ATTR Cardiac Amyloidosis*

Considerations for Identification and Diagnosis

*Also known as transthyretin amyloid cardiomyopathy or ATTR-CM.

ATTR-CM is an underrecognized cause of heart failure with preserved ejection fraction (HFpEF) in older adults[1]

DISEASE BURDEN

Heart failure (HF) is a leading cause of hospitalization and is associated with high morbidity and mortality postdiagnosis.[2] Many patients with heart failure present with multiple comorbidities.[3]

- **6.9 million** people are living with HF in the United States, and this number is expected to rise to nearly **8.5 million** by 2030[4†]
- Approximately **23% of Medicare patients** with a diagnosis of HF were readmitted to the hospital within 30 days[5‡]
- In one study, **51.5% of HF patients** had **HFpEF**[6]
- Once diagnosed, untreated patients with ATTR-CM have a median survival of ~3 to 5 years[7]

ATTR-CM is a life-threatening, progressive, infiltrative rare disease that can often be overlooked as a cause of heart failure.[8]

Abbreviation: ATTR, transthyretin amyloidosis.

†American Heart Association estimate.
‡Retrospective study of Medicare fee-for-service beneficiaries aged 65 years or older hospitalized with HF, acute myocardial infarction, or pneumonia from January 1, 2008, through December 31, 2014.[5]

SUSPICION OF ATTR CARDIAC AMYLOIDOSIS (ATTR-CM)

- More than **50% of hATTR patients and 39% of wtATTR patients received a misdiagnosis**[1]
- **~75%** of those patients received treatment for the misdiagnosed condition[1]

In Witteles et al, further evidence to support a suspicion of ATTR-CM includes the following **red flags**[1]:

- Reduction in longitudinal strain with apical sparing
- Discrepancy between left ventricular thickness and QRS voltage (with a lack of left ventricular hypertrophy on an electrocardiogram)
- Atrioventricular block, in the presence of increased left ventricular wall thickness
- Echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interatrial septum, and right ventricular free wall
- Marked extracellular volume expansion, abnormal nulling time for the myocardium, or diffuse late gadolinium enhancement on cardiac magnetic resonance imaging
- Symptoms of polyneuropathy and/or dysautonomia
- History of bilateral carpal tunnel syndrome
- Mild increase in troponin levels on repeated occasions

Patients affected by ATTR-CM may have multiorgan system involvement and may present with clinical symptoms related to various systems, including musculoskeletal, ocular, neurologic (peripheral and autonomic), and cardiovascular[2-4]

- ~1 in 10 patients over the age of 60 with HFpEF were found to have ATTR-CM[5,6]
- In one study, **1 in 6 patients aged 65 years and older** with severe symptomatic aortic stenosis undergoing transcatheter aortic valve replacement had ATTR-CM (16% overall and 22% of men)[7]
- 6% of patients with myocardial hypertrophy of unknown cause had hATTR[8]
- **69%** of patients diagnosed with ATTR-CM **had atrial fibrillation**[9]
- In 2 studies among patients with wtATTR, **46% to 49% had carpal tunnel syndrome**[10,11]
- **Total knee and hip arthroplasty** was **3 to 5 times more common** among patients with ATTR-CM than for age- and sex-matched controls[12]
- **24% of tissue samples removed during surgery for rotator cuff repair** were found to have wtATTR deposits[13]
- **ATTR** deposits have been identified in resected tissues in patients undergoing lumbar spinal stenosis surgery[14]

Abbreviations: ATTR, transthyretin amyloidosis; hATTR, hereditary ATTR-CM; HFpEF, heart failure with preserved ejection fraction; wtATTR, wild-type ATTR-CM.

SUSPICION AND DIAGNOSIS OF ATTR CARDIAC AMYLOIDOSIS (ATTR-CM)

A review of noninvasive and invasive approaches for suspicion and diagnosis of ATTR-CM[1]

Tools used to raise suspicion:

Echocardiogram

- Plays a major role in noninvasive diagnosis because of its assessment of structure and function and its pervasive use for patients with concerning cardiac symptoms[2]
- Showcases increased left ventricular wall thickness[2]
- Suspicion of ATTR-CM may include echocardiographic hypertrophic phenotype with associated infiltrative features, including increased thickness of the atrioventricular valves, interatrial septum, and right ventricular free wall[3]

Cardiac Magnetic Resonance (CMR)

- Plays an important role in noninvasive diagnosis because it provides tissue characterization in addition to high-resolution morphologic and functional assessment[2]
- Offers value in 2 clinical scenarios[2]:
  - Differentiation of cardiac amyloidosis from other cardiomyopathies
  - Potential early detection of cardiac amyloidosis
- CMR with late gadolinium enhancement may be relatively contraindicated in patients with suspected cardiac amyloidosis and concomitant renal failure[2]

Tools used to make a definitive diagnosis:

PYP Cardiac Imaging (Nuclear Scintigraphy)

- A noninvasive, readily available diagnostic tool with high sensitivity and specificity for ATTR-CM when combined with testing to rule out AL[4,5]
- Uses ^{99m}technetium pyrophosphate (^{99m}Tc-PYP), a radioactive tracer used as an adjunct in the diagnosis of ATTR-CM[4,5]
- A multicenter international study of scintigraphy at amyloidosis centers of excellence demonstrated 100% specificity for ATTR-CM using visual grade 2 or 3 with concurrent testing to rule out AL[5]

Endomyocardial Biopsy (EMB)

- An invasive, traditional approach for diagnosing cardiac amyloidosis; however, the need for specialized centers and expertise may contribute to diagnostic delay[4,5]
- Potential EMB complications, although rare, can include[6]:
  - Arrhythmia
  - Perforation with pericardial tamponade
  - Pneumothorax

ATTR-CM can be a burden to both patients and health systems because of its protracted diagnosis or misdiagnosis resulting from a poor understanding of the disease, heterogeneity of clinical characteristics, or misconceptions about diagnosis and treatment.[3]

Early and accurate diagnosis can improve patient care.[3]

Abbreviation: ATTR, transthyretin amyloidosis.

References

Page 1:

1. 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. doi:10.1093/eurheartj/ehv338 **2.** Lahoz R, Fagan A, McSharry M, Proudfoot C, Corda S, Studer R. Recurrent heart failure hospitalizations are associated with increased cardiovascular mortality in patients with heart failure in Clinical Practice Research Datalink. *ESC Heart Fail.* 2020;7(4):1688-1699. doi:10.1002/ehf2.12727 **3.** Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18). e895-e1032. doi:10.1161/cir.0000000000001063 **4.** Urbich M, Globe G, Pantiri K, et al. A systematic review of medical costs associated with heart failure in the USA (2014–2020). *PharmacoEconomics*. 2020;38(11):1219-1236. doi:10.1007/s40273-020-00952-0 **5.** Dharmarajan K, Wang Y, Lin Z, et al. Association of changing hospital readmission rates with mortality rates after hospital discharge. *JAMA*. 2017;318(3):270-278. doi:10.1001/jama.2017.8444 **6.** Avula HR, Leong TK, Lee KK, Sung SH, Go AS. Long-term outcomes of adults with heart failure by left ventricular systolic function status. *Am J Cardiol*. 2018;122(6):1008-1016. doi:10.1016/j.amjcard.2018.05.036 **7.** Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2023;81(11):1076-1126. doi:10.1016/j.jacc.2022.11.022 **8.** Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail.* 2019;7(8):709-716. doi:10.1016/j.jchf.2019.04.010

Page 2:

1. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail.* 2019;7(8):709-716. doi:10.1016/j.jchf.2019.04.010 **2.** González-López E, López-Sainz A, Garcia-Pavia P. Diagnosis and treatment of transthyretin cardiac amyloidosis. Progress and hope. *Rev Esp Cardiol*. 2017;70(11):991-1004. doi:10.1016/j.rec.2017.05.036 **3.** Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med*. 2018;28(1):10-21. doi:10.1016/j.tcm.2017.07.004 **4.** Mohty D, Damy T, Cosnay P, et al. Cardiac amyloidosis: updates in diagnosis and management. *Arch Cardiovasc Dis*. 2013;106(10):528-540. doi:10.1016/j.acvd.2013.06.051 **5.** 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. doi:10.1093/eurheartj/ehv338 **6.** Hahn VS, Yanek LR, Vaishnav J, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail.* 2020;8(9):712-724. doi:10.1016/j.jchf.2020.04.007 **7.** Castaño A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J.* 2017;38(38):2879-2887. doi:10.1093/eurheartj/ehx350 **8.** Damy T, Costes B, Hagège AA, et al. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. *Eur Heart J.* 2016;37(23):1826-1834. doi:10.1093/eurheartj/ehv583 **9.** Donnellan E, Wazni OM, Hanna M, et al. Atrial fibrillation in transthyretin cardiac amyloidosis: predictors, prevalence, and efficacy of rhythm control strategies. *JACC Clin Electrophysiol.* 2020;6(9):1118-1127. doi:10.1016/j.jacep.2020.04.019 **10.** Connors LH, Sam F, Skinner M, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation.* 2016;133(3):282-290. doi:10.1161/CIRCULATIONAHA.115.018852 **11.** 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. doi:10.1161/JAHA.113.000098 **12.** Rubin J, Alvarez J, Teruya S, et al. Hip and knee arthroplasty are common among patients with transthyretin cardiac amyloidosis, occurring years before cardiac amyloid diagnosis: can we identify affected patients earlier? *Amyloid.* 2017;24(4):226-230. doi:10.1080/13506129.2017.1375908 **13.** 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. doi:10.1016/j.humpath.2010.11.017 **14.** 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. doi:10.1038/modpathol.2014.102

Page 3:

1. 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. doi:10.1097/HCO.0000000000000547 **2.** Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2—evidence base and standardized methods of imaging. *Circ Cardiovasc Imaging*. 2021;14(7):e000029. doi:10.1161/HCI.0000000000000029. **3.** Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail*. 2019;7(8):709-716. doi:10.1016/j.jchf.2019.04.010 **4.** Bokhari S, Morgenstern R, Weinberg R, et al. Standardization of ^{99m}Technetium pyrophosphate imaging methodology to diagnose TTR cardiac amyloidosis. *J Nucl Cardiol.* 2018;25(1):181-190. doi:10.1007/s12350-016-0610-4 **5.** Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2016;133(24):2404-2412. doi:10.1161/CIRCULATIONAHA.116.021612 **6.** Narotsky DL, Castano 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. doi:10.1016/j.cjca.2016.05.008