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FULL RESEARCH PAPER
Heart failure and cardiomyopathies

Wild-type transthyretin cardiac amyloidosis is not rare in elderly subjects: the CATCH screening study

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Aims Wild-type transthyretin cardiac amyloidosis (ATTRwt-CA) affects older adults and is currently considered as a rare disorder. We investigated for the first time the prevalence of ATTRwt-CA in elderly individuals from the general population.

Methods and results General practitioners from Pisa, Italy, proposed a screening for ATTRwt-CA to all their patients aged 65–90 years, until 1000 accepted. The following red flags were searched: interventricular septal thickness ≥ 12 mm, any echocardiographic, electrocardiographic or clinical hallmark of CA, or high-sensitivity troponin T ≥ 14 ng/L. Individuals with at least one red flag ($n = 346$) were asked to undergo the search for a monoclonal protein and bone scintigraphy, and 216 accepted. Four patients received a non-invasive diagnosis of ATTRwt-CA. All complained of dyspnoea on moderate effort. A woman and a man aged 79 and 85 years, respectively, showed an intense cardiac tracer uptake (Grade 3), left ventricular (LV) wall thickening, Grade 2 and 3 diastolic dysfunction, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 1000 ng/L. Two other patients (a man aged 74 years and a woman aged 83 years) showed a Grade 2 uptake, an increased LV septal thickness, but preserved diastolic function, and NT-proBNP < 300 ng/L. The prevalence of ATTR-CA in subjects ≥ 65 years was calculated as 0.46% (i.e. 4 out of the 870 subjects completing the screening, namely 654 not meeting the criteria for Step 2 and 216 progressing to Step 2).

Conclusion Wild-type transthyretin cardiac amyloidosis is uncommon in elderly subjects from the general population, but more frequent than expected for a rare disease.

Lay summary Wild-type transthyretin cardiac amyloidosis (ATTRwt-CA) is a heart condition mostly found in older adults. Wild-type transthyretin cardiac amyloidosis is considered a rare disease, although no systematic screening has been performed yet. The study aimed to understand how common this disease is among the general population aged 65–90 years in Pisa, Italy. To do this, general practitioners offered screening for ATTRwt-CA to their patients within this age group. The initial step of the screening involved checking for certain warning signs (red flags), like abnormal thickness in a part of the heart called the interventricular septum, unusual heart function observed through various tests, or elevated levels of a specific heart protein. Out of 1000 individuals who began the screening process, 346 showed at least one of these red flags and

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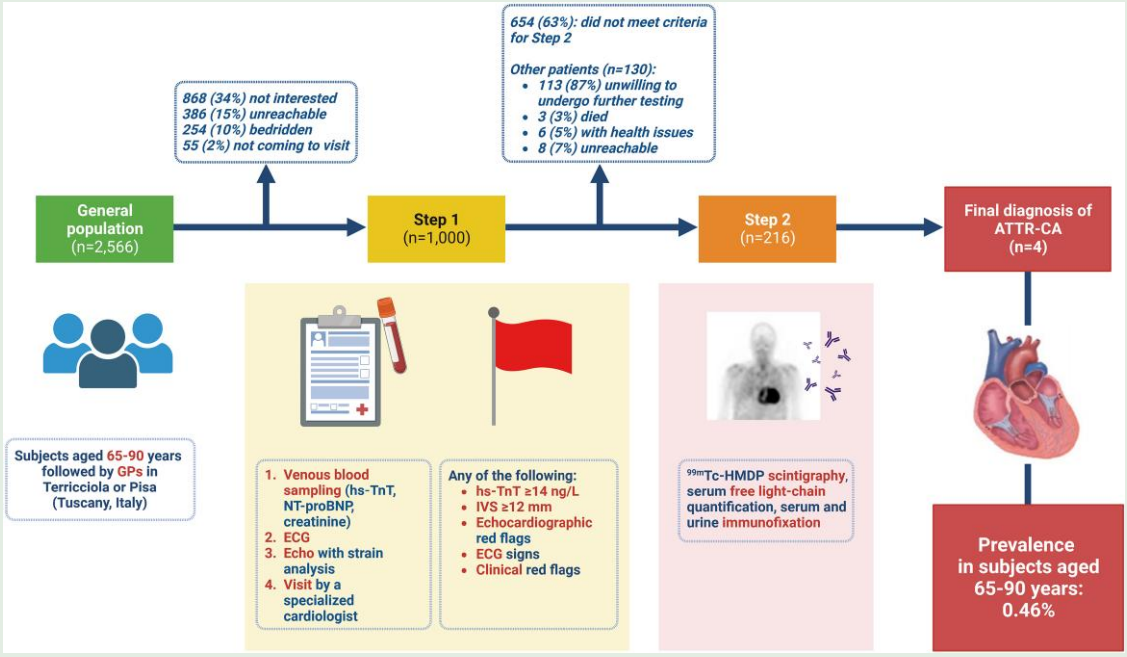
were further examined using bone scintigraphy (a type of imaging test) and tests for a specific protein related to this condition. Of these, 216 agreed to proceed with these additional tests. The results showed that four of these patients actually had ATTRwt-CA. Their conditions varied in severity, with some showing more intense signs of the disease on the heart scans, thicker heart walls, and higher levels of heart stress proteins. All four patients experienced mild difficulty in breathing during physical activity. Based on these findings, the study concluded that about 0.46% of elderly individuals in the general population might have ATTRwt-CA, indicating that the disease is somewhat more common in this age group than previously thought.

Graphical Abstract



Main findings of the CATCH study. ATTR-CA, transthyretin cardiac amyloidosis; ECG, electrocardiogram; GP, general practitioner; hs-TnT, high-sensitivity troponin T; IVS, interventricular septum; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Amyloidosis • Wild-type • Transthyretin cardiomyopathy • ATTR • Screening • Elderly • Disease prevalence

Introduction

Transthyretin cardiac amyloidosis (ATTR-CA) is currently considered as 'a rare but severe cause of restrictive cardiomyopathy'[1] caused by the accumulation of the serum protein TTR in the extracellular spaces of the heart. Wild-type (wt) ATTR-CA is a late-onset disease affecting older adults, attributed to age-related changes in protein homeostasis or the interaction between circulating proteins and the myocardium.[2] The progressive accumulation of amyloid leads to atrial and ventricular wall thickening, valve involvement, dysrhythmias and conduction disturbances, progressive diastolic and systolic dysfunction, and subsequent heart failure, initially with preserved ejection fraction.[3]

The number of diagnoses of ATTRwt-CA has increased rapidly over the last years, as confirmed by the experience of the UK National Amyloidosis Centre (NAC)[4] and data from the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry, which is the largest international registry of patients with ATTR-CA.[5] This rising prevalence can be attributed to a greater awareness of CA among physicians, a diagnostic algorithm limiting the need for tissue biopsy,[6] and the availability of a specific treatment.[7] While our knowledge of ATTRwt-CA epidemiology is progressively expanding, the prevalence of this condition in the general population remains unknown. Current estimates rely on inpatient or outpatient claim data[8,9] or systematic screenings in specific patient subsets.[10,11] Accurate data on the prevalence of ATTRwt-CA could help health system to re-design strategies for disease screening, patient care, and implementation of novel therapies in current practice. Furthermore, disease-modifying therapy is much more effective early in the course of the disease and that is significantly impacts survival and morbidity, which are drivers for early identification of affected individuals.

The Characterizing the burden of Amyloid Transthyretin CardiomyopatHy in the elderly (CATCH) study is the first attempt of systematic screening of ATTRwt-CA in a cohort of elderly subjects from the general population.

Methods

Recruitment and Step 1

The research protocol was approved by the Ethical Committee of Pisa and all participants gave written informed consent. The study was supported by unconditional funding by Pfizer and Eidos Therapeutics. The sponsors had

no role in the study design or result interpretation. Study investigators, general practitioners (GPs), and study participants did not receive any payment.

Subjects aged 65–90 years were asked to participate in the screening by GPs working either in the countryside or in an urban setting in an area of Tuscany (Italy), where there is no known cluster of *TTR* gene mutations. The only selection criterion was age. Typically, the elderly has been defined as the chronological age of 65 or older; the same upper age limit as in the ATTR-ACT study was chosen.[12] In Italy, everybody is registered with a GP. General practitioners were asked to propose study participation to all their patients (i.e. not only those presenting to their GP) through either in-person discussion or phone calls. We emphasized the importance of contacting all patients in this age group and asked to record the reasons why patients were unwilling to participate. The screening was conducted in the village of Terricciola (4414 inhabitants), about 40 km from Pisa, and in the city of Pisa (88 781 inhabitants). General practitioners from Terricciola were involved sequentially from March 2021 to December 2021. As per the study design, enrolment in Terricciola stopped when 500 subjects entered the study. General practitioners from Pisa were involved from March to December 2022 until further 500 subjects were enrolled in Pisa, for a total number of 1000 subjects entering the study.

Subjects accepting to enter the study and signing an informed consent underwent the first step of screening, which included the following exams, performed on the same day:

(1) clinical history and physical examination by a cardiologist with an expertise in CA (any of the following authors: A.A., V.C., I.F., F.G., and G.V.) using a form for data collection;
(2) twelve -lead electrocardiogram;
(3) transthoracic echocardiogram; and
(4) venous blood sampling for high-sensitivity troponin T (hs-TnT; ECLIA Elecsys, Roche Diagnostics), N-terminal pro-B-type natriuretic peptide (NT-proBNP; ECLIA Elecsys, Roche Diagnostics), and creatinine.

Step 2

We identified all patients meeting any of the following criteria after Step 1 examination:

(1) clinical criteria: history of carpal tunnel syndrome (either mono- or bilateral, operated or not), spontaneous tendon rupture, lumbar spine stenosis, any known plasma cell dyscrasia *and/or* symptoms compatible with peripheral or autonomic neuropathy;[13]
(2) electrocardiogram criteria: low QRS voltage (defined as a peak-to-peak QRS amplitude of less than 5 mm in the limb leads and/or less than 10 mm in the precordial leads) *or* deemed disproportionately low compared with left ventricular (LV) mass *and/or* pseudo-Q waves;[13]
(3) echo criteria: interventricular septal (IVS) thickness and/or posterior wall (PW) thickness in diastole ≥ 12 mm[12] *and/or* diastolic dysfunction grade 2 and 3 *and/or* a history of severe aortic stenosis (either operated or not); and
(4) laboratory criterion: hs-TnT ≥ 14 ng/L (i.e. the 99th percentile upper reference limit).[14]

When at least one criterion was met, the subject was to be referred to Step 2 exams (^{99m}Tc-hydroxymethylene diphosphonate scintigraphy and search for a monoclonal protein).[13] According to the standard diagnostic algorithm,[6,13] the combination of Grade 2 and 3 bone tracer uptake[15] and no monoclonal protein allowed to diagnose ATTR-CA. These patients then underwent the search for *TTR* gene mutations.

Scintigraphy examination and search for a monoclonal protein

See Supplementary material.

Statistical analysis

Normal distribution was assessed through the Shapiro–Wilk test. Continuous variables with normal distribution were presented as mean ± standard deviation and those with non-normal distribution as median and interquartile range. Mean differences among groups were evaluated through the unpaired Student's *t*-test or the Mann–Whitney *U* test, as appropriate. Categorical variables were presented as absolute numbers and percentages and compared by the chi-square test with Yates correction.

Table 1 Population characteristics

	All subjects *n* = 1000
Age (years)	74 (69–79)
Men, *n* (%)	518 (52)
White, *n* (%)	1000 (100)
BMI (kg/m^2)	26 (24–29)
NYHA Class I/II/III, *n* (%)	752/241/7 (75/24/1)
History of hypertension, *n* (%)	564 (56)
History of diabetes, *n* (%)	165 (17)
Carpal tunnel syndrome, *n* (%)	133 (13)
Monolateral	63 (6)
Bilateral	70 (7)
Operated	84 (8)
Lumbar spine stenosis, *n* (%)	26 (3)
Spontaneous tendon rupture, *n* (%)	25 (3)
Known plasma cell dyscrasia, *n* (%)	26 (3)
History or signs/symptoms of peripheral neuropathy, *n* (%)	92 (9)
Sinus rhythm, *n* (%)	944 (94)
Atrial fibrillation/flutter, *n* (%)	40 (4)
Paced rhythm, *n* (%)	20 (2)
Low/disproportionally low QRS voltage, *n* (%)	7 (1)
Q waves, *n* (%)	2 (0)
LVEF (%)	62 (58–66)
IVS (mm)	10 (9–11)
PW (mm)	9 (8–10)
LV wall thickness ≥ 12 mm, *n* (%)	218 (22)
LVMI (g/m^2)	87 (73–101)
Diastolic dysfunction Grade 2/3, *n* (%)	28/2 (3/0)
Severe aortic stenosis, *n* (%)	15 (2)
TAPSE (mm)	22 (20–25)
hs-troponin T (ng/L)	10 (8–15)
hs-troponin T ≥ 14 ng/L, *n* (%)	305 (31)
NT-proBNP (ng/L)	118 (60–235)
eGFR (mL/min/1.73 m^2)	75 (62–86)

BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; hs, high-sensitivity; IVS, interventricular septum; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PW, posterior wall; TAPSE, tricuspid annular plane systolic excursion.

P-values of <0.05 were considered as significant. The Bonferroni correction was applied to account for multiple testing. Predictors of ATTR-CA were searched through univariate logistic regression analysis. Only LV mass index (LVMI) and diastolic dysfunction grade had some missing values (1.7% and 2.6%, respectively); missing values were not imputed. Data were analysed using IBM SPSS Statistics (version 24).

Results

Recruitment of the 1000 study subjects

We sequentially involved six GPs (three from Terricciola and three from Pisa) to find 1000 subjects aged 65–90 years willing to undergo

Step 1 exams. To achieve this goal, GPs proposed study participation to a total of 2566 subjects. None of these 2566 subjects had been previously diagnosed with ATTR-CA according to their electronic health records. Among subjects not entering the study ($n = 1566$), 868 (55%) were not interested in the study or were reluctant to undergo the proposed examinations, 386 (25%) could not be contacted, and 254 (16%) were bedridden, severely ill, and/or in a nursing home. Finally, 55 subjects (4%) accepted to enter the study but did not come to the scheduled visit.

Step 1

The characteristics of the 1000 subjects undergoing Step 1 are reported in *Table 1*. Median age was 74 years (interquartile range 69–79). Men accounted for 52% of the cohort. Thirteen per cent had a history of carpal tunnel syndrome, 3% had lumbar spine stenosis, spontaneous tendon rupture, or known plasma cell dyscrasia, and 9% had some manifestations of peripheral or autonomic neuropathy. One per cent had low or disproportionally low QRS voltage. On echocardiographic examination, 3% of subjects had grade 2 or 3 diastolic dysfunction, and 15 (2%) had severe aortic stenosis. Finally, 31% of patients had hs-troponin T ≥ 14 ng/L. Compared with subjects enrolled in the city of Pisa, those from the countryside (Terricciola) had more often a history of carpal tunnel syndrome, lumbar spine stenosis and neuropathy, IVS thickness, and hs-troponin T levels (see Supplementary material online, *Table S1*).

Step 2

Among the 1000 subjects undergoing Step 1 exams, 346 (35%) met the pre-specified criteria to proceed to Step 2. Among them, 216 (62%) agreed to undergo further testing. Among the 130 subjects not proceeding to Step 2, three (3%) had died in the meanwhile, six (5%) did not accept because of serious health issues, eight (7%) could not be contacted, and the other 113 (87%) declined to undergo further testing, because of concerns about the radioactive tracer used for bone scintigraphy or for possible further invasive tests. Overall, the 130 subjects not proceeding to Step 2 were older, had higher NT-proBNP, and had worse renal function than those proceeding to Step 2 (see Supplementary material online, *Table S2*).

Thirteen subjects (6%) had a monoclonal component and were referred to haematological evaluation. None of these patients were ultimately diagnosed with AL-CA.

Final diagnoses of transthyretin cardiac amyloidosis

The main characteristics of four cases of ATTR-CA are reported in *Table 2*. A 79-year-old woman (Case #1) and an 85-year-old man (Case #2) showed an intense cardiac uptake (Grade 3; *Figure 1*) and no monoclonal protein, allowing a non-invasive diagnosis of ATTR-CA. A 74-year-old man (Case #3) showed a borderline Grade 2 uptake (as judged by two independent readers), and an intense tracer uptake in the septum and the basal segments of the lateral wall. He had no monoclonal protein and was unwilling to undergo endomyocardial biopsy. Upon discussion, there was a general agreement that he met the criteria for a non-invasive diagnosis of ATTR-CA (*Figure 2*). An 83-year-old woman (Case #4) displayed a Grade 2 uptake, with an intense uptake in the inferior wall confirmed by single photon emission computed tomography (SPECT) and SPECT/computed tomography (*Figure 2* and Supplementary material online, *Figure S1*), and again no monoclonal protein. *TTR* gene mutations were not found in any of the four patients.

Cases #1 and #2 showed clear evidence of structural heart disease, with LV wall thickening and diastolic dysfunction Grade 2 or 3. Case #2 even showed systolic dysfunction (LV ejection fraction 35%). N-terminal pro-B-type natriuretic peptide values were 1321 and 3941 ng/L, respectively.

Case #3 had an increased LV mass but no diastolic dysfunction and NT-proBNP 274 ng/L. Finally, Case #4 displayed a less prominent LV wall thickening, a preserved diastolic function, and NT-proBNP 249 ng/L (*Table 2*). The global longitudinal strain was mildly reduced, but no patient had an apical sparing pattern (see Supplementary material online, *Table S3*). No patient had low QRS voltage or Q waves (see Supplementary material online, *Figure S2*).

All patients complained of dyspnoea on effort [New York Heart Association (NYHA) Class II]. Three patients had previously undergone cardiac examinations: Case #1 because of atrial flutter and Cases #2 and #3 for the incidental detection of increased LV wall thickness during echocardiograms performed before non-cardiac surgery or as a screening examination in a hypertensive individual, respectively. No patient had previously performed the diagnostic workup for CA. Cases #1 and #2 were on low-dose furosemide therapy (0.54 and 0.31 mg/kg, respectively), and both were in the NAC Stage Ib.[16] Cases #3 and #4 were not on furosemide and then in the NAC stage Ia.

Prevalence of transthyretin cardiac amyloidosis in elderly subjects

The prevalence of ATTR-CA in elderly subjects aged 65–90 years from the general population was calculated as 4 out of 870 [i.e. 654 (Step 2 not proposed) + 216 (Step 2 performed)] = 0.46% (*Graphical Abstract*).

Predictors of transthyretin cardiac amyloidosis in elderly subjects

Among all the variables collected during Step 1, IVS and PW thickness, LVMI, diastolic dysfunction Grade 2 or 3, and NT-proBNP predicted ATTR-CA diagnosis in the whole cohort ($n = 1000$). The same predictors plus age were found in individuals completing the screening ($n = 870$). Interventricular septal thickness was a stronger predictor than PW thickness and LVMI (see Supplementary material online, *Table S4*).

Discussion

The CATCH study is the first attempt to establish the prevalence of ATTRwt-CA in a cohort of elderly subjects with phenotypical traits potentially suggestive of this condition. We designed a two-step screening starting with the assessment of unselected individuals and progressing to scintigraphy with bone tracers and the search for a monoclonal protein when at least one red flag was present. We found four patients meeting the criteria for a non-invasive diagnosis of ATTRwt-CA (i.e. an intense cardiac uptake of bone tracer and no monoclonal protein), with a final estimated prevalence of ATTRwt-CA of 0.46% among individuals aged 65–90 years. Among all the variables, IVS thickness was the stronger predictor of ATTR-CA.

The designation of tafamidis as an orphan drug and its associated market exclusivity provisions did not rely on solid epidemiological data but rather on prevalence data that could be largely underestimated.[17] The notion of ATTR-CA as a rare disease has been recently challenged based on the evidence of a high prevalence of ATTR-CA among patients with common conditions such as heart failure with preserved ejection fraction or severe aortic stenosis.[17] We report that ATTRwt-CA is relatively common among unselected elderly individuals, being found in four individuals out of 870 completing the screening (namely 654 not meeting the criteria for Step 2 and 216 progressing to Step 2). All diagnosed patients complained of dyspnoea on effort (NYHA Class II symptoms) and had evidence of structural heart disease, with increased wall thickness and LV mass and impaired LV global longitudinal strain. Overall, they displayed the combination of elements that we

Table 2 Main characteristics of patients with wild-type transthyretin cardiac amyloidosis

	Sex	Age (years)	CTS	Perugini grade	Kappa/ lambda ratio	Immuno-fixation (S/U)	*TTR* mutations	NYHA class	Furosemide dose (mg/kg)	LVEF (%)	IVS (mm)	LVMI (g/m^2)	Diastolic dysf. grade	Apical sparing	Low voltage	NT-proBNP (ng/L)	hs-troponin T (ng/L)	eGFR (mL/min/1.73 m^2)	NAC stage
Case #1	W	79	No	3	0.78	Negative	No	II	0.54	60	14	136	3	No	No	1321	30	68	Ib
Case #2	M	85	No	3	1.05	Negative	No	II	0.31	35	17	182	2	No	No	3941	57	75	Ib
Case #3	M	74	No	2	1.16	Negative	No	II	0	62	14	141	0	No	No	274	13	57	Ia
Case #4	W	83	Operated bilaterally	2	1.12	Negative	No	II	0	61	12	90	0	No	No	249	26	61	Ia

CTS, carpal tunnel syndrome; eGFR, estimated glomerular filtration rate; hs, high-sensitivity; IVS, interventricular septum; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; M, man; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; S/U, serum and urine; W, woman.

have proposed to define CA: (i) evidence of amyloid deposits in the heart (as assessed through either histological analysis or scintigraphy with bone tracers), (ii) structural heart disease, (iii) symptoms that can be attributed to cardiac disease.[11] Patients with Grade 3 uptake had severe diastolic dysfunction and elevated hs-troponin T and NT-proBNP, while those with Grade 2 uptake had no diastolic dysfunction and lower cardiac biomarkers plasma level. Interestingly, all patients were only mildly symptomatic for dyspnoea despite low diuretic doses, none of them displayed some typical red flags of CA,[18] namely apical sparing or Q waves, and even no discrepancy between QRS voltage and LV mass was present, suggesting a quite early diagnosis.

Another interesting finding is that women accounted for half of patients with ATTR-CA. Accordingly, the male sex was not even a univariate predictor of ATTR-CA. These findings suggest that women might be largely underdiagnosed. One possible reason is the notion of ATTRwt-CA as a disorder typically affecting men. Furthermore, the same cut-off for LV wall thickness (12 mm) was proposed as a gatekeeper to diagnosis in both men and women[9] despite lower normal LV wall thickness reference values in women than men, possibly delaying the diagnosis in women.[19]

In this screening study, we asked GPs to propose study participation to all their patients aged 65–90 years. General practitioners contacted on average 428 individuals, corresponding to 29% of the maximal number of adult patients (≥18 years) followed by GPs in Italy ($n = 1500$). Interestingly, individuals aged ≥65 and <90 years accounted for 30% of those aged ≥20 years in the province of Pisa in 2022, supporting the notion that virtually all individuals in this age range had been reached out.[20] We had to contact 2566 subjects to screen 1000, with an adherence rate of 39%, which is quite low but still higher than cancer screening programs in younger individuals (25–35%).[21] These subjects underwent first-line examinations that included a visit by a cardiologist with an expertise in CA, an electrocardiogram, blood sampling for cardiac biomarkers, and a transthoracic echocardiogram. We are well aware that a similar screening of elderly individuals cannot be implemented in the real world, but our goal was to establish the prevalence of ATTR-CA in the elderly population rather than finding a feasible and cost-effective screening protocol. Even the criteria for progressing to bone scintigraphy and the search for a monoclonal protein were designed to privilege sensitivity. For example, we adopted the same threshold of hs-troponin T (14 ng/L) identified as the upper limit of normal in healthy subjects from the general population, without interpreting these values on the light of renal function. Under this respect, we have recently reported that the combination of NT-proBNP < 180 ng/L and hs-troponin T < 14 ng/L reliably excludes the CA diagnosis, both in the overall population and subgroups referred for either AL-CA or cardiac (pseudo)hypertrophy.[14] We also screened all subjects with a history of carpal tunnel syndrome, thus including also subjects with a very low probability of CA, such as women with monolateral carpal tunnel syndrome.

Based on our results, ATTRwt-CA might not be a major cause of morbidity and reduced life expectancy even in many of the patients affected, as suggested by the NYHA Class II and the signs of an early-stage disease in all the individuals identified. On the other hand, all the patients diagnosed with ATTRwt-CA had no other apparent causes for their mild dyspnoea on effort, possibly indicating a causal role of cardiac amyloid deposition in patient symptoms, especially in the two patients with diastolic dysfunction. Furthermore, ATTRwt-CA may be an uncommon disorder in elderly subjects but should probably not be classified as a rare condition. When making the conservative assumption that we identified all cases of ATTRwt-CA across all age categories, the prevalence of ATTRwt-CA in the general population becomes 0.10%. Indeed, if we hypothesize that none of the 130 subjects unwilling to proceed to Step 2 had ATTRwt-CA and no individual aged <65 years (75% of the population in the province of Pisa)[20] was affected, the final prevalence of ATTRwt-CA becomes 4 out of 4,000, equal to 0.10%, which

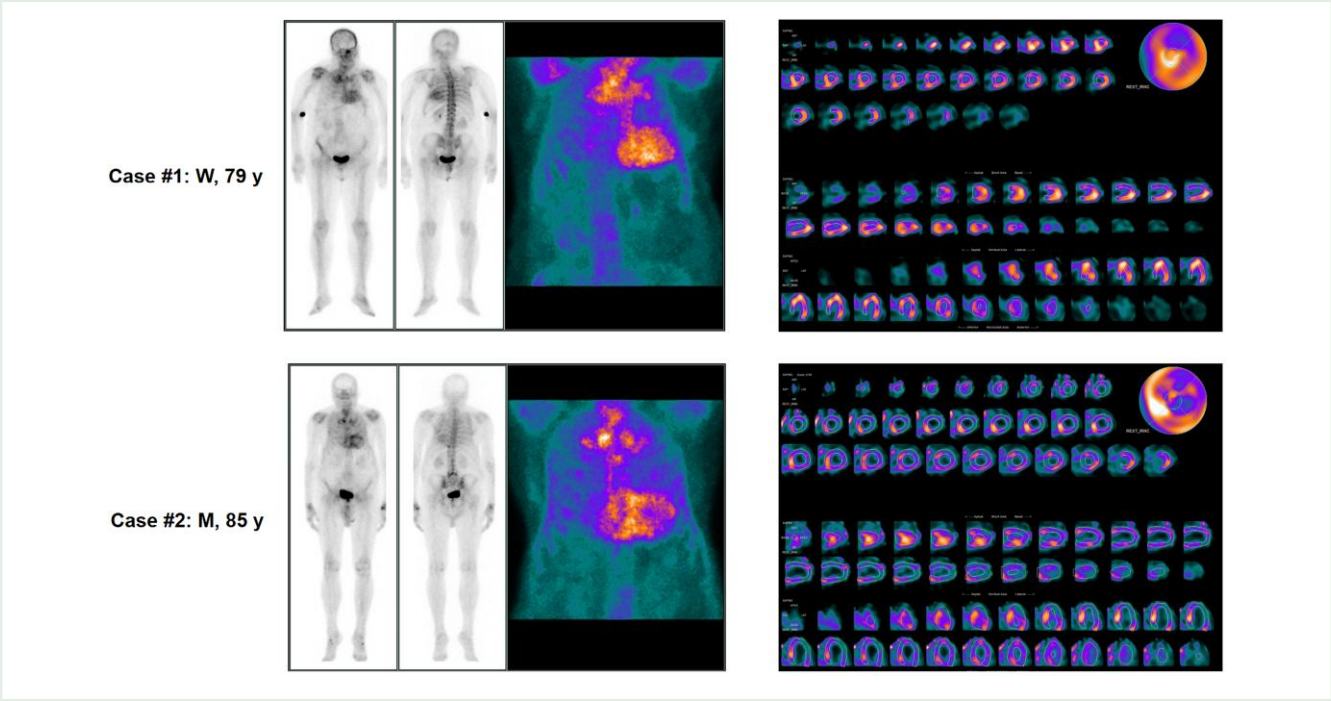


Figure 1 Scintigraphy findings in two patients diagnosed with wild-type transthyretin cardiac amyloidosis and Grade 3 uptake. Findings from a woman and a man receiving a non-invasive diagnosis of transthyretin cardiac amyloidosis are provided. See text for further details. Left: planar scintigraphy. Right: single-photon emission computed tomography. M, man; W, woman.

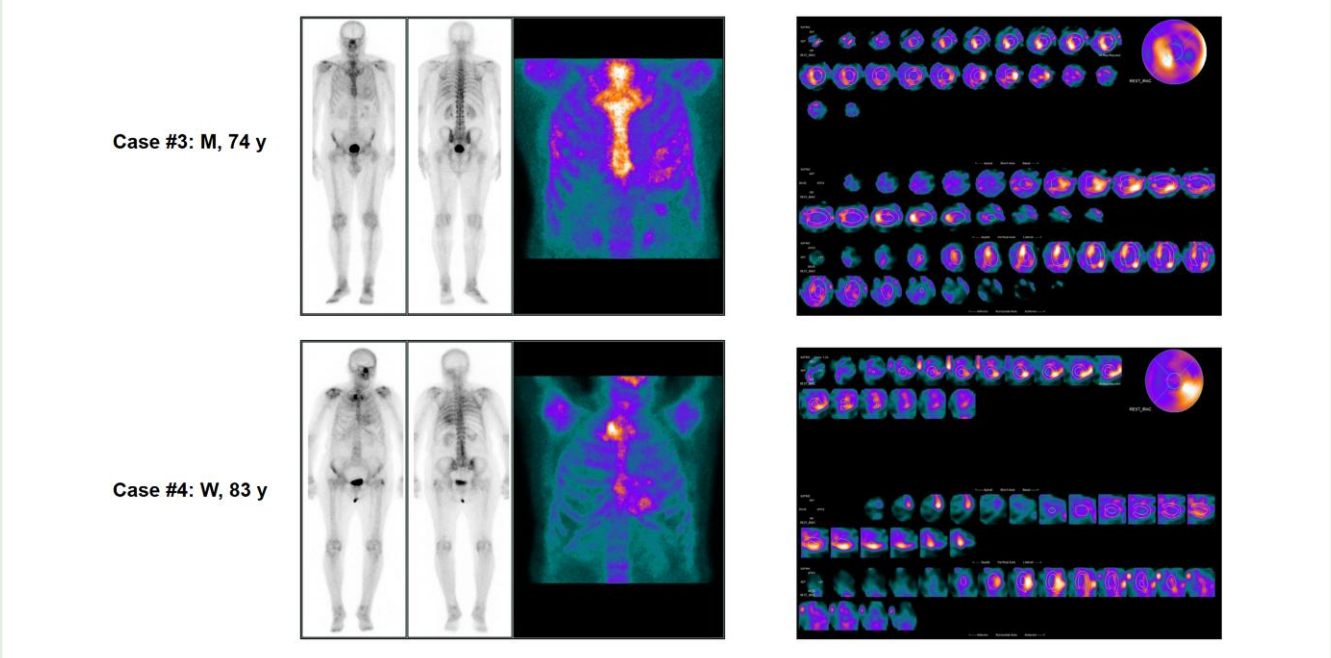


Figure 2 Scintigraphy findings in two patients diagnosed with wild-type transthyretin cardiac amyloidosis and Grade 2 uptake. Findings from a man and a woman receiving a non-invasive diagnosis of wild-type transthyretin cardiac amyloidosis are provided. Case #3 had a borderline Grade 2 uptake; see text for further details. Left: planar scintigraphy. Right: single-photon emission computed tomography. M, man; W, woman.

is two times higher than the thresholds defining a rare disorder in the European Union (0.05%)[22] or the USA (200 000 out of about 330 millions, corresponding to 0.06%).[23] While this conclusion relies on theoretical assumptions, it may inform screening strategies at the population level and provide regulatory agencies and industry with appropriate elements for defining public health or private insurance reimbursement.

Several limitations must be acknowledged. First, the pre-defined number of patients to be screened ($n = 1000$) was arbitrarily selected and relatively low for a rare disorder. Second, many subjects did not enter the study or did not accept Step 2 examinations, raising the question of participation bias. Notably, 254 individuals were bedridden, severely ill, and/or in a nursing home, and some individuals did not progress to Step 2 exams because of health issues. Had ATTR-CA been searched even in frailer individuals, the final prevalence might have been higher. Third, ATTR-CA was not searched in all enrolled individuals, but only in those meeting pre-defined criteria that privileged sensitivity (so that as many as 35% had at least one criterion to progress to Step 2). Some possible manifestations of CA (such as joint replacement)[24] were not considered, and we relied on a previous diagnosis of peripheral neuropathy or signs and/or symptoms suggestive of this condition rather than performing a dedicated neurological evaluation. Furthermore, the HFA-PEEF score was not employed as a diagnostic tool for ATTR-CA as it was proposed as a diagnostic tool for HF with preserved ejection fraction in patients with CA, rather than as a tool to diagnose CA in a general population or in patients with HF.[25] Fourth, ATTR-CA could hypothetically be found even in individuals without red flags: eventual additional cases would only increase the reported prevalence. Fifth, the proposed screening protocol cannot be transferred to a real-world scenario, and further studies are needed to identify a cost-effective screening strategy for ATTR-CA.

In conclusion, ATTRwt-CA has a prevalence of 0.46% in a cohort of elderly subjects from the general population. This condition is therefore uncommon but more frequent than expected for a rare disease.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

A.A. and G.V.: conception, data collection, and manuscript writing; V.C., I.F., A.B., F.G., Y.F.F.C., A.G., D.G., G.B., and M.F.: data collection and critical revision; M.P.,. S.M., M.F., C.P., and M.E.: critical revision; and C.R.: conception and critical input. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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