CARDIOHUB

CARDIO TOWN HALL AMYLOIDOSIS

Navigating Uncertainty in ATTR Amyloidosis Clinical Judgment and Shared Decisions:

KEY TAKEAWAYS

Cardiac Amyloidosis is characterized by protein infiltration into the myocardium that often leads to cardiomyopathy. It can be classified as:

- Immunoglobulin light chain amyloidosis (AL-CM)
- Transthyretin-mediated (ATTR), which may be either hereditary (ATTRv-CM) or Wild-type amyloidosis (ATTRwt-CM)

Symptoms	AL-CM	ATTRv-CM	ATTRwt-CM
Neuropathy	√	√√	√
Nephropathy	√		
GI involvement	√	√	√
Orthopedic issues		√	√√

Amyloidosis may affect several different systems in the body.

Cardiac

Heart failure

Atrial fibrillation

Bradyarrhythmias/ conduction abnormalities/ pacemakers

Musculoskeletal

Carpal tunnel syndrome

Back pain/lumbar spinal stenosis

Ruptured distal biceps tendon/ Popeye sign

Shoulder, knee, and hip pain or surgery

Trigger finger

Polyneuropathy

Painful neuropathy in hands and feet

Muscle weakness, difficulty walking, and falls

Autonomic Dysfunction

Orthostatic hypotension/ intolerance to blood pressure meds

Chronic diarrhea/ constipation/weight loss

Erectile dysfunction

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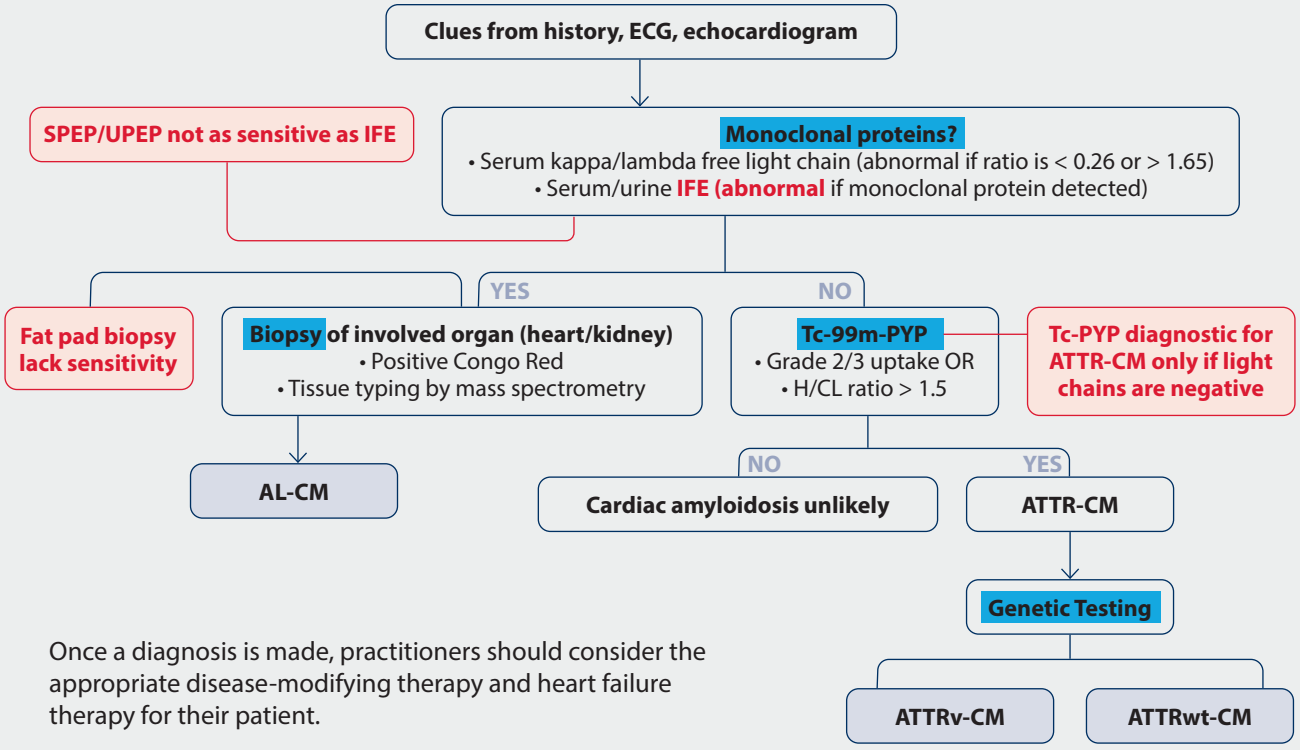
Following a step-by-step approach is key to making the correct diagnosis.



Once a diagnosis is made, practitioners should consider the appropriate disease-modifying therapy and heart failure therapy for their patient.

	TTR STABILIZERS		TTR SILENCERS
Trial	**ATTR-ACT trial**	**ATTRibute-CM trial**	**HELIOS-B**
Patients	441 patients with ATTR-CM, NYHA-I-III	632 patients with ATTR-CM, NYHA-I-III	655 patients with ATTR-CM, NYHA-I-III
Therapeutic Tenure	Tafamisis vs. placebo for 30 months	• Acoramidis vs. placebo for 30 months • 14.5% of patients started after enrollment	• Vutrisiran vs. placebo for 36 months • 40% of patients also on tafamidis at baseline and 13.5% started after enrollment
Death	43% to 30%	26% to 19%	26% to 18%
CV Hospitalization	61% to 52%	43% to 27%	CV events: 41% to 34%
Preservation	6MWD and QOL	6MWD and QOL	6MWD and QOL
FDA Approval	2019	November 2024	March 2025

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Clinical signs that may assist in selecting the appropriate DMT therapy for your patient.

Too Early for DMT

- Asymptomatic carriers of pathogenic *TTR* variants
- Noncardiac biopsy evidence of TTR amyloid deposition (ea, carpal tunnel or vertebral ligament issue) without cardiac disease

Monitoring and surveillance
- Biomarkers
- Echocardiogram
- Potential subsequent radionuclide imaging

Appropriate for DMT

- Confirmed ATTR-CM based on radionuclide scintigraphy in the absence of a monoclonal protein or biopsy with transthyretin amyloid
- Clinical history of HF
- NYHA Class I–III symptoms
- Patients with milder symptoms (earlier diagnosis) have best outcomes

HF Therapies
- Diuretics titrated to symptoms; avoid over-diuresis
- Caution with vasodilators and beta-blockers
- MRA and SGLT2 inhibitors assist in relief of congestion

Atrial Fibrillation
- Anticoagulation regardless of CHA_2DS_2-VASc score

Possibly Too Late for DMT

- NYHA Class IV symptoms
- NT-proBNP ≥8,500 pg/mL
- Severe kidney dysfunction (eGFR <15 mL/min/1.73 m^2)
- Significant functional impairment (6MWD <100–150 m)

- Referral for cardiac transplant if otherwise a candidate
- Palliative care consultation

ATTRv-CM with Cardiomyopathy and Polyneuropathy
- Vutrisiran
- Neurology consultation

ATTRwt-CM or ATTRv-CM without Polyneuropathy
- Tafamidis, acoramidis, or vutrisiran based on:
  - Cost/payer coverage
  - Access
  - Patient preference including route of administration
- Insufficient evidence to recommend combination therapy with TTR stabilizer and TTR silencer
- Insufficient evidence to change therapies if disease progression

DMT: disease-modifying therapy

While there are clearly established algorithms for diagnosis and several effective disease-modifying therapies, it's important to note that many unanswered questions remain.

Therapeutic Area	Question(s)	Potential Approaches to Address Emerging Questions
Initial therapy	• Stabilizer or silencer? • Which agent?	• Comparative effectiveness research using national data repositories or registries • Single- or multi-center collaborative research studies • Endpoints including progression of disease and costs in addition to mortality and CV events
Combination therapy and HF management	• Which combination? • Initially or in series? • Choice of HF therapies	• Randomized trials with active controls to determine efficacy of combination therapy compared with monotherapy • Comparison of combination therapy at diagnosis vs sequential initiation based on indicators of disease progression • Crossover studies comparing single and combination therapy • Randomized trials or prospective observational analyses to identify optimal combination of HF-focused therapies (including MRA and SGLT2 inhibitor)
Monitoring disease progression	• What is the optimal combination of metrics? • When to reassess?	• Determine contributions of potential indicators of therapeutic efficacy or disease progression in multiple complementary domains including circulating biomarkers (transthyretin/prealbumin, troponin, natriuretic peptides, eGFR), imaging biomarkers (echocardiogram GLS, CMR ECV, radionuclide scintigraphy), functional markers (6MWD, CPET-derived parameters), QOL (KCCQ)
Prevention of disease	• Can the development of ATTR-CM be prevented in at-risk individuals?	• Screening in at-risk populations (SCAN-MP; NCT03812172) • Randomized trials of stabilizers in carriers of pathogenic TTR variants approaching predicted age of disease onset (ACT-EARLY; NCT06563895) • Randomized trials of disease-modifying therapies in older adults with orthopedic transthyretin amyloid identification (carpal tunnel, spinal ligament)
Cost-effectiveness	• Costs to individuals as well as healthcare system	• Cost-effectiveness analysis regarding efficacy vs pricing • Analysis of access, administrative burden of the prescription process, regional variations in management

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