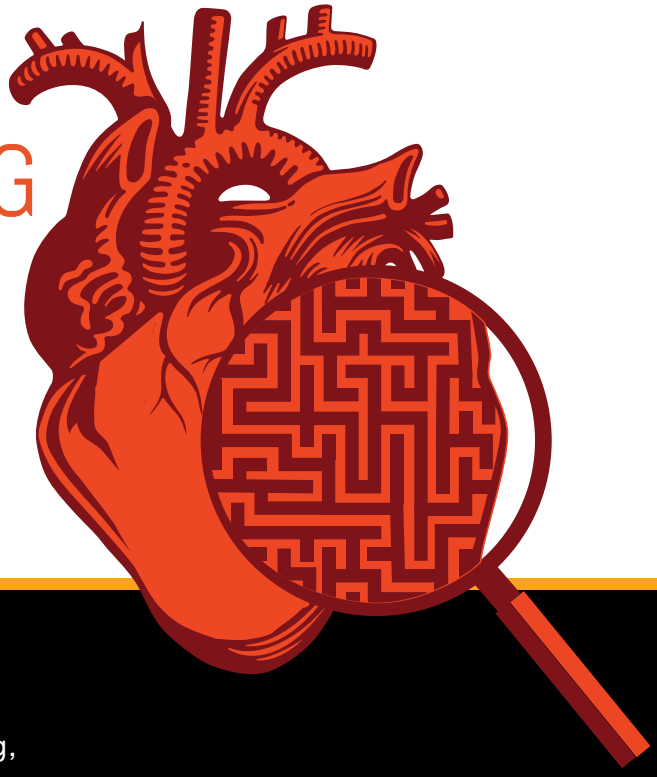
A LIFE-THREATENING DISEASE THAT CAN GO UNDETECTED



ATTR-CM: The Disease

- ATTR-CM is a rare condition that is life-threatening, underrecognised, and underdiagnosed[1-7]

Suspect the Signs of ATTR-CM

- The diagnosis of ATTR-CM is often delayed or missed[2,5,7]

Detect ATTR-CM Utilizing Nuclear Scintigraphy

- Tools used to diagnose ATTR-CM include nuclear scintigraphy (eg, [^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP] cardiac imaging), endomyocardial biopsy (EMB), and genetic testing[2,8]

^{99m}Tc-DPD, ^{99m}technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, ^{99m}technetium-labeled hydroxymethylene diphosphonate; ^{99m}Tc-PYP, ^{99m}technetium-labeled pyrophosphate.

ATTR-CM
SUSPECT & DETECT
UNCOVER THE CLUES FOR DIAGNOSIS

Pfizer Rare Disease

UNDERSTANDING TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM)

Amyloidosis is a group of diseases in which amyloid fibrils deposit into the extracellular spaces of different organs, which ultimately leads to progressive organ dysfunction.[1,9] The amyloid fibrils are formed by an aggregation of misfolded proteins. The most common amyloid fibril proteins that can infiltrate the heart and lead to cardiac amyloidosis[1] **are immunoglobulin light chain amyloid fibril protein (AL) and transthyretin amyloid fibril protein (ATTR)**.[2,9-11]

As for ATTR-CM specifically, it is found mostly in older patients, in whom misfolded transthyretin proteins deposit in the heart. This rare condition is life-threatening, underrecognised, and underdiagnosed.[1-7]

Most Common Types of Cardiac Amyloidosis

- Transthyretin amyloidosis (ATTR)[11]
  - Wild-type ATTR (ATTRwt)[11]
  - Hereditary ATTR (hATTR)[1] Also known as variant[1]
- Immunoglobulin light chain amyloidosis (AL)[11]

It is important to clinically differentiate between ATTR and AL, as they have different clinical courses.[11]

WILD-TYPE VS HEREDITARY ATTR-CM

WILD-TYPE ATTR-CM

Wild-type ATTR-CM (ATTRwt) is idiopathic[3] and is not considered to be a hereditary disease.[1] **It is thought to account for the majority of all ATTR-CM cases.[6]**

SOME PATIENT CONSIDERATIONS

- Ethnicity: predominantly white[3,6]
- Mostly men[3,4,6]
- Symptom onset typically over the age of 60 years[12]
- Heart failure[3,4,6]
- Cardiac arrhythmias, particularly atrial fibrillation[2-4,6]
- History of bilateral carpal tunnel syndrome[3,4,13]

PROGNOSIS

- Median survival: ~3.5 years[3,4,14]

HEREDITARY ATTR-CM

Hereditary ATTR-CM (hATTR)* is due to a mutation in the *TTR* gene.[1] Inherited mutations in *TTR* are common in patients of African (*Val122Ile*), Irish (*Thr60Ala*), Italian (*Ile68Leu*), and Danish (*Leu11Met*) descent.[2,12,15,16]

*Also known as variant hATTR.[1]

SOME PATIENT CONSIDERATIONS

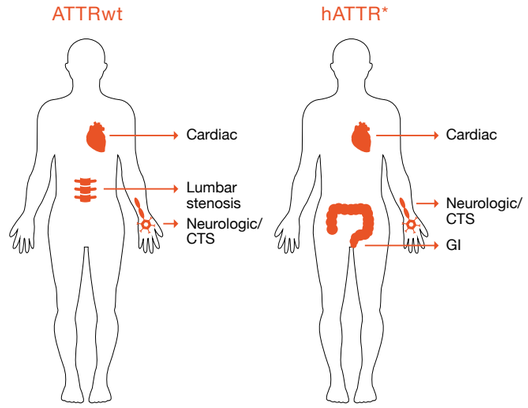
- Men and women[6]
- Symptom onset may occur as early as 50-60 years of age[12,17]
- Heart failure[6]
- Neurological symptoms (peripheral and autonomic)[6]
- Gastrointestinal symptoms[6]
- History of bilateral carpal tunnel syndrome[6]

PROGNOSIS

- Median survival: ~2 to 3 years[2]

COMMON SIGNS AND SYMPTOMS IN ATTRwt AND hATTR[3,4,6,10,18-21]*

Cardiac	• Fatigue • Shortness of breath • Edema	• Arrhythmias • HFpEF • Aortic stenosis
Soft Tissue	• Lumbar stenosis • Ruptured distal biceps tendon	
GI	• Diarrhoea • Constipation	• Nausea • Early satiety
Neurologic	• CTS • Peripheral neuropathy	• Orthostasis • Weakness



*Also known as variant hATTR.[1]

CTS, carpal tunnel syndrome; GI, gastrointestinal; HFpEF, heart failure with preserved ejection fraction.

H.I.D.D.E.N. IN PLAIN SIGHT

SUSPECT TRANSTHYRETIN CARDIAC AMYLOIDOSIS (ATTR-CM)

ATTR-CM is an underdiagnosed cause of heart failure, particularly heart failure with preserved ejection fraction (HFpEF) in older adults.[5,7]

CONSIDER THE FOLLOWING CLINICAL CLUES, ESPECIALLY IN COMBINATION, TO RAISE SUSPICION FOR ATTR-CM AND THE NEED FOR FURTHER TESTING

HFpEF — heart failure with preserved ejection fraction in patients typically over 60 years old[5-7]

INTOLERANCE — to standard heart failure (HF) therapies, ie, ACEi/ARBs and beta blockers[9,22,23]

DISCORDANCE — between QRS voltage and left ventricular (LV) wall thickness[24-26]

DIAGNOSIS — of carpal tunnel syndrome or lumbar spinal stenosis[3,11,13,20-22,27-29]

ECHO — showing increased LV wall thickness[6,11,26,30,31]

NERVOUS SYSTEM — autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss[6,11,17,32]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ECG, electrocardiography.

CLUES THAT MAY RAISE SUSPICION OF CARDIAC AMYLOIDOSIS

HFpEF: heart failure with preserved ejection fraction in patients typically over 60[5-7]

- In ATTR-CM, diastolic function is impaired due to amyloid fibril deposition in the myocardium resulting in thicker and inelastic ventricles, thereby decreasing the stroke volume. It is not until the later stages of ATTR-CM disease that ejection fraction drops.[33-35]
- Imaging clues, such as reduced longitudinal strain with apical sparing, may help increase suspicion[9,33]

INTOLERANCE to standard HF therapies, ie, ACEi/ARBs and beta blockers[9,22,23]

- Patients can develop a decrease in stroke volume, which can lead to low blood pressure. As a result, they can develop an intolerance to blood pressure–lowering therapies[22,23]

DISCORDANCE between QRS voltage and LV wall thickness[24-26]

- The classic ECG feature of ATTR-CM is a discordance between QRS voltage to LV mass ratio[9,12,25]

DIAGNOSIS of carpal tunnel syndrome or lumbar spinal stenosis[3,11,13,20-22,27-29]

- Carpal tunnel syndrome and lumbar spinal stenosis are often seen in ATTR-CM due to amyloid deposition in these areas[3,11,13,20,22,27-29]
- Carpal tunnel syndrome in ATTR-CM often precedes cardiac manifestations by several years[4,13,36]

ECHOCARDIOGRAPHY showing increased LV wall thickness[6,11,26,30,31]

- Increased wall thickness without a clear explanation (eg, hypertension) should raise suspicion for cardiac amyloidosis[9,37]
- Extracellular amyloid deposition results in an increased LV wall thickness that tends to be greater in ATTR-CM than in AL cardiac amyloidosis, with reported thicknesses for ATTR-CM often being more than 15 mm[11,25,26,31]

NERVOUS SYSTEM—autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss[6,11,17,32]

- Gastrointestinal complaints due to autonomic dysfunction include diarrhoea and constipation[10]
- Orthostatic hypotension due to autonomic dysfunction is another symptom that may occur with ATTR-CM[6,11,32]

IF YOU SUSPECT TRANSTHYRETIN AMYLOIDOSIS CARDIOMYOPATHY (ATTR-CM)

TOOLS FOR DIAGNOSIS

NONINVASIVE TESTING CAN DIAGNOSE ATTR-CM

NONINVASIVE

- **NUCLEAR SCINTIGRAPHY (^{99m}TC-PYP, ^{99m}TC-PYROPHOSPHATE; ^{99m}TC-DPD, ^{99m}TC-3,3-DIPHOSPHONO-1,2-PROPANODICARBOXYLIC ACID; ^{99m}TC-HMDP, ^{99m}TC-HYDROXYMETHYLENE DIPHOSPHONATE)[8]**
- **BLOOD AND URINE TESTING TO RULE OUT AL[8]***

INVASIVE

- **ENDOMYOCARDIAL BIOPSY (EMB) + AMYLOID TYPING[8]**

GENETIC TESTING[2]

NUCLEAR SCINTIGRAPHY IN COMBINATION WITH TESTING TO RULE OUT LIGHT CHAIN CAN DIAGNOSE ATTR-CM[8]

*Rule out AL: testing for presence of monoclonal protein via serum and urine immunofixation + serum free light chain assay.

DISCOVER THE TOOLS TO DIAGNOSE ATTR-CM

NUCLEAR SCINTIGRAPHY

- A noninvasive, readily available diagnostic tool with high sensitivity and specificity for ATTR-CM[8]
- Uses a radioactive bone tracer, ^{99m}technetium-labeled pyrophosphate (^{99m}Tc-PYP), ^{99m}technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), ^{99m}technetium-labeled hydroxymethylene diphosphonate (^{99m}Tc-HMDP), for detection of ATTR[8]
- A multicentre international study demonstrated 99% sensitivity for ATTR-CM (visual grade 1-3). A separate analysis within the study demonstrated 100% specificity for visual grade 2,3 with concurrent testing to rule out AL[8*†]

†Multicentre study conducted to determine the diagnostic value of bone scintigraphy in patients with ATTR-CM. Of 1217 evaluable patients, 374 underwent endomyocardial biopsy, and 843 were diagnosed with presence and type or absence of amyloid on basis of extracardiac histology combined with echocardiography with or without cardiac magnetic resonance imaging (CMR).

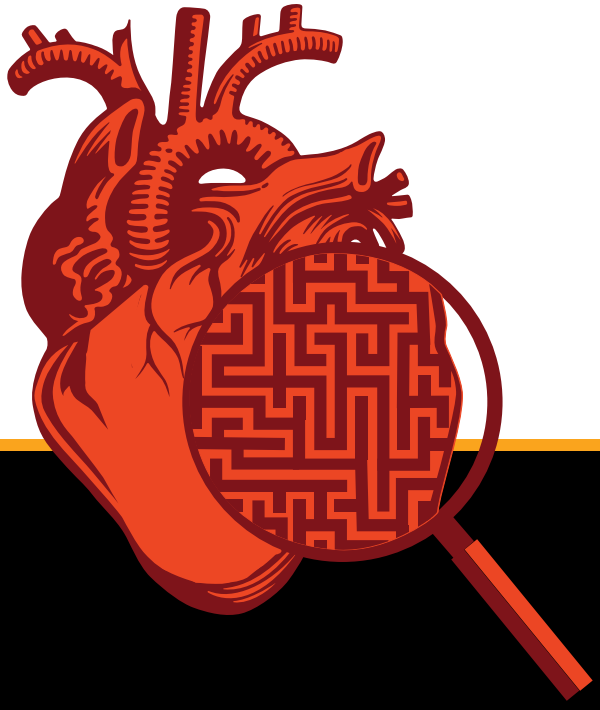
ENDOMYOCARDIAL BIOPSY (EMB)

- Diagnosis of cardiac amyloidosis requires the histology to show Congo red staining with apple-green birefringence[8,9]
- Additional tests to determine amyloid type are recommended following diagnosis of cardiac amyloidosis[8]
- Risk of complications and the need for specialised centres and expertise may contribute to a diagnostic delay[8,9]

GENETIC TESTING

- Used to determine if the disease is hereditary due to a mutation in the *TTR* gene[2‡]
- Genetic counseling and gene sequencing are recommended following confirmation of ATTR-CM[2]

‡Also known as variant ATTR.[1]



ATTR-CM

SUSPECT & DETECT

UNCOVER THE CLUES FOR DIAGNOSIS

References: 1. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines. *Amyloid*. 2016;23(4):209-213. **2.** Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. *Circulation*. 2017;135(14):1357-1377. **3.** Connors LH, Sam F, Skinner M, et al. Heart failure due to age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation*. 2016;133(3):282-290. **4.** Pinney JH, Whelan CJ, Petrie A, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. *J Am Heart Assoc*. 2013;2(2):e000098. **5.** Mohammed SF, Mirzoyev SA, Edwards WD, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. *JACC Heart Fail.* 2014;2(2):113-122. **6.** Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68(2):161-172. **7.** González-López E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J*. 2015;36(38):2585-2594. **8.** Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation.* 2016;133(24):2404-2412. **9.** Narotsky DL, Castaño A, Weinsaft JW, Bokhari S, Maurer MS. Wild-type transthyretin cardiac amyloidosis: novel insights from advanced imaging. *Can J Cardiol*. 2016;32(9):1166.e1-1166.e10. **10.** Nativi-Nicolau J, Maurer MS. Amyloidosis cardiomyopathy: update in the diagnosis and treatment of the most common types. *Curr Opin Cardiol.* 2018;33(5):571-579. **11.** Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation*. 2009;120(13):1203-1212. **12.** Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation*. 2012;126(10):1286-1300. **13.** Nakagawa M, Sekijima Y, Yazaki M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. *Amyloid.* 2016;23(1):58-63. **14.** Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol*. 2016;68:1014-1020. **15.** Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. *Amyloid*. 2015;22(3):171-174. **16.** Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. *Nat Rev Cardiol.* 2010;7(7):398-408. **17**. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. *Amyloid.* 2015;22(2):123-131. **18.** Galat A, Guellich A, Bodez D, et al. Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg? *Eur Heart J*. 2016;37(47):3525-3531. **19.** Geller HI, Singh A, Alexander KM, et al. Association between ruptured distal biceps tendon and wild-type transthyretin cardiac amyloidosis. *JAMA*. 2017;318(10):962-963. **20.** Westermark P, Westermark GT, Suhr OB, Berg S. Transthyretin-derived amyloidosis: probably a common cause of lumbar spinal stenosis. *Ups J Med Sci*. 2014;119(3):223-228. **21.** Yanagisawa A, Ueda M, Sueyoshi T, et al. Amyloid deposits derived from transthyretin in the ligamentum flavum as related to lumbar spinal canal stenosis. *Mod Pathol*. 2015;28(2):201-207. **22.** Brunjes DL, Castano A, Clemons A, Rubin J, Maurer MS. Transthyretin cardiac amyloidosis in older Americans. *J Card Fail.* 2016;22(12):996-1003. **23.** Castaño A, Drach BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. *Heart Fail Rev*. 2015;20(2):163-178. **24.** Carroll JD, Gaasch WH, McAdam KP. Amyloid cardiomyopathy: characterization by a distinctive voltage/mass relation. *Am J Cardiol.* 1982;49:9-13. **25.** Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. *Am J Cardiol*. 2014;114(7):1089-1093. **26.** Quarta CC, Solomon D, Uraizee I, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation.* 2014;129(18):1840-1849. **27.** Connors LH, Prokaeva T, Lim A, et al. Cardiac amyloidosis in African Americans: Comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. *Am Heart J*. 2009;158(4):607-614. **28.** Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol.* 2018;72(17):2040-2050. **29.** Sueyoshi T, Ueda M, Jono H, et al. Wild-type transthyretin-derived amyloidosis in various ligaments and tendons. *Hum Pathol*. 2011;42(9):1259-1264. **30.** Phelan D, Collier P, Thavendiranathan P, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart*. 2012;98(19):1442-1448. **31.** Ternacle J, Bodez D, Guellich A, et al. Causes and consequences of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2016;9(2):126-138. **32.** Coelho T, Maurer MS, Suhr OB. THAOS - The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr Med Res Opin.* 2013;29(1):63-76. **33.** Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med*. 2018;28(1):10-21. **34.** Rubin J, Steidley DE, Carlsson M, Ong ML, Maurer M. Myocardial contraction fraction by M-mode echocardiography is superior to ejection fraction in predicting mortality in transthyretin amyloidosis. *J Card Fail.* 2018;24(8):504-511. **35.** Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;2(6):670-679. **36.** Papoutsidakis N, Miller EJ, Rodonski A, Jacoby D. Time course of common clinical manifestations in patients with transthyretin cardiac amyloidosis: delay from symptom onset to diagnosis. *J Card Fail*. 2018;24(2):131-133. **37.** Rapezzi C, Lorenzini M, Longhi S, et al. Cardiac amyloidosis: the great pretender. *Heart Fail Rev*. 2015;20(2):117-124.

Pfizer Rare Disease