



Impact of Earlier Diagnosis in Cardiac ATTR Amyloidosis Over the Course of 20 Years

Adam Ioannou¹, MBBS, BSc*; Rishi K. Patel¹, MBBS, BSc*; Yousuf Razvi, MBChB, BSc; Aldostefano Porcari¹, MD; Gianfranco Sinagra¹, MD, FESC; Lucia Venneri, MD, PhD; Francesco Bandera, MD, PhD; Ambra Masi¹, MD; Georgina E. Williams, BSc; Sophie O'Beara¹, BSc (Hons); Sharmananthan Ganesanathan¹, BSc (Hons); Paolo Massa, MD; Daniel Knight¹, PhD; Ana Martinez-Naharro, PhD; Tushar Kotecha¹, PhD; Liza Chacko, MBBS, BSc; James Brown¹, MB, BChir; Muhammad U. Rauf¹, MBBS, BSc; Charlotte Manisty¹, MD, PhD; James Moon, MD, PhD; Helen Lachmann, MD; Ashutosh Wechelakar, MD; Aviva Petrie¹, MSc; Carol Whelan, MD; Philip N. Hawkins, MD, PhD; Julian D. Gillmore¹, MD, PhD†; Marianna Fontana¹, MD, PhD†

BACKGROUND: Diagnostic and therapeutic advances have led to much greater awareness of transthyretin cardiac amyloidosis (ATTR-CA). We aimed to characterize changes in the clinical phenotype of patients diagnosed with ATTR-CA over the past 20 years.

METHODS: This is a retrospective observational cohort study of all patients referred to the National Amyloidosis Centre (2002–2021) in whom ATTR-CA was a differential diagnosis.

RESULTS: We identified 2995 patients referred with suspected ATTR-CA, of whom 1967 had a diagnosis of ATTR-CA confirmed. Analysis by 5-year periods revealed an incremental increase in referrals, with higher proportions of patients having been referred after bone scintigraphy and cardiac magnetic resonance imaging (2% versus 34% versus 51% versus 55%, chi-square $P < 0.001$). This was accompanied by a greater number of ATTR-CA diagnoses, predominantly of the wild-type nonhereditary form, which is now the most commonly diagnosed form of ATTR-CA (0% versus 54% versus 67% versus 66%, chi-square $P < 0.001$). Over time, the median duration of associated symptoms before diagnosis fell from 36 months between 2002 and 2006 to 12 months between 2017 and 2021 (Mann–Whitney $P < 0.001$), and a greater proportion of patients had early-stage disease at diagnosis across the 5-year periods (National Amyloidosis Centre stage 1: 34% versus 42% versus 44% versus 53%, chi-square $P < 0.001$). This was associated with more favorable echocardiographic parameters of structure and function, including lesser interventricular septal thickness (18.0 ± 3.8 mm versus 17.2 ± 2.6 mm versus 16.9 ± 2.3 mm versus 16.6 ± 2.4 mm, $P = 0.01$) and higher left ventricular ejection fraction ($46.0\% \pm 8.9\%$ versus $46.8\% \pm 11.0\%$ versus $47.8\% \pm 11.0\%$ versus $49.5\% \pm 11.1\%$, $P < 0.001$). Mortality decreased progressively during the study period (2007–2011 versus 2012–2016: hazard ratio, 1.57 [95% CI, 1.31–1.89], $P < 0.001$; and 2012–2016 versus 2017–2021: hazard ratio, 1.89 [95% CI, 1.55–2.30], $P < 0.001$). The proportion of patients enrolled into clinical trials and prescribed disease-modifying therapy increased over the 20-year period, but even when censoring at the trial or medication start date, year of diagnosis remained a significant predictor of mortality (2012–2016 versus 2017–2021: hazard ratio, 1.05 [95% CI, 1.03–1.07], $P < 0.001$).

CONCLUSIONS: There has been a substantial increase in ATTR-CA diagnoses, with more patients being referred after local advanced cardiac imaging. Patients are now more often diagnosed at an earlier stage of the disease, with substantially lower mortality. These changes may have important implications for initiation and outcome of therapy and urgently need to be factored into clinical trial design.

Key Words: amyloidosis ■ prognosis ■ transthyretin

Editorial, see p XXX

Correspondence to: Marianna Fontana, MD, PhD, National Amyloidosis Centre, University College London, Royal Free Hospital, Rowland Hill Street, London NW3 2PF, United Kingdom. Email m.fontana@ucl.ac.uk

*A. Ioannou and R.K. Patel are joint first authors.

†J. D. Gillmore and M. Fontana are joint last authors.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.060852>.

For Sources of Funding and Disclosures, see page XXX.

© 2022 The Authors. *Circulation* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- There has been a substantial increase in the number of patients diagnosed with transthyretin cardiac amyloidosis in recent years, associated with greater proportions of patients referred after cardiac magnetic resonance imaging and bone scintigraphy.
- Patients with transthyretin cardiac amyloidosis are often now being diagnosed earlier in the disease process, evidenced by a shorter duration of symptoms before diagnosis, milder disease stage, and more favorable structural and functional echocardiographic changes at diagnosis.
- Mortality in transthyretin cardiac amyloidosis has improved substantially in recent times aside from any potential benefits from disease-modifying treatment or participation in clinical trials.

What Are the Clinical Implications?

- Transthyretin cardiac amyloidosis is now often diagnosed earlier in the disease process with improved prognosis. More data are needed to guide decisions on in whom and when to initiate treatment, and which treatments should be used at each disease stage.
- The described changes have important implications for contemporary clinical trials, given that predetermined end points on the basis of trials performed in the past may no longer be appropriate or sufficiently powered to evaluate the efficacy of new treatments.

Nonstandard Abbreviations and Acronyms

ATTR-CA	transthyretin cardiac amyloidosis
CA	cardiac amyloidosis
CMR	cardiac magnetic resonance
HR	hazard ratio
LV	left ventricular
NAC	National Amyloidosis Centre
NT-proBNP	N-terminal pro-B-type natriuretic peptide
^{99m}Tc-DPD	^{99m} technetium labelled 3,3-diphosphono-1,2-propanodicarboxylic acid
TTR	transthyretin

Transthyretin cardiac amyloidosis (ATTR-CA) is a progressive and ultimately fatal cardiomyopathy caused by deposition within the myocardial extracellular space of misfolded transthyretin in the form of amyloid fibrils, which progressively disrupt cardiac structure and function.¹ The sporadic, noninherited wild type is most prevalent and presents in later life with a median survival of 3 to 5 years. The hereditary form can present

much earlier in life and is caused by many different point mutations in the TTR gene; it is inherited dominantly with variable penetrance, clinical phenotype, and prognosis.²

The true incidence of ATTR-CA remains unknown. Although autopsy series have long demonstrated the presence of cardiac ATTR-amyloid deposits in up to 25% of elderly individuals, the entity of ATTR-CA diagnosed during life remains rare.³ However, diagnosis of ATTR-CA has increased markedly during the past 20 years through remarkable advances in cardiac imaging,⁴ in particular with respect to cardiac magnetic resonance (CMR) imaging and repurposed bone scintigraphy.^{5,6} In addition, awareness among clinicians has been driven by the development of disease-modifying therapies such as tafamidis,⁷ inotersen,^{8,9} and patisiran,¹⁰ which are all designed to inhibit ATTR-amyloid formation. However, although these novel pharmacological agents have given rise to the concept of ATTR-CA as a treatable cause of heart failure, important questions remain about clinicopathological correlations of the disease and its natural history, along with uncertainties relating to definitions of disease severity and stratification and clinically meaningful end points for clinical trials of new therapies.

We report here evolution of the clinical phenotype at diagnosis in a 20-year observational study of patients with ATTR-CA attending a national specialist center.

METHODS

Patient Population

This retrospective observational cohort study was set at the National Amyloidosis Centre (NAC), which is the single specialist center funded by the UK National Health Service for diagnosis and management of amyloidosis. In addition, the NAC laboratory provides the nationwide service for testing the TTR genotype, which is a mandated final step in diagnosis of ATTR-CA, corroborating that patients referred to the NAC represent the majority of the UK national caseload. All patients referred to the NAC between January 1, 2002, and December 31, 2021, in whom ATTR-CA was a differential diagnosis were included. We excluded patients in whom the final diagnosis was cardiac AL-amyloidosis. Between 2002 and 2005, the diagnosis of ATTR-CA was established on the basis of heart failure symptoms together with a characteristic cardiac amyloidosis (CA) echocardiogram and either direct endomyocardial biopsy proof of ATTR-amyloid or ATTR-amyloid in an extracardiac biopsy. From 2006 onward, CMR was added to the assessment if there was diagnostic doubt after echocardiography. From 2010 onward, ^{99m}technetium labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy was used, and a diagnosis established on the basis of ATTR-amyloid in an extracardiac biopsy with cardiac uptake on ^{99m}Tc-DPD scintigraphy; or grade 2 to 3 cardiac uptake on ^{99m}Tc-DPD scintigraphy in the absence of biochemical evidence of a plasma cell dyscrasia.⁶ All patients underwent genetic sequencing of the TTR gene and provided written consent for their data to be retrospectively analyzed and published, in line with the Declaration of Helsinki and

approval from the Royal Free Hospital ethics committee (REC 21/PR/0620).

Echocardiography

All echocardiograms were performed using GE Vivid machines and analyzed offline using the most up-to-date EchoPAC software at the time of image acquisition by qualified operators in accordance to current guidelines, and operators were blinded to the final diagnosis. For the purpose of our analysis, valvular regurgitation was deemed significant if at least moderate or severe.²

^{99m}Tc-DPD Bone Scintigraphy

Images were acquired by using the Discovery model NM/CT 670 hybrid gamma camera (GE Healthcare, Chicago, IL). Patients were intravenously injected with ~700 MBq (18.9 mCi) ^{99m}Tc-DPD. The protocol consisted of a planar whole-body acquisition performed at 3 hours after the injection, followed by single-photon emission computed tomography imaging of the thorax. A low-dose, noncontrast computed tomography scan was performed for attenuation correction and anatomic localization, generating a volume of interest for the whole heart. Intensity of myocardial uptake on the planar ^{99m}Tc-DPD scan was categorized as 0 to 3 according to the grading system described by Perugini et al.¹¹

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 25 (IBM, Somers, New York) apart from Kaplan Meier curves, which were constructed using Stata (StataCorp 2021, Stata Statistical Software Release 17, StataCorp LLC, College Station, TX). All continuous variables were tested for normal distribution (Shapiro-Wilk test) and presented as mean±SD or median (interquartile range). The independent *t*-test if the data were normally distributed in each group was used to compare means, or its nonparametric equivalent (Mann-Whitney U test) was used to compare the distribution of the 2 groups. The 1-way ANOVA if the data were normally distributed in each group was used to compare means, or its nonparametric equivalent (Kruskal-Wallis test) was used to compare the distribution of multiple groups. A significant result was followed by a post hoc Bonferroni-corrected pairwise comparison to establish where differences lay. NT-proBNP (N-terminal pro-B-type natriuretic peptide) was natural log-transformed, and following this was normally distributed; therefore, the ANOVA was used to compare the means of each group. Levene's test was used to check the homogeneity of variance in the *t*-test and ANOVA. Categorical data are presented as absolute numbers (*n*) and frequencies (%) and compared using the chi-square test.

All mortality data were obtained through the UK Office of National Statistics, which is the formal government registry for all deaths throughout the United Kingdom. The mortality end point was defined as time to death from baseline for all deceased patients and time to censor date (January 1, 2022) from baseline among the remainder. Follow-up was restricted to ≤60 months, after which patients were censored because of the majority of events occurring in the first 60 months, and a low number of patients at risk after 60 months. When accounting for the effect disease-modifying therapy or clinical

trials, patients were censored at their start date. Survival was evaluated using Cox proportional hazards regression analysis, providing estimated hazard ratios (HRs) with 95% CIs. The proportional hazards assumption was checked and confirmed. All Cox proportional hazards regression analyses used to assess the effect of each 5-year period of diagnosis on survival were adjusted for age. Three separate models were also constructed. One was adjusted for age to assess the effect of diflunisal on survival. A second was adjusted for age to assess the effect of each genotype on survival, and a third adjusted for age and presence of comorbidities (selected a priori on the basis of clinical relevance) as covariates, to assess the effect of genotype on survival. When accounting for the effect of disease-modifying therapy or enrollment into clinical trials, patients were censored at their start date. Kaplan-Meier curves were constructed, with statistical significance assessed with a log-rank test. Statistical significance was defined as *P*<0.01 to avoid spuriously significant results.

RESULTS

Over the 20-year study period, 2995 patients were referred with suspected CA (excluding patients in whom the final diagnosis was cardiac AL-amyloidosis), whereby ATTR-CA was a differential diagnosis, of whom 1967 patients (mean age, 75.52±8.40 years; male, 86.3%) were diagnosed with ATTR-CA, and 1028 were not diagnosed with ATTR-CA (mean age, 65.48±13.04 years; male, 70.6%). The 1967 patients with ATTR-CA were composed of the following: 1253 (63.7%) with wild-type ATTR-CA (mean age, 77.87±6.61 years; male, 94.4%); 212 (10.8%) with p.(T80A) hereditary ATTR-CA (mean age, 66.30±6.48 years; male, 71.2%); 433 (22.0%) with p.(V142I) hereditary ATTR-CA (mean age, 75.52±7.19 years; male, 72.3%); and 69 (3.5%) with other forms of hATTR (mean age, 61.31±14.05 years; male, 72.5%). Patients with non-p.(V142I), non-p.(T80A) hATTR had the following mutations: p.(Ala140Ser)=1, p.(Ala56Pro)=1, p.(Ala117Ser)=3, p.(Arg54Gly)=1, p.(Asp58Val)=1, p.(Asp59Val)=1, p.(Glu62Asp)=1, p.(Glu74Gly)=1, p.(Glu74Leu)=1, p.(Glu109Lys)=2, p.(Gly67Arg)=1, p.(Gly67Val)=5, p.(Gly73Ala)=1, p.(Gly77Arg)=1, p.(Gly87Arg)=1, p.(Gly26Ser)=2, p.(Ile127Val)=5, p.(Ile93Val)=1, p.(Phe53Ile)=1, p.(Phe53Val)=1, p.(Ser43Asn)=2, p.(Ser70Arg)=1, p.(Ser97Tyr)=15, p.(Ser117Tyr)=1, p.(Tyr134Cys)=1, p.(Val40Ile)=2, and p.(Val50Met)=15.

Referrals

The number of patients referred with a differential diagnosis that included ATTR-CA increased with each 5-year period (49 versus 349 versus 1024 versus 1573). In contrast with the increase in absolute number of referred patients confirmed to have ATTR-CA (35 versus 260 versus 704 versus 968), the relative proportion of patients referred with a possible

diagnosis of ATTR-CA fell (71.4% versus 74.5% versus 68.8% versus 65.7%, $P < 0.001$). This was secondary to a dramatic increase in the overall number of referrals, and an increasing proportion of patients referred in whom CA was excluded. The proportion referred by cardiologists increased, the proportion referred by hematologists remained constant, and the proportion referred by other specialties decreased over time (Figure 1).

A greater number of referrals were associated with a significant shift in local investigations that raised the suspicion of CA (Figure 2A). Echocardiography was responsible for the majority of referrals in the first two 5-year periods. However, over time, the proportion of patients referred because of echocardiography where ATTR-CA was finally confirmed decreased (Figure 2B). Furthermore, in the last 5-year period, echocardiography accounted for almost half of the referrals where ATTR-CA was excluded (Figure 2C). CMR was responsible for the majority of referrals in the last two 5-year periods (Figure 2A). Over time, the proportion of patients referred because of a CMR where ATTR-CA was finally confirmed increased significantly, with CMR accounting for more than half of the ATTR-CA confirmed cases in the last two 5-year periods (Figure 2B). However, the wider use of CMR was also associated

with a greater number of referrals where ATTR-CA was excluded (Figure 2C). The proportion of referrals after local bone scintigraphy also increased, albeit to a lesser degree (Figure 2A).

Diagnosis

The total number of patients diagnosed with ATTR-CA and with each main subtype increased at each 5-year period. The most marked upsurges were seen in those with wtATTR, who composed none of the population diagnosed with ATTR-CA between 2002 and 2006, 54.8% diagnosed between 2007 and 2011, and 66.9% of the total population diagnosed between 2012 and 2016. The largest increase in the total number of patients diagnosed with ATTR-CA occurred between the second (2007–2011) and third (2012–2016) 5-year periods, and increased by 170.8% ($n=444$). During the same time period, the number of patients with wild-type ATTR-CA increased by 236.4%, p.(T80A) increased by 56.1%, p.(V142I) increased by 108.1%, and non-p.(V142I), non-p.(T80A) hATTR increased by 300.0% (Figure 3). Over time, the use of endomyocardial biopsy and noncardiac biopsies for diagnostic confirmation decreased, whereas diagnoses confirmed using the nonbiopsy criteria increased (Table 1).

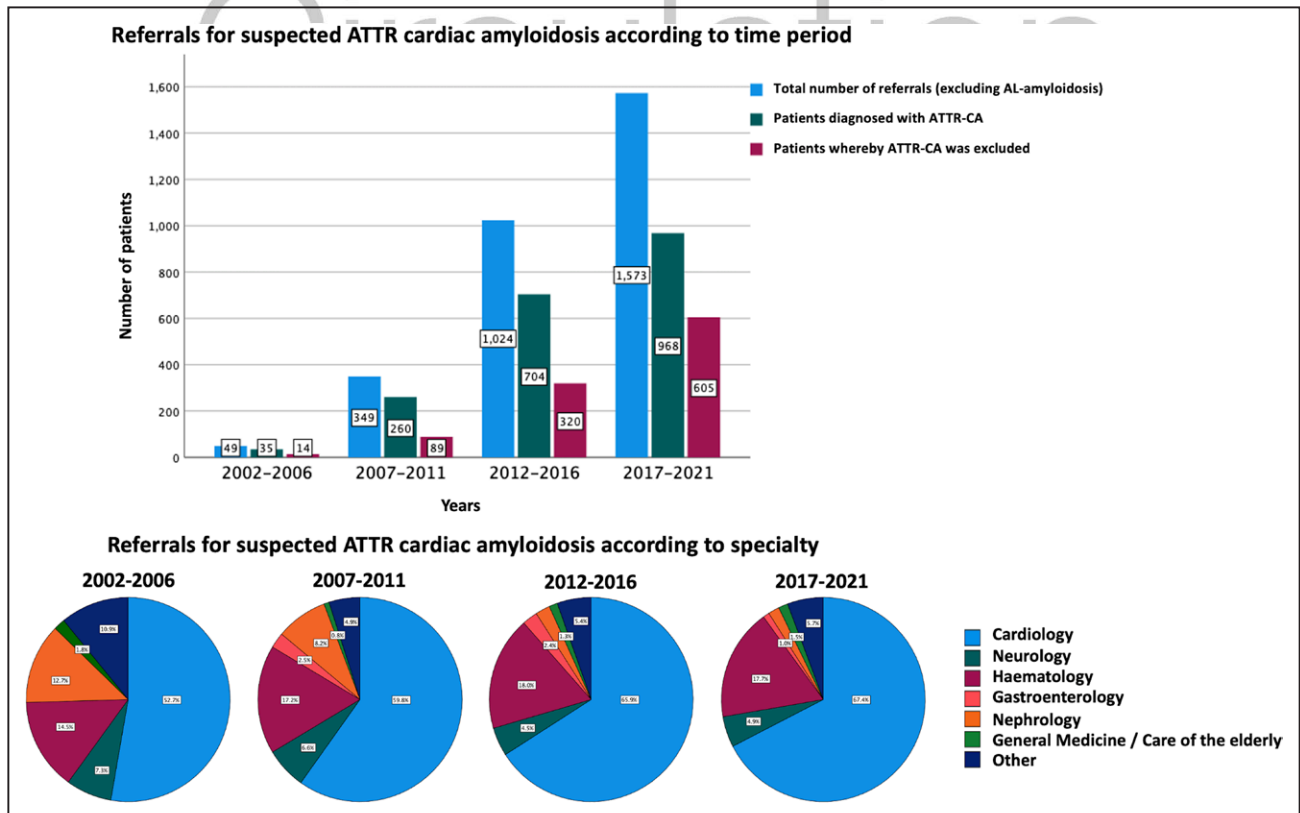


Figure 1. Total number of patients referred with suspected ATTR-CA between 2002 and 2021, and the proportion of whom were subsequently diagnosed with ATTR-CA.

Pie charts demonstrating the proportion of referrals made by different medical specialties between 2002 and 2021. ATTR-CA indicates transthyretin cardiac amyloidosis.

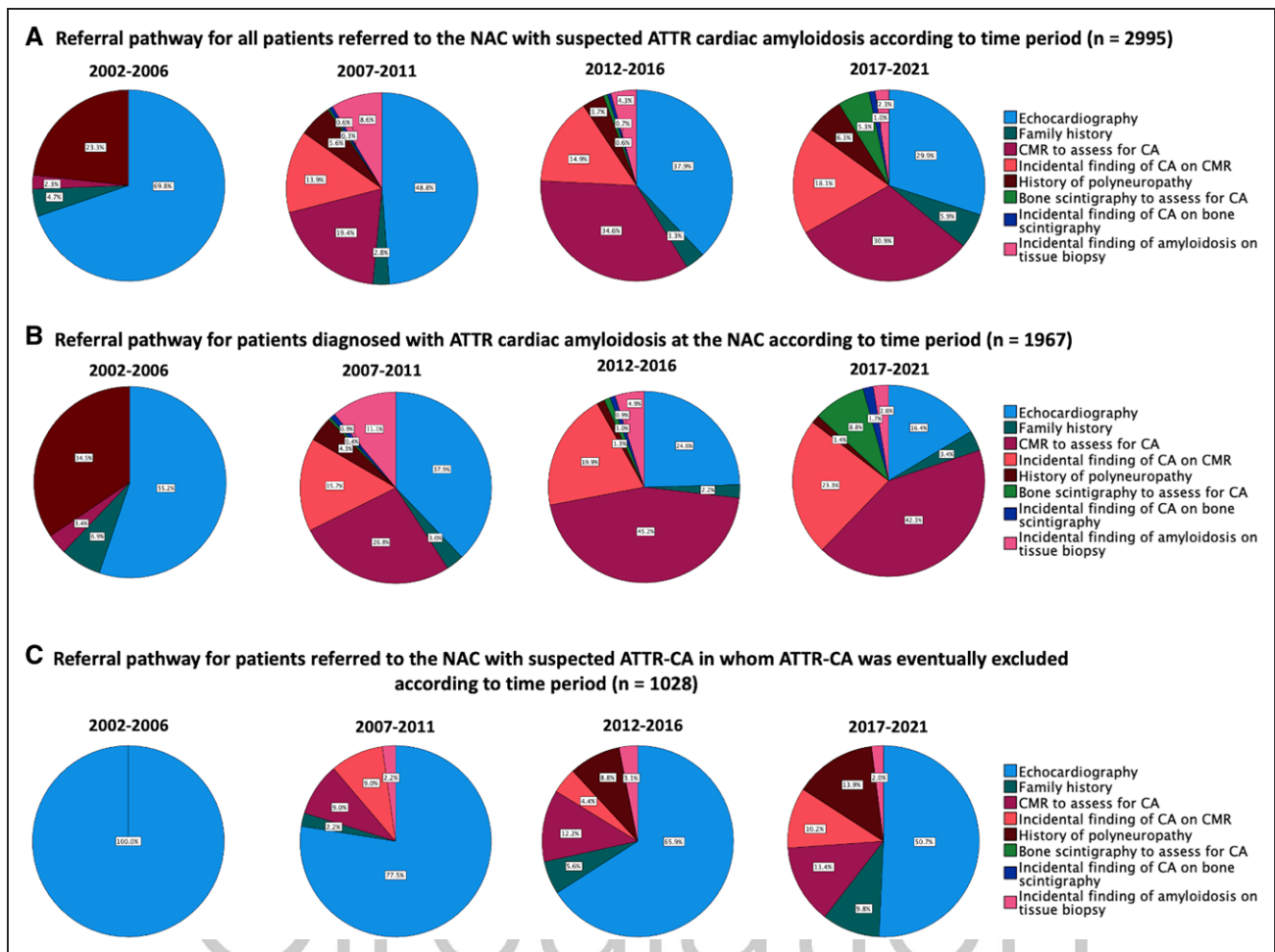


Figure 2.

A. Pie charts demonstrating the proportion of patients who were referred to the NAC with a suspected diagnosis of ATTR-CA after each local investigation. **B.** Pie charts demonstrating the proportion of patients who were subsequently diagnosed with ATTR-CA after each local investigation. **C.** Pie charts demonstrating the proportion of patients in whom a diagnosis of ATTR-CA was eventually excluded after each local investigation. ATTR-CA indicates transthyretin cardiac amyloidosis; CA, cardiac amyloidosis; CMR, cardiac magnetic resonance; and NAC, National Amyloidosis Centre.

Comorbidities and Conventional Heart Failure Therapy

The prevalence of cardiovascular risk factors was higher with each 5-year period, with patients in the most recent 5-year period having the most comorbidities. Use of β -blockers and statins was particularly low in the first 5-year period, but higher in subsequent periods. A higher proportion of patients in the third 5-year period were prescribed inhibitors of the renin-angiotensin system than in the fourth 5-year period, whereas loop diuretic use was lowest in the fourth 5-year period. Anticoagulation for atrial fibrillation changed significantly over time, with lower use of vitamin K antagonists and higher use of direct oral anticoagulants (Table 1). The prevalence of severe aortic stenosis was not significantly different across the study period (0.0% versus 1.2% versus 1.4% versus 1.0%, $P=0.960$), and neither was the proportion who underwent transcatheter aortic valve replacement (33.3% versus 25.0% versus 22.2%, $P=0.889$). When

split by genotype, p.(V142I) patients had a higher prevalence of diabetes and hypertension, and were prescribed more cardiovascular medications (Table S1).

Cardiac Phenotype at Diagnosis

Among the patients with ATTR-CA, age at diagnosis increased in contrast with severity of the cardiac phenotype, which became milder at each 5-year period. Evidence for the latter included better functional capacity measured by both New York Heart Association class, 6-minute walk test (% predicted corrected for age and height, 2012–2016 versus 2017–2021: 66.20 ± 26.31 versus 72.11 ± 27.30 , $P<0.001$) and higher blood pressure. At each 5-year period, the proportion of patients classified as NAC stage 1 (mild) increased, whereas the proportion with NAC stage 3 (severe) disease decreased (Table 1, Figure 4). This was driven by both a significantly lower NT-proBNP (median NT-proBNP [pg/L]: 4466 versus 3138 versus 3040 versus 2505, $P<0.001$) and

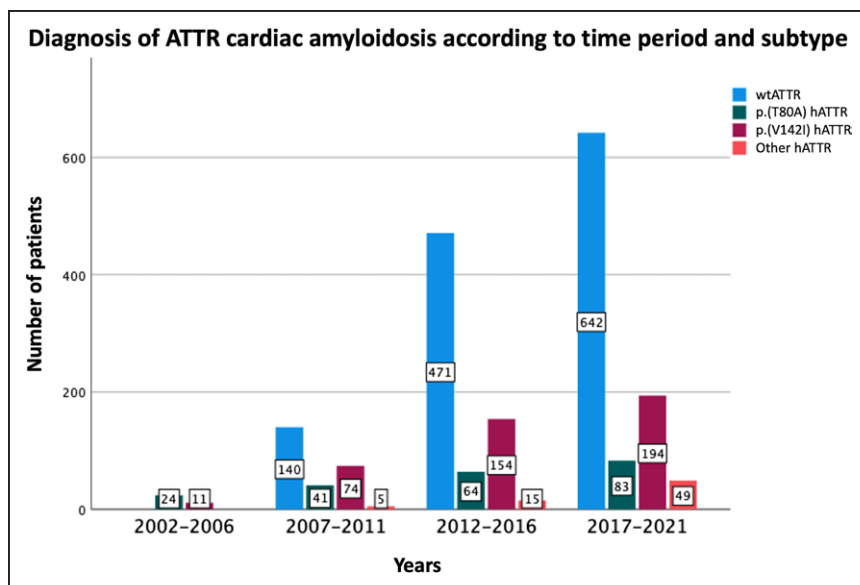


Figure 3. Number of patients diagnosed with each subtype of transthyretin cardiac amyloidosis between 2002 and 2021.

lower proportion of patients with chronic kidney disease stage 4 to 5. The milder cardiac phenotype was accompanied by a significant reduction in the duration of cardiac and/or neuropathic symptoms before diagnosis. On assessment of echocardiographic parameters, with each 5-year period, patients showed less pathological remodeling of their cardiac chambers, demonstrated by a significantly smaller left ventricular (LV) mass and interventricular septal wall thickness (Figure 5A), larger LV end-diastolic volume, and smaller biatrial size. This was accompanied by strikingly higher indices of biventricular systolic function across a range of deformation and nondeformation-based parameters, which was most pronounced when assessing stroke volume, LV ejection fraction (Figure 5B), longitudinal strain, and tricuspid annular plane excursion. Longitudinal strain became part of the echocardiographic protocol in the second 5-year period, routinely measured in all patients, unless it was not possible because of poor image quality. From this point onward, a high proportion of patients had strain assessments (0.0% versus 89.5% versus 94.2% versus 96.4%, $P < 0.001$). There was also a lower incidence of significant valvular regurgitation, lower pulmonary artery systolic pressure, and higher tricuspid annular plane excursion/pulmonary artery systolic pressure in the most recent 5-year period (Table 2).

When split by genotype, p.(V142I) patients had more advanced cardiac disease at diagnosis compared with wtATTR and p.(T80A). p.(V142I) patients also had worse renal function, with a greater proportion of patients having chronic kidney disease stage 3 to 5 (Table S1). On assessment of echocardiographic parameters, p.(V142I) patients had undergone a greater degree of concentric LV hypertrophy, with significantly higher indexed wall thickness and smaller LV end-diastolic volume compared with wtATTR, while also having larger biatrial size compared with p.(T80A). p.(V142I) patients had significantly

lower indices of biventricular systolic function, greater diastolic dysfunction, higher prevalence of significant mitral and tricuspid regurgitation, and a higher pulmonary artery systolic pressure compared with wtATTR and p.(T80A) (Table S2, Figure S1A and S1B). Over time, all 3 genotypes had a lower New York Heart Association class and NAC stage at diagnosis. On assessment of echocardiographic parameters, p.(V142I) patients were the only subgroup with a significantly higher LV ejection fraction, mitral annular plane systolic excursion, and tricuspid annular plane excursion (Tables S3 through S5).

The same trends were observed among patients referred to the NAC with suspected CA, in whom a diagnosis of ATTR-CA was eventually excluded. There was a smaller mean maximal wall thickness (mm; 15.50 ± 2.62 versus 15.75 ± 4.20 versus 13.08 ± 3.33 versus 12.67 ± 3.00 , $P < 0.001$), lower median NT-proBNP (ng/L; 1962 versus 1442 versus 947 versus 697, $P < 0.001$), and higher median estimated glomerular filtration rate (mL/min/1.73 m²; 44 versus 52 versus 60 versus 66, $P < 0.001$) across the study period.

Survival

At median follow-up of 30.6 months (limits of interquartile range, 15.1–55.1 months), 716 (36.7%) patients died. Assessment of each 5-year period revealed that 25 (73.5%) died between 2002 and 2006 (estimated median survival, 34.9 months [95% CI, 21.8–41.6]), 175 (67.6%) between 2007 and 2011 (estimated median survival, 38.9 months [95% CI, 32.1–41.8]), 372 (53.4%) between 2012 and 2016 (estimated median survival, 52.6 months [95% CI, 48.6–57.4]), and 144 (14.9%) between 2017 and 2021 (estimated median survival, >60 months [95% CI, >60.0 to >60.0]) (Figure 6A).

Among patients with wild-type ATTR-CA, assessment of each 5-year period revealed that 87 (62.1%)

Table 1. Baseline Characteristics and Treatment for Patients With ATTR-CA Diagnosed Between 2002 and 2021, by Year of Diagnosis (N=1967)

Variable	2002–2006 (n=35)	2007–2011 (n=260)	2012–2016 (n=704)	2017–2021 (n=968)	P value
Baseline characteristics					
Age	67.22±6.20*†‡	73.99±7.19§	75.81±7.72	76.03±9.01	<0.001
Male sex, n (%)	26 (74.3%)	224 (86.2%)	613 (87.1%)	834 (86.2%)	0.200
Body surface area	...	1.89±0.20	1.89±0.19	1.91±0.20	0.180
Ischemic heart disease	4 (11.4%)	35 (13.5%)	145 (20.6%)	198 (20.5%)	0.035
Diabetes	1 (2.9%)	23 (8.8%)§	125 (17.8%)	167 (17.3%)	<0.001
Hypertension	5 (14.3%)	39 (15.0%)§	224 (31.8%)¶	396 (40.9%)	<0.001
Stroke/transient ischemic attack	0 (0.0%)	23 (8.8%)	69 (9.8%)	115 (11.9%)	0.067
Chronic kidney disease					<0.001
Stages 1–2	18 (51.4%)	126 (48.5%)	334 (47.4%)	516 (53.3%)	
Stage 3	10 (28.6%)	113 (43.5%)	331 (47.0%)	405 (41.8%)	
Stage 4	3 (8.6%)	16 (6.2%)	34 (4.8%)¶	23 (2.3%)	
Stage 5	1 (2.9%)‡	2 (0.8%)	2 (0.3%)	2 (0.2%)	
Missing data	3 (8.6%)	3 (1.2%)	3 (0.4%)	22 (2.3%)	
Duration of symptoms before diagnosis (mo)	36 (24–48)*†‡	15 (9–36)§	12 (6–24)	12 (5–24)	<0.001
Diagnosis					
Cardiac biopsy	12 (34.3%)‡	103 (39.6%)§	146 (20.7%)¶	81 (8.4%)	<0.001
Noncardiac biopsy	23 (65.7%)‡	115 (44.2%)	355 (52.6%)¶	165 (17.0%)	<0.001
Nonbiopsy criteria	0 (0.0%)*†‡	42 (16.2%)§	203 (28.8%)¶	722 (74.6%)	<0.001
Heart failure severity					
New York Heart Association class					<0.001
I	0 (0.0%)	28 (10.8%)	83 (11.8%)	136 (14.0%)	
II	6 (17.1%)*†‡	120 (46.2%)§	444 (63.1%)	657 (67.9%)	
III	10 (28.6%)	75 (28.8%)	153 (21.7%)¶	134 (13.8%)	
IV	6 (17.1%)*†‡	19 (7.3%)§	17 (2.4%)¶	5 (0.5%)	
Missing data	13 (37.1%)	18 (6.9%)	7 (1.0%)	36 (3.7%)	
National Amyloidosis Centre stage					<0.001
1	12 (34.3%)	109 (41.9%)	309 (43.9%)¶	516 (53.3%)	
2	10 (28.6%)	101 (38.8%)	265 (37.7%)	302 (31.2%)	
3	8 (22.9%)	46 (17.7%)	126 (17.9%)¶	106 (11.0%)	
Missing data	5 (14.3%)	4 (1.5%)	4 (0.5%)	44 (4.9%)	
Six-minute walk test (meters)	327 (224–407)¶	368 (264–449)	<0.001
Six-minute walk test (% predicted)	66.20±26.31¶	74.00±26.27	<0.001
Systolic blood pressure (mmHg)	119.11±24.27	120.21±19.21	123.74±17.91¶	128.05±18.65	<0.001
Diastolic blood pressure (mmHg)	74.78±14.25	72.67±11.74	73.03±10.48¶	75.76±9.70	<0.001
N-terminal pro-B-type natriuretic peptide (pg/L)	4466 (1911–12 221)	3138 (1679–5683)	3040 (1569–5245)¶	2505 (1225–4562)	<0.001
Estimated glomerular filtration rate (mL/min/1.73 m ²)	68 (43–82)	59 (46–72)	58 (46–72)¶	61 (50–76)	0.004
Atrial fibrillation/flutter prevalence and management					
Atrial fibrillation/flutter prevalence	10 (28.6%)	127 (48.8%)	351 (49.8%)	469 (48.5%)	0.108
Anticoagulation	10 (100.0%)	114 (89.8%)	310 (88.3%)¶	451 (96.2%)	<0.001
Vitamin K antagonist	10 (100.0%)*†‡	110 (96.5%)§	203 (65.5%)¶	73 (16.2%)	<0.001
Direct oral anticoagulant	0 (0.0%)*†‡	4 (3.5%)§	107 (34.5%)¶	378 (83.8%)	<0.001
Atrial fibrillation/flutter ablation	0 (0.0%)	5 (3.9%)	12 (3.4%)	23 (4.9%)	0.665

(Continued)

Table 1. Continued

Variable	2002–2006 (n=35)	2007–2011 (n=260)	2012–2016 (n=704)	2017–2021 (n=968)	P value
Cardiac devices					
Permanent pacemaker	5 (14.3%)	43 (16.5%)	83 (11.8%)	107 (11.1%)	0.113
Implantable cardioverter-defibrillator	0 (0.0%)	8 (3.1%)	15 (2.1%)	22 (2.3%)	0.684
Cardiac resynchronization therapy defibrillator	0 (0.0%)	3 (1.2%)	11 (1.6%)	10 (1.0%)	0.704
Cardiac resynchronization therapy pacemaker	0 (0.0%)	5 (1.9%)	17 (2.4%)	11 (1.1%)	0.193
Cardiovascular medications					
β-Blocker	1 (2.9%)*†‡	97 (37.3%)§	360 (51.1%)	443 (45.8%)	<0.001
Calcium channel blocker	3 (8.6%)	16 (6.2%)	52 (7.3%)¶	111 (11.5%)	0.009
Angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker	12 (34.3%)	130 (50.0%)	352 (50.0%)¶	414 (42.8%)	0.007
Angiotensin receptor-neprilysin inhibitor	0 (0.0%)	0 (0.0%)	6 (0.9%)	21 (2.1%)	0.018
MRA	9 (25.7%)	113 (43.5%)	298 (42.3%)¶	309 (31.9%)	<0.001
Loop diuretic	25 (71.4%)	209 (80.4%)	578 (82.1%)¶	660 (68.2%)	<0.001
Sodium-glucose cotransporter-2 inhibitor	0 (0.0%)	0 (0.0%)	2 (0.3%)	13 (1.3%)	0.033
Statin	3 (8.6%)*†‡	94 (36.2%)	309 (43.9%)	419 (43.2%)	<0.001
Ezetimibe	0 (0.0%)	4 (1.5%)	5 (0.7%)	17 (1.8%)	0.263
Enrollment in ATTR-CA trials, prescription of disease modifiers and diflunisal					
Trials	0 (0.0%)‡	0 (0.0%)	17 (2.4%)¶	281 (29.0%)	<0.001
Disease modifiers	2 (5.7%)*	1 (0.4%)§	33 (4.7%)¶	159 (16.4%)	<0.001
Diflunisal	10 (28.6%)*†‡	28 (10.8%)§	36 (5.1%)¶	18 (1.9%)	<0.001

P values are provided for pairwise comparison. ATTR-CA indicates transthyretin cardiac amyloidosis.

* $P < 0.01$ for 2002 to 2006 versus 2007 to 2011.

† $P < 0.01$ for 2002 to 2006 versus 2012 to 2016.

‡ $P < 0.01$ for 2002 to 2006 versus 2017 to 2021.

§ $P < 0.01$ for 2007 to 2011 versus 2012 to 2016.

|| $P < 0.01$ for 2007 to 2011 versus 2017 to 2021.

¶ $P < 0.01$ for 2012 to 2016 versus 2017 to 2021.

died between 2007 and 2011 (estimated median survival, 41.6 months [95% CI, 37.4–49.7]), 229 (48.6%) between 2012 and 2016 (estimated median survival, 59.1 months [95% CI, 53.6 to >60.0]) and 81 (12.6%) between 2017 and 2021 (estimated median survival, >60.0 months [95% CI, >60.0 to >60.0]) (Figure 6B).

Among p.(T80A) patients, assessment of each 5-year period revealed that 16 (66.7%) died between 2002 and 2006 (estimated median survival, 50.0 months [95% CI, 25.2–57.5]), 23 (56.1%) between 2007 and 2011 (estimated median survival, 49.7 months [95% CI, 28.9 to >60.0]), 28 (43.8%) between 2012 and 2016 (estimated median survival, 57.1 months [95% CI, 47.0 to >60.0]), and 8 (9.6%) between 2017 and 2021 (estimated median survival, >60 months [95% CI, >60.0 to >60.0]) (Figure 6C).

Among p.(V142I) patients, assessment of each 5-year quartile revealed that 9 (81.8%) died between 2002 and 2006 (estimated median survival, 17.6 months [95% CI, 1.6–34.9]), 63 (85.1%) between 2007 and 2011 (estimated median survival, 25.6 months [95% CI, 21.3–32.0]), 108 (70.1%) between 2012 and 2016 (estimated median survival, 36.0 months [95% CI, 29.8–41.6]), and 51 (26.2%) between 2017 and 2021 (esti-

mated median survival, 56.3 months [95% CI, 53.0 to >60.0]) (Figure 6D).

When split by genotype, p.(V142I) patients overall had a significantly shorter estimated median survival (38.9 months [95% CI, 33.9–45.6]) than p.(T80A) (>60 months [95% CI, 49.7 to >60.0]) and wtATTR (>60 months [95% CI, 57.7 to >60.0]), and the increased risk associated with p.(V142I) was maintained when correcting for age (Figure S1C) and comorbidities (diabetes and hypertension) (p.[V142I] versus wtATTR: HR, 2.07 [95% CI, 1.74–2.43], $P < 0.001$). However, the p.(V142I) group demonstrated the greatest reduction in mortality. Those with wtATTR demonstrated a less marked but still significant reduction in mortality with each 5-year period. In contrast, those with p.(T80A) demonstrated no change in mortality between the first three 5-year periods (2002–2006 versus 2007–2011 versus 2012–2016) but demonstrated a significant reduction in mortality between 2012 to 2016 and 2017 to 2021.

Clinical Trials and Disease-Modifying Therapy

The proportion of patients enrolled into clinical trials and prescribed disease-modifying therapy significantly

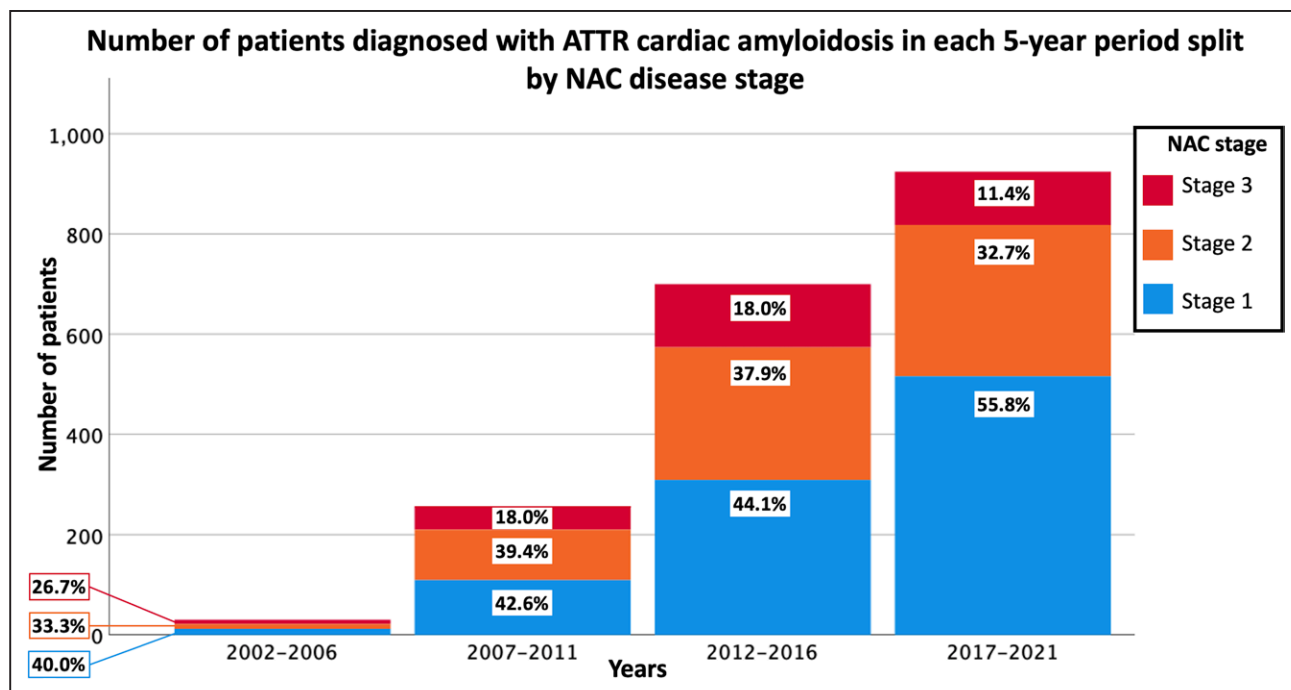


Figure 4. Number of patients diagnosed with transthyretin cardiac amyloidosis between 2002 and 2021, and the proportion of patients with each NAC disease stage for each 5-year period.

NAC indicates National Amyloidosis Centre.



increased over time. The only disease-modifying therapies approved by the National Institute for Health and Care Excellence in the United Kingdom are patisiran and inotersen, for patients with hATTR-polyneuropathy; whereas a minority accessed tafamidis through an early access to medicines scheme. A total of 94 patients were prescribed patisiran, 14 patients were prescribed inotersen, and 87 patients were prescribed tafamidis. When split by genotype, the populations with the greatest proportion in clinical trials were wtATTR, followed by p.(V142I) and p.(T80A). The populations with the greatest proportion on disease-modifying therapy were p.(T80A), followed by p.(V142I) and wtATTR.

When controlling for age, and censoring for the start date of clinical trials and disease-modifying therapy, year of diagnosis remained a significant predictor of mortality in the overall population (2012–2016 versus 2017–2021: HR, 1.05 [95% CI, 1.03–1.07], $P < 0.001$), and this was maintained on assessment of those with wtATTR (HR, 2.44 [95% CI, 1.83–3.24], $P < 0.001$) and p.(V142I) (HR, 1.93 [95% CI, 1.36–2.73], $P < 0.001$), but not p.(T80A) (HR, 3.30 [95% CI, 0.98–11.1], $P = 0.053$). Comparing each genotype, the increased mortality associated with p.(V142I) was maintained when censoring for the start date of clinical trials and disease-modifying therapy (Figure S1D).

A small minority were prescribed diflunisal ($n = 92$, 4.7%), 32 (34.8%) of whom died. Diflunisal use significantly decreased over time (Table 1), and when split by genotype, patients with p.(T80A) were most commonly

prescribed diflunisal (Table S1). When adjusting for age, diflunisal had no effect on survival (HR, 0.89 [95% CI, 0.62–1.29], $P = 0.533$).

DISCUSSION

This study has comprehensively identified substantial changes over the past 2 decades in the clinical phenotype of patients diagnosed to have ATTR-CA. Our study has demonstrated the following: (1) there has been a dramatic increase in referrals for suspected CA, in patients in whom the final diagnosis of ATTR-CA was confirmed but also in patients in whom ATTR-CA was excluded; (2) there was a significant shift in referral pathways, with a higher proportion of patients being referred after local CMR and bone scintigraphy; (3) ATTR-CA patients overall are now being diagnosed earlier in the disease process, as demonstrated by a shorter duration of symptoms before diagnosis, milder disease stage, and more favorable structural and functional echocardiographic changes at diagnosis; (4) ATTR-CA patients are now surviving for longer after diagnosis, even after censoring for the start date of clinical trials and disease-modifying therapy; and (5) p.(V142I) patients had the most advanced cardiac disease at diagnosis, and despite showing the most striking reduction in mortality had a poorer prognosis than wtATTR and p.(T80A).

There has been a dramatic increase in referrals to the NAC for suspected CA, indicating clinicians have developed a lower threshold for referring patients for further

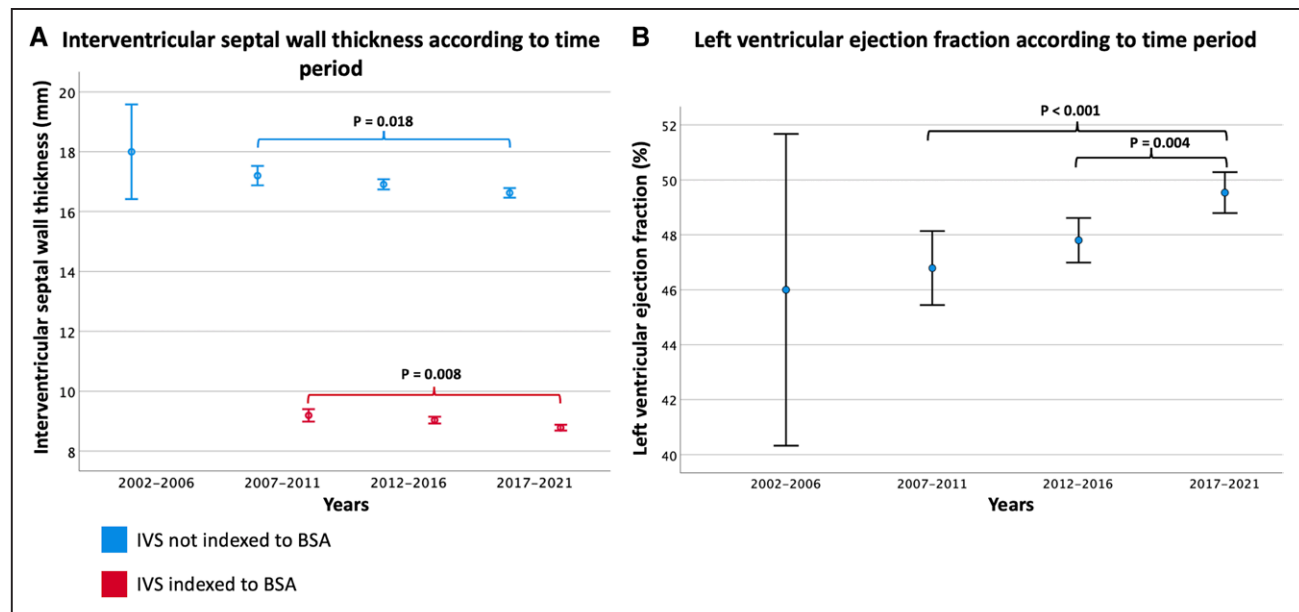


Figure 5.

A, Error bars demonstrating the change in mean interventricular septal (IVS) wall thickness (error bars representing 2×95% CI of the mean) between 2002 and 2021. **B**, Error bars demonstrating the change in mean left ventricular ejection fraction (error bars representing 2×95% CI of the mean) between 2002 and 2021.

investigations. This is supported by a reduced severity of cardiac disease across all referrals over time. This was observed in patients with ATTR-CA and in patients in whom a diagnosis of ATTR-CA was excluded. The potential reasons behind this increase in referrals and subsequent diagnoses are the following: increased awareness among clinicians, the increasing perception of ATTR-CA as a potentially treatable cause of heart failure with specific novel medicines, and greater use of advanced cardiac imaging (CMR and bone scintigraphy).^{12,13}

A higher proportion of patients are now being referred by cardiologists, with a majority referred after local CMR. Initially echocardiography was responsible for the majority of referrals, but more recently, the suspicion of CA has increasingly been raised by local CMR. Echocardiography remains a vital tool in detecting patients with a hypertrophic phenotype. As the first-line imaging modality in nearly all these patients, together with the clinical picture, echocardiography helps clinicians stratify the need to proceed with advanced cardiac imaging. However, it is possible that because of the overlap in imaging findings between different hypertrophic pathogeneses, echocardiography accounted for a high proportion of false-positive referrals. The characteristic changes on late gadolinium enhancement imaging allow differentiation of CA from other hypertrophic phenotypes, which may explain why CMR accounted for fewer false-positive referrals.^{14,15} The wider use of CMR was also associated with an increase in the referrals in which ATTR-CA was excluded, potentially because of some imaging overlap between CA and other hypertrophic phenotypes. Our data suggest that the increased use of CMR with late

gadolinium enhancement imaging in the assessment of other cardiovascular pathologies (such as ischemic heart disease) may also have resulted in an increased number of incidental or otherwise unanticipated diagnoses of ATTR-CA.^{6,16} In the United Kingdom, bone scintigraphy remains a specialist diagnostic test. Most patients are initially investigated locally with echocardiography and/or CMR. Once the suspicion of ATTR-CA is raised, patients across the United Kingdom are referred to the NAC for further investigations. At this point, ^{99m}Tc-DPD scintigraphy with single-photon emission computed tomography is used to confirm the diagnosis of ATTR-CA. Recent years (2017–2021) have seen increasing use of dedicated bone scintigraphy outside the NAC, after publication of a nonbiopsy pathway in 2016,⁶ but at present, CMR remains far more widely available, and is typically the source of most referrals. It is interesting that the increased use of local ^{99m}Tc-DPD scintigraphy was not associated with a significant increase in false-positive referrals. This is likely because of the specific bone scintigraphy technique used. In the United Kingdom, dedicated bone scintigraphy uses an intravenous injection of ^{99m}Tc-DPD followed by planar whole-body acquisition performed at 3 hours after the injection and single-photon emission computed tomography imaging of the thorax in almost all cases. This differs from clinical practice in the United States, where generally ^{99m}Tc-pyrophosphate is used as a radiotracer, and imaging takes place 1 hour after injection, with planar imaging being acquired often without single-photon emission computed tomography.¹⁷ In our study cohort, a high proportion of patients referred after local ^{99m}Tc-DPD scintigraphy were



Table 2. Echocardiographic Parameters for Patients With ATTR-CA Diagnosed Between 2002 and 2021, by Year of Diagnosis (N=1967)

Echocardiographic variable	2002–2006 (n=35)	2007–2011 (n=260)	2012–2016 (n=704)	2017–2021 (n=968)	P value
Interventricular septum in diastole (mm)	18.00±3.83	17.20±2.63	16.91±2.33	16.62±2.40	0.014
Interventricular septum in diastole, indexed (mm/m ²)	...	9.19±1.70	9.02±1.53	8.78±1.42	0.004
Posterior wall thickness in diastole (mm)	17.24±3.51	16.61±2.38	16.37±2.50	16.20±2.57	0.110
Posterior wall thickness in diastole, indexed (mm/m ²)	...	8.86±1.52	8.73±1.59	8.57±1.52	0.118
Left ventricle mass (g)	330.91±98.97	318.37±80.64‡	315.96±81.83§	294.58±93.76	<0.001
Left ventricle mass, indexed (g/m ²)	...	169.07±41.64‡	167.31±43.03§	157.06±38.74	<0.001
Left ventricular end diastolic volume (mL)	86.92±22.89	75.36±25.49‡	74.68±23.87§	82.39±29.00	<0.001
Left ventricular end diastolic volume, indexed (mL/m ²)	...	39.76±12.37‡	39.46±12.05§	43.02±13.97	<0.001
Left ventricular end systolic volume (mL)	52.75±19.77	40.85±18.15	39.52±17.15	42.53±20.15	0.006
Left ventricular end systolic volume, indexed (mL/m ²)	...	21.54±9.11	20.86±8.86	22.19±10.96	0.097
Stroke volume (mL)	34.46±10.80	34.51±12.80‡	35.24±12.38§	40.24±15.16	<0.001
Stroke volume, indexed (mL/m ²)	...	18.21±6.28‡	18.64±6.28§	21.02±7.37	<0.001
Ejection fraction (%)	46.00±8.93	46.79±10.98‡	47.80±10.97	49.53±11.13	<0.001
Longitudinal strain (%)	...	-10.25±3.83‡	-10.94±3.56	-11.21±3.89	0.001
Mitral annular plane systolic excursion (mm)	...	7.82±2.63	7.99±2.52	8.27±2.61	0.053
Tricuspid annular plane systolic excursion (mm)	...	14.38±4.82†‡	14.71±4.52§	15.98±5.21	<0.001
E/A	2.86±1.07	2.11±1.05	2.07±1.03	2.05±1.16	0.102
E/e' average	18.61±4.91	17.69±6.90	16.95±6.44	16.98±6.82	0.327
Left atrial area, measured in the 4-chamber view (cm ²)	23.33±6.03	26.66±5.65‡	26.58±5.49§	24.94±5.57	<0.001
Left atrial area, measured in the 4-chamber view, indexed (cm ² /m ²)	...	14.16±2.78‡	14.15±3.12§	13.16±2.94	<0.001
Right atrial area, measured in the 4-chamber view (cm ²)	18.6±7.78	25.36±6.74‡	24.37±6.37	23.38±6.58	<0.001
Right atrial area, measured in the 4-chamber view, indexed (cm ² /m ²)	...	13.40±3.27‡	12.91±3.31§	12.23±3.51	<0.001
Significant mitral regurgitation	0 (0.0%)	34 (13.1%)	113 (16.0%)§	87 (9.0%)	<0.001
Significant tricuspid regurgitation	1 (2.9%)	71 (27.3%)	143 (20.3%)§	101 (10.4%)	<0.001
Significant aortic stenosis	0 (0.0%)	4 (1.5%)	12 (1.7%)	19 (2.0%)	0.818
Pulmonary artery systolic pressure (mmHg)	48.46±13.41*	40.03±11.23	39.76±9.61	36.87±14.78	<0.001
Tricuspid annular plane systolic excursion/pulmonary artery systolic pressure	...	0.38±0.19‡	0.39±0.21§	0.64±0.84	0.001

P values are provided for pairwise comparison. ATTR-CA indicates transthyretin cardiac amyloidosis.

*P<0.01 for 2002 to 2006 versus 2017 to 2021.

†P<0.01 for 2007 to 2011 versus 2012 to 2016.

‡P<0.01 for 2007 to 2011 versus 2017 to 2021.

§P<0.01 for 2012 to 2016 versus 2017 to 2021.

subsequently confirmed to have ATTR-CA. Although these findings reflect referral practices across the United Kingdom, practices are likely to differ in other health care settings with different imaging modality availability, and where different radiotracers and image acquisition protocols are used.

CMR is the source of most referrals across all 3 genotypes. The main difference is that a greater proportion of P.(T80A) patients were referred with polyneuropathy or a family history of amyloidosis. In the United Kingdom, P.(T80A) is the most common cause of hATTR-polyneuropathy, and it is well established that neurological symptoms rather than cardiac symptoms often prompt investigation.¹⁸ However, the relatively low

proportion of p.(V142I) patients referred on the basis of their family history suggests that there is room for improvement, and potential for promoting earlier diagnosis still in this genotype.

Patients with ATTR-CA are being diagnosed significantly earlier in the evolution of the disease, as demonstrated by a shorter duration of symptoms before diagnosis, milder disease stage, and more favorable structural and functional echocardiographic changes at diagnosis. The most striking changes were in p.(V142I) patients, who were the only subgroup that demonstrated higher indices of systolic function over time. Despite these observations, p.(V142I) patients had more advanced cardiac disease at diagnosis. Although it is possible that advanced cardiac

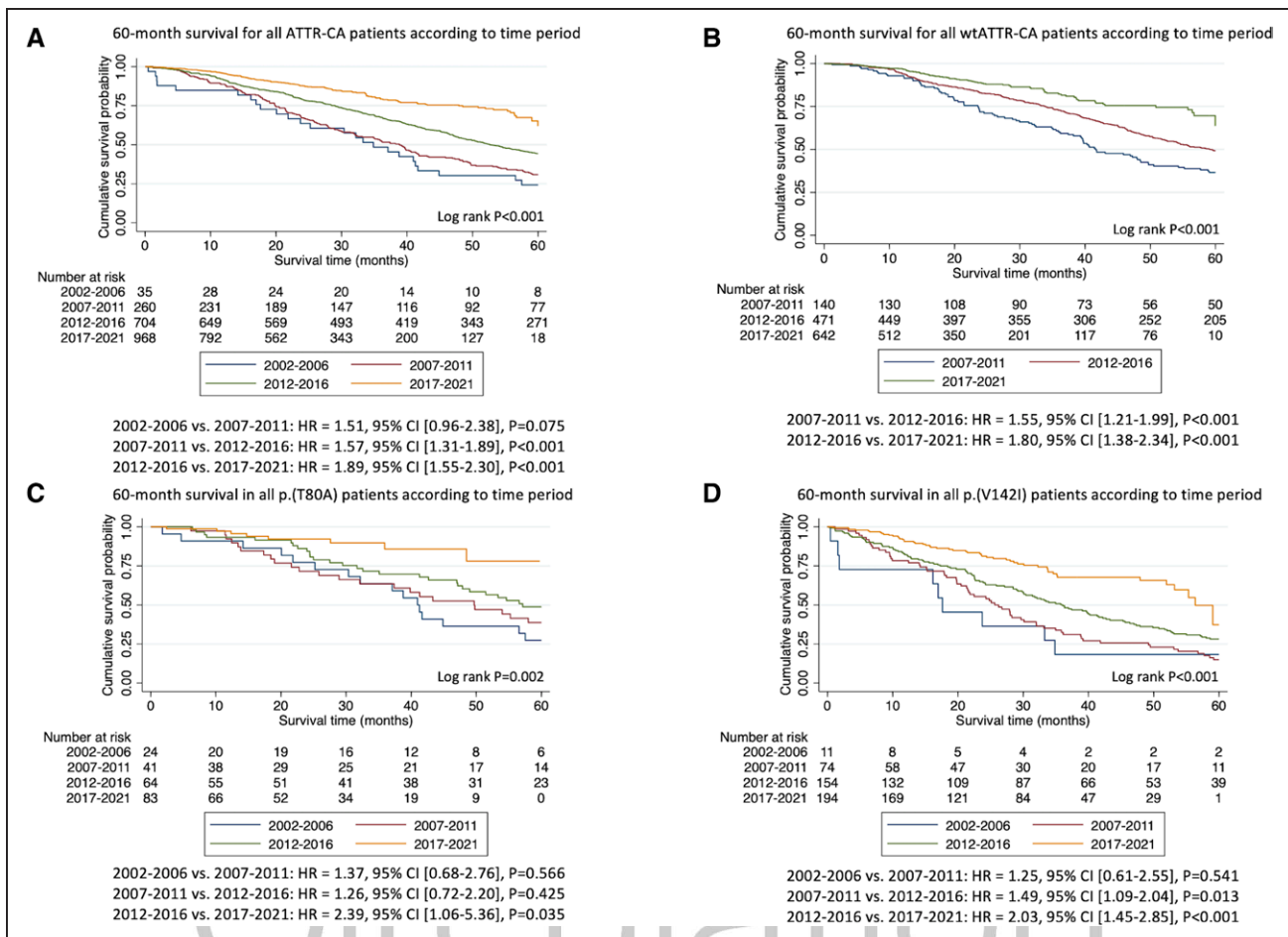


Figure 6. Kaplan-Meier curves demonstrating the prognostic effect of the year of diagnosis between 2002 and 2021, followed by multivariable Cox proportional hazards regression analysis, adjusted for age, comparing the risk of death in each 5-year interval between 2002 and 2021.

A, All patients with transthyretin cardiac amyloidosis (ATTR-CA). **B**, Patients with wild-type transthyretin cardiac amyloidosis (wtATTR-CA). **C**, Patients with p.(T80A) hereditary transthyretin cardiac amyloidosis (hATTR-CA). **D**, Patients with p.(V142I) hATTR-CA. HR indicates hazard ratio.

disease could be explained by intrinsic differences in disease biology between subtypes, with p.(V142I) patients having a more rapidly progressive phenotype,^{2,16} these differences could reflect a different propensity to seek medical attention and differences in referral practices across different populations. This is likely to be partially mitigated by the free nature of the National Health Service in the United Kingdom at point of care. However, earlier diagnosis in p.(V142I) patients remains a challenge, and further improvements are needed to bridge the gap.

There were no dramatic changes in the use of conventional cardiovascular therapies over the 20-year study period. The greatest change occurred between the third and fourth 5-year periods, with reduced use of β -blockers, medications that inhibit the renin-angiotensin system and loop diuretics. These changes may reflect the lower burden of heart failure symptoms and the milder cardiac phenotype observed in the most recent 5-year period.

Over the 20-year study period, there was a reduction in 60-month mortality in the overall population and each subgroup, which remained significant even when censor-

ing for the start date of clinical trials and disease-modifying therapy. The most substantial reduction in mortality was seen in p.(V142I) patients. Despite these improvements, the more severe cardiac disease associated with p.(V142I) resulted in an increased risk of mortality compared with both wtATTR and p.(T80A). Given that the reduction in mortality remained significant when censoring for the start date of clinical trials and disease-modifying therapy, it is likely the reduced mortality is related to a lead time bias (ie, because of earlier detection of ATTR-CA). This is further supported by the reduced symptom duration before diagnosis and milder cardiac phenotype at diagnosis. The past 2 decades have also seen substantial improvements in targeted supportive therapy of both heart failure and neuropathic disease in the ATTR population. Therefore, although patients are being diagnosed earlier in the disease process, it is possible that improvements in supportive therapy may have also contributed to the observed reduction in mortality.

The past 2 decades have seen a higher proportion of patients being recruited into clinical trials and prescribed

disease-modifying therapy. Funding decisions specific to the United Kingdom are likely to account for differences between genotypes, with p.(T80A) patients most commonly prescribed disease-modifying therapy. Current National Institute for Health and Care Excellence guidance has not approved tafamidis for treatment of ATTR-CA. The only patients in our cohort prescribed tafamidis were eligible through an early access to medicines scheme. In contrast, patisiran and inotersen were approved by the National Institute for Health and Care Excellence for treatment of hATTR-polyneuropathy, which is more common in p.(T80A) than p.(V142I).¹⁸ Therefore, p.(T80A) patients are more likely to meet eligibility criteria for treatment with patisiran or inotersen. However, it is important that the reduction in 60-month mortality remained significant even when censoring for the start date of clinical trials and disease-modifying therapy.

The changes in the clinical phenotype of patients with ATTR-CA over the past 20 years is of particular importance, given the current era of an ever-increasing number of clinical trials. Patients with ATTR-CA now have milder disease at diagnosis, and are living longer from the time of diagnosis. This is an important factor to consider in the design of contemporary clinical trials, given that predetermined end points on the basis of trials performed in the past may no longer be appropriate, or at least sufficiently powered, or of adequate duration to evaluate efficacy of novel agents. Our findings may in part explain the unexpected neutral outcome of the recent 12-month report of the Phase-III ATTRibute-CM trial of acoramidis.¹⁹ According to our data, the population included in the ATTR-ACT trial,⁷ which recruited patients from 2013 to 2015, are likely to have more advanced cardiac disease than those recruited into the more recent ATTRibute-CM, APOLLO-B, HELIOS-B, and CARDIO-TTRansform trials. Therefore, the same study design and trial end points used in the ATTR-ACT trial may no longer be applicable to the current population. In view of our data, it may be that future studies need to tailor their inclusion criteria to reflect the changes in cardiac phenotype (milder cardiac disease) and increase the number of patients and/or the length of follow-up. Last, given that ATTR-CA is now being diagnosed earlier, more data are needed to guide decisions on in whom and when to initiate treatment, and which treatments should be used at each disease stage.

Limitations

Limitations include the small sample size between 2002 and 2006, but this reflects a scarcity of advanced diagnostics during this time period, and represents an unavoidable limitation. Various echocardiographic measures were not available in this cohort. Indexing parameters to body surface area and using more advanced measures of disease severity became part of the echocardiographic protocol only in later years.

We acknowledge that there may be a small minority of UK patients with ATTR-CA who are not referred to the NAC. Nonetheless, the vast majority of patients continue to be referred to NAC even if a diagnosis of ATTR-CA has been confirmed locally, because tafamidis is not funded in the United Kingdom, and the NAC is the only UK center through which patients can be enrolled into clinical trials of disease-modifying therapy. Despite this limitation, the completely unique UK setup, whereby the NAC has been the only commissioned center for diagnosis and monitoring of amyloidosis nationally for >20 years, means that the cohort of patients presented in this study represents the closest example of a national ATTR-CA registry anywhere in the world.

CONCLUSIONS

In summary, ATTR-CA is being increasingly recognized and diagnosed earlier in the disease process, which has translated into reduced mortality from the time of diagnosis. Changes in the clinical phenotype of ATTR-CA ought to be factored into clinical practice, considered in the timing and use of disease-modifying therapy, and, importantly, the design, powering, and implementation of clinical trials.

ARTICLE INFORMATION

Received May 17, 2022; accepted September 22, 2022.

The data underlying this article cannot be shared publicly because of the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

Affiliations

National Amyloidosis Centre, University College London, Royal Free Campus, United Kingdom (A.I., R.K.P., Y.R., A. Porcari, L.V., A.M., G.E.W., S.O., S.G., P.M., D.K., A.M.-N., T.K., L.C., J.B., M.U.R., H.L., A.W., A. Petrie, C.W., P.N.H., J.D.G., M.F.). Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina, University of Trieste, Italy (A. Porcari, G.S., F.B.). Cardiology University Department, IRCCS Policlinico San Donato, Milan, Italy. St Bartholomew's Hospital, London, United Kingdom (C.M., J.M.).

Sources of Funding

None.

Disclosures

M.F. is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/18/21/33447) and has consulting income from Intellia, Novonordisk, Pfizer, Eidos, Prothena, Alnylam, Alexion, Janssen, and Ionis. D.K. is supported by a British Heart Foundation Clinical Research Leave Fellowship (FS/CRLF/20/23004). J.G. has consulting income from Ionis, Alexion, Eidos, Intellia, Alnylam, and Pfizer. A.W. has consulting income from Alexia, AstraZeneca, Janssen, Attralus, and Prothena. P.H. has consulting income from Alnylam. The other authors report no conflicts.

Supplemental Material

Figure S1
Tables S1–S5

REFERENCES

1. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:2872–2891. doi: 10.1016/j.jacc.2019.04.003

2. Chacko L, Martone R, Bandera F, Lane T, Martinez-Naharro A, Boldrini M, Rezk T, Whelan C, Quarta C, Rowczenio D, et al. Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis. *Eur Heart J*. 2020;41:1439–1447. doi: 10.1093/eurheartj/ehz905
3. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, Singleton A, Kiuru-Enari S, Paetau A, Tienari PJ, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med*. 2008;40:232–239. doi: 10.1080/07853890701842988
4. Ravichandran S, Lachmann HJ, Wechalekar AD. Epidemiologic and survival trends in amyloidosis, 1987–2019. *N Engl J Med*. 2020;382:1567–1568. doi: 10.1056/nejmc1917321
5. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, Kotecha T, Francis R, Hutt DF, Rezk T, et al. Magnetic resonance in transthyretin cardiac amyloidosis. *J Am Coll Cardiol*. 2017;70:466–477. doi: 10.1016/j.jacc.2017.05.053
6. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133:2404–2412. doi: 10.1161/CIRCULATIONAHA.116.021612
7. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379:1007–1016. doi: 10.1056/NEJMoa1805689
8. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Planté-Bordeneuve V, Barroso FA, Merlini G, Obici L, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:22–31. doi: 10.1056/NEJMoa1716793
9. Dasgupta NR, Rissing SM, Smith J, Jung J, Benson MD. Inotersen therapy of transthyretin amyloid cardiomyopathy. *Amyloid*. 2020;27:52–58. doi: 10.1080/13506129.2019.1685487
10. Fontana M, Martinez-Naharro A, Chacko L, Rowczenio D, Gilbertson JA, Whelan CJ, Strehina S, Lane T, Moon J, Hutt DF, et al. Reduction in CMR derived extracellular volume with patisiran indicates cardiac amyloid regression. *JACC Cardiovasc Imaging*. 2021;14:189–199. doi: 10.1016/j.jcmg.2020.07.043
11. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, Leone O, Farsad M, Ciliberti P, Bacchi-Reggiani L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol*. 2005;46:1076–1084. doi: 10.1016/j.jacc.2005.05.073
12. Gilstrap LG, Dominici F, Wang Y, El-Sady MS, Singh A, Di Carli MF, Falk RH, Dorbala S. Epidemiology of cardiac amyloidosis-associated heart failure hospitalizations among fee-for-service Medicare beneficiaries in the United States. *Circ Heart Fail*. 2019;12:e005407. doi: 10.1161/CIRCHEARTFAILURE.118.005407
13. Sepehrvand N, Youngson E, Fine N, Venner CP, Paterson I, Bakal J, Westerhout C, Mcalister FA, Kaul P, Ezekowitz JA. The incidence and prevalence of cardiac amyloidosis in a large community-based cohort in Alberta, Canada. *J Card Fail*. 2022;28:237–246. doi: 10.1016/j.cardfail.2021.08.016
14. Ioannou A, Patel R, Gillmore JD, Fontana M. Imaging-guided treatment for cardiac amyloidosis. *Curr Cardiol Rep*. 2022. doi: 10.1007/s11886-022-01703-7
15. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, Sheppard MN, Poole-Wilson PA, Hawkins PN, Pennell DJ. Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation*. 2005;111:186–193. doi: 10.1161/01.CIR.0000152819.978579D
16. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, Rowczenio DM, Gilbertson JA, Hutt DF, Rezk T, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation*. 2019;140:16–26. doi: 10.1161/CIRCULATIONAHA.118.038169
17. Hanna M, Ruberg FL, Maurer MS, Dispenzieri A, Dorbala S, Falk RH, Hoffman J, Jaber W, Soman P, Witteles RM, et al. Cardiac scintigraphy with technetium-99m-labeled bone-seeking tracers for suspected amyloidosis: JACC review topic of the week. *J Am Coll Cardiol*. 2020;75:2851–2862. doi: 10.1016/j.jacc.2020.04.022
18. Carr AS, Pelayo-Negro AL, Evans MR, Laura M, Blake J, Stancanelli C, Iodice V, Wechalekar AD, Whelan CJ, Gillmore JD, et al; UK ATTR study of the neuropathy associated with transthyretin amyloidosis (ATTR) in the UK. *J Neurol Neurosurg Psychiatry*. 2016;87:620–627. doi: 10.1136/jnnp-2015-310907
19. Topline Results from Phase 3 ATTRIBUTE-CM Study. BridgeBio.com. Accessed May 5, 2022. <https://bridgebio.com/news/bridgebio-pharma-reports-month-12-topline-results-from-phase-3-attribute-cm-study/>

Circulation
FIRST PROOF ONLY