EXPLORE ATTR-CM

MED-US-TTR-2500039

September 2025

ATTR-CM Disease State Slide Deck

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ATTR-CM, transthyretin amyloidosis with cardiomyopathy.

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About Transthyretin Amyloidosis (ATTR)

ATTR is a rapidly progressive, debilitating, and ultimately fatal multisystem disease caused by misfolded transthyretin (TTR) protein accumulating as amyloid deposits in multiple organs and tissues in the body, including the nerves and heart[1-6]

Due to the diverse sites of amyloid deposition, ATTR often presents with multisystem involvement, including cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) or a mixed combination of both[6-9]

There are 2 different types of ATTR[7,10]:

Hereditary ATTR (hATTR)
occurs due to inherited *TTR* gene variants and runs in families

Wild-type ATTR (wtATTR)
is nonhereditary, occurs spontaneously, and may be associated with aging

ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTR-PN, transthyretin amyloidosis with polyneuropathy; hATTR, hereditary transthyretin amyloidosis; TTR, transthyretin; wtATTR, wild-type transthyretin amyloidosis.

1. Rozenbaum MH, et al. *Cardiol Ther.* 2021;10:141-159; 2. Nativi-Nicolau JN, et al. *Heart Fail Rev.* 2022;27:785-793; 3. Lin X, et al. *BMC Neurol.* 2021;21:70; 4. Ioannou A, et al. *J Am Coll Cardiol.* 2024;83:1276-1291; 5. Gonzalez-Duarte A, Ulloa-Aguirre A. *Int J Mol Sci.* 2021;22:13158; 6. Adams D, et al. *Nat Rev Neurol.* 2019;15:387-404; 7. Maurer MS, et al. *J Am Coll Cardiol.* 2016;68:161-172; 8. Ruberg FL, et al. *J Am Coll Cardiol.* 2019;73:2872-2891; 9. Adams D, et al. Neurology. 2015;85:675-682; 10. Karam C, et al. Orphanet J Rare Dis. 2024;19:419.

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Differentiating Hereditary and Wild-Type ATTR[1-6]

	hATTR	wtATTR
Genetics[1]	Autosomal dominant, at least 1 *TTR* gene variant is present	Nonhereditary, no *TTR* gene variant
US prevalence	~46,000[a]	~125,000[a]
Age at symptom onset[2]	>20 years	>50 years
Male,[b] **%**[2]	76-86	91-97
Median survival following diagnosis, years	4.7[3]	2.5-5.5[4-6]
Clinical manifestations[2]		
Cardiac	Yes	Yes
Peripheral nerves	Yes	Occasionally
Autonomic nerves (including GI)	Yes	Rare
Kidney	Yes	Rare
Ophthalmologic	Vitreous deposition	Not prominent
Musculoskeletal	Yes	Yes

Table adapted from Gertz et al[2]

[a]Information based on Alnylam modeling data. [b]Male sex may be an overestimate as newer data suggest prevalence among females is higher than previously thought.[7]

ATTR, transthyretin amyloidosis; GI, gastrointestinal; hATTR, hereditary transthyretin amyloidosis; TTR, transthyretin; wtATTR, wild-type transthyretin amyloidosis.

1. Sekijima Y, Nakamura K. Hereditary transthyretin amyloidosis. Updated September 30, 2024. Accessed September 2025. https://www.ncbi.nlm.nih.gov/books/NBK1194/; 2. Gertz M, et al. *BMC Fam Pract.* 2020;21:198; 3. Swiecicki PL, et al. *Amyloid.* 2015;22:123-131; 4. Lane T, et al. *Circulation.* 2019;140:16-26; 5. Aus dem Siepen F, et al. *Clin Res Cardiol.* 2018;107:158-169; 6. Givens RC, et al. *Aging Health.* 2013;9:229-235; 7. Takashio S, et al. *J Cardiol.* 2022;79:50-57.

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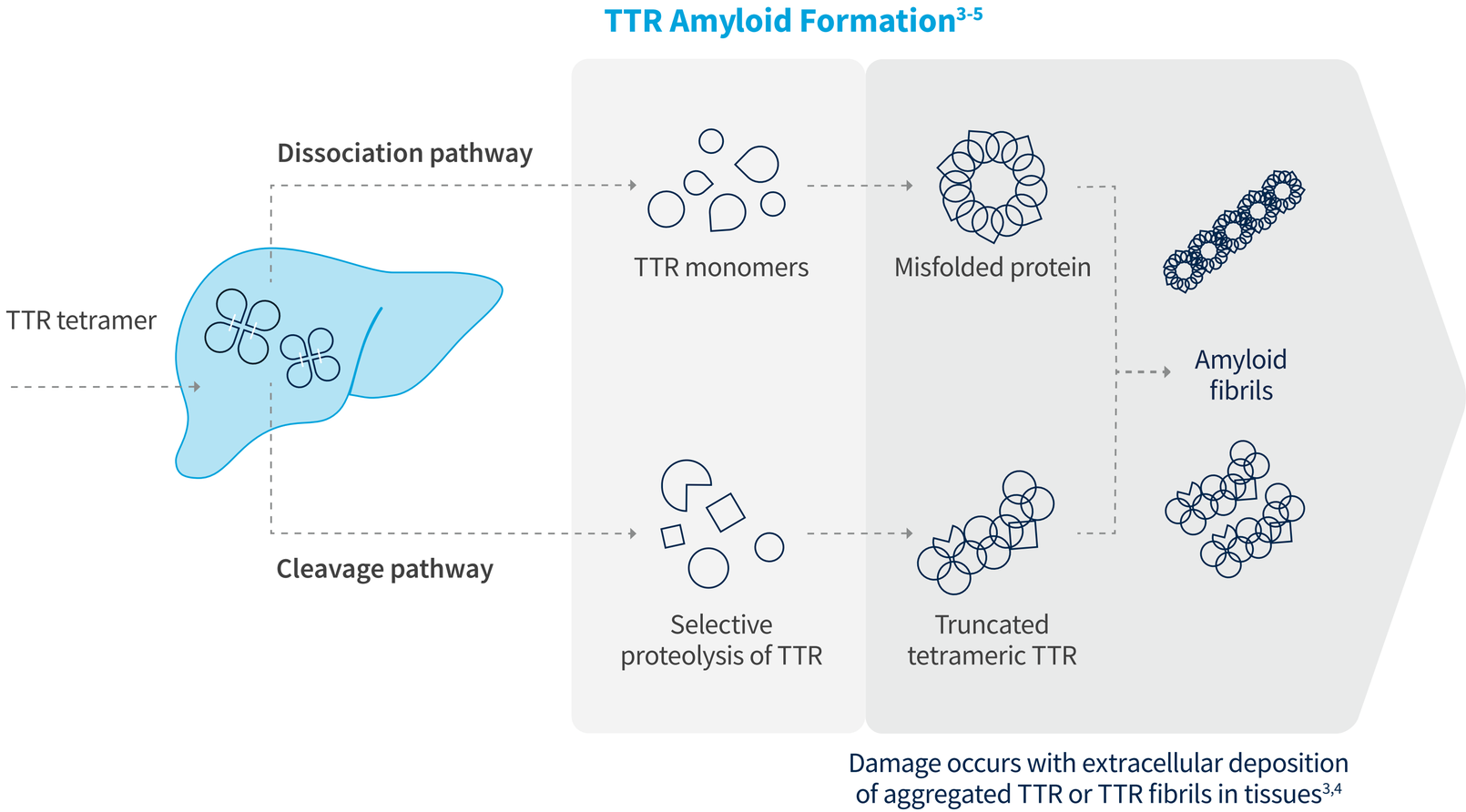
ATTR Is Driven by TTR Amyloid Formation[1-4]

TTR is a protein produced in the liver that normally circulates as a tetramer; its normal role is to bind and transport vitamin A and thyroxine (T4) around the body[1,2]

In ATTR, TTR tetramers can dissociate or are cleaved into monomers and other small fragments that misfold and aggregate to form amyloid fibrils[1-4]



ATTR, transthyretin amyloidosis; T4, thyroxine; TTR, transthyretin.

1. Adams D, et al. *Nat Rev Neurol.* 2019;15:387-404; 2. Koike H, Katsuno M. *Biomedicines.* 2019;7:11; 3. Porcari A, et al. *Cardiovasc Res.* 2023;118:3517-3535; 4. Ibrahim RB, et al. *Cell Mol Life Sci.* 2020;77:1421-1434; 5. Chen JJ, et al. *Cell Chem Biol.* 2016;23:1282-1293.

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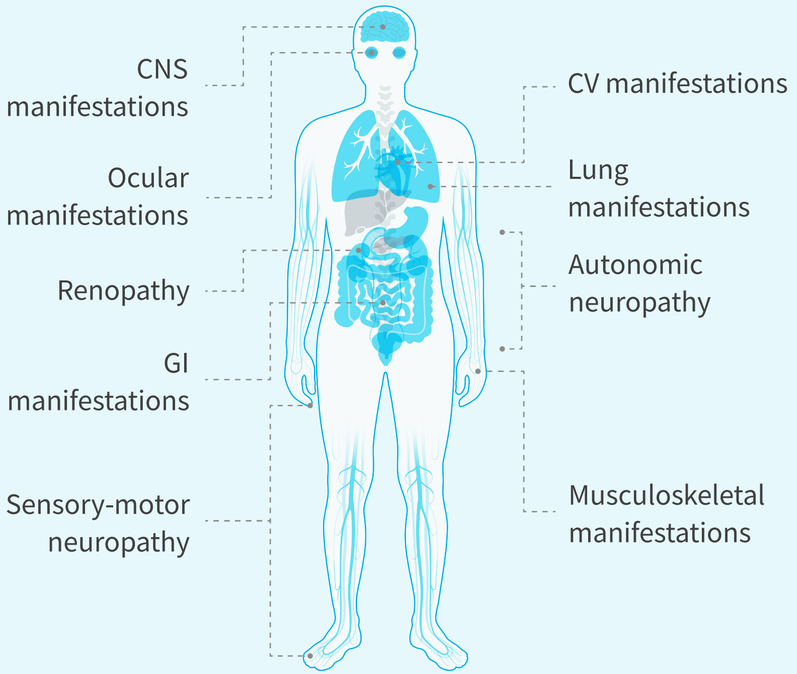
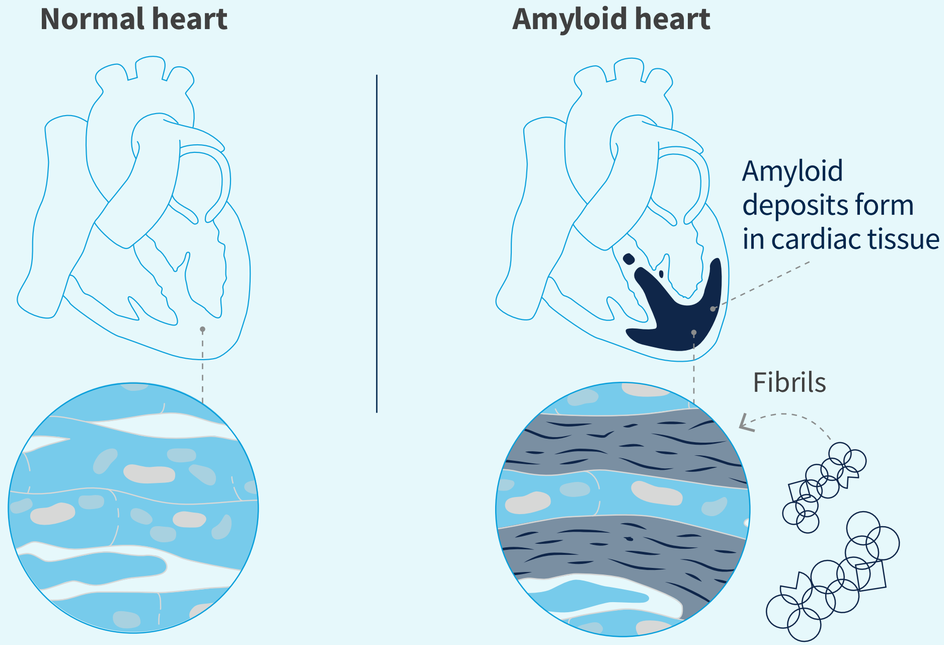
Clinical Manifestations of ATTR-CM Result From Amyloid Deposition in the Cardiac Tissue[1-3]

Damage occurs when extracellular deposition of TTR aggregates and amyloid fibrils occurs in tissues in the body[1,4-6]

Extracellular amyloid deposition in nerves, cardiac tissue, and other systems leads to the clinical manifestations of ATTR[2,7-9]:



In ATTR-CM, amyloid deposits accumulate in the cardiac tissue,[1] making the myocardium stiff and rigid and eventually affecting the heart's mechanical function.[3] Patients commonly present with signs of heart failure, diastolic dysfunction, and arrhythmias[1]



ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CNS, central nervous system; CV, cardiovascular; GI, gastrointestinal; TTR, transthyretin.

1. Porcari A, et al. *Cardiovasc Res.* 2022;118:3517-3535; 2. Nativi-Nicolau JN, et al. *Heart Fail Rev.* 2022;27:785-793; 3. Jain A, Zahra F. Transthyretin amyloid cardiomyopathy (ATTR-CM). Updated April 27, 2023. Accessed September 2025. https://www.ncbi.nlm.nih.gov/books/NBK574531/; 4. Adams D, et al. *Nat Rev Neurol.* 2019;15:387-404; 5. Koike H, Katsuno M. *Biomedicines.* 2019;7:11; 6. Ibrahim RB, et al. *Cell Mol Life Sci.* 2020;77:1421-1434; 7. Gertz M, et al. *BMC Fam Pract.* 2020;21:198; 8. Conceição I, et al. *J Peripher Nerv Syst.* 2016;21:5-9; 9. Ussavarungsi K, et al. *Eur Respir J.* 2017;49:1602313.

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ATTR Is Rapidly Progressive With Significant Morbidity and Mortality[1-3]

In ATTR, cardiac involvement is the most critical determinant of survival, with cardiac involvement at diagnosis associated with a poor prognosis[4-6]

Life expectancy for patients with ATTR-CM is

2 to 6 years

from the point of diagnosis, if untreated[7-9]

ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy.

1. Lane T, et al. *Orphanet J Rare Dis.* 2015;10(Suppl 1):O26; 2. Adams D, et al. *Neurology.* 2015;85:675-682; 3. Adams D, et al. *Curr Opin Neurol.* 2016;29(Suppl 1):S14-S26; 4. Shams P, Ahmed I. *Cardiac amyloidosis.* Updated May 3, 2025. Accessed September 2025. https://www.ncbi.nlm.nih.gov/books/NBK580521/; 5. Tozza S, et al. *J Peripher Nerv Syst.* 2021;26:155-159; 6. Porcari A, et al. *Cardiovasc Res.* 2023;118:3517-3535; 7. Lane T, et al. *Circulation.* 2019;140:16-26; 8. Grogan M, et al. *J Am Coll Cardiol.* 2016;68:1014-1020; 9. Gillmore JD, et al. *Eur Heart J.* 2018;39:2799-2806.

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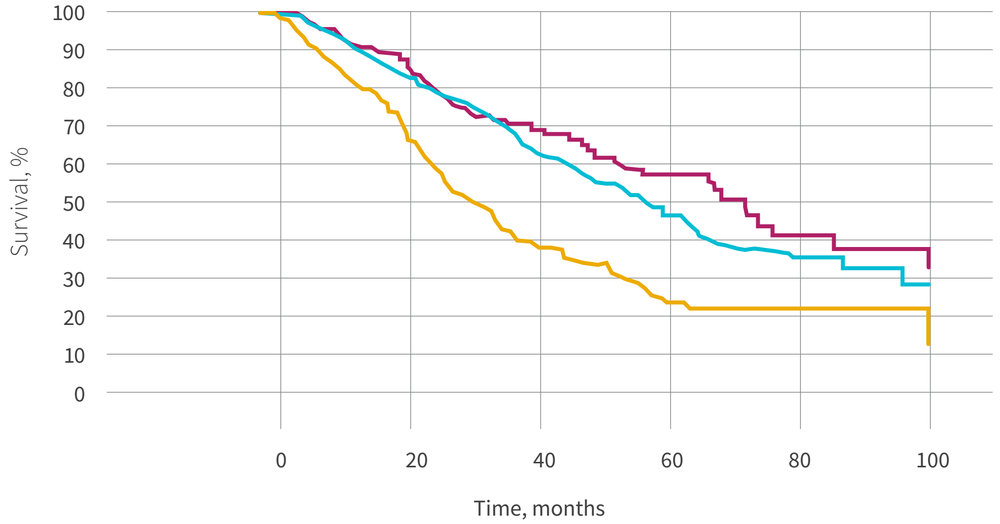
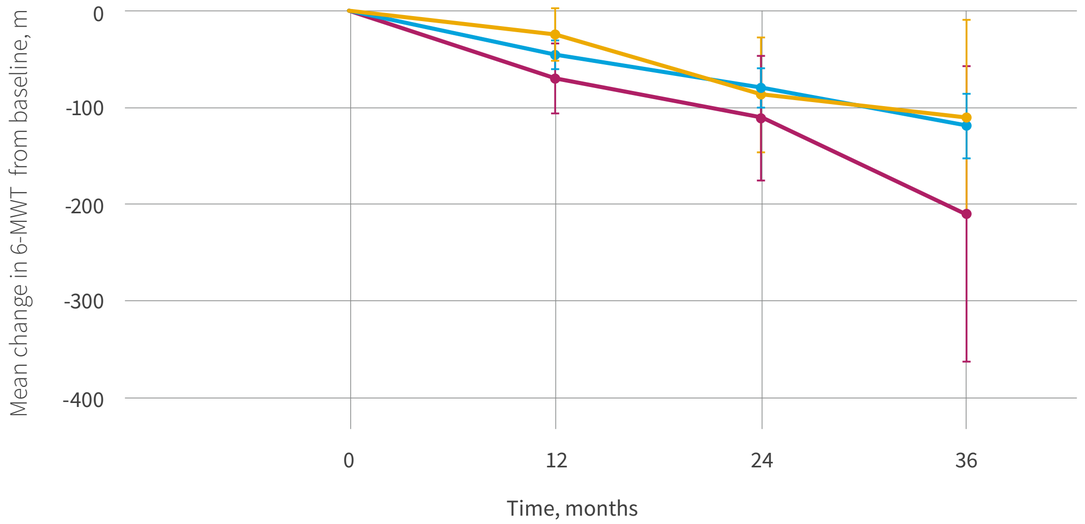
Patients With ATTR-CM Have Reduced Overall Survival and Progressive Decline in Physical Functioning[1,2]

Survival From Diagnosis of ATTR-CM[2,a]



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

6-MWT Decline in Patients With ATTR-CM Over 36 Months[2]



Numbers at risk			
Non-V122I-hATTR-CM	32	17	9
V122I-hATTR-CM	61	31	11
wtATTR-CM	289	175	66

Figures adapted from Lane et al.[2]

[a]Analysis from data including 1034 patients with ATTR-CM from 2000 to 2017 at the United Kingdom National Amyloidosis Centre.[2]

6-MWT, 6-minute walk test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; wtATTR-CM, wild-type transthyretin amyloidosis with cardiomyopathy.

1. Ruberg FL, et al. *Am Heart J.* 2012;164:222-228; 2. Lane T, et al. *Circulation.* 2019;140:16-26.

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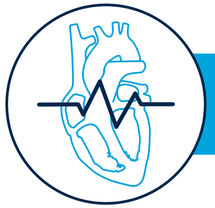
ATTR Disease Presentation Is Often Nonspecific, Heterogeneous, and Multisystemic[1,2]

A range of manifestations can develop over many years[1]; symptoms may start more than **10 years** before diagnosis[1,3,4]

In ATTR-CM, awareness of common early signs and symptoms in patients should raise suspicion of the disease[1,5]

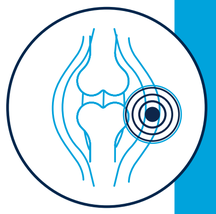
Awareness of high-risk populations may also help in the early diagnosis of ATTR-CM, for example patients with[6-11]:



Atrial fibrillation

Left ventricular hypertrophy

Aortic stenosis



Extracardiac musculoskeletal manifestations, including carpal tunnel syndrome, spinal stenosis, or spontaneous biceps tendon rupture

HFpEF

ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; HFpEF, heart failure with preserved ejection fraction.

1. Nativi-Nicolau JN, et al. *Heart Fail Rev.* 2022;27:785-793; 2. Porcari A, et al. *Cardiovasc Res.* 2023;118:3517-3535; 3. Karam C, et al. Poster presented at: XVIII Meeting of the International Society of Amyloidosis; September 4-8, 2022; Heidelberg, Germany. P192; 4. Karam C, et al. *Neurol Clin Pract.* 2019;9:309-313; 5. Witteles RM, et al. *JACC Heart Fail.* 2019;7:709-716; 6. Griffin JM, et al. *JACC CardioOncol.* 2021;3:488-505; 7. Brito D, et al. *Glob Heart.* 2023;18:59; 8. Gonzalez-Lopez E, et al. *Eur Heart J.* 2015;36:2585-2594; 9. Castano A, et al. *Curr Cardiovasc Risk Rep.* 2017;11:17; 10. Damy T, et al. *Eur Heart J.* 2016;37:1826-1834; 11. Castano A, et al. *Eur Heart J.* 2017;38:2879-2887.

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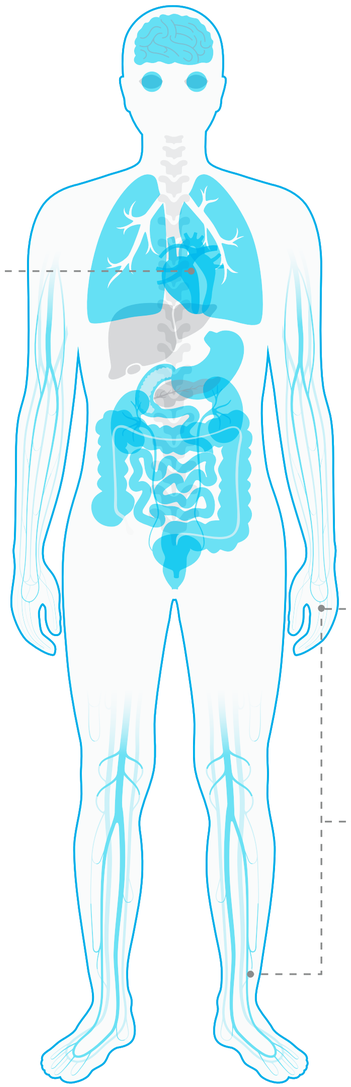
Common Signs and Symptoms of ATTR-CM

- Reduction in longitudinal strain with apical sparing
- Discrepancy between LV thickness and QRS voltage
- Atrioventricular block, in the presence of increased LV wall thickness
- Echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interatrial septum, and RV free wall
- Marked extracellular volume expansion, abnormal nulling time for the myocardium, or diffuse late gadolinium enhancement on CMR
- Mild increase in troponin levels on repeated occasions



- Bilateral carpal tunnel syndrome

- Symptoms of polyneuropathy and/or dysautonomia

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CMR, cardiac magnetic resonance; LV, left ventricular; RV, right ventricular.

Witteles RM, et al. *JACC Heart Fail.* 2019;7:709-716.

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Identification and Diagnosis of ATTR-CM

Once early signs and symptoms have been identified, cardiac assessment tools can be used to diagnose ATTR[1-6]

A diagnosis of ATTR can be confirmed by tissue biopsy or scintigraphy if cardiac involvement is suspected[3-6]

ACC Diagnostic Algorithm for Suspected Cardiac Amyloidosis[5,6]

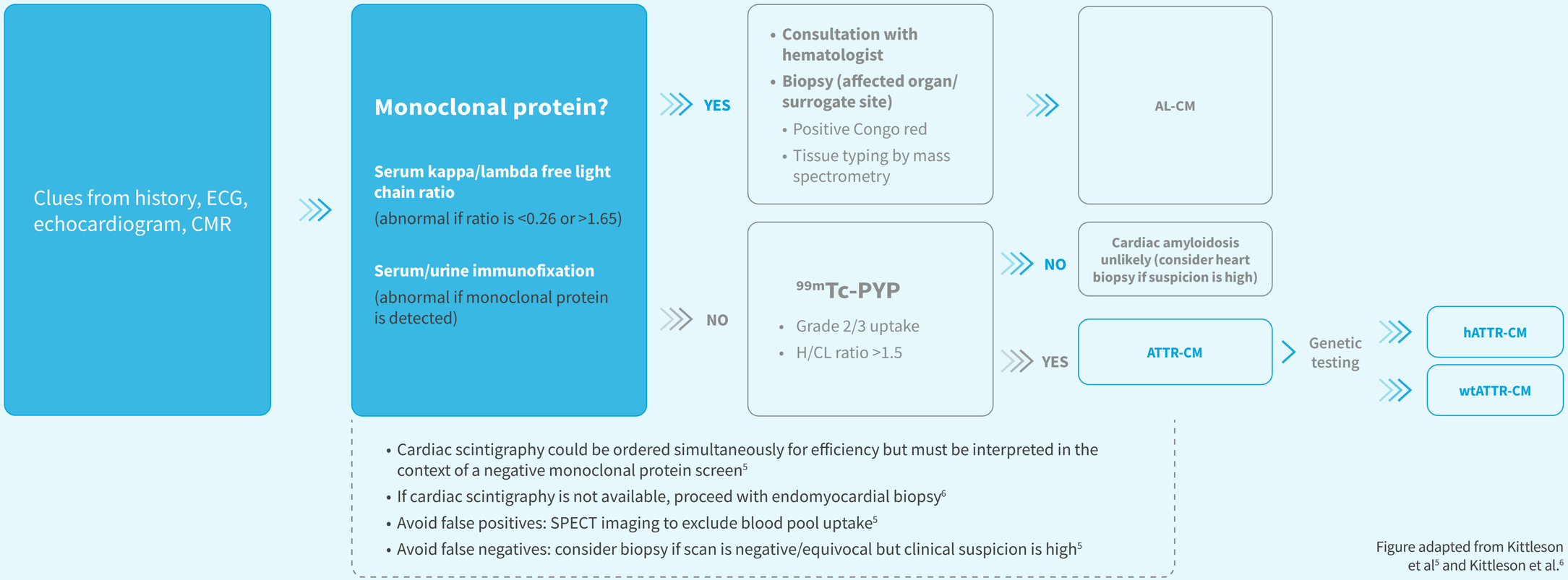

Figure adapted from Kittleson et al[5] and Kittleson et al.[6]

^{99m}Tc-PYP, 99m-technetium-pyrophosphate; ACC, American College of Cardiology; AL-CM, primary/amyloid light chain cardiac amyloidosis; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CMR, cardiac magnetic resonance; ECG, electrocardiogram; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; H/CL, heart/contralateral chest ratio; SPECT, single-photon emission computed tomography; wtATTR-CM, wild-type transthyretin amyloidosis with cardiomyopathy.

1. Dharmarajan K, Maurer MS. *J Am Geriatr Soc.* 2012;60:765-774; 2. Shin SC, Robinson-Papp J. *Mt Sinai J Med.* 2012;79:733-748; 3. Carroll A, et al. *J Neurol Neurosurg Psychiatry.* 2022;93:668-678; 4. Adams D, et al. *J Neurol.* 2021;268:2109-2122; 5. Kittleson MM, et al. *J Am Coll Cardiol.* 2023;81:1076-1126; 6. Kittleson MM, et al. *Circulation.* 2020;142:e7-e22.

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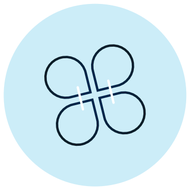
Summary



ATTR is a rapidly progressive, debilitating, and ultimately fatal multisystem disease caused by misfolded TTR protein accumulating as amyloid deposits in multiple organs and tissues in the body[1]

ATTR often presents with multisystem involvement, including cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) or a mixed combination of both[2,3]

In ATTR-CM, amyloid deposits accumulate in the cardiac tissues.[4] Patients with ATTR-CM commonly present with signs of heart failure, diastolic dysfunction, and arrhythmias[4]

ATTR-CM has a profound impact on quality of life and functional capacity.[5] Additionally, patients with ATTR-CM have a life expectancy of 2 to 6 years from the point of diagnosis, if untreated[5–7]

Recognizing the common signs and symptoms and identifying patients at elevated risk, coupled with the use of cardiac assessment tools and tissue biopsy or scintigraphy, can support earlier diagnoses of ATTR-CM[1,8]

ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTR-PN, transthyretin amyloidosis with polyneuropathy; TTR, transthyretin.

1. Nativi-Nicolau J, et al. *Heart Fail Rev.* 2022;27:785–793; 2. Maurer MS, et al. *J Am Coll Cardiol.* 2016;68:161-172; 3. Ruberg FL, et al. *J Am Coll Cardiol.* 2019;73:2872-2891; 4. Porcari A, et al. *Cardiovasc Res.* 2022;118:3517-3535; 5. Lane T, et al. *Circulation.* 2019;140:16-26; 6. Grogan M, et al. *J Am Coll Cardiol.* 2016;68:1014-1020; 7. Gillmore JD, et al. *Eur Heart J.* 2018;39:2799-2806; 8. Kittleson MM, et al. *J Am Coll Cardiol.* 2023;81:1076-1126.

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