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EDITORIAL

Early-stage amyloid transthyretin cardiomyopathy: uncertainties and opportunities

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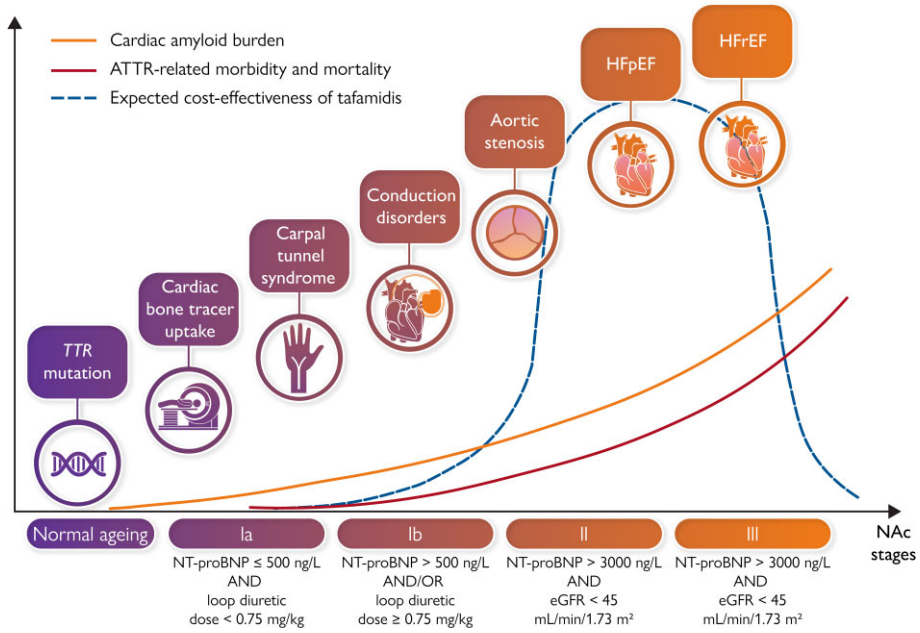
This editorial refers to 'Characteristics and natural history of early-stage cardiac transthyretin amyloidosis', by S. Law *et al.*, https://doi.org/10.1093/eurheartj/ehac259.

Graphical Abstract



Natural history of amyloid transthyretin cardiomyopathy (ATTR-CM).
The figure provides a schematic representation of the progression of tissue amyloid deposits, disease manifestations, the burden of morbidity and mortality, and the expected cost-effectiveness of tafamidis from normal ageing to National Amyloidosis Centre (NAC) Stage III disease. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal probrain natriuretic peptide.

Amyloid transthyretin cardiomyopathy (ATTR-CM) used to be considered a rare disorder whose diagnosis required a tissue biopsy and which had no treatment options. As a result, most cases were diagnosed only in late stages or remained undiagnosed. Over the last few years, greater disease awareness, the introduction of an algorithm for non-invasive diagnosis,[1] and the recent approval of

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tafamidis as the first specific treatment have led to a dramatic increase in the number of diagnoses of ATTR-CM, and particularly its wild-type (wt) form. Studies trying to establish the prevalence of ATTR-CM have pursued two main approaches: (i) the systematic assessment of subgroups with a high likelihood of overt disease [mainly heart failure (HF) with preserved ejection fraction and severe aortic stenosis]; or (ii) the screening of individuals with a high likelihood of subclinical disease (in particular carriers of *TTR* gene mutations, individuals operated on for carpal tunnel syndrome, or those undergoing bone scintigraphy for non-cardiac reasons). Several studies have examined the natural history, predictors of outcome, and response to tafamidis of patients in the first group, while reliable data on subjects with early disease are lacking.

In this issue of the *European Heart Journal*, Law *et al.* provide novel evidence on the natural history of patients with untreated 'early-stage' ATTR-CM.[2] This study is a retrospective analysis of patients from the UK National Amyloidosis Centre (NAC) cohort ($n = 623$) and the French Amyloidosis Mondor Network ($n = 256$). These patients had ATTRwt or ATTR due to the cardiac-specific p.V142I variant, NAC Stage I disease [N-terminal probrain natriuretic peptide (NT-proBNP) $\leq$3000 ng/L and estimated glomerular filtration rate (eGFR) $\geq$45 mL/min/1.73 m^2], and were not receiving any disease-modifying treatment. The authors identified a Stage Ia corresponding to NT-proBNP $\leq$500 ng/L (or $\leq$1000 ng/L in the presence of atrial fibrillation) and a daily loop diuretic equivalent dose $<$0.75 mg/kg. Survival free from all-cause death was compared with patients in Stage Ib (i.e. those with Stage I disease not meeting the criteria for Stage Ia) and survival data on age- and gender-matched individuals from the UK. Individuals with stage Ia ATTR-CM had longer survival than those with Stage Ib disease, and not significantly different from that of the general population. Nevertheless, Stage Ia subjects displayed some evidence of disease progression over a median follow-up of 28 months: for example, 26% progressed to Stage Ib and 18% to Stage II, the percentage of patients with New York Heart Association class $\geq$II increased from 62% to 82%, and median NT-proBNP increased by 145 ng/L per year.[2]

The authors should be congratulated for proposing new diagnostic criteria for early-stage ATTR-CM and for comparing—for the first time—the survival of individuals with early-stage disease vs. matched individuals from the general population. As with all studies introducing novel concepts, this study generates many questions that may prompt new investigations.

What is the time-course of the progression from asymptomatic cardiac disease to overt clinical disease?

It is currently unclear how much time is needed for amyloid deposits to become large and confluent, then for extracellular spaces to enlarge, and eventually for left ventricular (LV) pseudohypertrophy to develop. This lack of evidence translates, for example, into the vague recommendation that *TTR* mutation carriers be screened starting from ~10 years before the age of disease onset in affected family members.[3] Most of the few data about the early stages of ATTR-CM come from the follow-up of *TTR* mutation carriers, from subjects with unexpected cardiac uptake of a bone tracer during a scintigraphy requested for other reasons (who generally have ATTRwt), from patients with carpal tunnel syndrome, or from those with incidental finding of amyloid deposits on tissue specimens from different kinds of surgery. Based on this sparse evidence, we can conclude that: (i) amyloid deposition in the transverse carpal ligament precedes by 3–10 years the development of ATTR-CM; (ii) cardiac uptake of bone tracers may precede (sometimes by several years) the development of LV pseudohypertrophy; and (iii) cardiac amyloid accumulation manifests first with subtle abnormalities in myocardial contraction that can be detected through LV and possibly also left atrial strain.[4]

Plasma natriuretic peptides probably start to increase during early disease stages following the two triggers for release, namely increased myocardial wall tension and the toxicity of amyloid precursors and pre-fibrillary aggregates.[5,6] The study by Law *et al.* shows that NT-proBNP is a strong and independent predictor of outcome even in patients with Stage I disease, which is one of the reasons why the investigators chose an NT-proBNP cut-off to discriminate two subsets of Stage I patients with a different prognosis. Dedicated studies would also be welcome to assess the role of contemporary troponin assays, potentially able to detect cardiomyocyte damage following amyloid deposition and myocardial tissue remodelling.

What are the best criteria to define early-stage ATTR-CM?

As discussed by the authors, the definition of Stage Ia broadly reflects the entry criteria of clinical trials on ATTR amyloidosis, which included NT-proBNP cut-offs and a history of HF or clinical evidence of HF (ATTR-ACT, ATTRIBUTE-CM, APOLLO-B, HELIOS-B, ION-CS2, and ITL-2001-CL-001).[2] The identification of an NT-proBNP cut-off is further supported by the prognostic value of NT-proBNP, as discussed above.[2] On the other hand, the specific cut-off values of NT-proBNP and loop diuretic equivalent dose were chosen arbitrarily. Furthermore, the two variables provide partially overlapping information on pulmonary and systemic congestion, and the loop diuretic dose introduces an element of subjectivity, as it may vary according to the policy of single centres and individual physicians. Additionally, a combination of two dichotomous variables can be easily evaluated in clinical practice, but provides a rather simplistic view of the patient's status. Multidimensional scores combining clinical, imaging, and laboratory data and considering continuous variables might be considered at least in research settings for more accurate patient phenotyping and risk prediction.

What is the life expectancy and the natural history of elderly subjects with early-stage ATTR-CM?

A strength of this study is the comparison with data from age- and gender-matched individuals from the same country. The first

interesting result is that there is no difference in overall survival during a median follow-up period of 21 months.[2] This conclusion is supported by several population studies searching for Val122Ile mutation carriers among black Americans,[7–9] where the mutation status was not associated with shorter survival, even though patients were much younger than in the present study (e.g. 62 years in the REGARDS cohort vs. 75 years in the cohort of Law *et al.*).[2,7] Therefore, we are starting to diagnose ATTR-CM even in older individuals whose life expectancy will not be affected by this slowly progressing disorder.

While early-stage ATTR-CM does not seem to affect the life expectancy of these patients, it still displayed an appreciable progression during the <2 year median follow-up. For example, a quarter of patients progressed from Stage Ia to Stage Ib, and slightly less than a fifth to Stage II or III.[2] Accordingly, in the population studies on black American individuals, mutation carriers had a much higher risk of incident HF than matched individuals,[7–9] and this association was confirmed even after extensive adjustment for potential confounders.[7] An important limitation of these studies is that they simply excluded individuals with known HF at baseline, and did not search for echocardiographic or laboratory signs of cardiac disease.[7–9] We therefore do not know how many of them would have met the NT-proBNP criterion for Stage Ia disease. Nonetheless, we may reasonably conclude that subjects with early-stage disease have a higher risk of incident HF than age-matched individuals. HF hospitalization is clearly a softer endpoint than all-cause mortality, but remains an important determinant of morbidity and worse quality of life in patients with ATTR-CM.[10]

Translating these concepts from the clinical setting to the design of randomized clinical trials, we might conclude that reducing the rates of HF hospitalization is a reasonable goal in subjects with early-stage ATTR-CM, while efforts to reduce mortality are likely bound to fail.

Does a disease-modifying therapy have an acceptable cost-effectiveness profile in patients with early-stage ATTR-CM?

Tafamidis is the only approved treatment for cardiac amyloidosis patients without polyneuropathy. The criteria for prescription usually reflect the inclusion criteria of ATTR-ACT, which basically corresponds to the definition of Stage Ib ATTR-CM.[11] Subjects with Stage Ia disease were thus not enrolled in ATTR-ACT and are not eligible for tafamidis therapy because of the lack of demonstrated prognostic benefit from this drug. On the other hand, tafamidis seemed more effective in less symptomatic patients, and treatment initiation in early-stage ATTR-CM might be equally as effective, at least when assessing the impact on HF hospitalization and quality of life. It is not unreasonable to propose clinical trials on patients with early-stage disease (either ATTRwt or ATTRv with a cardiac phenotype) with the goal of reducing the burden of HF hospitalizations and improving the quality of life. A major hindrance to such trials is the high cost of these drugs making them not cost-effective even in patients with more advanced disease,[12] where they can reduce mortality rates.

Conflict of interest: none declared.

References

1. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, *et al.* Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016;**133**:2404–2412.
2. 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.
3. 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.
4. Rapezzi C, Aimo A, Pavasini R. Longitudinal strain in the management of cardiac AL amyloidosis: do we need it? *Eur Heart J* 2022;**43**:342–344.
5. Castiglione V, Franzini M, Aimo A, Carecci A, Lombardi CM, Passino C, *et al.* Use of biomarkers to diagnose and manage cardiac amyloidosis. *Eur J Heart Fail* 2021;**23**:217–230.
6. Bourgault S, Choi S, Buxbaum JN, Kelly JW, Price JL, Reixach N. Mechanisms of transthyretin cardiomyocyte toxicity inhibition by resveratrol analogs. *Biochem Biophys Res Commun* 2011;**410**:707–713.
7. Parcha V, Malla G, Ivin MR, Armstrong ND, Judd SE, Lange LA, *et al.* Association of transthyretin Val122Ile variant with incident heart failure among black individuals. *JAMA* 2022;**327**:1368–1378.
8. Quarta CC, Buxbaum JN, Shah AM, Falk RH, Claggett B, Kitzman DW, *et al.* The amyloidogenic V122I transthyretin variant in elderly black Americans. *N Engl J Med* 2015;**372**:21–29.
9. Buxbaum J, Alexander A, Koziol J, Tagoe C, Fox E, Kitzman D. Significance of the amyloidogenic transthyretin Val 122 Ile allele in African Americans in the Arteriosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Am Heart J* 2010;**159**:864–870.
10. Aimo A, Rapezzi C, Perfetto F, Cappelli F, Palladini G, Obici L, *et al.* Quality of life assessment in amyloid transthyretin (ATTR) amyloidosis. *Eur J Clin Invest* 2021;**51**:e13598.
11. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, *et al.* Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016.
12. Kazi DS, Bellows BK, Baron SJ, Shen C, Cohen DJ, Spertus JA, *et al.* Cost-effectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. *Circulation* 2020;**141**:1214–1224.