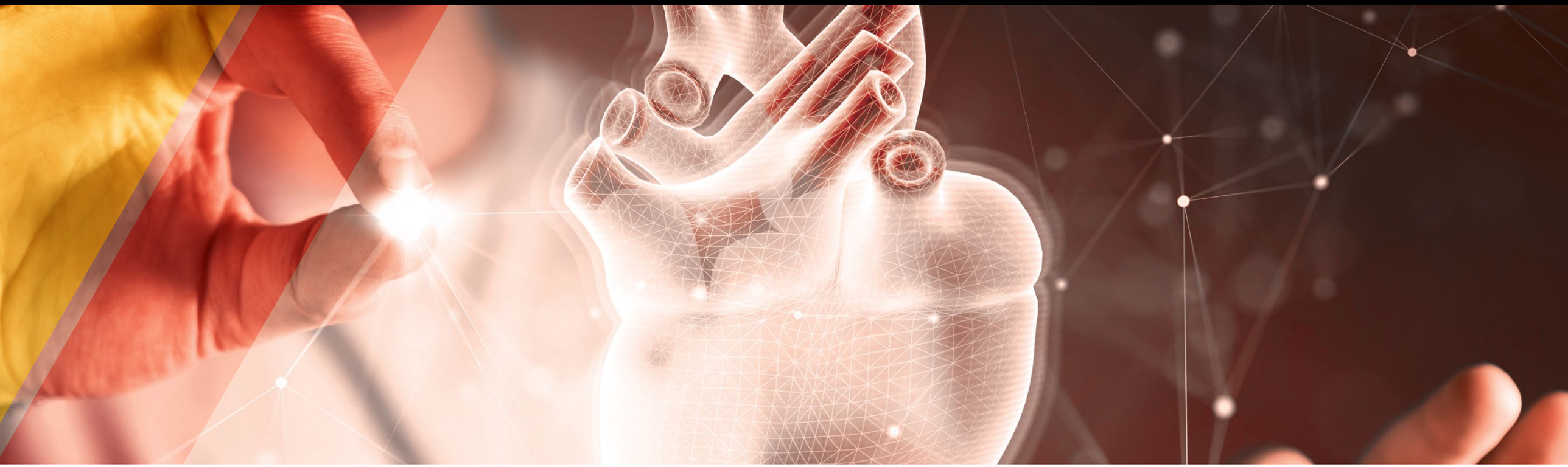
ATTR-CM

SUSPECT & DETECT

Key investigational steps



TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM)

ATTR-CM the disease

A rare condition that is life-threatening, under-recognized, and under-diagnosed[1]

SUSPECT the signs of ATTR-CM

The diagnosis of ATTR-CM is often delayed or missed[1,2]

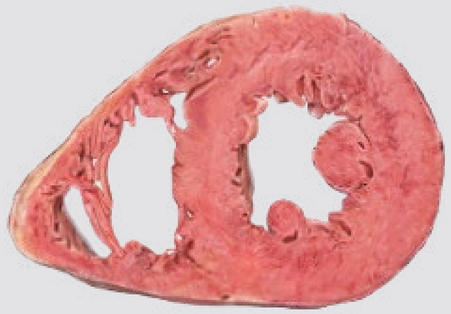
DETECT ATTR-CM

Tools used to diagnose ATTR-CM include nuclear scintigraphy (e.g., [^{99m}Tc-PYP] cardiac imaging), endomyocardial biopsy (EMB), and genetic testing[1]

^{99m}Tc-PYP = ^{99m}technetium-labelled pyrophosphate.

Understanding transthyretin amyloid cardiomyopathy (ATTR-CM)[1,3]

- ATTR is a form of infiltrative cardiomyopathy in which a specific precursor protein pathologically misfolds, aggregates, and forms amyloid fibrils that deposit extracellularly within various organs
- In the heart, the infiltration of amyloid fibrils into myocardial tissue results in progressive ventricular stiffness, wall thickening, and diastolic filling abnormalities, which typically manifest as heart failure (HF) with preserved ejection fraction and restrictive physiology, eventually leading to organ failure



Normal heart*

Amyloid heart*

- When the disease is severe and advanced, systolic dysfunction might also be seen
- It is a potentially **fatal cause of heart failure and other cardiovascular manifestations**

ATTR-CM has the ability to disguise itself clinically as common cardiovascular disease states[1]

- ~10% of HFpEF patients referred to a single centre had ATTR-CM confirmed by endomyocardial biopsy[4†]
- ~13% of hospitalized patients with HFpEF and increased LV wall thickness had wild-type ATTR-CM confirmed by scintigraphy[5‡]
- 16% of patients who undergo transcatheter aortic valve replacement for severe aortic stenosis, and
- 5% of patients with presumed hypertrophic cardiomyopathy

Thus, it is **believed to be underdiagnosed** and the true incidence and prevalence are uncertain.[1]

HFpEF = heart failure with preserved ejection fraction

* Illustrative representation.

† Prospective analysis in 108 patients seen at the John Hopkins HFpEF Clinic who underwent endomyocardial biopsy to evaluate myocardial tissue histopathology.

‡ Prospective, cross-sectional, single-centre study at a tertiary university hospital in Madrid, Spain that included 120 patients admitted for HFpEF, with LV ejection fraction ≥50% and LV hypertrophy ≥12 mm. ^{99m}Tc-DPD (^{99m}technetium-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid) scintigraphy was used to confirm ATTR-CM.

WHAT ARE THE TYPES OF ATTR-CM?

ATTR-CM is categorized into two subtypes:[3]

1 a **hereditary** subtype, due to one of numerous disease-causing genetic mutations, and

> Recent reports have demonstrated that median survival depends on the hereditary ATTR-CM (hATTR) mutation and stage at diagnosis; it can range from 2-5 years from initial presentation in untreated patients[6,7]

2 a **wild-type**, in which a mutation is not present

> Recent reports have demonstrated median survival is approximately 3.5 years after initial evaluation[4]

> The prevalence of wild-type ATTR-CM (wtATTR) is unknown, but it is thought to be relatively high compared to hATTR-CM[2]

Demographic profiles of common subtypes of cardiac amyloidosis[1]

Wild-type ATTR-CM	■ Median age of onset >70 years ■ Male predominance ■ Prevalence/incidence unknown; increases with age
Hereditary ATTR-CM	■ Age of onset variable, depends on genotype ■ No clear predominance by sex ■ Most common gene mutations in North America: Val122Ile (West African descent), Thr60Ala (Northern Ireland descent), Val30Met (Swedish, Portuguese, Japanese descent) ■ Prevalence/incidence variable; depends on genotype
Light chain amyloidosis (AL)	■ Median age of onset >60 years ■ Slight male predominance ■ Annual incidence 10 per million; increases with age

Adapted from Fine *et al*.[1]

Practical tip. In general, ATTR cardiac amyloidosis is a slowly progressive disorder that is most common in older men. In comparison, AL cardiac amyloidosis generally has a more rapidly progressive course, a relatively younger age of onset, and less of a male predominance.[1]

AL = light chain amyloidosis; hATTR = hereditary transthyretin amyloidosis; wtATTR = wild-type transthyretin amyloidosis.

WHAT ARE SOME OF THE SYMPTOMS OF ATTR-CM?

Select extracardiac manifestations of common subtypes of cardiac amyloidosis[1]

MANIFESTATION	AL	wtATTR	hATTR
Renal	■ Renal insufficiency ■ Nephrotic syndrome	■ Milder renal involvement (mainly due to heart failure)	
Autonomic		■ Orthostatic hypotension ■ Gastroparesis, diarrhea and/or constipation ■ Sexual dysfunction ■ Sweating abnormalities	
Neurologic		■ Peripheral sensorimotor neuropathy (might be predominant feature of hATTR) ■ Carpal tunnel syndrome (bilateral)	
		■ Spinal stenosis (predominantly lumbar)	
Musculoskeletal	■ Pseudohypertrophy (i.e., macroglossia)	■ Biceps tendon rupture	
Hematologic	■ Bleeding and easy bruising (i.e., periorbital)		

Adapted from Fine *et al*.[1]

Please see the CCS/CHFS guidelines for complete information.

It is important to clinically differentiate between AL and ATTR, as they have different clinical courses.[1]

AL = light chain amyloidosis; hATTR = hereditary transthyretin amyloidosis; wtATTR = wild-type transthyretin amyloidosis.

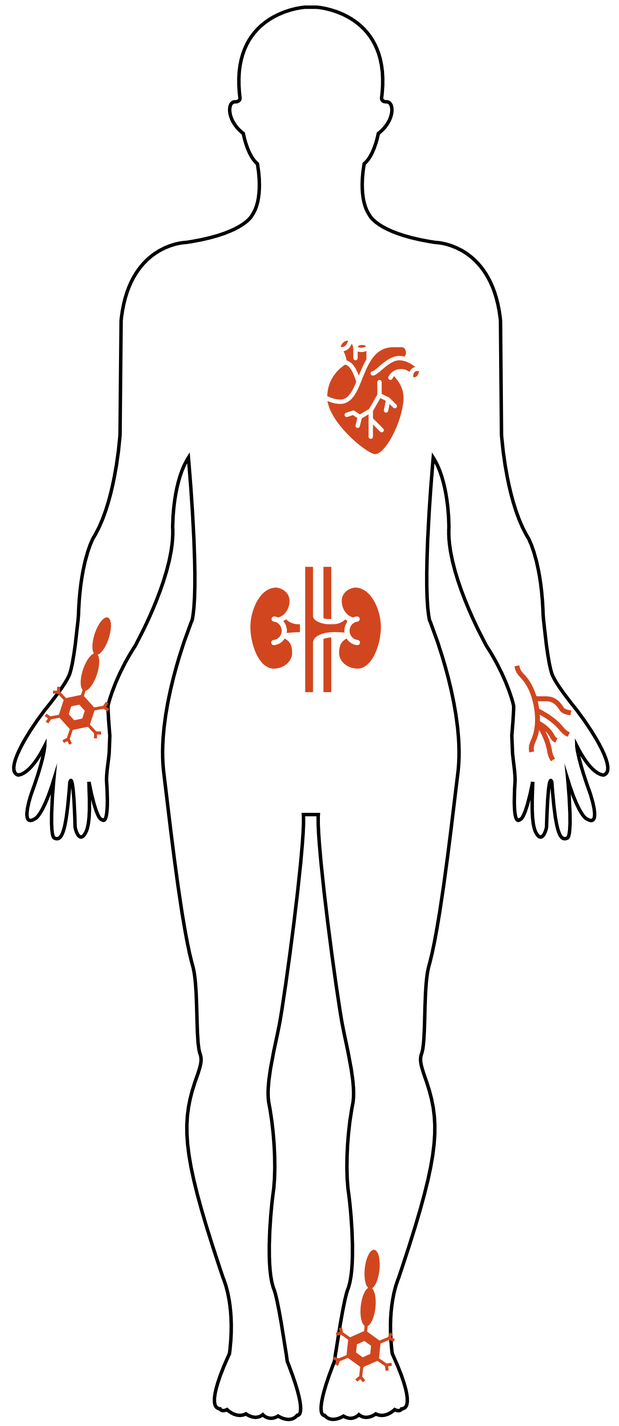
WHEN TO SUSPECT ATTR-CM?

Key clinical features to trigger a diagnostic workup for cardiac amyloidosis[1]

SUSPECT CARDIAC AMYLOIDOSIS WHEN PATIENTS PRESENT WITH SIGNS AND SYMPTOMS OF HEART FAILURE WITH ≥1 OF THE FOLLOWING

(Strong Recommendation, Moderate-Quality Evidence)

- Unexplained increased LV wall thickness
  Older than 60 years of age with low-flow low-gradient AS and LVEF >40%
- Established AL or ATTR in non-cardiac organ/system
  (i.e., renal AL amyloidosis causing nephrotic syndrome)
- History of carpal tunnel syndrome (bilateral)
- Unexplained peripheral sensorimotor neuropathy and/or dysautonomia



Adapted from Fine *et al*.[1]

AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; LVEF = left ventricular ejection fraction.

Differential diagnostic algorithm for evaluating suspected ATTR-CM[1]

Cardiac amyloidosis suspected based on standard HF workup, including cardiac imaging with either echocardiography and/or CMR, troponin and BNP/NTproBNP

↓

Screen for plasma cell dyscrasia – serum and urine protein electrophoresis with immunofixation, serum free light chain assay

↓

AL amyloidosis suspected
monoclonal protein present

↓

Hematology referral
biopsy of involved organ, typically EMB, renal, BMB or fat pad (which cannot exclude systemic amyloidosis) with MS or IHC if positive†

↓

AL cardiac amyloidosis
(or other type by EMB with MS or IHC)‡

Cardiac amyloidosis excluded*

ATTR amyloidosis suspected
monoclonal protein absent

↓

Tc-^{99m}-PYP scan
if unavailable, perform EMB with MS or IHC, if positive†

↓

ATTR-CM
perform TTR genetic testing

↓

Positive
Hereditary ATTR-CM

Negative
Wild-type ATTR-CM

Cardiac amyloidosis excluded –
if equivocal results, consider EMB*

Adapted from Fine *et al*.[1]

BMB = bone marrow biopsy; BNP = B-type natriuretic peptide;
CMR = cardiovascular magnetic resonance imaging; EMB = endomyocardial biopsy;
IHC = immunohistochemistry; LGE = late gadolinium enhancement; MS = mass spectrometry;
NTproBNP = N-terminal pro-B-type natriuretic peptide; PYP = pyrophosphate; sFLC = serum free light chain.

* Endomyocardial biopsy should be performed if non-invasive evaluation is equivocal or negative despite a high index of clinical suspicion.
† Tissue biopsy analysis includes Congo red staining for amyloid deposits.
‡ A diagnosis of AL cardiac amyloidosis should prompt urgent hematology referral.

Adapted from Fine *et al*.[1]

Summary of diagnosis recommendations from the Canadian Cardiovascular Society/Canadian Heart Failure Society joint position statement on the evaluation and management of patients with cardiac amyloidosis:[1]*

Routine investigations are recommended for the evaluation of HF in patients who present with suspected cardiac amyloidosis, including 12-lead ECG, troponin, and BNP/NTproBNP (Strong Recommendation, Moderate-Quality Evidence).

Echocardiography with longitudinal LV strain measurement, or CMR with LGE and T1 mapping imaging is recommended to be performed in all patients with suspected cardiac amyloidosis to evaluate for characteristic features of cardiac amyloidosis or alternative causes of HF (Strong Recommendation, Moderate-Quality Evidence).

Serum and urine protein electrophoresis with immunofixation and sFLC assay is recommended to be performed in all patients with suspected cardiac amyloidosis to evaluate for possible AL amyloidosis or other plasma cell dyscrasia (Strong Recommendation, Moderate-Quality Evidence).

Nuclear scintigraphy with bone-seeking radiotracer (if available) is recommended to evaluate for cardiac involvement when ATTR cardiac amyloidosis is suspected after exclusion of AL (Strong Recommendation, Moderate-Quality Evidence).

Endomyocardial biopsy is recommended for diagnosis and subtyping with mass spectrometry or immunohistochemistry/immunofluorescence (if available) when the existing diagnostic workup for cardiac amyloidosis is equivocal or discordant with clinical suspicion (Strong Recommendation, Low-Quality Evidence).

For patients with a diagnosis of ATTR cardiac amyloidosis, genetic testing is recommended to differentiate hATTR from wtATTR (Strong Recommendation, Moderate-Quality Evidence).

* Please consult the position statement for complete recommendations.

References:

1. Fine NM *et al.* Canadian Cardiovascular Society/Canadian Heart Failure Society joint position statement on the evaluation and management of patients with cardiac amyloidosis. *Can J Cardiol* 2020;36:322-34.

2. Maurer MS *et al.* Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail* 2019;12:e006075.

3. O'Meara E *et al.* CCS/CHFS heart failure guidelines: clinical trial update on functional mitral regurgitation, SGLT2 inhibitors, ARNI in HFpEF, and tafamidis in amyloidosis. *Can J Cardiol* 2020;36:159-69.

4. Hahn VS *et al.* Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail* 2020;8(9):712-24.

5. González-López E *et al.* Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;36(38):2585-94.

6. Maurer MS *et al.* Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. *Circulation* 2017;135(14):1357-77.

7. Donnelly JP *et al.* Cardiac amyloidosis: An update on diagnosis and treatment. *Cleve Clin J Med* 2017;84 (12 Suppl 3):12-26.

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