Symptoms and Disease Burden of ATTR

MED-US-DZSTATE-2400016

ATTR Disease State Slide Deck

- This resource provides information about ATTR.
- This resource is intended to be viewed in its entirety to support scientific exchange and is not intended as recommendations for clinical practice.
- This resource may contain hyperlinks that are not functional in this format.
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II Symptoms and Burden of Disease

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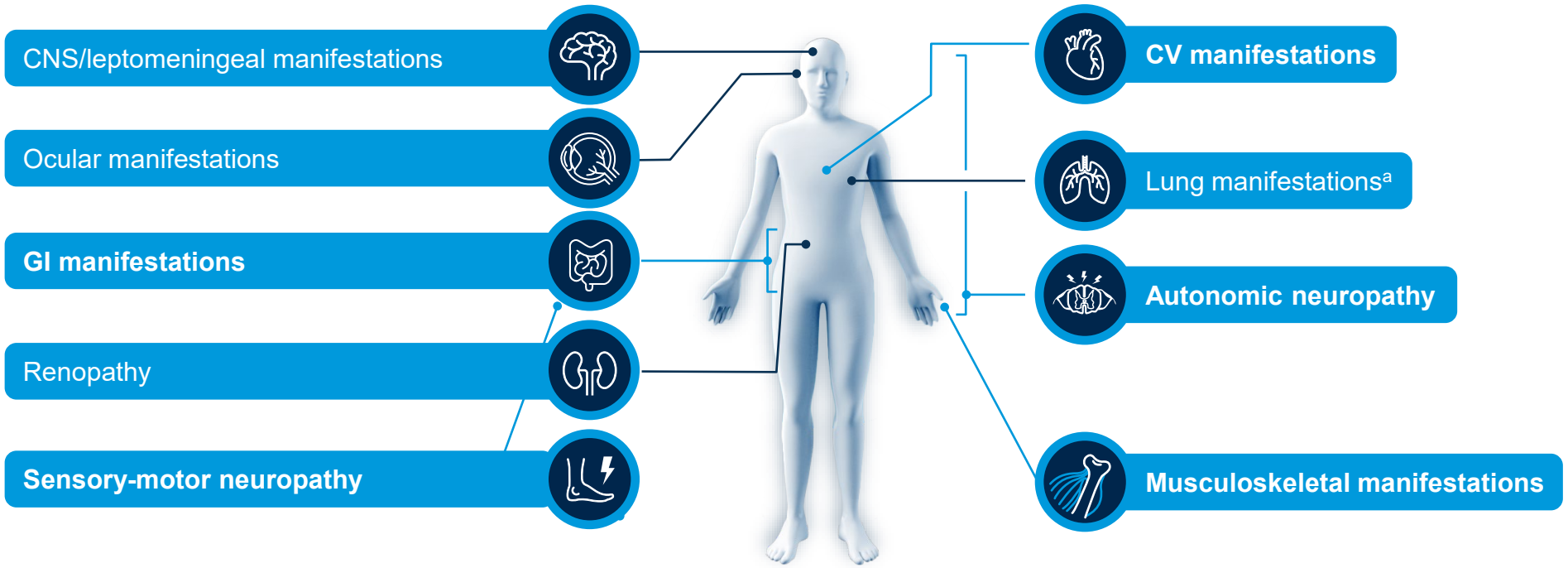
Overall Symptoms and Manifestations of ATTR [1-5]



ATTR disease presentation is often non-specific, heterogeneous, and multisystemic[1-3]

[a]Individual case reports
ATTR, transthyretin amyloidosis; CNS, central nervous system; CV, cardiovascular; GI, gastrointestinal.
1. Gertz et al. *BMC Fam Pract.* 2020;21(1):198; 2. Conceição et al. *J Peripher Nerv Syst.* 2016;21(1):5–9; 3. Nativi-Nicolau et al. *Heart Fail Rev.* 2022;27(3):785–93; 4. Ussavarungsi et al. *Eur Respir J.* 2017;49(2):1602313; 5. Zhang et al. American Society of Surgery of the Hand Annual Meeting. September 30, 2022; Boston MA.

CNS/leptomeningeal manifestations

- Progressive dementia
- Headache
- Ataxia
- Seizures
- Spastic paresis
- Stroke-like episodes
- Hemorrhage

CNS, central nervous system.

1. Conceição et al. *J Peripher Nerv Syst.* 2016;21(1):5–9.

Ocular manifestations

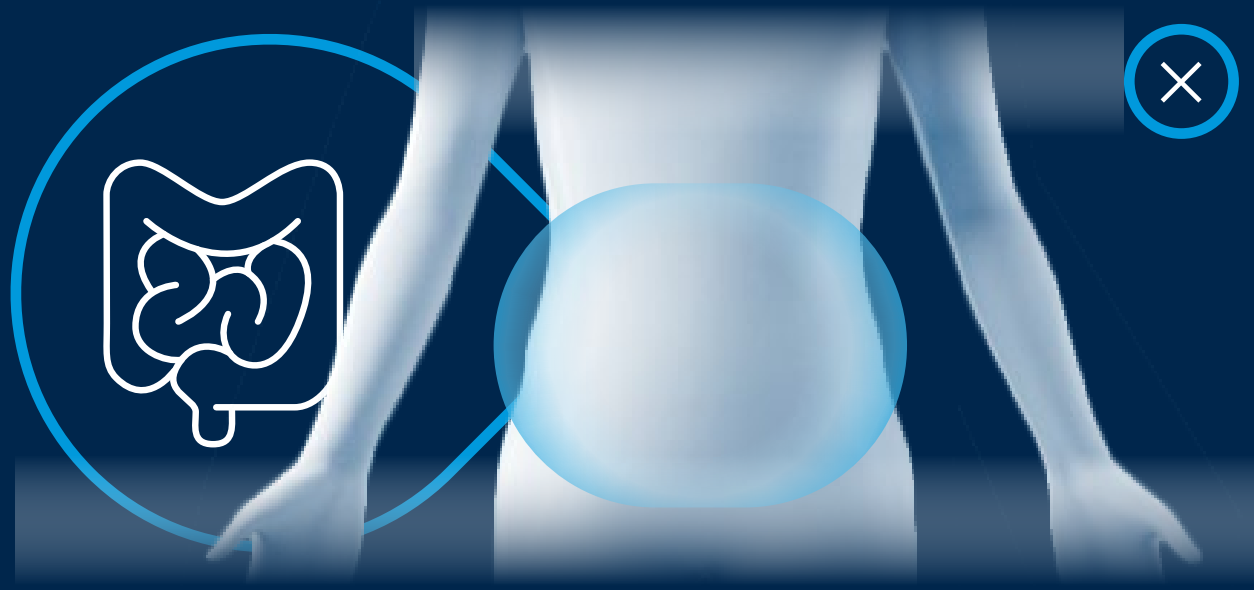
- Vitreous opacification
- Glaucoma
- Abnormal conjunctival vessels
- Pupillary abnormalities

ATTR, transthyretin amyloidosis.

1. Conceição et al. *J Peripher Nerv Syst.* 2016;21(1):5–9.

GI manifestations

- Nausea and vomiting
- Changes in GI motility (ie, diarrhea, constipation, gastroparesis, early satiety)
- Unintentional weight loss



ATTR, transthyretin amyloisosis; GI, gastrointestinal.

1. Gertz et al. *BMC Fam Pract.* 2020;21(1):198.

Renopathy

- Proteinuria
- Renal failure

ATTR, transthyretin amyloidosis.

1. Gertz et al. *BMC Fam Pract.* 2020;21(1):198.

Sensory-motor neuropathy

- Neuropathic pain
- Altered sensation (ie, change in sensitivity to pain and temperature)
- Numbness and tingling
- Muscle weakness
- Impaired balance
- Difficulty walking

1. Conceição et al. *J Peripher Nerv Syst.* 2016;21(1):5–9.

CV manifestations

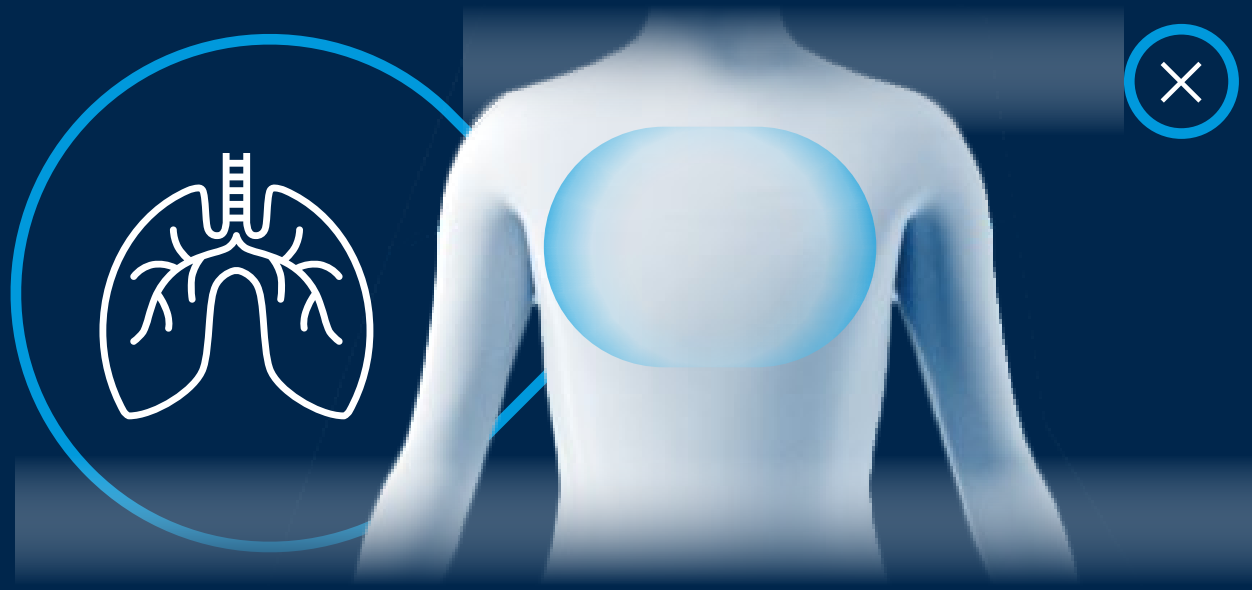
- Conduction blocks
- Cardiomyopathy
- Mild regurgitation
- Shortness of breath
- Edema
- Heart failure
- Atrial fibrillation
- Palpitations and arrhythmia
- Sinus node dysfunction

ATTR, transthyretin amyloidosis; CV, cardiovascular.

1. Nativi-Nicolau et al. *Heart Fail Rev.* 2022;27(3):785–93.

Lung manifestations[a]

- Amyloid deposition with organizing pneumonia
- Diffuse alveolar septal amyloidosis



[a]Individual case reports

1. Ussavarungsi et al. *Eur Respir J.* 2017;49(2):1602313.

Autonomic neuropathy

- Orthostatic intolerance
- Syncope
- Recurrent UTI (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities
- Vasomotor dysfunction
- Pupillomotor abnormalities
- Cardiac conduction disturbances and arrhythmias

ATTR, transthyretin amyloidosis; UTI, urinary tract infection.

1. Conceição et al. *J Peripher Nerv Syst.* 2016;21(1):5–9.

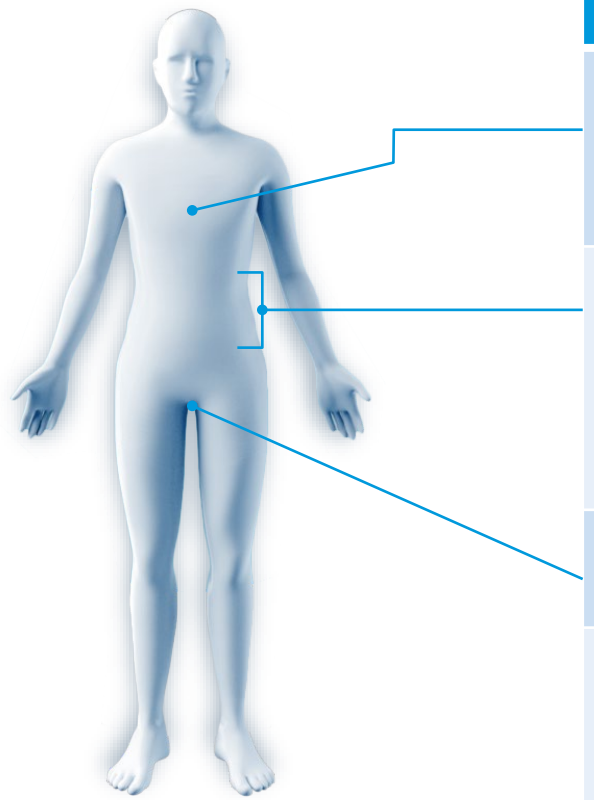
Musculoskeletal manifestations

- Carpal tunnel syndrome
- Lumbar spinal stenosis
- Spontaneous biceps tendon rupture
- Rotator cuff injury
- Osteoarthritis
- Finger tenosynovitis/ trigger finger

ATTR, transthyretin amyloidosis.

1. Zhang et al. American Society of Surgery of the Hand Annual Meeting. September 30, 2022; Boston MA.

Autonomic Symptoms and Manifestations of ATTR



There are a wide range of symptoms of autonomic neuropathy in ATTR	
CV manifestations[1-5] *CV manifestations may also result from amyloid deposition in cardiac tissues and structural defects*[4]	Reduced HRV, abnormal BP regulation, orthostatic intolerance, palpitations, arrhythmias and syncope
GI manifestations[1,6,7]	Nausea and vomiting, changes in GI motility (diarrhea/constipation), unintentional weight loss, early satiety
Genitourinary[2,8]	Recurrent UTIs, neurogenic bladder, sexual dysfunction
Other[8-10]	Ocular manifestations (pupillomotor), vasomotor dysfunction, sweating abnormalities (sudomotor)

ATTR, transthyretin amyloisosis; BP, blood pressure; CV, cardiovascular; GI, gastrointestinal; HRV, heart rate variability; UTI, urinary tract infection.

1. Gonzalez-Duarte. *Clin Auton Res.* 2019;29:245–51; 2. Maurer et al. *J Am Coll Cardiol.* 2016;68:161–72; 3. Ando & Suhr. *Amyloid.* 1998;5:288–300; 4. Niklasson et al. *Acta Neurol Scand.* 1989;79:182–7; 5. Olofsson et al. *Amyloid.* 1994;1:240–6; 6. Ebenezer et al. *Ann Neurol.* 2017;82:44−56; 7. Wixner et al. *Orphanet J Rare Dis.* 2014;9:61 8. Conceição et al. *J Peripher Nerv Syst.* 2016;21:5–9; 9. Gonzalez-Duarte et al. *Clin Auton Res.* 2019;29(Suppl. 1):S1–9; 10. Obayashi & Ando. *Amyloid.* 2012;19:28–9.

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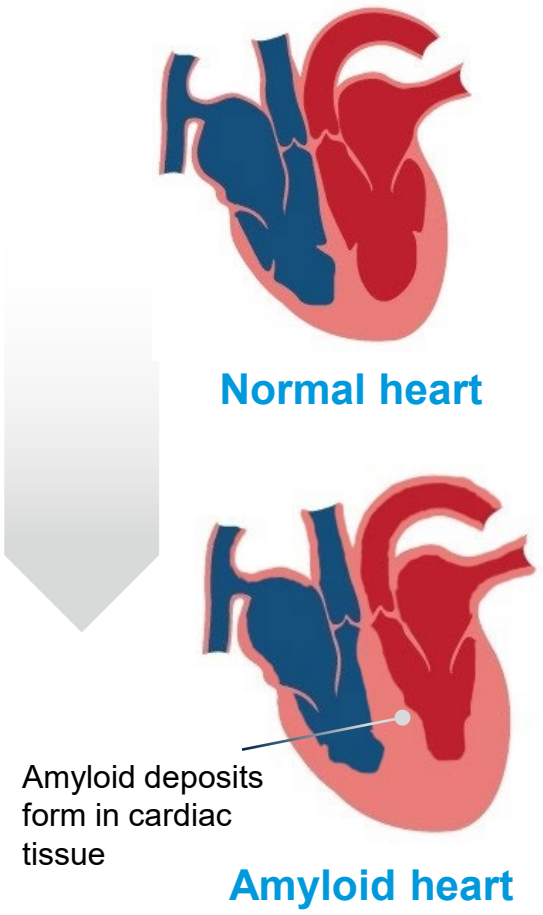
Cardiac Manifestations of ATTR[1]



Clinical	Electrical	Imaging	Laboratory
• Fatigue • Shortness of breath[2] • Edema[2] • Palpitations and arrhythmias[2] • Heart failure symptoms • Family history of heart failure	• Conduction system disease/pacemaker • Atrial fibrillation • Pseudoinfarct pattern • Discordant QRS voltage for degree of increased left ventricular wall thickness on imaging	• Increased left ventricular wall thickness • Grade 2 or worse diastolic function • Abnormal longitudinal strain with apical sparing • Diffuse subendocardial or transmural late gadolinium enhancement on cardiac magnetic resonance imaging with increased extracellular volume fraction	• Persistent low-level troponin elevation • Elevated B-type natriuretic peptide or NT-proBNP

ATTR, transthyretin amyloidosis; NT-proBNP, *N*-terminal prohormone of brain-type natriuretic peptide.

1. Kittleson et al. *JACC*. 2023; 81(11):1076–176; 2. Adams D, et al. *Orphanet J Rare Dis*. 2021;16(1):411.

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Common Amyloidosis Symptoms and Diagnostic Challenges

A global online patient survey conducted by the Amyloidosis Research Consortium

hATTR

Organs most affected in patients

Nervous system **78%**

Heart **71%**

GI system **53%**

Kidneys **10%**

Top 3 initial symptoms

Numbness/Tingling in hands or feet **53%**

Carpal tunnel syndrome **33%**

Fatigue **28%**

wtATTR

Organs most affected in patients

Heart **97%**

Nervous system **24%**

GI system **15%**

Kidneys **10%**

Top 3 initial symptoms

Shortness of breath **51%**

Irregular heart rate or palpitations **45%**

Fatigue **38%**

hATTR, hereditary ATTR; wtATTR, wild-type ATTR.

1. Amyloidosis Research Consortium. ARC 2022 Community Survey Results. Published 2022. Accessed November 6, 2023. https://arci.org/arc-2022-community-survey/#wild

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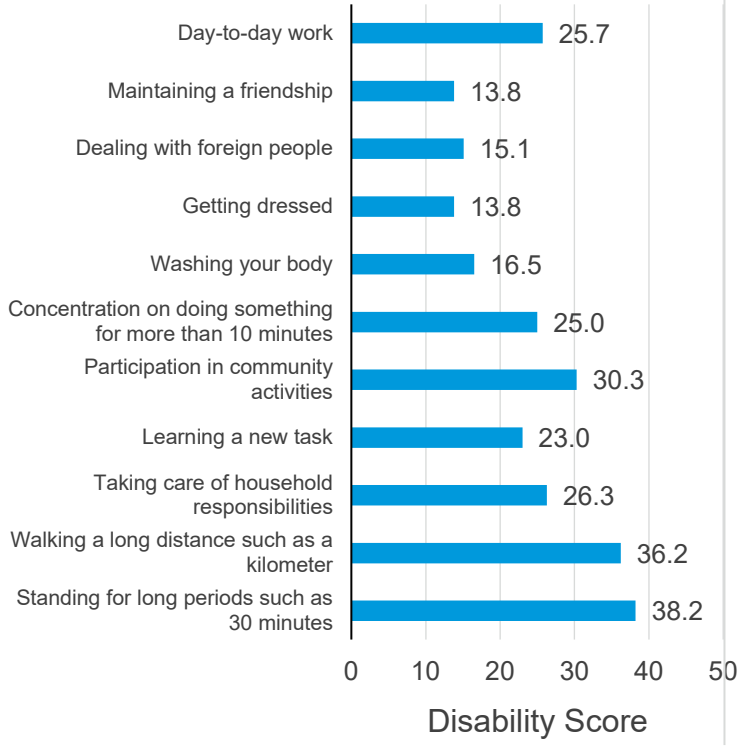
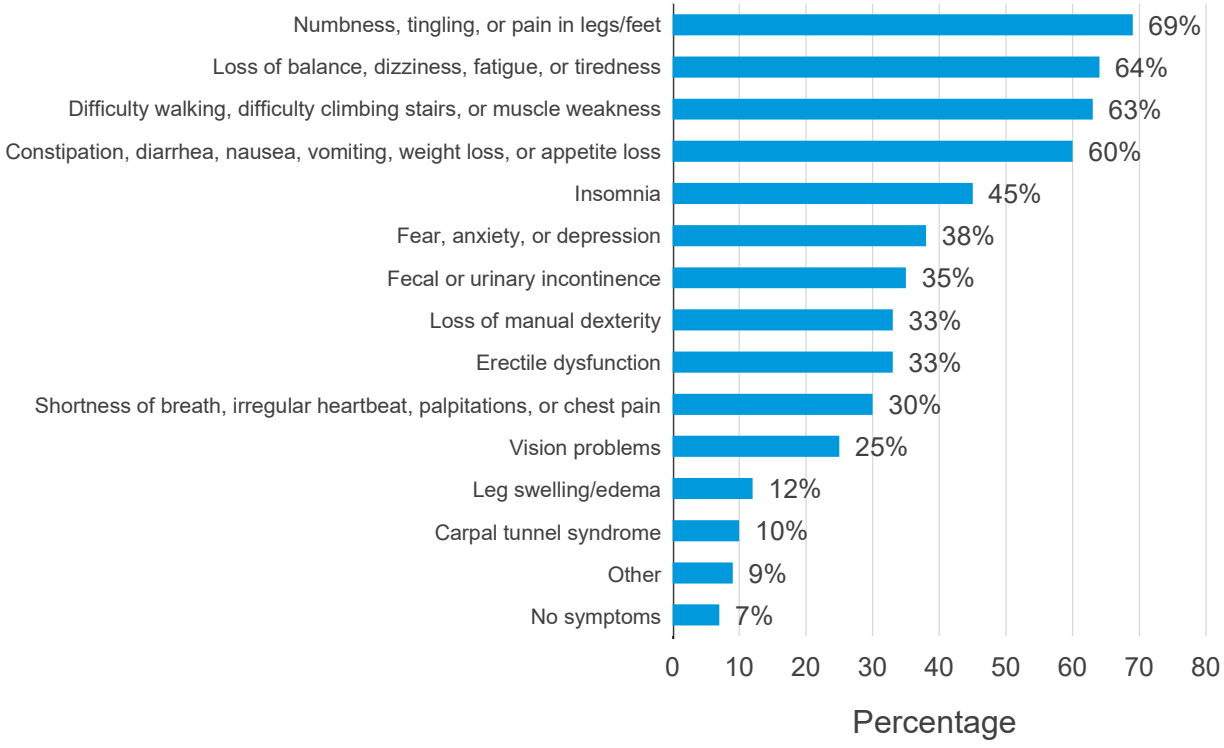
hATTR-PN is Relentlessly Progressive and can Lead to Physical and Emotional Disability[1]

Functional impairment reported by patients with hATTR-PN (N=38)[2]



hATTR-PN patient-reported multisystemic disease burden (N=113)[3]



ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR; hATTR-PN, hereditary ATTR with polyneuropathy; QoL, quality of life; QoL-DN, quality of life diabetic neuropathy.

1. Mariani et al. *Ann Neurol.* 2015;78:901–16; 2. Bolte et al. *Orphanet J Rare Dis* 2020;15:287; 3. Hsu et al. Congresso Paulista de Neurologia. May 29 – June 1, 2019. Guaruja, Brazil.

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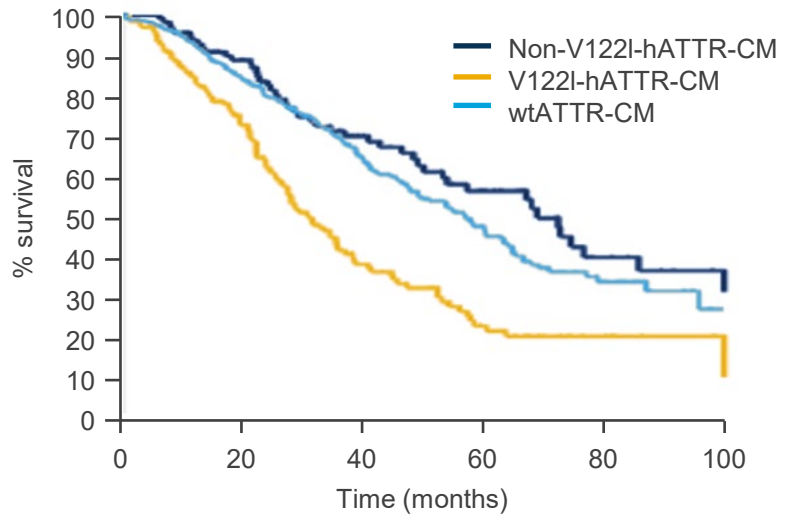
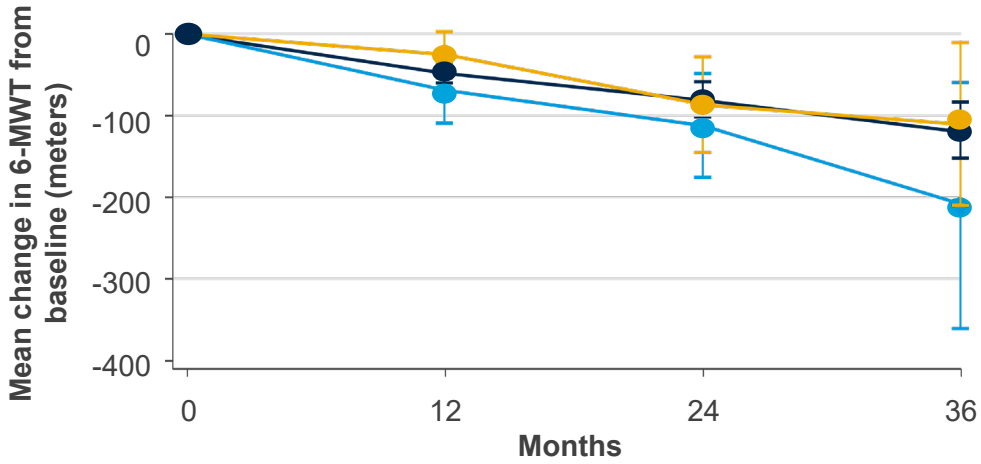
Patients with ATTR-CM Experience a Reduced Overall Survival and Gradual Progressive Decline in Physical Functioning[1,2]

Survival from diagnosis of ATTR[2,a]



Numbers at risk						
Non-V122I-hATTR	118	87	52	34	14	7
V122I-hATTR	205	122	42	18	7	3
wtATTR	711	415	188	76	24	2

6-MWT decline in patients with ATTR with cardiomyopathy over 36 months[2]



Number			
V122I-hATTR-CM	61	31	11
wtATTR-CM	289	175	66
Non-V122I-hATTR-CM	32	17	9

Quality of life measures reported by patients with ATTR[2]

[a]Analysis from data including 1034 patients with ATTR amyloidosis with cardiomyopathy from 2000-2017 at the United Kingdom National Amyloidosis Center.
6MWT, 6 minute walk test; ATTR, transthyretin amyloidosis ATTR-CM, ATTR with cardiomyopathy; hATTR, hereditary ATTR; wtATTR, wild-type ATTR.
1. Ruberg et al. *Am Heart J.* 2012;64:222–8; 2. Lane et al. *Circulation* 2019; 140:16–26.

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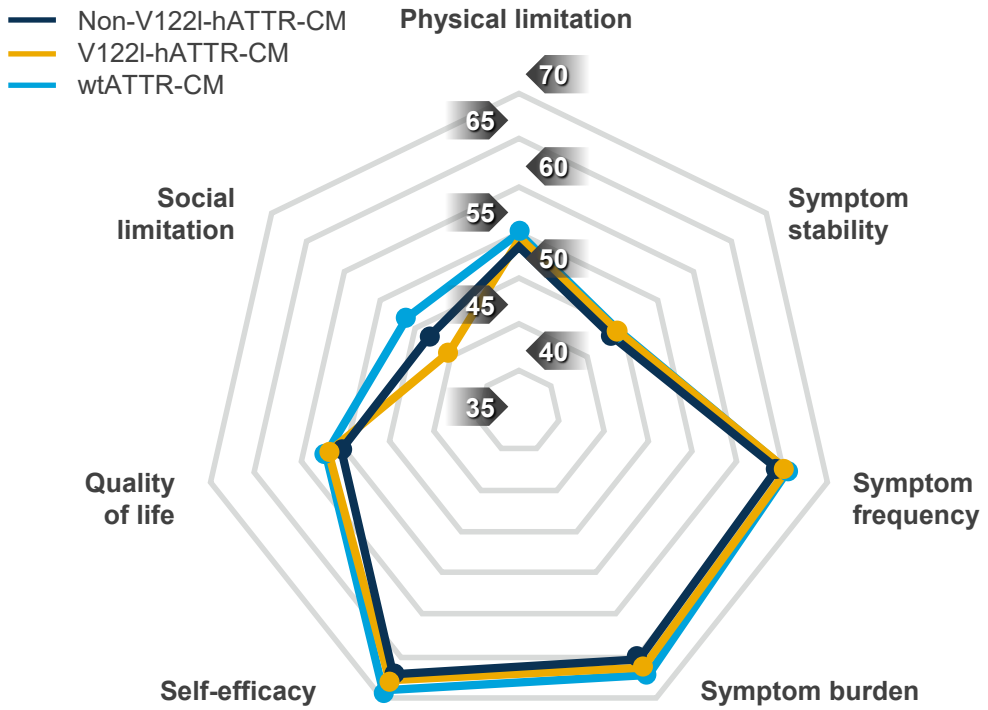
Health-related quality of life measured by the KCCQ[1,a]



[a]Analysis from data including 1034 patients with ATTR-CM from 2000-2017 at the UK National Amyloidosis Center. Overall KCCQ domain scores at 12 months post diagnosis were available in 158 patients.
ATTR, transthyretin amyloidosis; ATTR-CM, ATTR withcardiomyopathy; hATTR, hereditary ATTR; hATTR-CM, hereditary ATTR with cardiomyopathy; wtATTR, wild-type ATTR; wtATTR-CM, wild-type ATTR with cardiomyopathy; KCCQ, Kansas City Cardiomyopathy Questionnaire.

1. Lane et al. *Circulation.* 2019;140:16-26.

Summary

- ATTR 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 remains underdiagnosed or misdiagnosed[4,9,10]
- Patients with ATTR 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[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 amyloidosis; hATTR, hereditary ATTR; wtATTR, wild-type ATTR; 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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