RESEARCH LETTER

doi:10.1002/ejhf.3186

Prevalence of wild-type transthyretin amyloidosis in a prospective heart failure cohort with preserved and mildly reduced ejection fraction: Results of the Amylo-VIP-HF study

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underrecognized fatal disease characterized by extracellular deposition of misfolded transthyretin proteins causing heart failure (HF).[1] Previous studies on ATTR-CM prevalence have mostly been performed retrospectively and in selected cohorts.[2–4] A recent community screening study found that ATTR-CM, defined in this study by a Perugini grade ≥2 out of three cardiac tracer uptake on bone scintigraphy, was present in 6% of patients older than 60 years with HF with preserved ejection fraction (HFpEF) and left ventricular hypertrophy (LVH).[5] Early distinction of ATTR-CM from other common HFpEF types is crucial, especially with disease-specific treatment available.[6] Cardiac magnetic resonance (CMR) imaging is frequently used for myocardial characterization to determine the aetiology of HF. Prospective ATTR-CM CMR studies have mostly been performed in amyloidosis referral cohorts prone to referral bias and lacking proper control groups. We therefore aimed to establish the prevalence of ATTR-CM prospectively in a broad cohort of patients with HFpEF or HF with mildly reduced ejection fraction (HFmrEF) and to investigate the ability of CMR to distinguish ATTR-CM from other types of HFpEF/HFmrEF.

Patients with mild or moderate symptoms of HF (compatible with New York Heart Association functional class II–III), left ventricular ejection fraction >40% (HFpEF/HFmrEF) and evidence of functional and/or structural alterations on echocardiography (septal or posterior wall thickness ≥11 mm, and/or mean septal and lateral e' <9 cm/s or E/e' ≥13 and/or a left atrial volume index ≥34 ml/m^2) were prospectively included between January 2015 and December 2019. Unlike previous studies we did not mandate LVH defined by a specific intraventricular septal thickness (IVST) ≥12 mm for inclusion. No pre-selection based on red flags or symptoms suggestive of cardiac amyloidosis was made. Patients with (an indication for) a cardiac implantable electronic device (CIED), a life expectancy <1 year, recent myocardial infarction, a percutaneous coronary intervention or coronary artery bypass graft <3 months, or complex congenital heart disease were excluded from the study. Additional details regarding study design, in- and exclusion criteria and CMR protocol have been described previously.[7] ^{99m}Technetium-hydroxymethylene-diphosphonate (^{99m}Tc-HDP) planar and single photon emission computed tomography/computed tomography (SPECT/CT) bone scintigraphy was performed. Cardiac ^{99m}Tc-HDP retention was visually scored according to the Perugini grading.[1] ATTR-CM was diagnosed according to the European Society of Cardiology position statement.[1] The study complies with the Declaration of Helsinki, the University Medical Centre Groningen ethics committee approved the study (registration number 2013/483), and all patients provided written informed consent. The National Amyloidosis Centre (NAC) disease stage, ranging from Ia–III, was calculated based on N-terminal pro-brain natriuretic peptide (NT-proBNP), estimated glomerular filtration rate, and for NAC stage Ia/b additionally the presence of atrial fibrillation and furosemide equivalent diuretic dose.[8,9] Red flags[1] and risk scores for presence of ATTR-CM were calculated for patients with wild-type ATTR-CM (ATTRwt-CM).[10,11]

Overall, 104 of the included 113 patients underwent bone scintigraphy and were included for further analyses; characteristics are shown in *Table 1*. Mean age was 72 ± 8 years with an equal gender distribution. Seven of these patients had cardiac tracer uptake on bone scintigraphy: four Perugini grade 1, two Perugini grade 2 and one Perugini grade 3. Five patients of the total cohort (4.8%; 95% confidence interval [CI] 2.2–8.7%) were diagnosed with ATTRwt-CM. Three ATTRwt-CM patients were diagnosed non-invasively and two ATTRwt-CM patients with Perugini grade 1 invasively by a positive subcutaneous fat aspirate. All five ATTRwt-CM patients had HFpEF and LVH (13.2% of all patients with HFpEF with LVH [*n* = 38]; 95% CI 5.2–25.8%). Four ATTRwt-CM patients were NAC stage Ib (80%) and one NAC stage II (20%). The diagnosis of ATTR-CM could not be established by subcutaneous abdominal fat tissue biopsy in two patients with Perugini grade 1 tracer uptake. Tracer uptake in these patients did not show evolution after a follow-up of 2 and 5 years. For further analyses, these patients were excluded. In all patients with cardiac tracer uptake on bone scintigraphy light-chain amyloidosis was excluded with blood and urine immunofixation and serum free light chain assessment. Hereditary types of amyloidosis were excluded using gene panel analysis.

Mean age was higher in ATTRwt-CM patients and they were predominantly male. On echocardiography, LVEF was comparable between ATTRwt-CM and ATTRwt-CM negative HFpEF/HFmrEF patients. All five patients with ATTRwt-CM had an LVEF >50% (i.e. HFpEF). Seventy-two (74%) of ATTRwt-CM negative patients had HFpEF, the other ATTRwt-CM negative patients had and LVEF between 40% and 50% (i.e. HFmrEF). IVST was slightly increased in ATTRwt-CM. CMR was performed in the majority of patients, one patient with ATTRwt-CM refused because of claustrophobia. Late gadolinium enhancement (LGE) was present in two (50%) ATTRwt-CM patients and in 26 (34%) ATTRwt-CM negative HFpEF/HFmrEF patients. Native midventricular myocardial T1 was longer in ATTRwt-CM.

One ATTRwt-CM patient with Perugini grade 3 cardiac tracer uptake and NAC stage II, had a subendocardial LGE pattern, abnormal gadolinium kinetics and a prolonged (1131 ms) T1 value. One patient with Perugini grade 2 cardiac tracer uptake and NAC stage Ib had a subendocardial LGE pattern, normal gadolinium kinetics and a prolonged (1116 ms) T1 value. Two ATTRwt-CM patients with Perugini grade 1 cardiac tracer uptake and NAC stage Ib had no LGE, normal gadolinium kinetics and T1 values of 1006 and 916 ms. None of the patients with Perugini grade 1 cardiac

Table 1 Baseline characteristics of the Amylo-VIP-HF study

Variables	All subjects ($n = 104$)	ATTRwt-CM ($n = 5$)	ATTRwt-CM negative HFpEF/HFmrEF ($n = 97$)
Patient characteristics			
Age, years	72 ± 8	80 ± 6	72 ± 8
Male sex, *n* (%)	51 (49)	4 (80)	46 (47)
BMI, kg/m^2	29 [26–34]	32 [27–33]	29 [26–34]
Smoking, *n* (%)	64 (62)	2 (40)	61 (63)
Medical history, *n* (%)			
HT	78 (75)	2 (40)	76 (78)
CAD	35 (34)	1 (20)	34 (35)
DM2	42 (40)	1 (20)	41 (42)
AF	54 (52)	3 (60)	51 (53)
Medication use, *n* (%)			
β–blocker	86 (83)	5 (100)	80 (82)
ACEi	38 (37)	2 (40)	35 (36)
ARB	28 (27)	0 (0)	27 (28)
MRA	41 (39)	2 (40)	37 (38)
Diuretics	93 (90)	4 (80)	88 (91)
Functionality, *n* (%)			
NYHA class			
II	57 (55)	3 (60)	53 (55)
III	47 (45)	2 (40)	44 (45)
NAC stage			
Ib		4 (80)	
II		1 (20)	
Laboratory values			
eGFR, ml/min/1.73 m^2	47 [37–71]	55 [53–56]	46 [36–72]
NT-proBNP, ng/L	789 [403–1497]	1014 [760–1174]	784 [360–1500]
hs-troponin T, ng/L	19 [13–33]	28 [22–42]	18 [12–34]
ECG			
AV block, *n* (%)	10 (10)	2 (40)	8 (8)
Bundle branch block, *n* (%)	23 (22)	2 (40)	21 (22)
QTc, ms	436 [419–461]	451 [425–471]	435 [419–462]
Low QRS voltage (≤15 mm), *n* (%)	8 (8)	0 (0)	8 (8)
Echocardiography			
LVEF, %	55 [50–58]	55 [53–56]	55 [49–58]
HFpEF, *n* (%)	78 (75)	5 (100)	72 (74)
IVST, mm	11 [10–13]	13 [12–21]	11 [10–13]
IVST ≥12 mm, *n* (%)	51 (49)	5 (100)	45 (46)
LVPWT, mm	10 [8–11]	12 [10–19]	10 [8–11]

Table 1 (Continued)

Variables	All subjects ($n = 104$)	ATTRwt-CM ($n = 5$)	ATTRwt-CM negative HFpEF/HFmrEF ($n = 97$)
RWT	0.42 [0.37–0.50]	0.51 [0.41–0.90]	0.42 [0.37–0.49]
LVMI, g/m^2	99 [78–127]	130 [91–235]	99 [78–125]
TAPSE, mm	20 [17–24]	20 [18–27]	20 [17–24]
E lateral, cm/s	8.8 [6.8–10.9]	10.9 [6.1–13.3]	8.5 [6.8–10.7]
E septal, cm/s	6.6 [5.2–8.0]	7.0 [4.2–8.3]	6.6 [5.2–8.0]
E/e'	10.5 [8.2–14.9]	11.6 [7.0–17.9]	10.1 [8.2–14.9]
LAVI, ml/m^2	43 [37–55]	57 [41–70]	43 [36–53]
Echocardiographic red flags[a], *n* (%)			
0	20 (19)	0 (0)	20 (21)
1	43 (41)	2 (40)	41 (42)
2	25 (24)	1 (20)	24 (25)
≥3	16 (15)	2 (40)	12 (12)
CMR			
GLSS performed, *n* (%)	96 (92)	4 (80)	90 (93)
GLSS, %	−16 [−13 to −20]	−17 [−11 to −19]	−16 [−13 to −21]
LGE performed, *n* (%)	83 (80)	4 (80)	77 (79)
LGE positive, *n* (%)	28 (27)	2 (50)	26 (27)
T1 mapping performed, *n* (%)	74 (71)	4 (80)	69 (71)
Native mid-myocardial T1, ms	1035 [1002–1053]	1061 [936–1127]	1034 [1001–1050]
Bone scintigraphy, *n* (%)			
Perugini grade 0	97 (93)	0 (0)	97 (100)
Perugini grade 1	4 (4)	2 (40)	0 (0)
Perugini grade 2	2 (2)	2 (40)	0 (0)
Perugini grade 3	1 (1)	1 (20)	0 (0)
Risk scores, *n* (%)			
Davies *et al.* risk score[b]			
Low (<6 points)	82 (79)	2 (40)	79 (81)
High (≥ 6 points)	22 (21)	3 (60)	18 (19)
T-Amylo ATTR-CM risk score[c]			
Unlikely (0–2 points)	52 (50)	1 (20)	51 (53)
Inconclusive (3–6 points)	52 (50)	4 (80)	46 (47)
Very likely (7–11 points)	0 (0)	0 (0)	0 (0)

Continuous variables are displayed as median [interquartile range] to be able to compare HFpEF/HFmrEF and ATTR–CM optimally, due to the small number of patients for the ATTR–CM group.

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; AV, atrio-ventricular; BMI, body mass index; CAD, coronary artery disease; CMR, cardiac magnetic resonance; DM2, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; GLSS, global longitudinal systolic strain; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; hs, high-sensitivity; HT, hypertension; IVST, intraventricular septal thickness; LAVI, left atrial volume index; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVPWT, left ventricular posterior wall thickness; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; QTc, corrected QT interval; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion.

[a]Red flags on echocardiography are defined as an intra-atrial septal thickness ≥5 mm, pericardial effusion, restrictive filling pattern, granular sparkling and AV valve thickness ≥5 mm; information on apical sparing was not present from echocardiography.[1]

[b]Davies *et al.* risk score adds 2 points if 60–69 years, 3 if 70–79 years, 4 if ≥80 years, 2 for male sex, −1 for hypertension, 1 for EF < 60%, 1 for IVST≥12 mm and 2 for RWT >0.57.[10]

[c]T-Amylo risk score adds 3 points for CTS history, 1 if ≥80 years, 3 if male, 2 if IVST ≥16 mm, 2 if low QRS voltage.[11]

tracer uptake and NAC stage Ib qualified as a high-risk score for ATTRwt-CM.

Wild-type ATTR-CM was diagnosed in 5% ($n = 5$) of all HFpEF/HFmrEF patients ($n = 104$), but only in patients with HFpEF and LVH ($n = 38$). The overall prevalence is lower than in two previous prospective studies,[2,3] most likely due to the inclusion of patients with HFmrEF, without LVH, a lower mean age and the exclusion of patients with CIED. Conversely, including patients with Perugini grade 1 cardiac tracer uptake on bone scintigraphy and positive tissue biopsy might have avoided missing early ATTRwt-CM cases, whereas other studies deemed Perugini grade 1 or even grade 2 as negative.[2,3] Unlike prior studies, we did not mandate a specific IVST for inclusion. Although we expected that especially early ATTRwt-CM can be present in the absence of LVH, no ATTRwt-CM was present in patients without LVH, thus supporting current screening criteria warranting further investigations for ATTRwt-CM.[1] Two of the early stage ATTRwt-CM patients would have not been identified using existing risk models.

Characteristic CMR findings of ATTRwt-CM were only found in one advanced ATTRwt-CM patient. In the remaining three patients with early-stage disease, no CMR characteristics were present. Therefore, CMR alone seems less suitable for distinguishing early-stage ATTRwt-CM from other types of HFpEF/HFmrEF.

The most important limitation of this study is the small number of patients and exclusion of patients with a CIED, which could potentially lead to a lower prevalence of transthyretin amyloidosis in our study.[12] Overall and subgroup conclusions should therefore be cautiously interpreted and statistical analyses were not performed. Due to the NYHA class II–III and NT-proBNP inclusion criterium, no pre-symptomatic ATTRwt-CM patients were included and potential NAC stage Ia patients could have been missed.

This prospective multicentre study demonstrated that ATTRwt-CM is present in 5% of HFpEF/HFmrEF patients. CMR was not able to reliably distinguish early ATTRwt-CM from other causes of HFpEF/HFmrEF, underscoring the need for a comprehensive diagnostic work-up without relying solely on CMR.

Funding

The VIP-HF study (ClinicalTrials.gov Identifier NCT01989299) was financially supported by an unrestricted grant from Abbott–Netherlands and Pfizer to the University Medical Centre Groningen. Abbott–Netherlands and Pfizer were neither involved in the conduction of the study, nor in the writing of the manuscript.

Conflict of interest: O.C.M. reports a relationship with AstraZeneca, Boehringer Ingelheim and Novartis that includes consulting or advisory. M.R. reports consultancy fees from Bayer, InCarda Therapeutics to the institution; unrestricted research grant from ZonMW and the Dutch Heart Foundation; DECISION project 848 090 001; unrestricted research grants from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation; RACE V (CVON 2014–9), RED-CVD (CVON2017-11); unrestricted research grant from Top Sector Life Sciences & Health to the Dutch Heart Foundation (PPP Allowance; CVON-AI [2018B017]); unrestricted research grant from the European Union's Horizon 2020 research and innovation programme under grant agreement; EHRA-PATHS (945260). R.H.J.A.S. reports independent research grants from Pfizer. H.L.A.N.: the UMCG, which employs H.L.A.N., has received consultancy fees and speaking honorarium from Pfizer and Alnylam. All other authors have nothing to disclose.

Alwin Tubben[1,2], Hendrea S.A. Tingen[2,3], Niek H.J. Prakken[4], Vanessa P.M. van Empel[5], Thomas M. Gorter[1], Laura M.G. Meems[1], Olivier C. Manintveld[6], Michiel Rienstra[1], Robert G. Tieleman[1,7], Andor W.J.M. Glaudemans[3], Dirk J. van Veldhuisen[1], Riemer H.J.A. Slart[2,3], Hans L.A. Nienhuis[2,8], and Peter van der Meer[1,2]*

[1]Department of Cardiology, University Medical Centre Groningen, Groningen, The Netherlands; [2]Amyloidosis Centre of Expertise, University Medical Centre Groningen, Groningen, The Netherlands; [3]Department of Nuclear Medicine and Molecular Imaging, University Medical Centre Groningen, Groningen, The Netherlands; [4]Department of Radiology, University Medical Centre Groningen, Groningen, The Netherlands; [5]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Medical University Centre Maastricht, Maastricht, The Netherlands; [6]Department of Cardiology, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands; [7]Department of Cardiology, Martini Hospital, Groningen, The Netherlands; and [8]Department of Internal Medicine, University Medical Centre Groningen, Groningen, The Netherlands

*Email: p.van.der.meer@umcg.nl

References

1. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, *et al.* Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail* 2021;**23**:512–526. https://doi.org/10.1002/ejhf.2140
2. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, *et al.* Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;**36**:2585–2594. https://doi.org/10.1093/eurheartj/ehv338
3. Bennani Smires Y, Victor G, Ribes D, Berry M, Cognet T, Méjean S, *et al.* Pilot study for left ventricular imaging phenotype of patients over 65 years old with heart failure and preserved ejection fraction: The high prevalence of amyloid cardiomyopathy. *Int J Cardiovasc Imaging* 2016;**32**:1403–1413. https://doi.org/10.1007/s10554-016-0915-z
4. Bay K, Gustafsson F, Maiborg M, Bagger-Bahnsen A, Strand AM, Pilgaard T, *et al.* Suspicion, screening, and diagnosis of wild-type transthyretin amyloid cardiomyopathy: A systematic literature review. *ESC Heart Fail* 2022;**9**:1524–1541. https://doi.org/10.1002/ehf2.13884
5. AbouEzzeddine OF, Davies DR, Scott CG, Fayyaz AU, Askew JW, McKie PM, *et al.* Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. *JAMA Cardiol* 2021;**6**:1267–1274. https://doi.org/10.1001/jamacardio.2021.3070
6. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, *et al.*; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016. https://doi.org/10.1056/NEJMoa1805689
7. van Veldhuisen DJ, van Woerden G, Gorter TM, van Empel VPM, Manintveld OC, Tieleman RG, *et al.* Ventricular tachyarrhythmia detection by implantable loop recording in patients with heart failure and preserved ejection fraction: The VIP-HF study. *Eur J Heart Fail* 2020;**22**:1923–1929. https://doi.org/10.1002/ejhf.1970
8. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, *et al.* A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018;**39**:2799–2806. https://doi.org/10.1093/eurheartj/ehx589
9. Law S, Bezard M, Petrie A, Chacko L, Cohen OC, Ravichandran S, *et al.* Characteristics and natural history of early-stage cardiac transthyretin amyloidosis. *Eur Heart J* 2022;**43**:2622–2632. https://doi.org/10.1001/jamacardio.2022.1781
10. Davies DR, Redfield MM, Scott CG, Minamisawa M, Grogan M, Dispenzieri A, *et al.* A simple score to identify increased risk of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. *JAMA Cardiol* 2022;**7**:1036. https://doi.org/10.1001/jamacardio.2022.1781
11. Arana-Achaga X, Goena-Vives C, Villanueva-Benito I, Solla-Ruiz I, Rengel Jimenez A, Gaspar TI, *et al.* Development and validation of a prediction model and score for transthyretin cardiac amyloidosis diagnosis: T-Amylo. *JACC Cardiovasc Imaging* 2023;**16**:1567–1580. https://doi.org/10.1016/j.jcmg.2023.05.002
12. López-Sainz Á, de Haro-del Moral FJ, Dominguez F, Restrepo-Cordoba A, Amor-Salamanca A, Hernandez-Hernandez A, *et al.* Prevalence of cardiac amyloidosis among elderly patients with systolic heart failure or conduction disorders. *Amyloid* 2019;**26**:156–163. https://doi.org/10.1080/13506129.2019.1625322