CARDIAC AMYLOIDOSIS; CURRENT STATUS OF DIAGNOSIS

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I THE DIAGNOSTIC PARADIGM SHIFT (GILLMORE ALGORITHM / ESC 2021-2023 / ACC 2023)

- **Two Dominant Clinical Subtypes (>95% of All Cardiac Amyloidosis):**
  - **Immunoglobulin Light-Chain (AL) Amyloidosis:** Clonal plasma cell dyscrasia secreting misfolded **lambda (75–80%) or kappa (20–25%)** immunoglobulin light chains; medical emergency with <6-month untreated survival if severe cardiac involvement is present.
  - **Transthyretin (ATTR) Amyloidosis:** Misfolding of hepatic **transthyretin (prealbumin)** tetramers into amyloid fibrils, divided into **Wild-Type ATTR (ATTRwt, formerly "senile systemic amyloidosis")** (predominantly older men >=65 yr) and **Hereditary/Variant ATTR (ATTRv)** (autosomal dominant *TTR* gene mutations such as **Val122Ile [p.Val142Ile]**, **Thr60Ala**, and **Val30Met**).
  - **The Non-Invasive Diagnostic Revolution:** Based on the landmark validation by **Gillmore et al. (*Circulation* 2016)**, **ATTR Cardiac Amyloidosis can be diagnosed with ~100 percent specificity and positive predictive value WITHOUT an invasive biopsy** when **Grade 2 or 3 myocardial uptake on bone-avid radiotracer scintigraphy** is combined with **complete absence of a monoclonal protein in serum and urine**.

II EXTRACARDIAC AND CARDIOVASCULAR "RED FLAGS" (WHEN TO SUSPECT AMYLOIDOSIS)

- **Orthopedic and Soft-Tissue Red Flags (Frequently Precede Heart Failure by 5 to 10 Years in ATTR):**
  - **Bilateral Carpal Tunnel Syndrome** (most common early sign, present in ~50% of ATTRwt 5 to 10 years before cardiac diagnosis).
  - **Lumbar Spinal Canal Stenosis** (ligamentum flavum amyloid infiltration).
  - **Spontaneous Distal Biceps Tendon Rupture ("Popeye Sign")** (present in ~33% of ATTRwt) and trigger finger / total hip or knee arthroplasty.
  - **Pathognomonic Mucocutaneous Signs of AL Amyloidosis: Macroglossia** (tongue enlargement with lateral dental indentations) and **periorbital purpura ("raccoon eyes")** after minor coughing/Valsalva, alongside nephrotic-range proteinuria and hepatomegaly.
  - **Neurological Red Flags: Sensorimotor peripheral polyneuropathy** (ascending numbness/pain, classic in **ATTRv** and AL) and **dysautonomia** (profound orthostatic hypotension, postprandial diarrhea/constipation, erectile dysfunction, and urinary retention).
  - **Cardiovascular Phenotypic Clues:**
  - **Voltage-to-Mass Discordance:** Marked concentric biventricular wall thickening (**>=12 to 14 mm**) on echocardiography paired with **low QRS voltage** (all limb leads <=5 mm or precordial leads <=10 mm; present in ~50–60% of AL and ~25–30% of ATTR) or **absence of expected LVH voltage** with a **"pseudo-infarction" QS pattern** in anterior/inferior leads (present in 50 to 70% despite clean coronary arteries).
  - **"Auto-Cure" of Hypertension and GDMT Intolerance:** A previously hypertensive patient whose blood pressure spontaneously normalizes or who develops severe hypotension/bradycardia on low doses of **ACEi/ARB/ARNI or Beta-Blockers**.
  - **Specific High-Prevalence Cohorts: 13 to 16 percent of elderly patients undergoing TAVR for severe Aortic Stenosis** (especially **Low-Flow, Low-Gradient severe AS**), **13 to 17 percent of hospitalized HFpEF patients with LV wall thickness >=12 mm**, and middle-aged/older adults with unexplained **Complete Heart Block** or **Atrial Fibrillation**.

III STEP 1: MANDATORY LABORATORY EXCLUSION OF AL AMYLOIDOSIS (ALL THREE TESTS REQUIRED)

- **The Cardinal Rule:** Because **up to 20 to 30 percent of patients with AL Cardiac Amyloidosis can also show false-positive Grade 1, 2, or 3 myocardial uptake on Tc-99m PYP/DPD bone scintigraphy**, **a bone scan can NEVER be interpreted in isolation without simultaneously ordering the Monoclonal Protein Triad**:
- **Serum Free Light Chain (sFLC) Assay (Quantitative Kappa and Lambda Free Light Chains + Kappa/Lambda Ratio):** Normal serum kappa/lambda ratio is **0.26 to 1.65** (extended to **0.37 to 3.10 in severe CKD / eGFR <30 mL/min** because free light chains are renally cleared).
- **Serum Protein Electrophoresis with Immunofixation (SPIE / SIFE)**.
- **24-Hour (or Spot) Urine Protein Electrophoresis with Immunofixation (UPIE / UIFE)**.
- **Crucial Exam Trap:** Standard Serum Protein Electrophoresis (**SPEP**) alone is **insufficient** (sensitivity only ~50 to 70% in AL because the monoclonal light-chain spike is often too small to form an M-band on standard SPEP); combining **sFLC + SIFE + UIFE achieves >99 percent sensitivity for detecting AL Amyloidosis**.

IV STEP 2: MULTIMODALITY ECHOCARDIOGRAPHY AND CARDIAC MRI

- **Transthoracic Echocardiography and 2D Speckle-Tracking Strain:**
  - **Structural Hallmarks:** Concentric **LV and RV free-wall thickening (>=12 mm; RV free wall >5 mm)**, **thickened interatrial septum and AV valve leaflets**, bi-atrial dilation, small pericardial effusion, and Grade III restrictive mitral inflow (**E/A >2.0, deceleration time <150 ms, e' <5 cm/s, E/e' >15**).
  - **The "Cherry-on-Top" Apical Sparing Bull's-Eye Pattern:** Profound impairment of longitudinal strain in the basal and mid-ventricular segments with **preserved strain at the LV apex (Relative Apical Longitudinal Strain ratio = [Average Apical LS] / [Average Basal LS + Average Mid LS] >= 1.0)**.
  - **Cardiac Magnetic Resonance (CMR — Reference Tissue Characterization):**
  - **Late Gadolinium Enhancement (LGE) and Nulling Kinetics:** Diffuse circumferential **subendocardial or transmural LGE** (often involving the right ventricle and both atria) accompanied by **abnormal gadolinium inversion-time (TI) kinetics**—on the TI scout sequence, the amyloid-infiltrated **myocardium reaches the null point (turns black) BEFORE or simultaneously with the LV blood pool**.
  - **Parametric Mapping:** Markedly elevated **Native T1 (>1,100 to 1,150 ms at 1.5T)** and **massively expanded Extracellular Volume (ECV >= 40 percent, often 50 to 70 percent)**—the highest ECV values seen in any cardiomyopathy.

Diagnostic Step / Modality	Specific Finding / Cut-off	Clinical Action / Interpretation
Step 1: Monoclonal Screen	**sFLC (Kappa/Lambda ratio) + SIFE + UIFE**	If **ANY test is abnormal** -> **Non-invasive pathway STOPS**; urgent Hematology + **Tissue Biopsy with Mass Spectrometry**

Diagnostic Step / Modality	Specific Finding / Cut-off	Clinical Action / Interpretation
Step 2: Echo & CMR	Wall thickness >=12 mm + **Apical Sparing GLS ("Cherry-on-Top")**; CMR **subendocardial/transmural LGE, abnormal TI nulling, & ECV >=40%**	Confirms cardiac amyloid phenotype; does **not** reliably differentiate AL from ATTR (requires Step 1 + Step 3)
Step 3: Tc-99m PYP / DPD / HMDP Bone Scintigraphy + SPECT	**Perugini Grade 2 or 3** (Heart/Contralateral Lung [H/CL] ratio >=1.5 at 1h or >=1.3 at 3h) **+ Negative sFLC/SIFE/UIFE**	**100% Specificity & PPV for ATTR Cardiac Amyloidosis** (**No biopsy required**)
Step 4: *TTR* Gene Sequencing	Sanger / NGS sequencing of the ***TTR* gene**	**Class I Mandatory** in all confirmed ATTR-CM to distinguish **ATTRwt** from **ATTRv** (cascade family screening)

V STEP 3: BONE-AVID RADIOTRACER SCINTIGRAPHY (THE NON-INVASIVE ATTR CONFIRMATION)

- **Radiotracers: Technetium-99m Pyrophosphate (Tc-99m PYP)**, **Tc-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (Tc-99m DPD)**, or **Tc-99m Hydroxymethylene Diphosphonate (Tc-99m HMDP)**. (**Crucial Exam Trap: Tc-99m MDP [Methylene Diphosphonate]**, the standard orthopedic bone scan tracer used in many general radiology departments, has **low sensitivity for cardiac ATTR and must NOT be used**.)
- **Perugini Visual Grading Scale (at 1 or 3 Hours Post-Injection) + Mandatory Tomographic SPECT:**
  - **Grade 0:** No myocardial uptake and normal bone/rib uptake.
  - **Grade 1:** Myocardial uptake **less than** rib uptake.
  - **Grade 2:** Myocardial uptake **equal to** rib uptake.
  - **Grade 3:** Myocardial uptake **greater than** rib uptake with mild or absent rib uptake.
  - **Mandatory SPECT Confirmation:** Planar Heart-to-Contralateral Lung (**H/CL >= 1.5 at 1 hour or >= 1.3 at 3 hours**) ratios alone can be **falsely positive due to residual radiotracer in the LV blood pool** (especially in low-output heart failure or CKD); therefore, **3D SPECT/CT imaging is mandatory** to verify that radiotracer uptake is truly within the **left ventricular myocardium** rather than the cavity blood pool.
  - **The Non-Invasive Diagnostic Rule (Class I): Perugini Grade 2 or 3 myocardial uptake on SPECT** + **Negative sFLC, Negative SIFE, and Negative UIFE** confirms **ATTR Cardiac Amyloidosis with 100% specificity without endomyocardial biopsy**.

VI STEP 4: WHEN INVASIVE BIOPSY AND MASS SPECTROMETRY ARE REQUIRED, PLUS TTR GENOTYPING

- **Strict Indications for Histological Biopsy (Endomyocardial Biopsy or Surrogate Fat Pad / Bone Marrow Biopsy):**
  - **Scenario A — Positive Monoclonal Protein Screen (Abnormal sFLC, SIFE, or UIFE):** Regardless of whether the PYP scan is Grade 0 or Grade 2/3 (since **MGUS coexists in 20 to 40 percent of elderly ATTRwt patients**, and AL can show Grade 2/3 PYP uptake), **histological biopsy with fibril typing is mandatory** before starting chemotherapy or TTR stabilizers. (Note: **Abdominal fat pad aspirate** has ~80–85% sensitivity in systemic **AL**, ~45–65% in **ATTRv**, and **only ~15% in ATTRwt**; therefore, **Endomyocardial Biopsy [EMB]** is often required when fat pad biopsy is negative.)
  - **Scenario B — Negative Monoclonal Screen with Equivocal Grade 1 PYP Scan** (or Grade 0 PYP scan when high suspicion of rare *TTR* variants like Phe64Leu/Ser77Tyr or ApoA-I amyloidosis exists).
  - **Histopathology and Gold-Standard Fibril Typing:**
  - **Congo Red Staining:** Demonstrates salmon-pink deposits under light microscopy and pathognomonic **apple-green birefringence under cross-polarized light** (or Thioflavin T/S fluorescence).
  - **Laser Microdissection and Liquid Chromatography–Tandem Mass Spectrometry (LMD-LC-MS/MS):** The **gold standard (near-100 percent specificity)** for definitive amyloid precursor protein typing on biopsy tissue (superior to immunohistochemistry, which can yield false results due to serum protein contamination).
  - **Mandatory *TTR* Gene Sequencing (Class I in All Confirmed ATTR-CM):** Every patient diagnosed with ATTR Cardiac Amyloidosis—regardless of age—must undergo ***TTR* genetic sequencing** to differentiate **wild-type (ATTRwt)** from **hereditary/variant (ATTRv)** disease, triggering cascade genetic testing of first-degree relatives and unlocking access to *TTR* gene silencers.

KEY REFERENCES

- **Gillmore JD, Maurer MS, Falk RH, et al.:** Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis, *Circulation*, 2016.
- **Garcia-Pavia P, Rapezzi C, Adler Y, et al.:** Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases, *European Heart Journal*, 2021.
- **Kittleson MM, Ruberg FL, Ambardekar AV, et al.:** 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis, *Journal of the American College of Cardiology*, 2023.