CARDIAC AMYLOIDOSIS; CURRENT GUIDELINE RECOMMENDATIONS IN MANAGEMENT

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Last reviewed: October 2026

I HEART FAILURE AND HEMODYNAMIC MANAGEMENT (THE "GDMT PARADOX" — ESC 2021/2023 & ACC 2023 CONSENSUS)

- **Pathophysiological Basis (Fixed Stroke Volume & Autonomic Neuropathy):** Amyloid fibril infiltration produces a thick-walled, small-cavity, severely restrictive left and right ventricle with a **steep diastolic pressure-volume curve** and a **fixed, low stroke volume**. Because stroke volume cannot increase, **cardiac output is strictly heart-rate dependent (CO = Fixed SV x HR)**, while concomitant amyloid autonomic neuropathy impairs compensatory baroreceptor vasoconstriction.
- **Cornerstone Volume Management (Class I):** Judicious **Loop Diuretics** (preferring **Torsemide** or **Bumetanide** over Furosemide due to superior oral bioavailability in right-sided gut edema) combined with **Mineralocorticoid Receptor Antagonists (Spironolactone or Eplerenone)** (supported mainly by observational data) and **SGLT2 Inhibitors (Dapagliflozin/Empagliflozin)**, while avoiding aggressive over-diuresis that drops preload and precipitates prerenal azotemia and hypotension.
- **Standard HFrEF Neurohormonal Blockers That Are Poorly Tolerated or Contraindicated:**
  - **Non-Dihydropyridine Calcium Channel Blockers (Verapamil, Diltiazem — Avoid):** Bind avidly to extracellular amyloid fibrils, causing severe negative inotropy, high-grade **AV block**, and cardiogenic shock.
  - **Digoxin (Avoid / Use Only with Extreme Caution):** Binds directly to extracellular **amyloid fibrils**, resulting in elevated myocardial tissue concentrations and **fatal arrhythmias / conduction block even when serum digoxin levels are within the "normal" therapeutic range**.
  - **Beta-Blockers:** Poorly tolerated and generally **deprescribed/avoided** in restrictive cardiac amyloidosis because blunting compensatory sinus tachycardia immediately drops cardiac output and precipitates decompensated heart failure and syncope.
  - **ACE Inhibitors, ARBs, and ARNI:** Frequently precipitate severe **orthostatic hypotension** by blocking compensatory angiotensin-II vasoconstriction in patients with autonomic dysfunction. (For disabling orthostatic hypotension, **Midodrine**, **Droxidopa**, or compression stockings are used.)

II ARRHYTHMIA AND THROMBOEMBOLISM MANAGEMENT

- **Universal Anticoagulation in Atrial Fibrillation / Flutter Irrespective of CHA2DS2-VASc Score (Class I):** Amyloid infiltration of the left and right atria causes **severe atrial myopathy, loss of atrial mechanical contraction ("atrial electromechanical dissociation"), and left atrial appendage (LAA) stasis**, resulting in a **20 to 30 percent prevalence of intracardiac thrombi**. Therefore, **lifelong Oral Anticoagulation (DOACs or Warfarin) is Class I mandatory in ANY patient with Cardiac Amyloidosis and clinical or subclinical Atrial Fibrillation/Flutter, regardless of a CHA2DS2-VASc score of 0 or 1**.
- **Mandatory Transesophageal Echocardiography (TEE) Before Cardioversion:** Because **LAA thrombus is found far more often in Cardiac Amyloidosis than in other AF patients, even after >=3 weeks of therapeutic oral anticoagulation**, a **pre-procedural TEE (or Cardiac CT) is mandatory before every electrical cardioversion or catheter ablation**, regardless of anticoagulation duration.
- **Rhythm Control:** Restoring sinus rhythm improves symptoms in early disease; **Amiodarone** is the safest antiarrhythmic drug (and **Catheter Ablation** is increasingly effective when performed in NYHA Class I–II before advanced atrial dilation).

III DISEASE-MODIFYING THERAPIES FOR TRANSTHYRETIN (ATTR) CARDIAC AMYLOIDOSIS

- **TTR Tetramer Stabilizers (Bind the Thyroxine-Binding Site to Prevent Tetramer Dissociation into Monomers):**
  - **Tafamidis (Class I, Level B — ATTR-ACT Trial, *NEJM* 2018):** In 441 patients with **ATTRwt or ATTRv** cardiomyopathy, oral **Tafamidis** (80 mg meglumine or 61 mg free acid once daily) reduced **all-cause mortality by 30 percent (HR 0.70)** and **cardiovascular hospitalizations by 32 percent** over 30 months, while slowing decline in 6MWD and KCCQ score (with survival curves diverging at **18 months**; ESC 2023 Class I for **NYHA I–II**; ACC/AHA 2022 Class IIa for NYHA I–III).
  - **Acoramidis (AG10 — ATTRibute-CM Trial, *NEJM* 2024; FDA Approved Nov 2024):** Next-generation, enthalpically driven TTR stabilizer mimicking the super-stabilizing protective ***TTR* Thr119Met** genetic variant (achieving >90% TTR stabilization). In **ATTRibute-CM** (n = 632), oral **Acoramidis (800 mg twice daily)** significantly won on the primary 4-step hierarchical endpoint (**Win Ratio 1.8; p < 0.0001**), reducing **cardiovascular hospitalizations by 50 percent** and composite all-cause mortality or CV hospitalization.
  - **Hepatic *TTR* mRNA Gene Silencers (RNA Interference [siRNA] & Antisense Oligonucleotides [ASO]):**
  - **Vutrisiran (GalNAc-Conjugated siRNA — HELIOS-B Trial, *NEJM* 2024; FDA Approved March 2025 for ATTR-CM):** Subcutaneous **Vutrisiran (25 mg every 3 months)** silences hepatic *TTR* mRNA (>80–85% TTR knockdown). In the landmark Phase III **HELIOS-B Trial** (n = 655 patients with **ATTRwt or ATTRv cardiomyopathy**, 40% of whom were on background Tafamidis), Vutrisiran **significantly reduced the primary composite of all-cause mortality and recurrent cardiovascular events by 28 percent overall (HR 0.72; p = 0.01) and by 33 percent in the monotherapy population**, while reducing all-cause mortality by **35 percent** over 42 months and preserving 6MWD and KCCQ. (**Mandatory Vitamin A Supplementation [2,500–3,000 IU/day]** is required with all TTR silencers because TTR transports retinol-binding protein.)
  - **Patisiran (APOLLO-B Trial, *NEJM* 2023) and Eplontersen (NEURO-TTRansform / CARDIO-TTRansform):** IV **Patisiran** (every 3 weeks) preserved 6MWD and KCCQ at 12 months in APOLLO-B (FDA approved for ATTRv polyneuropathy), while the monthly subcutaneous GalNAc-ASO **Eplontersen** (approved for ATTRv polyneuropathy) **did not meet its primary endpoint** of CV mortality and recurrent CV events in the Phase III **CARDIO-TTRansform** trial (n = 1,432; ESC 2026).
  - **Investigational Gene Editing and Amyloid Depletors:**
  - **In-Vivo CRISPR-Cas9 Gene Editing (Nexiguran Ziclumeran / NTLA-2001 — MAGNITUDE Trial):** A single intravenous lipid-nanoparticle infusion permanently knocks out the hepatic *TTR* gene, achieving a sustained **~90 percent reduction in serum TTR** (the MAGNITUDE trial was placed on FDA clinical hold in October 2025 after severe liver laboratory abnormalities in a participant).
  - **Anti-ATTR Depleting Monoclonal Antibodies (Coramitug / PRX004, ALXN2220 / NI006):** Target cryptic epitopes exposed only on misfolded ATTR fibrils to trigger **macrophage-mediated antibody-dependent phagocytosis** and clear existing myocardial deposits.

Therapeutic Class & Agent	Molecular Mechanism & Route	Landmark Trial	Primary Clinical Outcome & Approval Status
Tafamidis (TTR Stabilizer)	Binds T4 pocket of TTR tetramer; oral **61 mg / 80 mg OD**	**ATTR-ACT** (*NEJM* 2018)	**30% reduction in mortality**, **32% reduction in CV hospitalizations**; **ESC Class I** (NYHA I–II)

Therapeutic Class & Agent	Molecular Mechanism & Route	Landmark Trial	Primary Clinical Outcome & Approval Status
Acoramidis (TTR Stabilizer)	Mimics protective *Thr119Met* variant (>90% stabilization); oral **800 mg BD**	**ATTRibute-CM** (*NEJM* 2024)	**Win Ratio 1.8 (p <0.0001)**; **50% reduction in CV hospitalizations**; **FDA approved (2024)** for ATTR-CM
Vutrisiran (*TTR* siRNA Silencer)	GalNAc-siRNA cleaves hepatic *TTR* mRNA; **25 mg SC every 3 months** (+ Vitamin A)	**HELIOS-B** (*NEJM* 2024)	**28% reduction in death/CV events** (35% mortality reduction at 42 mo); **FDA approved (2025)** for ATTR-CM & ATTRv-PN
Daratumumab + CyBorD (**AL Amyloidosis**)	Anti-CD38 mAb + Cyclophosphamide, Bortezomib, Dexamethasone	**ANDROMEDA** (*NEJM* 2021)	**53.3% vs. 18.1% complete hematologic response**; doubled cardiac organ response; **Class I** for AL

IV MANAGEMENT OF IMMUNOGLOBULIN LIGHT-CHAIN (AL) CARDIAC AMYLOIDOSIS

- **Medical Oncology Emergency (Class I):** Untreated AL cardiac amyloidosis (where circulating free light chains exert **direct p38-MAPK cardiotoxic oxidative stress** in addition to fibril infiltration) has a median survival of **less than 6 months** from heart failure onset.
- **First-Line Standard of Care — Daratumumab-CyBorD (ANDROMEDA Trial, *NEJM* 2021):** Subcutaneous **Daratumumab (anti-CD38 plasma-cell monoclonal antibody)** added to **Bortezomib (proteasome inhibitor), Cyclophosphamide, and Dexamethasone** tripled the complete hematologic response rate (**53.3 percent vs. 18.1 percent**), doubled 6-month cardiac organ response (**41.5 percent vs. 22.2 percent**, measured by >=30% and >=300 pg/mL drop in NT-proBNP), and improved major organ deterioration progression-free survival. (Monitor closely for bortezomib/dexamethasone fluid retention and cardiotoxicity.)

V CONDUCTION SYSTEM PACING, ICDS AND TRANSPLANTATION

- **Permanent Pacing and CRT / Conduction System Pacing (Class I):** High-grade AV block is common (especially after TAVR in dual aortic stenosis + ATTRwt); if significant right ventricular pacing burden (>20 to 40 percent) is anticipated, **Cardiac Resynchronization Therapy (CRT) or Left Bundle Branch Area Pacing (LBBAP)** is preferred over right ventricular apical pacing because dyssynchronous RV pacing acutely reduces stroke volume in a small restrictive LV.
- **Restricted Role of Primary-Prevention ICDs:** Routine primary-prevention ICD implantation based solely on LVEF <=35% is **not generally recommended** in advanced Cardiac Amyloidosis because sudden death in end-stage amyloidosis is frequently due to **Electromechanical Dissociation (Pulseless Electrical Activity [PEA]) or complete heart block/asystole** rather than shockable VT/VF; **ICDs are Class I recommended for secondary prevention** (sustained VT or resuscitated VF arrest with >1-year life expectancy).
- **Orthotopic Heart Transplantation:** Feasible in selected younger patients with isolated advanced **ATTR-CM** (combined with post-transplant TTR stabilizer/silencer therapy) or **AL-CM** (accompanied or followed by **Autologous Stem Cell Transplantation [ASCT]** / Dara-CyBorD to prevent recurrent graft amyloidosis).

KEY REFERENCES

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