Circulation

ON MY MIND

Screening for Cardiac Involvement in Carriers of Pathogenic *TTR* Variants: Proposal for an Approach Based on High-Sensitivity Troponin

Alberto Aimo, MD, PhD; Chiara Sanguinetti, PhD; Maria Franzini, PhD

Amyloidosis is a systemic disorder caused by the deposition of misfolded proteins in various organs. Genetic variants that reduce TTR (transthyretin) stability cause the variant (v) form of TTR amyloidosis (ATTRv). ATTRv amyloidosis can manifest as early as the fifth decade of life with isolated cardiac disease (characterized by heart failure and/or conduction disturbances), isolated peripheral or autonomic neuropathy, or both. Besides 2 stabilizing and protective *TTR* variants, around 140 *TTR* variants are reported as pathogenic. Their incomplete penetrance and variable expressivity pose challenges for the screening of variant carriers, who may develop subclinical, and then overt, cardiac or neurologic disease.[1,2]

Cardiac biomarkers (troponins and natriuretic peptides) represent a possible way to detect myocardial damage, regardless of the specific variant. The evidence is basically limited to a study reporting that heterozygous carriers of *TTR* V142I display both increased high-sensitivity troponin (hs-Tn) I values and increased risk for incident heart failure.[3] Despite the lack of solid evidence, both the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) recommend serial measurements of cardiac biomarkers in *TTR* variant carriers. The ESC suggests measuring hs-Tn and NT-proBNP (N-terminal pro-B-type natriuretic peptide), echocardiography, and ECG Holter monitoring, beginning ≈10 years before the age of onset in the proband (predicted age of disease onset). Scintigraphy with a bone tracer and cardiac magnetic resonance (CMR) imaging should be performed every 3 years or when other tests are abnormal.[1] The ACC proposes instead a baseline cardiac screening including ECG, cardiac biomarkers, and echocardiography with strain, to be repeated "based on symptoms." Cardiac screening and neurology consultations are advised when cardiac screening is abnormal.[2] Both the ESC and ACC documents lack clear guidelines on what constitutes abnormal findings that require further investigation. This is particularly relevant for cardiac biomarkers, which are possibly the most sensitive indicators of myocardial remodeling, but expose also to the risk of false positive findings.

A slight elevation of cardiac biomarkers may signal an ongoing myocardial damage, which will eventually lead to structural and functional cardiac disease, and ultimately, signs and symptoms of cardiac disease. Similarly, even small increases in cardiac biomarkers over time may signal a progression of cardiac disease. Such increases should be greater than the analytic variability (ie, the changes over repeated measures of the biomarker in a same sample), plus the intra-individual biologic variability (ie, the random changes in biomarker values, in samples collected at different times, around the setting point of each individual). The reference change value (RCV) is a measure that incorporates both sources of variability. It is calculated as $RCV = 2.77 \times \sqrt{(CVa^2 + CVi^2)}$, where *CVa* and *CVi* represent the coefficients of analytical and intraindividual variability, respectively.[4] Few data on the biologic variability of NT-proBNP are available. Individuals without known heart disease have typically hs-Tn values <99th percentile upper reference level. By definition, hs-Tn methods exhibit a CVa <10% for biomarker

Key Words: amyloidosis ■ heart diseases ■ investigational therapies ■ prealbumin ■ troponin

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Alberto Aimo, MD, PhD, Interdisciplinary Center for Health Sciences, Scuola Superiore Sant'Anna, and Cardiology Division, Fondazione Toscana Gabriele Monasterio, Piazza Martiri della Libertà 33, 56124 Pisa, Italy. Email a.aimo@santannapisa.it or aimoalb@ftgm.it

For Sources of Funding and Disclosures, see page 1658.

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

values at the upper reference level.[4] Based on reference datasets (https://biologicalvariation.eu/), CVi values for hs-TnT and hs-TnI are 11.4% and 12.7%, respectively. By applying the CVa and CVi values to the aforementioned formula, we calculate an RCV of 42% for the single hs-TnT assay and an average RCV of 45% for hs-TnI assays. This indicates that increased hs-TnT >42% or increased hs-TnI >45% in the same individual cannot be attributed to random fluctuations in biomarker values. Instead, these increases signify ongoing and worsening cardiac damage. The availability of point-of-care assays for troponins with the analytic performance of high-sensitivity methods increases the possibility of repeated measurement.

Based on these premises, we propose the following screening algorithm: hs-Tn should be measured beginning 10 years before the predicted age of disease onset; if hs-Tn remains stable or increases <50% in 1 year (rounding up from the previously noted values 42% to 45%), another measurement after 1 year may suffice, and additional tests may not be essential. An hs-Tn value that increases ≥50% in 1 year in the absence of possible causes (eg, worsening renal function), suggests cardiomyocyte damage related to amyloid deposition. This may warrant searching for extracellular volume expansion or regional bone tracer uptake via CMR or single-photon emission computed tomography with bone tracer, respectively (Figure).

When there is laboratory and imaging evidence of heart disease, starting a treatment that halts or slows ATTR progression is reasonable to stop amyloid deposition and prevent further cardiac remodeling. However, phase 3 trials for cardiac amyloidosis have only recruited symptomatic patients with NT-proBNP values ≥300 ng/L. Therefore, there are no approved drugs for patients with subclinical cardiac amyloidosis who do not have clinically evident neuropathy, which in and of itself indicates the need for therapy.[1,2]

The ongoing ACT-EARLY (Acoramidis Transthyretin Amyloidosis Prevention Trial in the Young) study is investigating the potential to prevent the development of symptomatic disease by administering acoramidis treatment to *TTR* variant carriers, beginning 10 years before the anticipated onset of the disease based on the proband's age of onset.[5] If this study yields positive results, the standard approach for managing carriers will involve administering acoramidis 10 years before the expected onset of the disease. However, if the ACT-EARLY results are neutral, negative, or inconclusive, alternative studies should be pursued to explore treatment options for patients with asymptomatic heart disease. A possible strategy involves the screening algorithm proposed above: annual measurement of hs-TnT/I through standard or point-of-care assays, followed by CMR or single-photon emission computed tomography with a bone tracer if troponin levels increase >50% from the previous year. Treatment should be initiated if both troponin changes and imaging findings indicate cardiac involvement. Prospective studies are required to determine the proportion of carriers with ≥50% annual change who have evidence of subclinical cardiac involvement on imaging, and whether treatment initiation in this stage can stop disease progression and has a favorable cost-effectiveness profile.

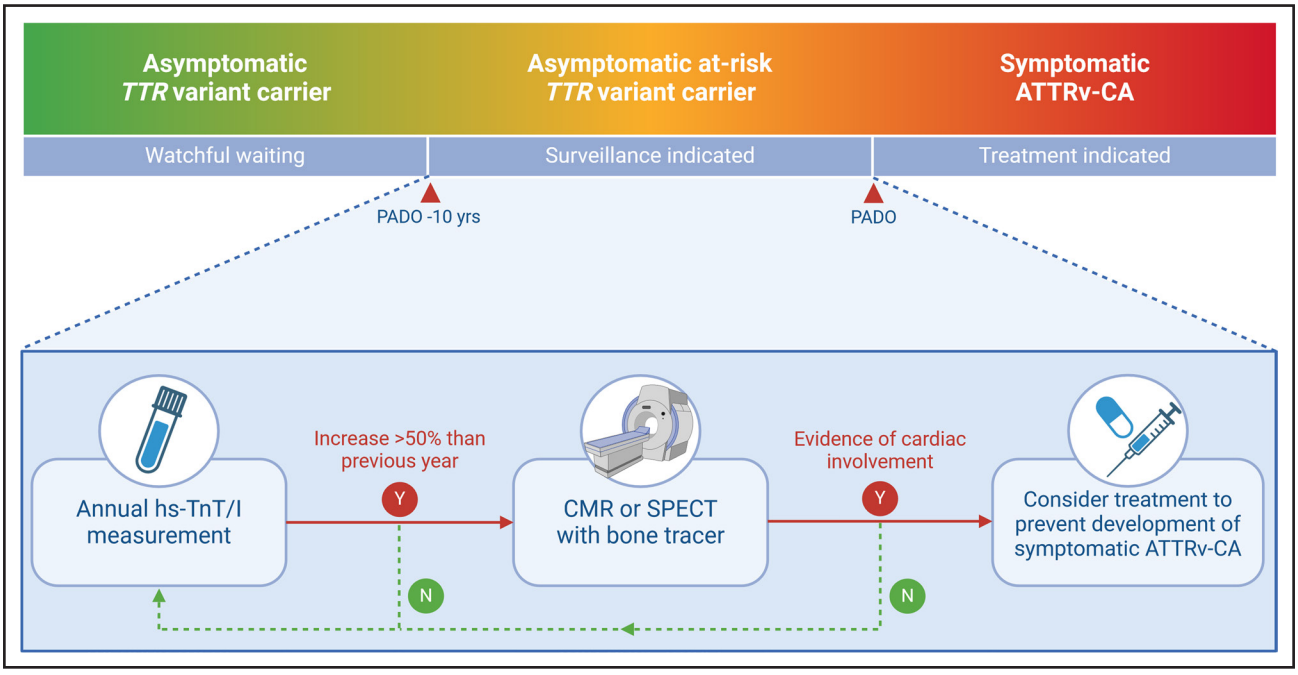

Figure. Proposed screening strategy for cardiac disease in carriers of *TTR* gene variants.
ATTRv indicates transthyretin amyloidosis variant; CA, cardiac amyloidosis; CMR, cardiac magnetic resonance; hs-TnT/I, high-sensitivity troponin T/I; N, No; PADO, predicted of age disease onset; SPECT, single-photon emission computed tomography; TTR, transthyretin; and Y, Yes.

ARTICLE INFORMATION

Affiliations

Health Sciences Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy (A.A.). Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy; (A.A.) Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Italy (C.S., M.F.).

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, Burazor I, Caforio ALP, Damy T, Eriksson U, 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. doi: 10.1002/ejhf.2140
2. Kittleson MM, Ruberg FL, Ambardekar AV, Brannagan TH, Cheng RK, Clarke JO, Dember LM, Frantz JG, Hershberger RE, Maurer MS, et al; Writing Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81:1076–1126. doi: 10.1016/j.jacc.2022.11.022
3. Coniglio AC, Segar MW, Loungani RS, Savla JJ, Grodin JL, Fox ER, Garg S, de Lemos JA, Berry JD, Drazner MH, et al. Transthyretin V142I genetic variant and cardiac remodeling, injury, and heart failure risk in Black adults. *JACC Heart Fail*. 2022;10:129–138. doi: 10.1016/j.jchf.2021.09.006
4. Burtis CA, Bruns DE. *Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics*. 7th Edition. 2015; Elsevier Missouri, Saunders: 364–370.
5. Garcia-Pavia P, Gillmore JD, Adams D, Conceicao I, Coelho T, Judge DP, Maurer MS, Ruberg FL, Solomon S, Masri A, et al. Rationale and design of ACT-EARLY, the acoramidis transthyretin amyloidosis prevention trial. Presented at: 2024 International Symposium on Amyloidosis; May 26–30, 2024, Rochester, MN.