ATTR Amyloidosis Disease Management

MED-US-DZSTATE-2400019

ATTR Amyloidosis Disease State Slide Deck

- This resource provides information about ATTR amyloidosis.
- This resource is intended to be viewed in its entirety to support scientific exchange and is not intended as recommendations for clinical practice.
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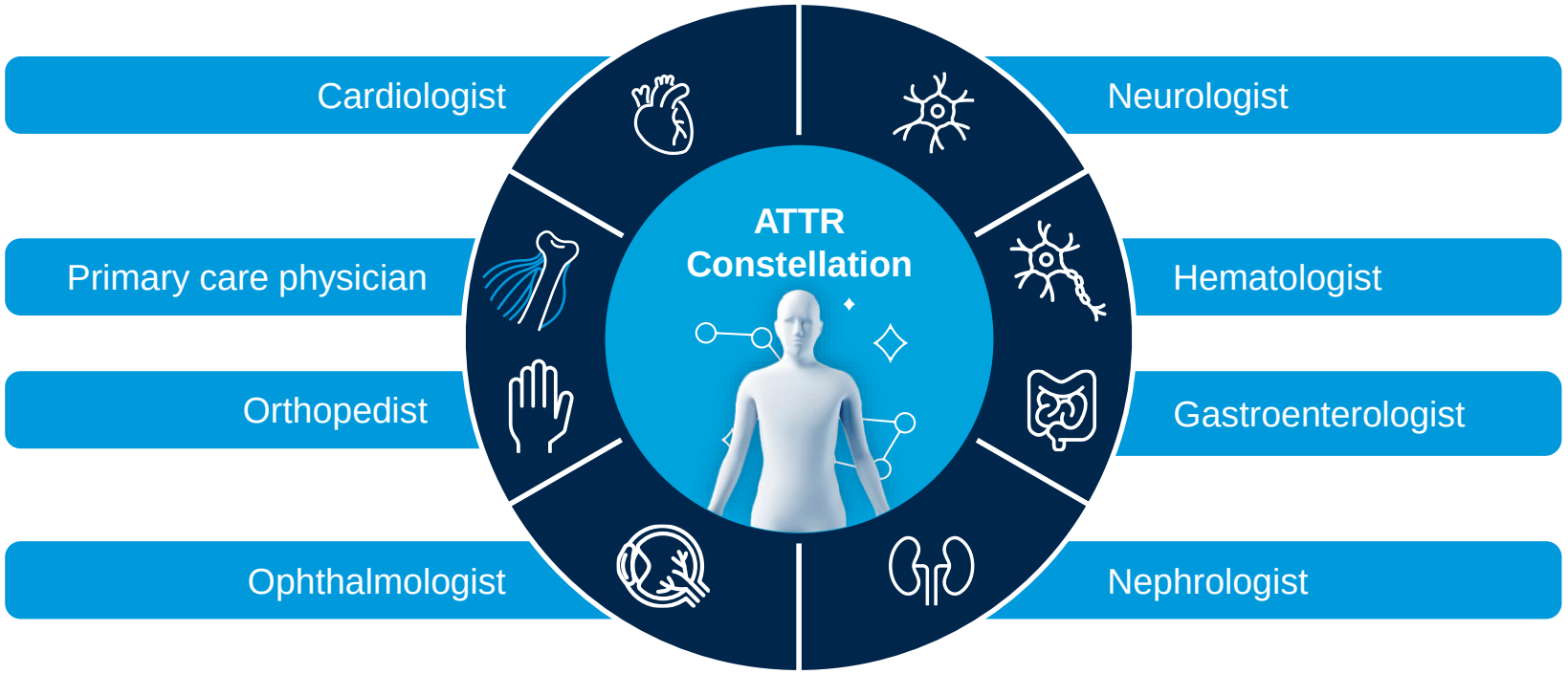
Management

The Multisystemic Nature of ATTR Amyloidosis Requires a Multidisciplinary Approach for Assessment, Diagnosis, and Management[1-3]



Advanced-practice providers, for example nurses, pharmacists, dieticians, geneticists, and social workers, also contribute to the treatment and care of amyloidosis patients.[4,5]

ATTR, transthyretin-mediated.

1. Nativi-Nicolau et al. *Heart Fail Rev.* 2022;27(3):785–93; 2. Ando et al. *Amyloid.* 2022;29(3):143–55; 3. Karam et al. *Meeting of the International Society of Amyloidosis* 2022; Poster P192; 4. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 5. Nativi-Nicolau et al. *Clin Med Insights Cardiol.* 2021;15:1–10.

hATTR Amyloidosis ISA Guideline Recommendations for Symptomatic Therapy

Symptom	Therapy
Neuropathic pain	• **First line:** SNRI, gabapentinoids, trialed in 4-6-week period with 2 weeks at max tolerated dose • **Second line:** weak opioid analgesics, topical agents • **Third line:** strong opioids
Gastrointestinal disturbances	• Dietary changes • Prokinetics with erythromycin or domperidone • Metoclopramide for acute attacks of recurrent vomiting • Osmotic laxatives and polyethylene glycol • Linaclotide, lubiprostone, and prucalopride when laxatives have failed • Rifaximin followed by probiotics • Octreotide or opium tincture for chronic diarrhea refractory to loperamide
Cardiac involvement	• Low dose loop diuretics or mineralocorticoid receptor antagonists in case loop diuretics fail • Beta blockers, ACE inhibitors, or angiotensin receptor blockers if no clear contraindications • Anticoagulation with warfarin or other oral anticoagulant for rhythm disturbances • Pacing for significant bradycardia and certain AV blocks • ICD is not indicated as sudden cardiac death in ATTR-CM may result
Orthostatic hypotension	• **Nonpharmacologic interventions:** compression stockings, removal of aggravating hypotensive medications, increasing water intake • **Pharmacologic:** norepinephrine replacers, fludrocortisone, octreotide • In case of CHF, avoid fludrocortisone
Ocular involvement	• Ocular lubrication, vitrectomy or trabeculectomy
Renal failure	• Treatment in line with guidelines for chronic kidney failure • Hemodialysis for end stage disease

Symptomatic management in hATTR amyloidosis is of major importance due to its impact on patient quality of life as well as social, economic, and psychological well-being.

ACE, angiotensin-converting enzyme; ATTR-CM, transthyretin amyloidosis cardiomyopathy; AV, atrial-ventricular; CHF, congestive heart failure; hATTR, hereditary transthyretin-mediated; ICD, implantable cardioverter defibrillator; ISA, International Society of Amyloidosis; SNRI, serotonin-norepinephrine reuptake inhibitors.

1. Ando et al. *Amyloid.* 2022; 29(3):143–55.

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Current Therapeutic Strategies for ATTR Amyloidosis

Strategies include both approved therapies and investigational treatments in clinical trials

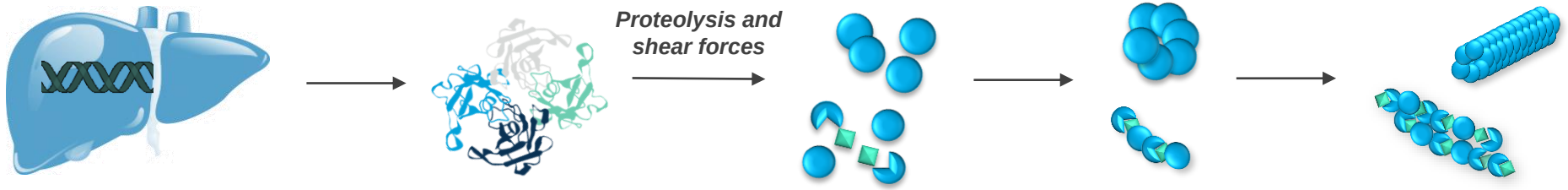
Suppression of TTR synthesis:

Gene silencing (siRNA, ASO)
Gene editing (CRISPR-Cas9)

TTR stabilizers

Amyloid fibril degradation/reabsorption:

Anti-misfolded-TTR monoclonal antibody



TTR* gene expressed in liver** → **TTR tetramer** → ***Proteolysis and shear forces → **TTR monomers** → **Truncated and misfolded TTR** → **Amyloid fibrils**

Image adapted from Ando et al. 2022[1]

ASO, antisense oligonucleotide; ATTR, transthyretin-mediated; CRISPR, clustered regularly interspaced short palindromic repeats; siRNA, small interfering ribonucleic acid; TTR, transthyretin.

1. Ando et al. *Amyloid.* 2022; 29(3):143–55.

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Monitoring Patients With hATTR Amyloidosis Following Diagnosis and Treatment Initiation

Patients presenting with one class of symptoms should schedule a yearly follow-up with appropriate specialists to monitor the other classes of hATTR amyloidosis symptoms.

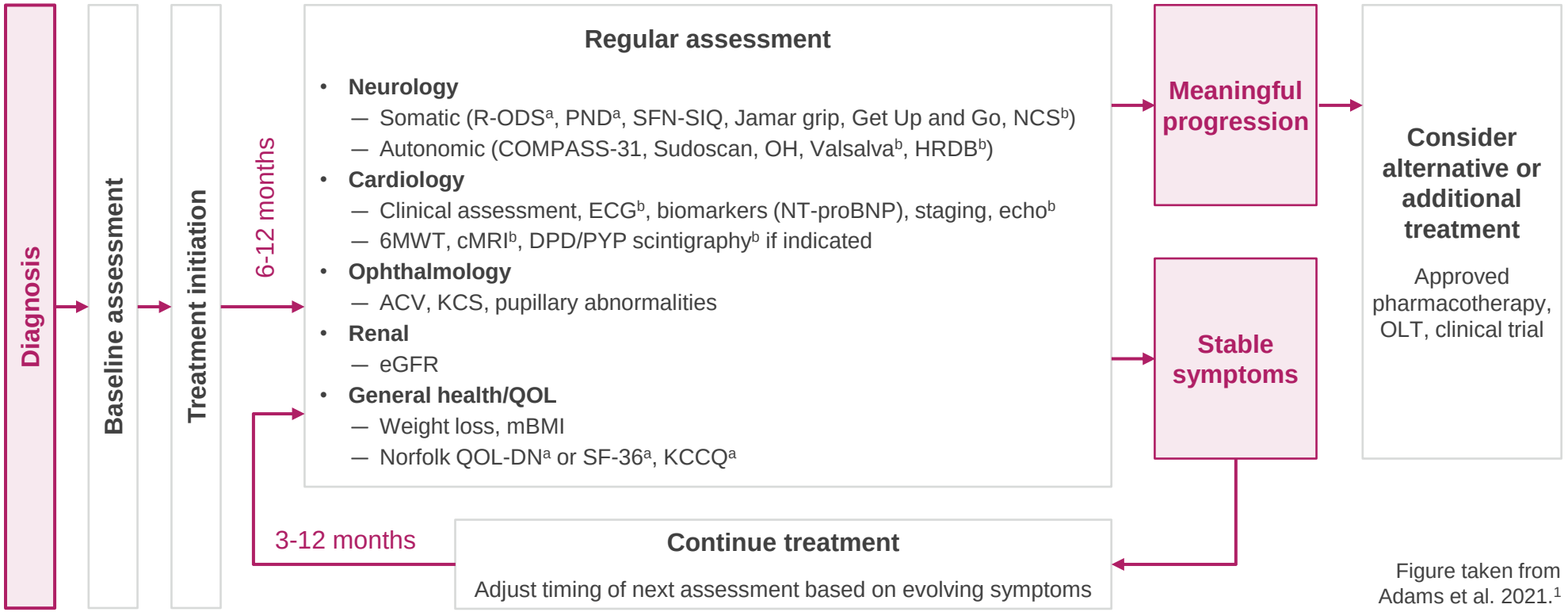

Figure taken from Adams et al. 2021.[1]

[a]Questionnaire to be performed prior to consultation. [b]Additional test.
6MWT, 6-min walk test; ACV, abnormal conjunctival vessel; cMRI cardiac magnetic resonance imaging; COMPASS-31, Composite Autonomic Symptom Score-31; DPD, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin-mediated; HRDB, heart rate deep breathing; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCS, keratoconjunctivitis sicca; mBMI, modified body mass index; NCS, nerve conduction study; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide; OH, orthostatic hypotension; OLT, orthotopic liver transplantation; PND, polyneuropathy disability; PYP, ^{99m}Tc-pyrophosphate; QOL, quality of life; R-ODS, Rasch-built Overall Disability Scale; SF-36, 36-item Short-Form Health Survey; SFN-SIQ, small-fiber neuropathy and symptom inventory questionnaire.

1. Adams et al. *Orphanet J Rare Dis.* 2021;16:411

Assessment of Disease Progression Is an Unmet Need in the Management of ATTR Amyloidosis

What is known?

ATTR amyloidosis is a progressively debilitating and ultimately fatal disease[1,2]

ATTR amyloidosis progresses silently and rapidly[1,3]

As the disease progresses, patients experience increasingly severe symptoms, disability, and mortality[1]

ATTR amyloidosis is underdiagnosed and often misdiagnosed[1–4]

Patients are often diagnosed when they already have late-stage manifestations[3,4]

Early diagnosis and treatment may improve patient outcomes[1–4]

What are the data and knowledge gaps?

How to define disease progression in ATTR amyloidosis[1,3,4]

There is limited consensus on how to monitor symptomatic patients[1]

There are no validated criteria to determine if a patient is responding to treatment[4]

Understanding of the early stages of disease[3]

The profile of progression is not well characterized from the very early stages of disease[3]

Improved disease awareness is required to diagnose patients earlier and gain a more complete understanding of the disease[1–3]

There is an urgent clinical need to identify widely applicable markers of disease progression that can be used by HCPs to accurately monitor progression and help guide decisions on when to initiate or modify therapy[1,5]

ATTR, transthyretin-mediated; HCP, healthcare professional.

1. Adams et al. *Orphanet J Rare Dis* 2021;16(1):411; 2. Nativi-Nicolau et al. *ESC Heart Fail* 2021;8(5):3875–84; 3. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23(6):895–905; 4. Ando et al. *Amyloid* 2022;29(3):143–55; 5. Ioannou et al. *J Am Coll Cardiol* 2024;83(14):1276–91.

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Recent Recommendations and Literature Updates on Assessment of ATTR Amyloidosis Disease Progression

2021

Garcia-Pavia et al.

Eleven measurable features for monitoring progression in patients with ATTR-CM are proposed and discussed by a group of experts in cardiac amyloidosis. The experts also include a recommended threshold indicating progression for each feature[1]

2021

Adams et al.

Experts discuss the importance of a multisystem approach to managing hATTR amyloidosis, and include guidance for assessing progression in neuropathy and cardiac dysfunction, as well as their opinions on the sensitivity of these assessments in detecting progression[2]

hATTR-PN **hATTR-CM**

2022

Ando et al.

Experts propose guidelines for monitoring hATTR amyloidosis disease progression in response to therapy, including a proposed common minimum set of evaluation to monitor the course of polyneuropathy[3]

2024

Ioannou et al.

A landmark survival analysis is evaluated to assess the prognostic importance of an increase in NT-proBNP and outpatient diuretic intensification (ODI) as markers of disease progression in ATTR-CM[4]

= Additional info

These guidelines represent the opinions of experts in ATTR amyloidosis. These slides and pop-ups only present a top-line summary of certain aspects of each publication. This resource should not be used alone to guide assessment of disease progression. The full references can be accessed using the blue underlined links above.

ATTR, transthyretin-mediated; ATTR-CM, ATTR amyloidosis with cardiomyopathy; hATTR, hereditary ATTR; hATTR-CM, hereditary ATTR amyloidosis with cardiomyopathy; hATTR-PN, hereditary ATTR amyloidosis with polyneuropathy; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide.

1. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23(6):895–905; 2. Adams et al. *Orphanet J Rare Dis* 2021;16(1):411; 3. Ando et al. *Amyloid* 2022;29(3):143–55; 4. Ioannou et al. *J Am Coll Cardiol* 2024;83(14):1276–91.

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Expert Consensus for Monitoring Progression in ATTR Amyloidosis with Cardiomyopathy

Eleven clinical parameters for monitoring disease progression in ATTR amyloidosis with cardiomyopathy were identified by experts and deemed to be feasible and clinically meaningful

The experts recommended that the presence of one marker from each of the following three specified domains met the minimum requirements for defining disease progression:

Domain 1
Clinical and functional endpoints

Any hospitalization (related to HF decompensation) in a 6-month period

One class increase in NYHA Class[a]

Five-point decrease in KCCQ (deterioration); ten-point decrease in KCCQ (moderate deterioration); 10% decrease in EQ-5D score (deterioration)

Decrease of 30–40 m every 6 months in the 6-MWT[b]

+

Domain 2
Biomarkers and laboratory markers

30% increase in troponin (high-sensitivity assay)

30% increase in NT-proBNP with 300 pg/mL cut-off[c]

Advance in NAC staging score

+

Domain 3
Imaging and electrocardiographic parameters

≥2 mm increase in LV wall thickness

≥5% decrease in LV ejection fraction; ≥5 mL decrease in stroke volume and ≥1% increase in LV global longitudinal strain

Stepwise increase in diastolic functioning grade; consistent deterioration in diastolic function

New-onset bundle branch block, or AV block (of any degree); sinus pauses, sinus node dysfunction, AF with a very slow ventricular response without pharmacologic treatment (<50 bpm)

[a]Must be measured during a 30-day period of stability. [b]In the absence of an obvious non-cardiovascular cause. [c]To be measured during a 30-day period of clinical stability and under the same atrial rhythm. 6-MWT, 6-minute walk test; AF, atrial fibrillation; ATTR, transthyretin-mediated; AV, atrioventricular; EQ-5D, EuroQol five dimensions; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Garcia-Pavia et al. *Eur J Heart Fail* 2021;23(6):895–905.

Expert Opinion for Monitoring Progression in hATTR Amyloidosis with Polyneuropathy

As hATTR amyloidosis with polyneuropathy progresses, organs become more impaired, and most neuropathy symptoms worsen in a linear fashion.
The appearance of new symptoms or the worsening of existing signs or symptoms may indicate progression. The rate of worsening is also an important consideration

Authors identified assessments for monitoring progression in somatic and autonomic neuropathy in recommended order of importance, and rated their sensitivity to progression[a]:

	Indicators of progression in somatic neuropathy (top three most important only)	Indicators of progression in autonomic neuropathy (top three most important only)
1	Change in gait speed of 0.05–0.10 m/s in the 10-MWT OR an increase of 15% over 6 months (or 30% over 12 months) in the time taken to stand up, walk across the room, and sit down (Timed Get Up and Go Test) (**Sensitivity: High**)	Reduction on two consecutive examinations of the feet using Sudoscan® (sudomotor testing)[c] (**Sensitivity: High**)
2	Change in PND disease stage[b] (**Sensitivity: Low in early-onset V30M, high in late-onset V30M**)	Change from age-adjusted normal value to abnormal value in the heart rate deep breathing assessment (**Sensitivity: High**)
3	Reduction in grip strength of 4–6 kg over 12 months in the Jamar Hand Dynamometer—both hands grip strength test (**Sensitivity: High**)	Reduction of total CADT score (CADT questionnaire[d]) by two points or reduction of any subscore by one point OR increase by one point in a year in the COMPASS-31 questionnaire[d] (**Sensitivity: Low**)

[a]Sensitivity based on the authors' clinical experience. [b]Not sensitive to small changes in progression but useful to assess during monitoring visits as a change in score indicates increased functional impairment. [c]Rarely performed but useful for monitoring patients with V30M and early-onset disease. [d]These scales are non-linear, so the impact of a specific score change may differ according to the patient's starting level.
10-MWT, 10-meter walk test; CADT, Compound Autonomic Dysfunction Test; COMPASS-31, Composite Autonomic Symptom Score-31; hATTR, hereditary transthyretin-mediated; PND, polyneuropathy disability.
Adams et al. *Orphanet J Rare Dis* 2021;16(1):411.

Expert Opinion for Monitoring Progression in hATTR Amyloidosis with Cardiomyopathy

Cardiac symptoms do not always worsen in a linear fashion and instead may have thresholds or may even be reversible in the short/medium-term with symptomatic treatment such as diuretics. This makes it difficult to use worsening of cardiac symptoms or NYHA classification alone to evaluate progression in hATTR amyloidosis with cardiomyopathy

Authors identified assessments for monitoring progression in cardiac dysfunction and rated their sensitivity to progression[a]:

Clinical, functional, and biomarker assessments	Cardiac structure and conduction assessments (high sensitivity only, please see reference for full list)
New signs and symptoms of chronic heart failure; unplanned cardiac hospitalization; uncontrolled heart failure that would require increased diuretic dosage or IV diuretics (**Sensitivity: High**)	New arrhythmias, burden of atrial fibrillation, need for pacing, or ventricular tachycardia/ventricular fibrillation on Holter ECG[b]
Decrease of 20–30 m in the 6-MWT (if no disabling neuropathy) (**Sensitivity: High**)	New bundle branch block or AV block; new microvoltage or pseudo-myocardial infarction pattern; or new arrhythmias on 12-lead ECG[c]
Persistent change in the patient's Grogan or Gillmore stage (**Sensitivity: Medium**)	Changes in longitudinal relaxation time, extracellular volume, wall thickness, or ejection fraction on cardiac MRI[d]
Trend increase in NT-proBNP, troponin I, troponin T (**Sensitivity: High**)	PYP or DPD cardiac uptake using qualitative Perugini grading 1–3, quantification by scintigraphy with bone tracers using H/L ratio[d,e]

[a]Sensitivity based on the authors' clinical experience. [b]If new syncope: repeat Holter for sinus dysfunction, atrial fibrillation, atrial or ventricular arrhythmias, and consider EPS. [c]High/medium sensitivity. [d]Cardiac imaging should be performed at different visits by the same operator or radiologist, on the same machine, using the same software. [e]Repeat scan only if initial scan was negative, and if >3 years since last scan, and echo shows significant increase in wall thickness.

6-MWT, 6-minute walk test; AV, atrioventricular; DPD, 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiogram; EPS, electrophysiologic study; hATTR, hereditary transthyretin-mediated; H/L, heart-to-lung; IV, intravenous; LV, left ventricular; MRI, magnetic resonance imaging; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PYP, 99mTc-pyrophosphate.

Adams et al. *Orphanet J Rare Dis* 2021;16(1):411.

Recommendations for Monitoring Progression in hATTR Amyloidosis with Polyneuropathy

A common minimum set of evaluation is necessary to monitor the course of polyneuropathy in response to therapy. In the authors' opinion, this monitoring should include, every 6–12 months (12 months for COMPASS-31), an evaluation of PND score, 6-MWT or 10-MWT (depending on the severity of the neuropathy), composite clinical NIS, mBMI estimation, a questionnaire on autonomic manifestation (preferably COMPASS-31), and functional assessment of the patient's ability in daily life using R-ODS[1]

Indicators of progression for the above tests, along with the sensitivity to progression[a], were part of recommendations published by Adams et al. 2021 and are highlighted below[1,2]:

PND score	6-MWT or 10-MWT	NIS[b]
A change in disease stage indicates progression, with low sensitivity in early-onset V30M and high sensitivity in late-onset V30M	A change in gait speed of 0.05–0.10 m/s or an increase of 30% over 12 months in the time to walk 10 m indicates progression, with high sensitivity	A change of 7–16 points over 12 months, or worsening on two consecutive consultations 6 months apart, indicates progression, with high sensitivity in late-onset V30M

mBMI	COMPASS-31 questionnaire[b]	R-ODS[b]
Reduction in mBMI of 12% over 18 months (the decline observed in placebo-treated patients in the APOLLO study[3]) could be an indicator of disease progression	An increase by one point in a year indicates progression, but with low sensitivity	Worsening of R-ODS score by 3–8 points over 12 months, or worsening of the score on two consecutive consultations 6 months apart, indicates progression, with high sensitivity

[a]Sensitivity to progression based on the authors' (Adams et al. 2021) clinical experience. [b]These scales are non-linear, so the impact of a specific score change may differ according to the patient's starting level. 6-MWT, 6-minute walk test; 10-MWT, 10-meter walk test; COMPASS-31, Composite Autonomic Symptom Score-31; hATTR, hereditary transthyretin-mediated; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; R-ODS, Rasch-built Overall Disability Scale.

1. Ando et al. *Amyloid* 2022;29(3):143–55; 2. Adams et al. *Orphanet J Rare Dis* 2021;16(1):411; 3. Adams et al. *N Engl J Med* 2018;379(1):11–21.

Assessment of Markers of Disease Progression in ATTR Amyloidosis with Cardiomyopathy

This retrospective study used a landmark survival analysis, based on worsening of NT-proBNP and requirement of ODI between time of diagnosis and a 1-year visit, to assess the prognostic importance of an increase in NT-proBNP and ODI as markers of disease progression in ATTR amyloidosis with cardiomyopathy[1]

NAC cohort (n=1,598); external validation cohort (n=677)[1]

NT-proBNP progression[1]

Defined as NT-proBNP absolute increase >700 ng/L and relative increase >30%

~30% of patients experienced NT-proBNP progression (in both cohorts)

NT-proBNP progression was associated with a **1.8-fold higher risk of mortality[a]**

ODI[1]

Defined as any post-diagnosis initiation or increment in the dose of loop diuretic (furosemide equivalent)

~28% of patients in the NAC cohort and **~45%** of patients in the external validation cohort experienced ODI

ODI was associated with a **~2-fold higher risk of mortality[b,c]**

NT-proBNP progression + ODI

= **~3-fold higher risk of mortality compared with patients with a stable diuretic dose and stable NT-proBNP[d,1]**

Combining NT-proBNP progression and ODI produces a simple, universally applicable model that detects disease progression[1]

A validated measure of disease progression could have clinical relevance for informing prognosis and patient discussions on disease status, referral to amyloid centers, and guidance of treatment strategies. There could also be application in clinical trials[2]

[a]Vs patients who did not experience NT-proBNP progression. [b]Vs patients who did not experience ODI. [c]1.9-fold higher risk in the NAC cohort and 2.1-fold higher risk in the external validation cohort. [d]3.0-fold higher risk in the NAC cohort and 3.2-fold higher risk in the external validation cohort.
ATTR, transthyretin-mediated; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; ODI, outpatient diuretic intensification.
1. Ioannou et al. *J Am Coll Cardiol* 2024;83(14):1276–91; 2. Alexander. *J Am Coll Cardiol* 2024;83(14):1292–94

Summary

- ATTR amyloidosis is a multisystemic, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR accumulating as amyloid deposits in multiple organs and tissues including nerves, heart, and GI tract [1-4]
  - Patients diagnosed with hATTR and wtATTR amyloidosis have a median survival of 4.7[5] and 2.5-5.5 years,[6-8] respectively
- ATTR amyloidosis remains underdiagnosed or misdiagnosed[4,9,10]
- Patients with ATTR amyloidosis experience substantial burden, including reduced QoL[11-14] and functional impairment[6,15]

There remains a need for health care professionals to:

1	2	3	4
Recognize the constellation of red-flag symptoms of ATTR amyloidosis[16,17]	**Collaborate with a multidisciplinary team for a potential diagnosis[16,17]**	**Employ the diagnostic algorithm and confirmatory diagnostic tools to verify diagnosis[17-19]**	**Assess progression of disease following treatment and provide patient with holistic care (mental, physical, and social support)[20,21]**

ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated; wtATTR, wild-type transthyretin-mediated; GI, gastrointestinal; QoL, quality of life; TTR, transthyretin.

1. Hanna. *Curr Heart Fail Rep.* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis.* 2013;106:528–40; 3. Adams et al. *Neurology.* 2015;85:675–82; 4. Maurer et al. *Circ Heart Fail.* 2019;12:e006075; 5. Swiecicki et al. *Amyloid.* 2015;22:123–31; 6. Lane et al. *Circulation.* 2019;140:16–26; 7. Aus dem Siepen et al. *Clin Res Cardiol.* 2018;107(2):158–69; 8. Givens et al. *Aging health.* 2013;9(2):229–35; 9. Hawkins et al. *Ann Med.* 2015;47:625–38; 10. Castano et al. *Heart Fail Rev.* 2015;20:163–78; 11. Coehlo et al. *Muscle Nerve.* 2017;55:323–32; 12. Vinik et al. *J Peripher Nerv Syst.* 2014;19:104–14; 13. Ines et al. *ISPOR Congress* 2015. Poster N21; 14. Obici et al. *Amyloid.* 2020;27:153–62; 15. Bolte et al. *Orphanet J Rare Dis* 2020;15:287; 16. Nativi-Nicolau et al. *Heart Fail Rev*. 2022;27(3):785–93; 17. Kittleson et al. *JACC.* 2023; 81(11):1076–176; 18. Namiranian and Geisler. *Am J Med.* 2022;135 Suppl 1:S13–19; 19. Ando et al. *Orphanet J Rare Dis.* 2013;8:31; 20. Adams et al. *Orphanet J Rare Dis.* 2021;16:411; 21. Obici et al. *BMJ Open.* 2023;13:e073130.

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