# 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]**

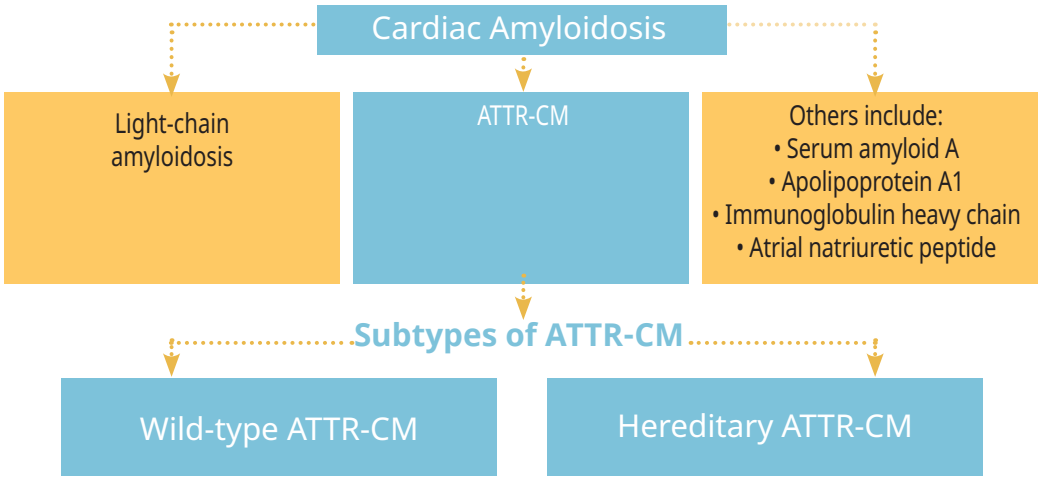
**Abbreviation:** ATTR, transthyretin amyloidosis.

†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]

# ATTR CARDIAC AMYLOIDOSIS (ATTR-CM) OVERVIEW

## Two types of cardiac amyloidosis (CA)—light-chain amyloidosis (AL) and ATTR-CM—make up ~95% of all CA diagnoses[1]

### Main types of CA[1-3]




## There are 2 types of ATTR-CM—wild type and hereditary[1]:

### Wild-type ATTR-CM*
**(wtATTR)**

**Associated with aging[4,5]**

- Most often affects White men over the age of 60[6-8]
- May be the most common form of ATTR-CM[8]

### Hereditary ATTR-CM†
**(hATTR)**

**Caused by a change** (or "mutation") **in one of your genes[9]**

- Passed down from a relative[7]
- Affects both men and women, with symptoms beginning as early as **50 to 60** years old[10]
- There are more than 120 known mutations that cause hATTR; the most common mutation in the United States is V122I[1,3]

**Abbreviation:** ATTR, transthyretin amyloidosis.

*Formerly known as senile cardiac amyloidosis, senile systemic amyloidosis, or age-related amyloidosis.[6]

†May also be known as mutant variant ATTR, ATTRm amyloidosis, mutant ATTR amyloidosis, or hereditary amyloidosis.[1]

# 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.

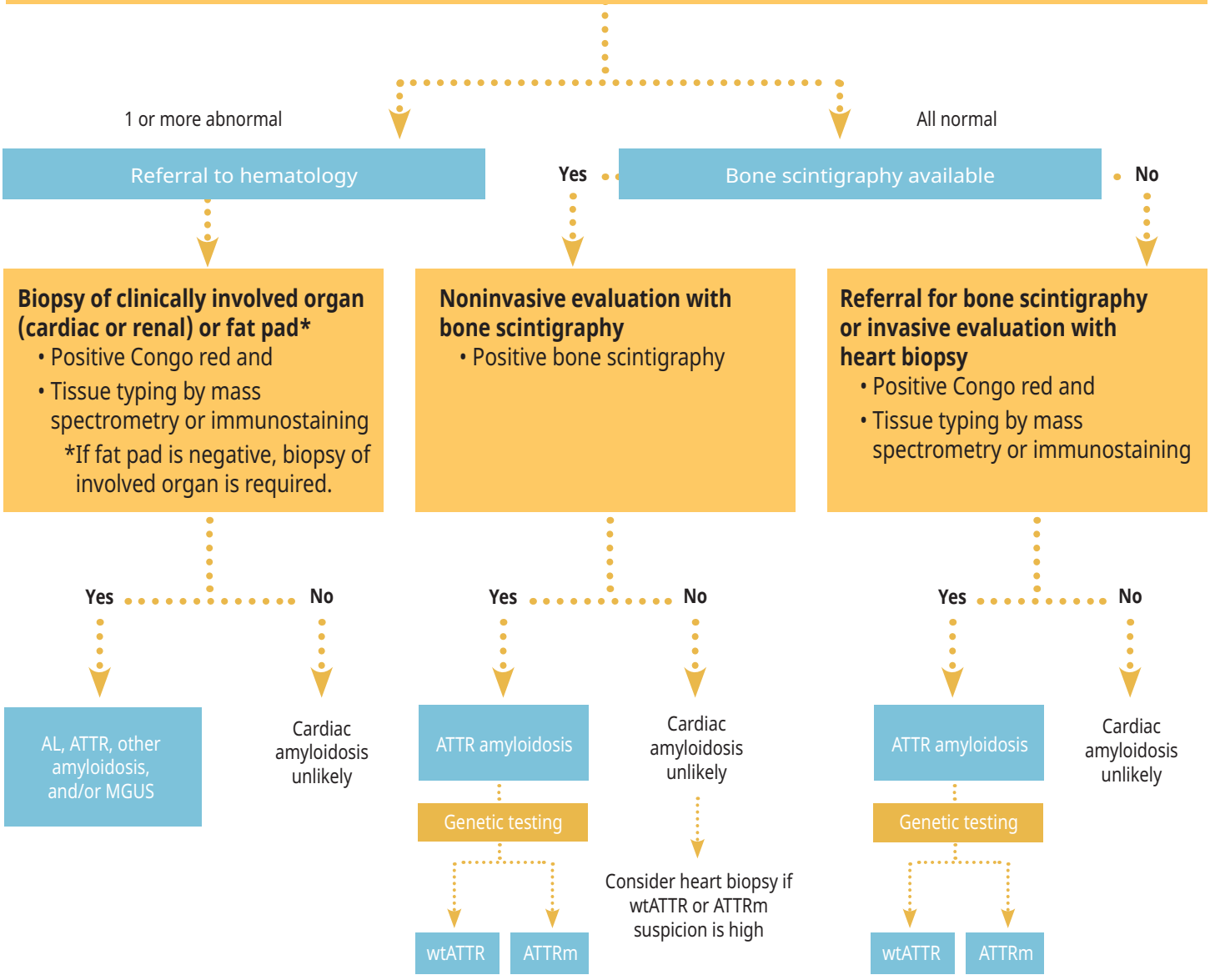
# DIAGNOSIS OF ATTR CARDIAC AMYLOIDOSIS (ATTR-CM)

## Once ATTR-CM is suspected, a definitive diagnosis can be achieved through a noninvasive or invasive diagnostic approach[1,2]

Symptoms, ECG, echocardiogram, MRI, or biomarkers suggestive of cardiac amyloidosis[1,2]

**Screen for the presence of a monoclonal protein. Order the following 3 tests:**

- Serum kappa/lambda free light-chain ratio (abnormal if ratio is <0.26 or >1.65)
- Serum protein immunofixation (abnormal if monoclonal protein is detected)
- Urine protein immunofixation (abnormal if monoclonal protein is detected)




**Abbreviations:** AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; ATTRm, mutant transthyretin amyloidosis; ECG, electrocardiogram; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; wtATTR, wild-type ATTR-CM.

Reproduced with permission from Nativi-Nicolau J and Maurer MS.[2]

# 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.

**THERE ARE MANY EXCELLENT RESOURCES ON ATTR CARDIAC AMYLOIDOSIS (ATTR-CM) FOR YOU, YOUR PATIENTS, AND THEIR LOVED ONES. FIND SUPPORT FROM THESE TRUSTED AMYLOIDOSIS ORGANIZATIONS:**

## Amyloidosis Support Groups

**www.amyloidosissupport.org**

- Provides education for patients through live support groups in 30 cities
- Provides patient education through virtual webinars and patient support groups on Facebook

## Amyloidosis Research Consortium

**www.arci.org**

- Provides comprehensive support and information for patients
- Accelerates development of and access to new and innovative treatments
- Drives research that will have the greatest impact on patients

## Amyloidosis Foundation

**www.amyloidosis.org**

- Supports research for an earlier diagnosis
- Educates medical professionals
- Provides patients with a comprehensive range of services

## Additional Resources

| PROGRAM | DESCRIPTION | HOW TO ACCESS |
|---|---|---|
| **Your Heart's Message** | **To learn more about ATTR-CM and the resources available to patients** (support groups) | **www.yourheartsmessage.com** |
| **Transthyretin Cardiac Amyloidosis** | **Website HCPs can access for ATTR-CM information** | **https://transthyretincardiacamyloidosis.pfizerpro.com** |

**Click here to get more information on ATTR-CM:**

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