

## RESEARCH LETTER

doi:10.1002/ejhf.70030

## High prevalence of wild-type transthyretin cardiac amyloidosis in older adults with carpal tunnel syndrome, heart failure or increased left ventricular mass: The CAPTURE study

Amyloidosis is characterized by the extracellular deposition of amyloidogenic proteins that cause tissue dysfunction, organ failure, and death.<sup>1</sup> Transthyretin (TTR) and light-chains of immunoglobulins account for most forms of amyloid cardiomyopathy (ATTR- and AL-CM, respectively).<sup>2</sup> ATTR-CM predominantly affects older adult males.<sup>3–5</sup> Its most common form, wild-type (wt) ATTR-CM, is believed to be caused by ageing-related changes that promote the dissociation of the TTR tetramer into its monomeric subunits, leading to their tissue accumulation. Autopsy studies have revealed cardiac amyloid deposits in 25% of individuals aged  $\geq 85$  years,<sup>6</sup> and in as many as 43% of individuals aged  $\geq 75$  years.<sup>7</sup> Although amyloid deposition does not always become clinically evident, these data suggest that ATTR-CM remains substantially under-diagnosed in the elderly.

Accurately defining the prevalence of ATTR-CM in older adults is becoming ever more critical as populations age and multiple disease-modifying therapies enter clinical practice. In the Italian multicentre AC-TIVE study, including patients aged  $\geq 55$  years with at least one red flag on echocardiography, the prevalence of ATTR-CM was 24% among subjects with suspected amyloid CM.<sup>8</sup> The CATCH study, a prospective screening of unselected subjects aged 65–90 years, involved the search for a monoclonal protein and bone scintigraphy in subjects with at least one red flag, and found a prevalence of ATTRwt-CM of 0.46%.<sup>9</sup>

The CAPTURE study (Cardiac Transthyretin Amyloidosis in the Elderly: Unmasking its Prevalence in Individuals with Cardiac Hypertrophy, Heart Failure, and Carpal Tunnel

**Table 1** Main characteristics of the whole cohort and the subgroups with final diagnoses of amyloid transthyretin or light-chain cardiomyopathy

Characteristics	Subjects screened (n = 1215)	ATTR-CM (n = 311)	AL-CM (n = 32)
Age, years, mean $\pm$ SD	77 $\pm$ 5	80 $\pm$ 4	69 $\pm$ 10
Male sex, %	70	90	62
Hypertension, %	85	91	66
Diabetes, %	24	28	25
MGUS, %	30	10	80
LV hypertrophy and HF, %	55	65	45
LV hypertrophy alone, %	31	33	25
HF alone, %	14	2	30

AL-CM, light-chain cardiomyopathy; ATTR-CM, amyloid transthyretin cardiomyopathy; HF, heart failure; LV, left ventricular; MGUS, monoclonal gammopathy of unknown significance.

Syndrome) was conceived to investigate an elder population, as in CATCH, while placing additional emphasis on the clinical red flag of carpal tunnel syndrome (CTS)<sup>10</sup> in addition to the presence of heart failure (HF) and/or left ventricular (LV) hypertrophy. To be eligible, participants had to meet all of the following criteria: age  $\geq 65$  years; history of mono- or bilateral CTS, whether surgically treated or not; history of HF and/or increased LV mass index relative to current echocardiographic cut-offs,<sup>11</sup> regardless of possible causes (e.g. arterial hypertension); no prior diagnosis of amyloid CM. The study involved the following referral centres for amyloid CM in Italy: Pisa, Trieste, Brescia, Ferrara, Siena, Padua. Each centre established a collaboration with general practitioners who were asked to identify suitable patients and to refer them to the nearest amyloidosis centre for the standard diagnostic workup.<sup>12</sup> A total of 1215 patients were enrolled over 2 years (70% men, age 77  $\pm$  5 years). Their main characteristics are reported in Table 1. More than half of subjects (n = 668, 55%) had both HF and LV hypertrophy, while 377 (31%) had LV hypertrophy but not HF, and 170 (14%) had HF but not LV hypertrophy. ATTR-CM was diagnosed in 311 patients (90% men, age 80  $\pm$  4 years), corresponding to a 26% prevalence of ATTR-CM. The vast majority of these patients presented with the wt form (n = 297, 95%), and 261 (84%) were diagnosed through the non-invasive approach, as they presented with Perugini score 2–3

and no monoclonal protein.<sup>12</sup> An additional 32 subjects (3%) were diagnosed with AL-CM based on a tissue-based protocol, yielding an overall prevalence of amyloid CM of 28%. The prevalence of amyloid CM was 34% in patients with HF and LV hypertrophy, 26% in those with LV hypertrophy alone, and 14% in those with HF alone.

The CAPTURE study provided novel insight on the prevalence of ATTR-CM in older adults presenting with specific red flags, including CTS, HF and/or increased LV mass. Across Italian referral centres, 1215 participants were enrolled, and 26% were diagnosed with ATTR-CM; most of them had the wt form. These results align with the AC-TIVE study, which found a prevalence of ATTR-CM of 24% among individuals aged  $\geq 55$  years whose echocardiograms suggested amyloid CM.<sup>8</sup> Together, the two studies underscore the substantial disease burden in this high-risk group and the critical need for heightened clinical surveillance and earlier diagnosis. Although much less frequent, AL-CM was still detected in 3% of study participants. Interestingly, 11 of these patients had a history of multiple myeloma or monoclonal gammopathy of unknown significance. These haematologic disorders are often not linked to cardiac symptoms unless overt red flags are recognized, also because of the lack of specific recommendations on cardiac screening in patients with plasma cell disorders.<sup>13</sup> Therefore, a diagnosis of AL-CM can still be missed despite prior haematologic follow-up,

underscoring the value of systematic cardiac screening in high-risk populations.

The global prevalence of amyloid CM (ATTR- or AL-CM) in CAPTURE was 28%, again mirroring the 29% prevalence among suggestive echocardiograms in AC-TIVE.<sup>8</sup> LV hypertrophy seemed to drive the diagnostic yield more than HF, as demonstrated by the much higher yield of the screening in patients with LV hypertrophy (with or without HF) than in those with HF alone (41% vs. 14%). This suggests that increased LV mass should prompt screening for amyloid CM in elderly individuals with CTS even in the absence of overt HF. This is also in agreement with the current diagnostic algorithm.<sup>12</sup>

Several limitations must be acknowledged. Our study had an intrinsic selection bias by enrolling only subjects previously undergoing a cardiology examination resulting in a diagnosis of HF and/or LV hypertrophy. While checking that the previous cardiology exams allowed adjudicating LV hypertrophy and/or HF, we did not repeat these examinations and therefore did not reclassify patients into these categories. In many cases, the prior cardiology evaluation had apparently not even identified a possible aetiology. As a result, alternative diagnoses (e.g. hypertensive cardiomyopathy) were often unclear and not systematically recorded. Among the patients diagnosed with amyloid CM according to the current diagnostic algorithm,<sup>12</sup> conditions such as long-standing hypertension may have contributed to the HF or LV hypertrophy phenotype. The timing of CTS diagnosis was not recorded in the majority of cases, therefore this study cannot give further insight on the time from CTS diagnosis to amyloid CM development. Additionally, the number and characteristics of eligible patients who declined participation were not systematically recorded, as these individuals did not provide consent for data collection. This represents a potential source of selection bias, as their clinical profiles remain unknown. We also acknowledge the absence of an age-matched comparator group without red flags, which would have added valuable context.

In summary, CAPTURE reinforces that amyloid CM, particularly the ATTRwt form, is common rather than exceptional in older adults who present with CTS, HF, and/or increased LV mass. The combination of a high diagnostic yield and the operational setbacks encountered in primary care emphasizes the need to streamline the process by documenting red flags in electronic health records,

raising clinical suspicion (possibly through automated alerts), and establishing clear, rapid referral pathways to specialist amyloidosis centres. Implementing such measures will be crucial to shorten the diagnostic workup, initiate disease-modifying therapy while cardiac function is still preserved, and ultimately improve outcomes in this growing patient population.

### Acknowledgement

Open access publishing facilitated by Scuola Superiore Sant'Anna, as part of the Wiley - CRUI-CARE agreement.

### Funding

The study received unconditional funding from Pfizer.

**Conflict of interest:** none declared.

**Alberto Aimo<sup>1,2\*</sup>, Giuseppe Vergaro<sup>1,2</sup>, Maria Concetta Pastore<sup>3</sup>, Daniela Tomasoni<sup>4</sup>, Vincenzo Castiglione<sup>1,2</sup>, Riccardo Saro<sup>5,6</sup>, Elisa Zaro<sup>5,6</sup>, Antonio Maria Sammartino<sup>4</sup>, Elisa Giacomini<sup>3</sup>, Matteo Serenelli<sup>7</sup>, Alberto Cipriani<sup>8,9</sup>, Aldostefano Porcari<sup>5,6</sup>, Andrea Di Lenarda<sup>6</sup>, Marco Metra<sup>4</sup>, Gianfranco Sinagra<sup>5,6</sup>, Matteo Cameli<sup>3</sup>, Marco Merlo<sup>5,6</sup>, and Michele Emdin<sup>1,2</sup>**

<sup>1</sup>Interdisciplinary Center of Health Sciences, Scuola Superiore Sant'Anna, Pisa, Italy; <sup>2</sup>Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy; <sup>3</sup>Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy; <sup>4</sup>Cardiology, ASST Spedali Civili di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; <sup>5</sup>European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart (ERN GUARD-Heart); <sup>6</sup>Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy; <sup>7</sup>Cardiologic Center, University of Ferrara, Ferrara, Italy; <sup>8</sup>Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua, Padua, Italy; and <sup>9</sup>Cardiology Unit, University Hospital of Padua, Padua, Italy

\*Emails: a.aimo@santannapisa.it; aimoalb@ftgm.it

### References

- Flodrova P, Flodr P, Pika T, Vymetal J, Holub D, Dzubak P, et al. Cardiac amyloidosis: From clinical suspicion to morphological diagnosis. *Pathology* 2018;**50**:261–268. <https://doi.org/10.1016/j.pathol.2017.10.012>
- Maleszewski JJ. Cardiac amyloidosis: Pathology, nomenclature, and typing. *Cardiovasc Pathol*

- 2015;**24**:343–350. <https://doi.org/10.1016/j.carpath.2015.07.008>
- Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: A prospective, observational cohort study. *Circulation* 2016;**133**:282–290. <https://doi.org/10.1161/CIRCULATIONAHA.115.018852>
- Pinney JH, Whelan CJ, Petrie A, Dzung J, Banyersad SM, Sattianayagam P, et al. Senile systemic amyloidosis: Clinical features at presentation and outcome. *J Am Heart Assoc* 2013;**2**:e000098. <https://doi.org/10.1161/JAHA.113.000098>
- Givens RC, Russo C, Green P, Maurer MS. Comparison of cardiac amyloidosis due to wild-type and V122I transthyretin in older adults referred to an academic medical center. *Aging Health* 2013;**9**:229–235. <https://doi.org/10.2217/ahe.13.10>
- Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, 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. <https://doi.org/10.1080/07853890701842988>
- Porcari A, Bussani R, Merlo M, Varrà GG, Pagura L, Rozze D, et al. Incidence and characterization of concealed cardiac amyloidosis among unselected elderly patients undergoing post-mortem examination. *Front Cardiovasc Med* 2021;**8**:749523. <https://doi.org/10.3389/fcvm.2021.749523>
- Merlo M, Pagura L, Porcari A, Cameli M, Vergaro G, Musumeci B, et al. Unmasking the prevalence of amyloid cardiomyopathy in the real world: Results from phase 2 of the AC-TIVE study, an Italian nationwide survey. *Eur J Heart Fail* 2022;**24**:1377–1386. <https://doi.org/10.1002/ejhf.2504>
- Aimo A, Vergaro G, Castiglione V, Fabiani I, Barison A, Gentile F, et al. Wild-type transthyretin cardiac amyloidosis is not rare in elderly subjects: The CATCH screening study. *Eur J Prev Cardiol* 2024;**31**:1410–1417. <https://doi.org/10.1093/eurjpc/zwae093>
- Milandri A, Farioli A, Gagliardi C, Longhi S, Salvi F, Curti S, et al. Carpal tunnel syndrome in cardiac amyloidosis: Implications for early diagnosis and prognostic role across the spectrum of aetiologies. *Eur J Heart Fail* 2020;**22**:507–515. <https://doi.org/10.1002/ejhf.1742>
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1–39.e14. <https://doi.org/10.1016/j.echo.2014.10.003>
- 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 ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2021;**42**:1554–1568. <https://doi.org/10.1093/eurheartj/ehab072>
- Dimopoulos MA, Terpos E, Boccadoro M, Moreau P, Mateos MV, Zweegman S, et al. EHA-EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma. *Nat Rev Clin Oncol* 2025;**22**:680–700. <https://doi.org/10.1038/s41571-025-01041-x>