significant ($p < 0.001$).

who notably presented a similar number of times to hospital service providers (median 16 in the 3 years preceding diagnosis among patients with ATTRwt-CM). From a demographic perspective, 88.6% of ATTRwt-CM patients were Caucasian, and only 2.2% were Afro-Caribbean. There was no significant difference in blood pressure at diagnosis between the two genotypic cohorts. However, there was a greater prevalence of atrial fibrillation/flutter in patients with ATTRwt-CM (45.5%) than in those with ATTRv-CM (28.1%, $p < 0.001$).

Despite the close matching for NT-proBNP and eGFR (expected given matching for NAC Stage), median serum troponin was higher in p.(V142I)-ATTRv-CM (78 vs 62 ng/L, $p < 0.001$) and there was a greater degree of liver dysfunction.

Despite larger hearts based on echocardiography among the cohort with ATTRwt-CM compared to p.(V142I)-ATTRv-CM (IVSd: 17.2 vs. 16.8 mm and LV mass: 343.6 vs. 296.1 g), almost all measures of biventricular function were significantly less impaired in those with ATTRwt-CM. Furthermore, significant regurgitant valvular heart disease was almost 10-fold more common in p.(V142I)-ATTRv-CM than ATTRwt-CM. Further characterization by CMR in a sub-group of patients (91 ATTRv-CM, 141 ATTRwt-CM) demonstrated a higher amyloid burden by ECV mapping (58% vs. 56%, $p = 0.027$) but lower myocyte cell volume (53 vs. 59 ml/m^2, $p = 0.002$) in p.(V142I)-ATTRv-CM than in ATTRwt-CM (*Figure 1*). These findings were consistent with our histological findings from EMBs, albeit in a small number of cases (six p.(V142I)-ATTRv-CM and five ATTRwt-CM), in which there was a greater degree of myocyte vacuolization and atrophy accompanied by a greater degree of capillary rarefaction in p.(V142I)-ATTRv-CM. There was also deeper amyloid infiltration typically extending beyond the subendocardial layer in the EMBs from patients with p.(V142I)-ATTRv-CM whereas among those with ATTRwt-CM amyloid was typically confined to the subendocardium, spared the vasculature, and associated with myocyte hypertrophy rather than atrophy.

Median survival by Kaplan–Meier analysis in p.(V142I)-ATTRv-CM was substantially poorer at 31.2 versus 59.9 months ($p < 0.001$) in ATTRwt-CM (*Figure 3*). Multivariable Cox regression analysis in the whole cohort of ATTR-CM patients (both ATTRv and ATTRwt) using the same variables used in the earlier multivariable analysis of p.(V142I)-ATTRv-CM patients (*Table 3*) but with the addition of genotype indicated that presence of the p.(V142I) variant was the single most powerful predictor of mortality (HR 2.47, 95% CI 1.88–3.24, $p < 0.001$).

Discussion

Amyloid cardiomyopathy is the most common cause of restrictive cardiomyopathy and remains relatively unique in the realm of heart failure. ATTR-CM is an increasingly recognized cause of heart failure globally, with multiple novel specific anti-amyloid treatments in clinical use or under investigation within clinical trials. To our knowledge, our study represents to largest and most comprehensively phenotyped cohort of p.(V142I)-ATTRv-CM patients in the published literature; notably there have been no studies exploring phenotypic characteristics with CMR and histology with comparison to an appropriately matched ATTRwt-CM cohort. This is a patient cohort of particular importance, since p.(V142I) is the most common pathogenic TTR variant, as well as the most common cause of variant ATTR-CM. Indeed, large scale genomic studies have demonstrated a 3–4% mutation carrier rate in populations of African descent.[3] The UK National Amyloidosis Centre is the single nationwide centre specially commissioned for the assessment, diagnosis, and treatment of all patients with suspected amyloidosis. The Centre's database therefore represents a *de facto*

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national registry. Furthermore, analysis of national referral patterns and temporal trends over the past two decades during which there have been diagnostic advances have been extremely consistent such that there is no reason to suspect significant selection bias.[20]

Transthyretin cardiomyopathy has so far been considered as a single disease entity with different genotypic variants typically associated with diagnosis at different stages of disease on the basis of echocardiography or CMR.[12,21] For example, a study comparing the echocardiographic phenotype of ATTR-CM associated with three different TTR variants indicated that patients with p.(V142I)-ATTRv-CM typically have more advanced cardiomyopathy at diagnosis than patients with ATTRwt-CM or p.(T80A) ATTRv-CM, accounting for a poorer prognosis.[12] Whilst this study is unable to exclude the fact that this may indeed be true, it also suggests that p.(V142I)-ATTRv-CM is a phenotypically different disease to ATTRwt-CM characterized by a more extensive pattern of right-sided cardiac amyloid infiltration and hepatic congestion which is accompanied by frequent regurgitant valvular disease and greater functional impairment. The particular importance of right-sided cardiac dysfunction is highlighted by the prognostic significance of TAPSE and indexed right atrial area in our multivariable analysis and almost 10-fold higher burden of significant tricuspid regurgitation with higher right-sided pressures in p.(V142I)-ATTRv-CM patients relative to their matched wild-type counterparts. This is in stark contrast to previous studies demonstrating that global longitudinal strain and indexed stroke volume were independent predictors of prognosis when the same variables were selected for analysis.[12] The high burden of right-sided cardiac dysfunction in this genotypic subgroup is consistent with our centre's clinical experience of p.(V142I)-ATTRv-CM in which oedema and congestive hepatopathy are frequently observed. Interestingly, atrial dimensions were not significantly elevated in patients with p.(V142I)-ATTRv-CM despite the high frequency of regurgitant mitral and tricuspid valvular disease. A higher indexed right atrial area was highly prognostic in our multivariable analysis, and from echocardiographic assessment we were able to establish that right-sided pressures were markedly raised. A possible mechanistic explanation for this combination of findings is increased stiffness of the atrial walls from atrial amyloid infiltration; a feature that has been highlighted in previous studies.[17]

The fact that patients with p.(V142I)-ATTRv-CM have a worse prognosis than their ATTRwt-CM counterparts has already been extensively reported; nonetheless the striking prognostic significance of carrying the p.(V142I) TTR variant highlights both the severity of the disease, and in a health system that is free at the point of care, supports the idea that it is a more biologically aggressive form of ATTR-CM (*Graphical Abstract*).[12,22] CMR studies and histological analyses of EMB samples in this study indicated novel and previously undescribed contrasting pathological features in ATTRwt-CM and p.(V142I)-ATTRv-CM; the former was associated with myocyte hypertrophy and less amyloid per unit of total cardiac volume whereas the latter was associated with myocyte atrophy and more amyloid per unit of total cardiac volume. In addition, the small number of available EMBs from patients with p.(V142I)-ATTRv-CM showed evidence of endothelial dysfunction and ischaemic injury, notably absent in ATTRwt-CM, which might go some way to explaining the myocyte findings and are consistent with the different values of high-sensitivity troponin T despite closely matched NT-proBNP and GFR values between the genotypic subgroups. The explanation for this so-called 'differential myocyte response' could simply be related to the speed of amyloid deposition but may also be related to different toxicity of differently structured amyloid fibrils. Further large scale *in vitro* and *in vivo* studies are required to explore these hypotheses further. One notable finding was the absence of myocardial oedema in either genotypic subgroup which is an important observation, since it supports the concept that ECV represents true cardiac amyloid burden, as opposed to being a composite of oedema and amyloid infiltration.

Our study indicates that homozygosity for the pathogenic p.(V142I) TTR variant is associated with earlier disease onset but that the disease course of ATTRv-CM is similar to that in p.(V142I) TTR heterozygotes; nonetheless, given the earlier disease onset, homozygotes with ATTRv-CM died a median of 10 years earlier than their heterozygous counterparts in our study. Notably, one could expect the younger homozygous patients to live longer, in view of their younger age and therefore likely lower burden of non-amyloid comorbidity with potential for greater capacity for physiological compensation. This does suggest the homozygous disease phenotype itself is more aggressive in p.(V142I) ATTRv-CM and therefore associated with a more morbid disease course; a phenomenon well recognized across all Mendelian diseases.[23] Physiologically this would be unsurprising, given that all of the circulating TTR in such patients is conformationally variant with high amyloidogenic potential. Larger studies are required to determine in more detail whether the organ tropism differs between homozygous and heterozygous carriers of the p.(V142I) TTR variant and whether the earlier onset of ATTRv-CM observed among homozygotes in this study holds true across the entire spectrum of variant ATTR-CM. However, this study suggests that homozygous p.(V142I)-ATTRv-CM patients should be afforded closer clinical monitoring from a younger age than their heterozygous counterparts.

Racial disparities and socioeconomic inequality particularly in ethnic minorities have been widely published to be factors contributing to poorer access to healthcare.[24] Recent studies have shown the significance of socioeconomic and income disparities highlighting the negative impact on health and life expectancy of low income in the 21st century.[25] Our data, from the United Kingdom NHS, which is free at the point of access, showed that p.(V142I)-ATTRv-CM patients attended healthcare providers an equal number of times in the 3 years prior to diagnosis as patients with ATTRwt-CM suggesting that the disparity in outcomes in this study was related to disease biology. It is conceivable that the disparity in outcomes may be even greater in healthcare systems in which access to health care is directly influenced by socioeconomic status and income. Interestingly, a recent UK study of diagnostic trends and outcomes in ATTR amyloidosis over the last 20 years, showed that patients with p.(V142I)-ATTRv-CM potentially derived the greatest survival benefit from early diagnosis, reinforcing the need for equitable access to healthcare and early diagnosis in ATTR-CM regardless of TTR genotype.[20]

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Our study has limitations. Most importantly, only a subgroup of patients had CMRs ($n = 231$) and EMBs ($n = 11$) performed. Nonetheless, the CMR and histological data do corroborate the comprehensive echocardiographic, functional and biomarker data from the whole cohort to support our hypothesis that ATTRwt-CM and p.(V142I)-ATTRv-CM are different diseases. However, the authors acknowledge that the findings are hypothesis-generating rather than conclusive. Furthermore, detailed information on the nature of healthcare visits preceding diagnosis is not readily available (i.e. whether these healthcare visits were elective outpatient visits, or emergency hospitalizations). We acknowledge that further granularity on healthcare visits would be useful in determining pre-diagnostic morbidity of our cohort of patients. Finally, accurate data on comorbidities was not readily available for comparison between the patient cohorts.

In conclusion, the past decade has seen landmark developments in understanding of ATTR amyloid pathogenesis, imaging-based diagnosis of ATTR-CM, and amyloid-specific therapy which have transformed what was once considered a rare untreatable condition into an important cause of heart failure for which life-prolonging treatments exist. Whilst poorer outcomes among patients with p.(V142I)-ATTRv-CM compared to ATTRwt-CM have been extensively reported, the two conditions, along with all the other TTR variants causing ATTR-CM are widely considered to be a single disease entity. Here, we provide evidence to support the hypothesis that the disease biology differs substantially between these two cardiomyopathic TTR variants which may be of relevance in an age of patient-tailored therapy.

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