



# Symptoms and Disease Burden of ATTR

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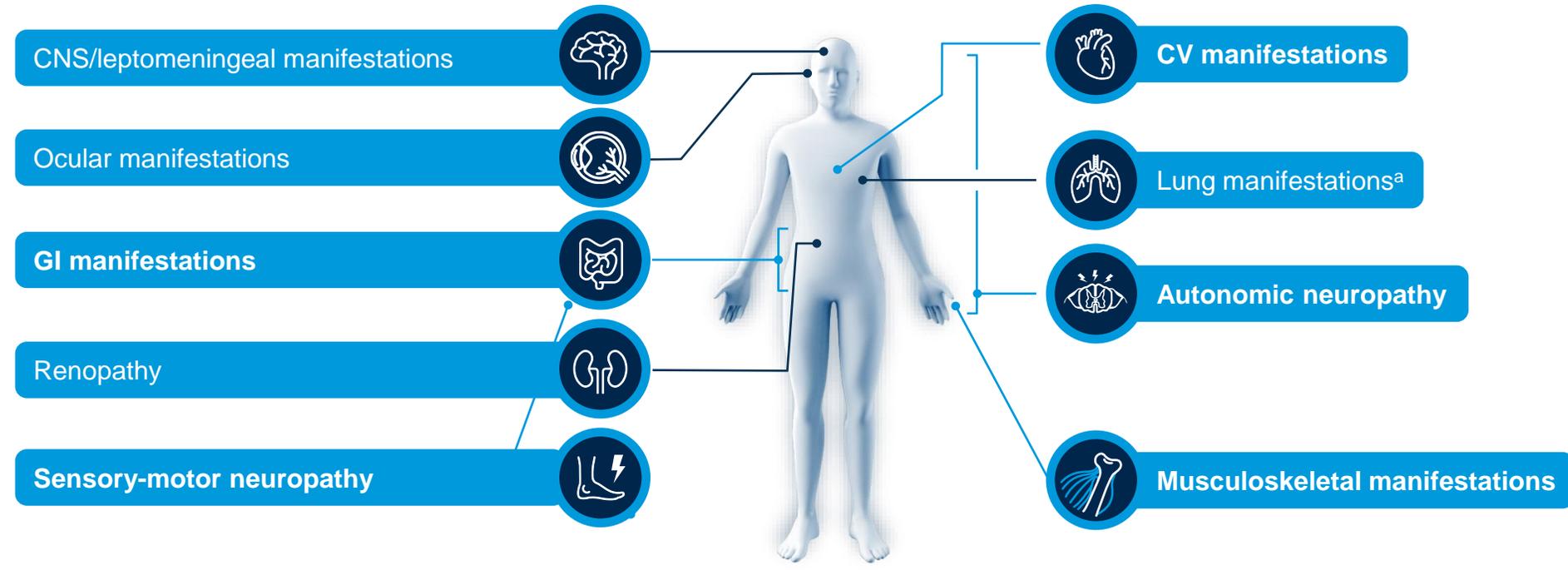


## ATTR Disease State Slide Deck

- 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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## || Symptoms and Burden of Disease

# Overall Symptoms and Manifestations of ATTR 1-5



ATTR disease presentation is often non-specific, heterogeneous, and multisystemic<sup>1-3</sup>

<sup>a</sup>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

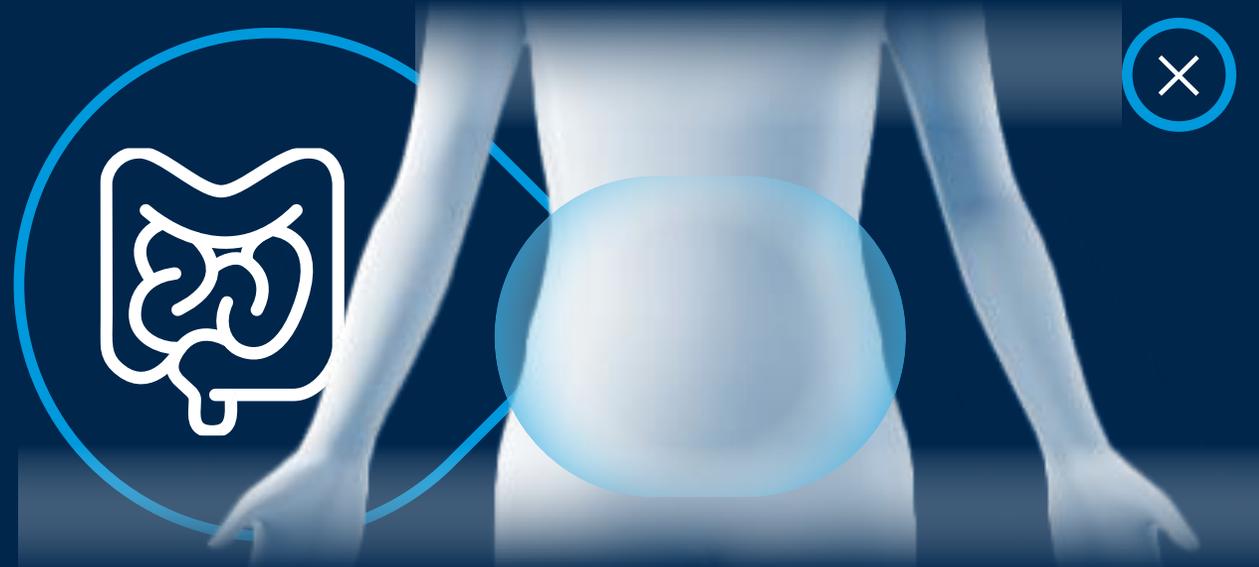


ATTR, transthyretin amyloidosis.

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

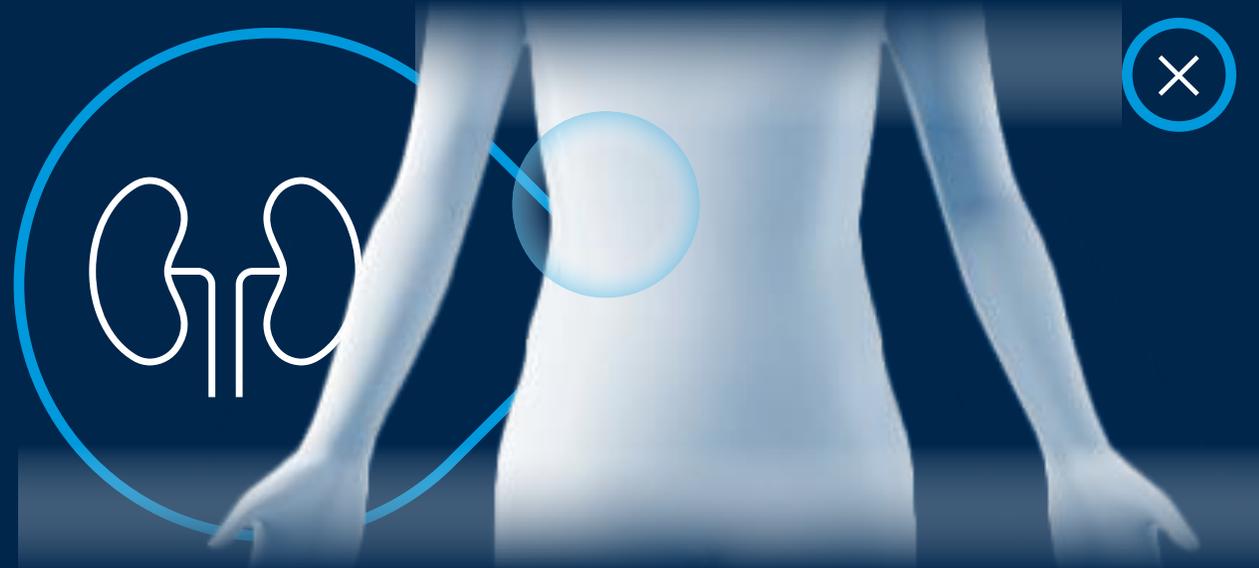
# GI manifestations

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



# 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



# CV manifestations

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



# Lung manifestations<sup>a</sup>

- Amyloid deposition with organizing pneumonia
- Diffuse alveolar septal amyloidosis



<sup>a</sup>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



# Musculoskeletal manifestations

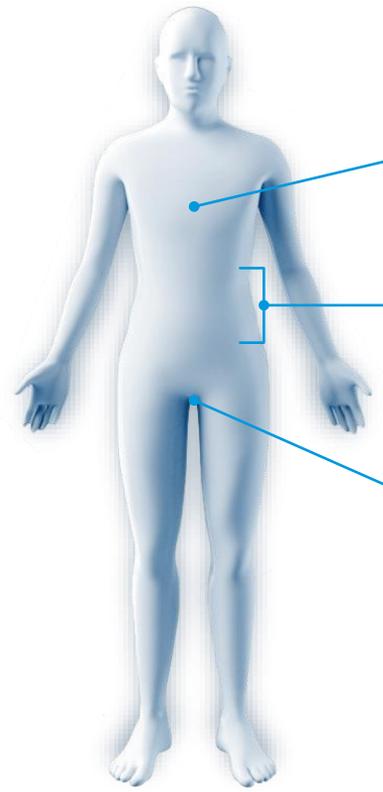
- Carpal tunnel syndrome
- Lumbar spinal stenosis
- Spontaneous biceps tendon rupture
- Rotator cuff injury
- Osteoarthritis
- Finger tenosynovitis/trigger finger



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

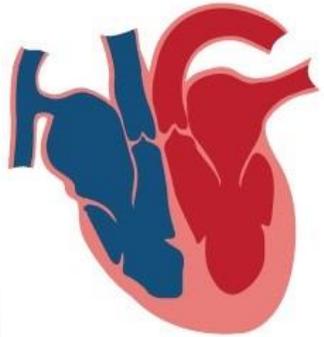


**There are a wide range of symptoms of autonomic neuropathy in ATTR**

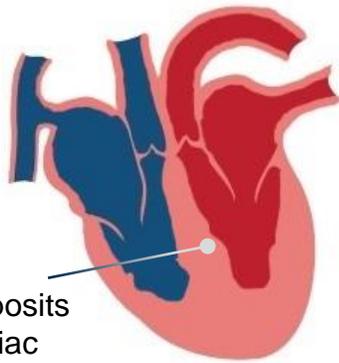
<p><b>CV manifestations<sup>1-5</sup></b>  <i>CV manifestations may also result from amyloid deposition in cardiac tissues and structural defects<sup>4</sup></i></p>	<p>Reduced HRV, abnormal BP regulation, orthostatic intolerance, palpitations, arrhythmias and syncope</p>
<p><b>GI manifestations<sup>1,6,7</sup></b></p>	<p>Nausea and vomiting, changes in GI motility (diarrhea/constipation), unintentional weight loss, early satiety</p>
<p><b>Genitourinary<sup>2,8</sup></b></p>	<p>Recurrent UTIs, neurogenic bladder, sexual dysfunction</p>
<p><b>Other<sup>8-10</sup></b></p>	<p>Ocular manifestations (pupillomotor), vasomotor dysfunction, sweating abnormalities (sudomotor)</p>

ATTR, transthyretin amyloidosis; 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.

# Cardiac Manifestations of ATTR<sup>1</sup>



Normal heart



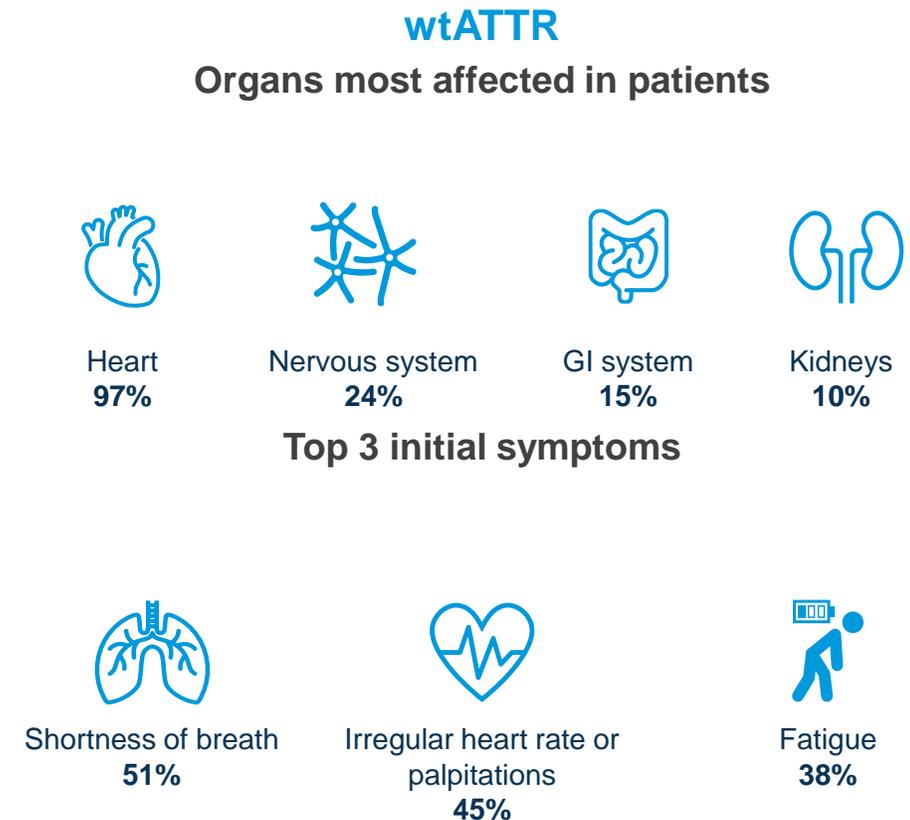
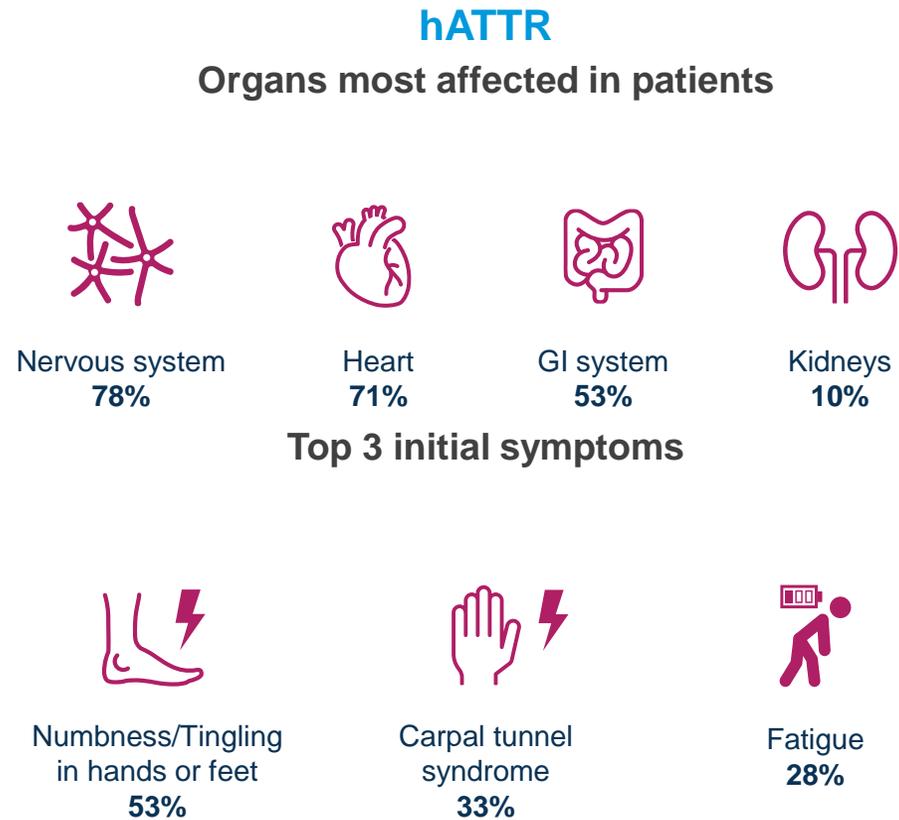
Amyloid deposits form in cardiac tissue

Amyloid heart

 Clinical	 Electrical	 Imaging	 Laboratory
<ul style="list-style-type: none"> <li>• Fatigue</li> <li>• Shortness of breath<sup>2</sup></li> <li>• Edema<sup>2</sup></li> <li>• Palpitations and arrhythmias<sup>2</sup></li> <li>• Heart failure symptoms</li> <li>• Family history of heart failure</li> </ul>	<ul style="list-style-type: none"> <li>• Conduction system disease/pacemaker</li> <li>• Atrial fibrillation</li> <li>• Pseudoinfarct pattern</li> <li>• Discordant QRS voltage for degree of increased left ventricular wall thickness on imaging</li> </ul>	<ul style="list-style-type: none"> <li>• Increased left ventricular wall thickness</li> <li>• Grade 2 or worse diastolic function</li> <li>• Abnormal longitudinal strain with apical sparing</li> <li>• Diffuse subendocardial or transmural late gadolinium enhancement on cardiac magnetic resonance imaging with increased extracellular volume fraction</li> </ul>	<ul style="list-style-type: none"> <li>• Persistent low-level troponin elevation</li> <li>• Elevated B-type natriuretic peptide or NT-proBNP</li> </ul>

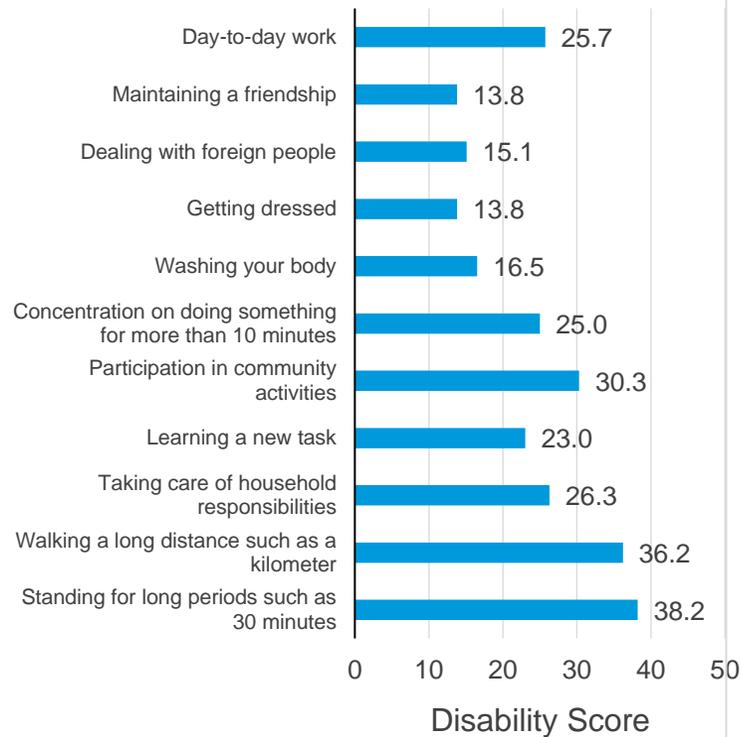
# Common Amyloidosis Symptoms and Diagnostic Challenges

A global online patient survey conducted by the Amyloidosis Research Consortium

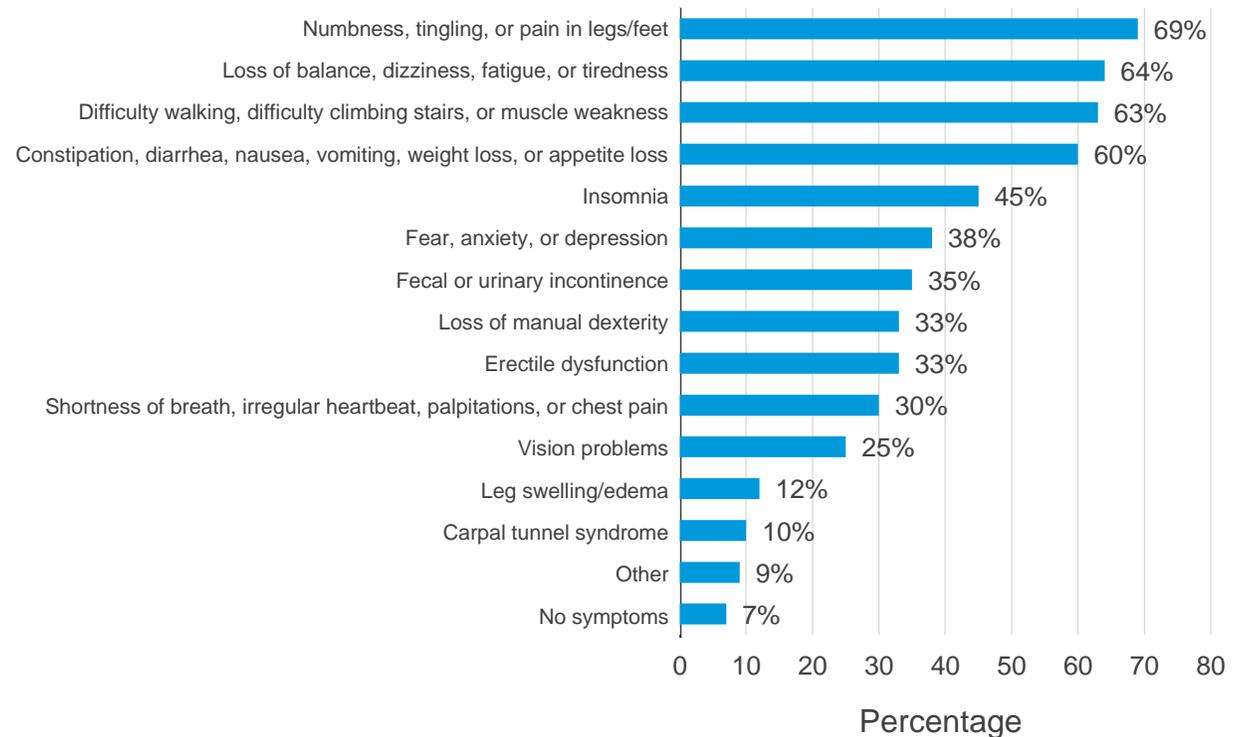


# hATTR-PN is Relentlessly Progressive and can Lead to Physical and Emotional Disability<sup>1</sup>

Functional impairment reported by patients with hATTR-PN (N=38)<sup>2</sup>



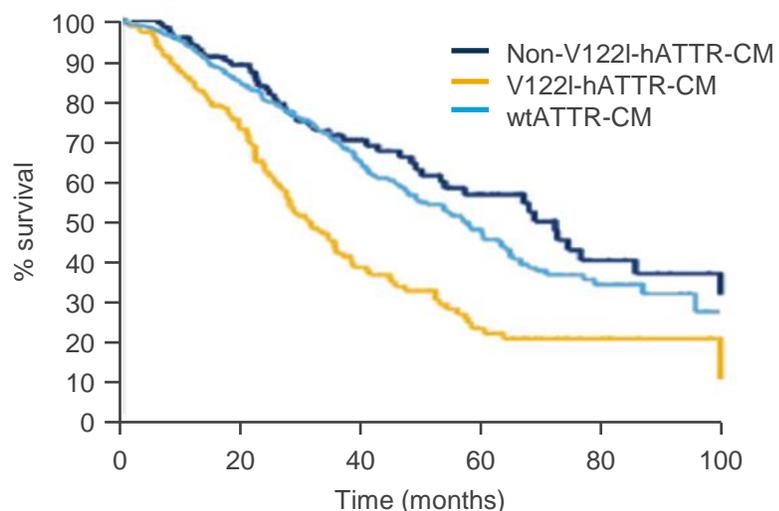
hATTR-PN patient-reported multisystemic disease burden (N=113)<sup>3</sup>



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. Guarujá, Brazil.

# Patients with ATTR-CM Experience a Reduced Overall Survival and Gradual Progressive Decline in Physical Functioning<sup>1,2</sup>

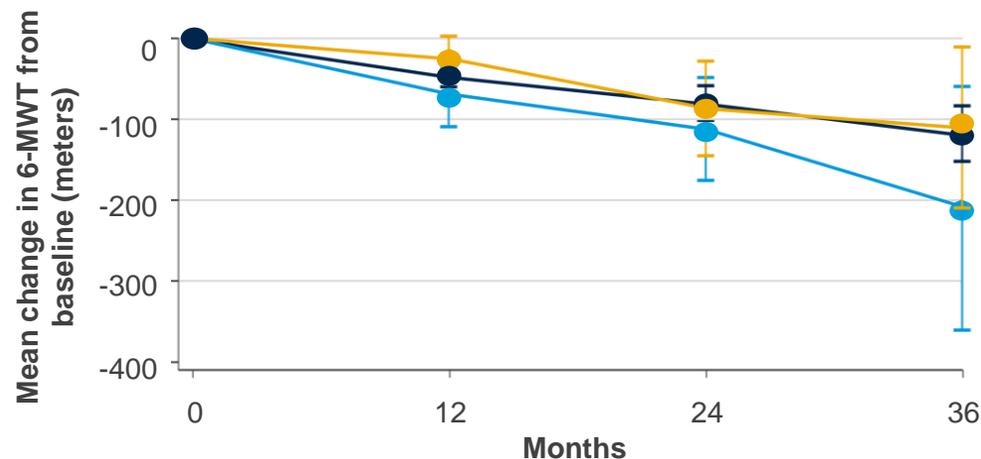
Survival from diagnosis of ATTR<sup>2,a</sup>



**Numbers at risk**

	0	20	40	60	80	100
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<sup>2</sup>



**Number**

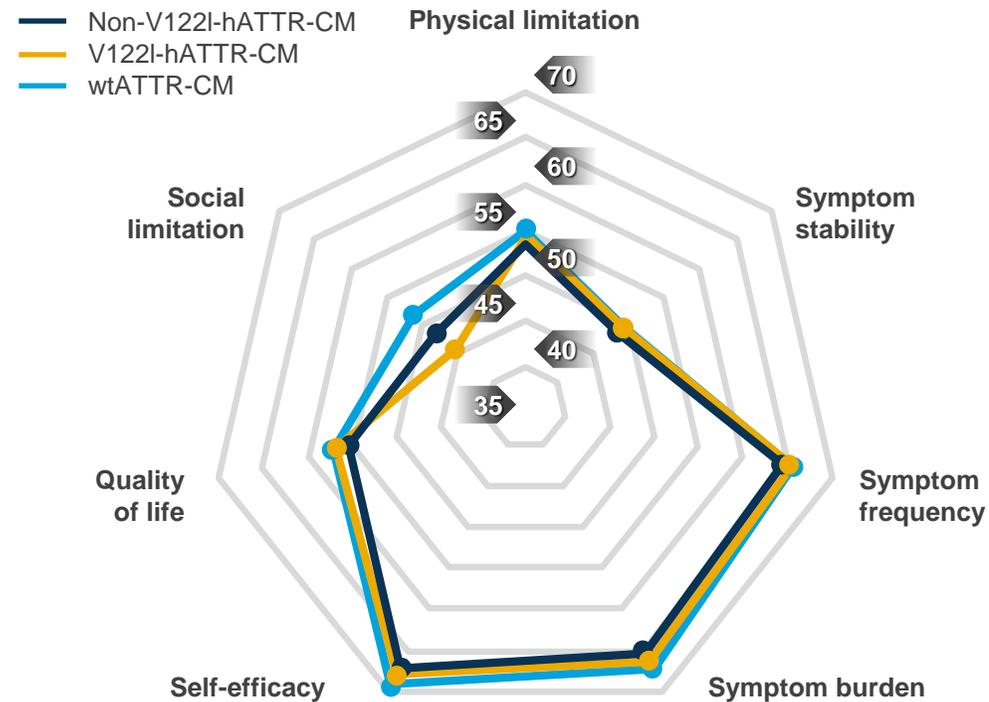
	12	24	36
V122I-hATTR-CM	61	31	11
wtATTR-CM	289	175	66
Non-V122I-hATTR-CM	32	17	9

Quality of life measures reported by patients with ATTR<sup>2</sup>



<sup>a</sup>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.

# Health-related quality of life measured by the KCCQ<sup>1,a</sup>



<sup>a</sup>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 with cardiomyopathy; 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<sup>1-4</sup>
  - Patients diagnosed with hATTR and wtATTR amyloidosis have a median survival of 4.7<sup>5</sup> and 2.5-5.5 years,<sup>6-8</sup> respectively
- ATTR remains underdiagnosed or misdiagnosed<sup>4,9,10</sup>
- Patients with ATTR experience substantial burden, including reduced QoL<sup>11-14</sup> and functional impairment<sup>6,15</sup>

There remains a need for health care professionals to:

1

Recognize the constellation of red-flag symptoms of ATTR<sup>16,17</sup>

2

Collaborate with a multidisciplinary team for a potential diagnosis<sup>16,17</sup>

3

Employ the diagnostic algorithm and confirmatory diagnostic tools to verify diagnosis<sup>17-19</sup>

4

Assess progression of disease following treatment and provide patient with holistic care (mental, physical, and social support)<sup>20,21</sup>

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. Coelho 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. Namirani 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.* 2016;11:411; 21. Obici et al. *BMJ Open.* 2023;13:e073130.