Review Article

Management of Cardiac Amyloidosis: A Narrative Review

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Abstract

Amyloidosis is a multi-system disorder in which cardiac involvement often manifests with heart failure and/or arrhythmias. Recognition of cardiac amyloidosis is important as it is a potentially treatable cause of cardiomyopathy. While the approach to a case of suspected cardiac amyloidosis was discussed in a prior article, this one focuses on the management of its two main types (AL and ATTR). This is an area of active research with the advent of newer therapies such as RNA silencers and gene editing. We shall also discuss the management of heart failure and arrhythmias specific to amyloidosis.

Keywords: Abnormal light, abnormal transthyretin, cardiac amyloidosis, cardiac transplant, gene editing, RNA silencers, tafamidis

Introduction

Cardiac amyloidosis (CA) is an under-recognized disease, due to late presentation, a lack of clinical suspicion, and the dearth of specialized diagnostic modalities, especially in resource-constrained settings. The diagnosis and management of amyloidosis require multidisciplinary coordination. The approach to diagnosing and classifying CA was discussed in detail in a prior article.[1] This article deals with the current management of cardiac involvement in amyloidosis. We shall focus on the management of the two main types of CA- light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). The last section deals with the management of cardiac manifestations of the disease (heart failure and arrhythmias). Figure 1 depicts an overview of the current management of CA.

Methods

We searched the PubMed and ScienceDirect databases for studies on the treatment of CA, AL, and ATTR, published till June 16, 2025. Our initial search revealed 46,748 articles. We included original articles pertaining to the treatment of CA, which limited our search to 36 studies. We also reviewed the latest guidelines and consensus statements in the management of CA and compiled these data to write a narrative review.[2,3]

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Abnormal Light Chain Amyloidosis

Briefly, AL amyloidosis is diagnosed in suspected cases based on monoclonal protein assays, followed by a biopsy (surrogate site/affected organ) for demonstration of amyloid deposits and a bone marrow biopsy for the assessment of the plasma cell burden, evidence of multiple myeloma, and detection of the rarer B-cell lymphoproliferative disorders (e.g., Waldenstrom macroglobulinemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma). Since it is most commonly due to an underlying low-level plasma cell clonal proliferation, the goal of therapy is to eradicate the abnormal clone and remove circulating light chains from circulation. Treatment involves chemotherapy, immunotherapy, and stem cell transplantation (SCT). The choice of therapy depends on efficacy and toxicity in view of multisystem involvement in amyloidosis [Figure 2]. Once the diagnosis of AL amyloidosis is established, the first step is to assess the patient for eligibility for SCT. This is the standard of care at present and offers

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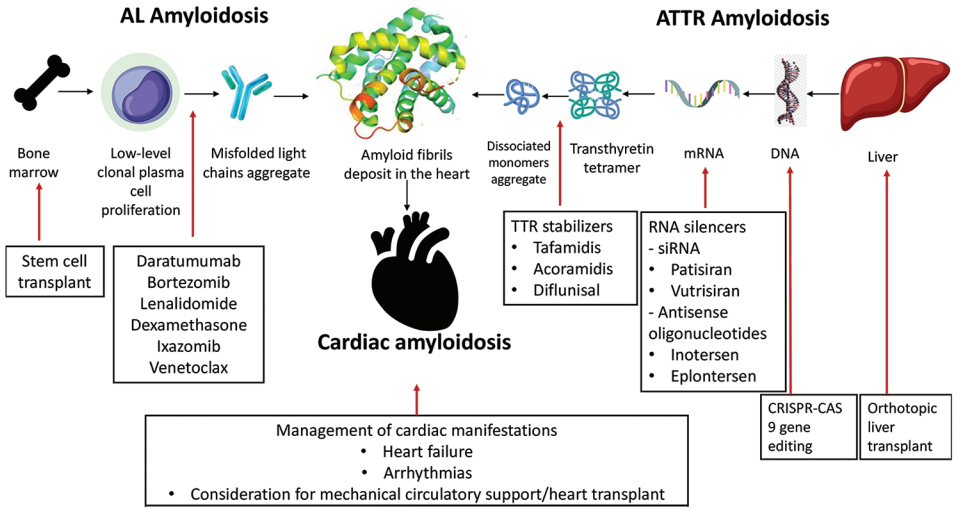

Figure 1: Overview of the current management of cardiac amyloidosis. Red arrows depict the target site of action of various therapies. AL amyloidosis: Light chain amyloidosis, ATTR amyloidosis: Transthyretin amyloidosis. siRNA: Small interfering RNA.

long-lasting remission and organ response. In general, the eligibility criteria for autologous SCT are as follows, though these may vary from center to center:[4]

- Adequate performance status
- Left ventricular (LV) Ejection Fraction >45%
- Systolic blood pressure (SBP) ≥90 mm Hg
- Troponin T <0.06 ng/ml or hs Troponin T <75 ng/ml
- NT proBNP <5000 pg/ml
- Creatinine clearance >50 ml/min (unless on chronic dialysis)
- Bilirubin <2 mg/dl
- Diffusion capacity of the lungs for carbon monoxide (DLCO) >50%
- No more than two organs significantly involved.

Only around 25% of AL amyloidosis patients fulfill these criteria and are deemed eligible for SCT due to advanced heart failure or involvement of other organs in the majority.[5] Importantly, patients with heart failure with reduced ejection fraction would be ineligible for stem cell transplant due to the risk of significant hemodynamic decompensation.[6] The eligible patients are treated with high-dose melphalan (HDM) followed by SCT. In patients with bone marrow plasma cell burden of more than 10%, administration of 2–4 cycles of a bortezomib-based regimen is advisable for induction.[7] In 421 AL amyloidosis patients treated with HDM–SCT at Boston University, mortality was 11% overall and decreased to 6% in the last 5 years of the study.[8] The median event-free survival was 2.6 years, and the overall survival was 6.3 years. The survival was better in patients with a complete response to therapy, as expected. Eighty-one patients died within the 1st year after HDM-SCT and were not evaluable for hematologic and organ response. One year after treatment, 43% of evaluable patients achieved a complete hematological response, and 78% experienced an organ response. Hematological relapses or progression after HDM–SCT occur in 36%–38% of patients at a median of 2.0–4.3 years after treatment.[9]

The patients deemed ineligible for stem cell transplant are treated with plasma cell-directed therapies, though these may soon supplant SCT, with accumulating evidence favoring their safety.[2] The preferred regimen for management of SCT-ineligible patients is daratumumab, cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD).[2] Daratumumab is a monoclonal antibody targeting the CD38 molecule on the plasma cell surface. The ANDROMEDA (A Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib, and Dexamethasone [CyBorD] Compared to CyBorD Alone in Newly Diagnosed Systemic Amyloid Light Chain [AL] Amyloidosis) Study, an open label randomized trial showed significantly improved hematologic response with addition of daratumumab (53.3% vs. 18.1%, relative risk ratio 2.9; 95% confidence interval [CI]: [2.1–4.1]; $P < 0.001$).[10] The incidence of adverse events was nearly the same in both arms. It is less cardiotoxic and nephrotoxic than the other therapeutic agents. The role of daratumumab with low-dose dexamethasone in patients with advanced cardiac involvement (NT proBNP levels >8500 pg/ml) is being studied (NCT04131309). Other chemotherapeutic options include bortezomib, melphalan, and dexamethasone and Dara-dex.[2,11] In patients with refractory disease or relapse after initial therapy, options include daratumumab (if not used before), or immunomodulatory drugs, such as thalidomide, lenalidomide, or pomalidomide. Ixazomib is an oral proteasome inhibitor and could be a potential option.[12] Another drug, venetoclax, inhibits the antiapoptotic B-cell lymphoma-2 protein that facilitates programmed cell death. It is most useful in patients with the t(11;14) cytogenetic alteration with a worse prognosis.[13]

A trial evaluating birtamimab, a monoclonal antibody that eliminates toxic light chain aggregates, was terminated early

for futility.[14] Table 1 summarizes the major drugs for treatment of AL amyloidosis

Response to treatment of AL amyloidosis is assessed based on hematologic and organ-specific response. In general, a hematologic response is seen within 3–6 months of treatment initiation, whereas an organ-specific response is noted 6–12 months after the hematologic response. The criteria for response are as follows:[16]

Hematologic response

- Complete response: Both criteria must be met-absence of amyloidogenic light chains, defined by negative Serum immunofixation electrophoresis (SIFE) and Urine immunofixation electrophoresis (UIFE), and either a Free light chains (FLC) ratio within reference range or an uninvolved FLC concentration greater than the involved FLC concentration, with or without an abnormal FLC ratio
- Very good partial response: dFLC (difference between involved and uninvolved FLC) < 40 mg/dl

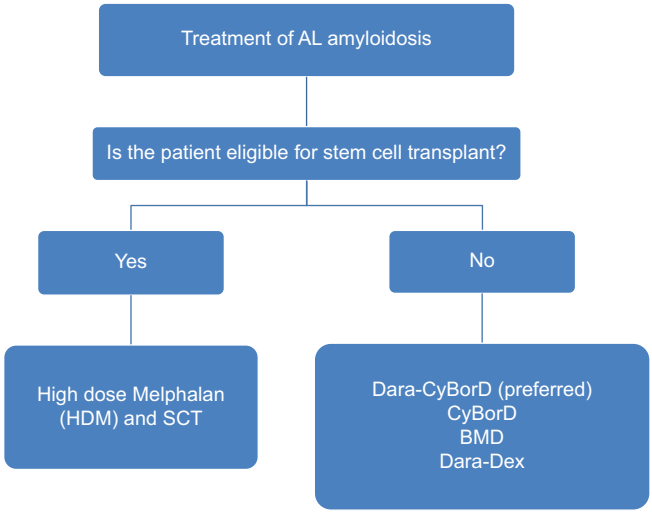

Figure 2: Simplified approach to management of AL amyloidosis.

- Partial response: dFLC decrease by ≥50%
- No response: dFLC <50%.

Organ response

- Cardiac response: Decrease in NT proBNP by >30% and <300 ng/l (if baseline NT proBNP >650 ng/l)
- Renal response: At least 30% reduction in proteinuria or a drop below <0.5 g/24 h, in the absence of renal progression (>25% decrease in estimated glomerular filtration rate [eGFR])
- Hepatic response: 50% reduction in abnormal alkaline phosphatase or a decrease in radiographic liver size by ≥2 cm.

Abnormal Transthyretin Amyloidosis

Transthyretin (TTR) is a protein synthesized in the liver that transports thyroxine and retinol-binding protein. ATTR amyloidosis is caused by abnormal dissociation of tetramers into intermediates, which misassemble into oligomers, protofilaments, and amyloid fibrils. Two main classes of drugs have been used in amyloidosis: TTR stabilizers and TTR silencers [Figure 3]. Table 2 depicts the various drugs along with evidence for their efficacy.

Transthyretin stabilizers

As of now, Tafamidis, a TTR stabilizer, is the only Food and Drug Administration (FDA) approved drug for the management of ATTR CA. It is a benzoxazole derivative that binds to the thyroxine-binding site of TTR and stabilizes it, thus preventing its dissociation. The ATTR-ACT (Safety and Efficacy of Tafamidis in Patients with TTR Cardiomyopathy) showed lower all-cause mortality and decreased heart failure hospitalizations with tafamidis compared to placebo.[17] At month 30, there was a significantly lower rate of decline in 6-min walk distance (6mWD) and in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score. The benefit was noted irrespective of ATTR wild type (ATTRwt) or variant (ATTRv) status. A surprising finding was an increase

Table 1: Drugs in the treatment of light chain amyloidosis with supporting evidence

Drug	Study	Results	Remarks
CyBorD	Observational data[15] (n=230)	Hematologic response in 60%; 43% achieved a very good partial response	Regimen of choice in combination with Daratumumab in those ineligible for SCT
Daratumumab	ANDROMEDA[10] Daratumumab (n=195) versus placebo (n=193) Along with CyBorD	Improvement in complete hematologic response (53.3% vs. 18.1%, RRR 2.9; 95% CI [2.1–4.1]; P<0.001) Improved cardiac response at 6 months (41.5% vs. 22.2%)	Similar adverse effects in both arms Less cardiotoxic than other drugs
Ixazomib	TOURMALINE-AL1 NCT01659658[12] Ixazomib (with dexamethasone) versus physician choice; in relapsed/refractory AL	Complete response rate: 26 versus 18% (P=0.22) Median time to mortality or vital organ deterioration: 34.8 versus 26.1 months (HR: 0.53; 95% CI, 0.32–0.87; P=0.01)	Reserved for relapsed/refractory disease
Venetoclax	Retrospective cohort of relapsed/refractory AL (n=43)[13]	Hematologic response rate 68%; 63% achieved VGPR/CR	Reserved for relapsed/refractory disease, especially those with t(11;14)

SCT: Stem cell transplantation, CyBorD: Cyclophosphamide, Bortezomib, and Dexamethasone, CI: Confidence interval, RRR: Relative risk ratio, AL: Light chain amyloidosis, VGPR: Very good partial response, CR: Complete response, HR: Hazard ratio

Table 2: Therapies in transthyretin amyloid cardiomyopathy with supporting evidence

Drug	Study	Results	Remarks
		RNA stabilizers	
Tafamidis	ATTR-ACT[17] Tafamidis (*n*=264) versus placebo (*n*=177)	Reduction in all-cause mortality (78 of 264 [29.5%] vs. 76 of 177 [42.9%]; HR, 0.70; 95% CI, 0.51–0.96) Reduction in heart failure hospitalizations (RR 0.68 (0.48/year vs. 0.70/year; 95% CI, 0.56–0.81)	Only FDA-approved drug at present for ATTR-CM Main adverse effect: Diarrhea, mostly mild-moderate (similar in both groups)
Acoramidis	ATTRibute-CM[18] Acoramidis (n=421) versus placebo (n=211)	Improvement in primary four-step hierarchical analysis (all-cause death, cardiovascular hospitalizations, change in NT-proBNP, change in 6mWD): Win ratio 1.8, 95% CI, 1.4–2.2, *P*<0.001)	Maximum ratio of wins to losses in NT-proBNP pairwise comparisons (23.3% vs. 7.0%) Fewer serious adverse events with acoramidis (54.6% vs. 64.9%)
Diflunisal	Observational data	Improved survival and halted echocardiographic progression of disease	Contraindicated in renal dysfunction, (eGFR <45 mL/min/1.73 m^2) or recent GI bleed Caution in recent decompensated heart failure
		RNA silencers	
Patisiran	APOLLO-B Patisiran (*n*=181) versus placebo (*n*=179)	Significantly lower decline in 6mWD with Patisiran (*P*=0.02) Significant improvement in KCCQ-OS score (*P*=0.04) No significant improvement in composite of death, CV events or decline in 6mWD	Approved for ATTRv neuropathy
Vutrisiran	HELIOS-B[19] Vutrisiran (*n*=326) versus placebo (*n*=329)	Reduction in all-cause death and cardiovascular events (HR 0.67, 95% CI 0.49–0.93, *P*=0.02) Reduction in all-cause mortality (HR 0.65, 95% CI 0.46–0.90, *P*<0.01) Significantly lower decline in 6mWD and KCCQ-OS	Fewer serious adverse events with Vutrisiran (62% vs. 67%)
Inotersen	Single-arm interventional study[20] (no randomized data)	Improvement in 6mWD and reduction in LV mass at 3 years	Adverse effects: thrombocytopenia, glomerulonephritis, infusion site reactions Requires Vitamin A supplementation Has been shown to improve quality of life in ATTR neuropathy
Eplontersen	CARDIO-TTRansform[21] Eplontersen versus placebo	Enrollment completed Primary outcome: Composite of CV mortality and recurrent CV events	Similar adverse event profile to Inotersen

ATTR: Transthyretin amyloidosis, CV: Cardiovascular, 6mWD: 6-min walk distance, CI: Confidence interval, HR: Hazard ratio, RR: Risk ratio, Nt-proBNP: N-terminal prohormone of brain natriuretic peptide, eGFR: Estimated glomerular filtration rate, LV: Left ventricular, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire: Overal Summary

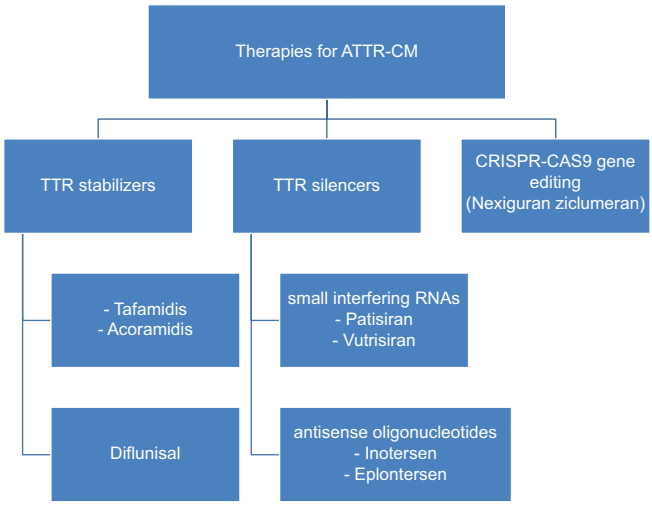

Figure 3: Therapies in transthyretin amyloid cardiomyopathy.

in cardiovascular (CV) hospitalizations in New York Heart Association (NYHA) III patients, which was likely due to a longer duration of severe illness in these patients. The usual dose of tafamidis is 61 mg once daily (or tafamidis meglumine 80 mg once daily).

ATTRibute-CM (efficacy and safety of AG10 in subjects with TTR amyloid cardiomyopathy) was a multinational RCT including 632 patients (2:1 ratio) with wild-type or variant symptomatic ATTR CM randomized either to oral acoramidis (800 mg twice daily) or placebo for 30 months.[18] There was a significant improvement in the primary composite outcome (including death, CV hospitalizations, change in NTproBNP, and 6mWD) with acoramidis. There were fewer serious adverse events in the acoramidis arm. This drug is a promising alternative to tafamidis in the treatment of ATTR cardiomyopathy (ATTR-CM). To the best of our knowledge, there are no head-to-head comparisons between acoramidis and tafamidis, though pharmacokinetic data suggest that acoramidis may be more potent at stabilizing TTR at the cost of a shorter half-life, faster metabolism, and moderate oral bioavailability.[22]

Diflunisal, a nonsteroidal anti-inflammatory drug, is a more cost-effective alternative to tafamidis as a TTR

stabilizer, and has been used in amyloid neuropathy at a dose of 250 mg twice daily.[23] A single-center retrospective analysis suggests efficacy for ATTR-CM in terms of improved survival and retardation of echocardiographic progression.[24] It is, however, contraindicated in patients with renal dysfunction (eGFR <45 ml/min/1.73 m^2) or a history of recent gastrointestinal bleed. It should be used with caution in patients with recent decompensated heart failure.

Transthyretin silencers

Another group of drugs, TTR silencers, including small interfering RNAs and antisense oligonucleotides, targets TTR mRNA for cleavage, thereby reducing its availability for translation to protein [Figure 2]. These drugs have been approved for ATTRv neuropathy,[25] and recent evidence has shown promise in ATTR-CM as well.

Small-interfering RNA

The APOLLO-B trial was a phase 3 trial evaluating patisiran (given at a dose of 0.3 mg/kg body weight intravenously once every 3 weeks) in patients with ATTR-CM (80% wild type ATTR), which showed significant improvement in 6mWD reduction and KCCQ-OS score, but an insignificant benefit in time to death, urgent heart failure visits, or all-cause hospitalizations over 12 months.[26] HELIOS-B trial has shown an improvement in the composite of all-cause death and CV events as well as all-cause mortality alone with Vutrisiran (25 mg subcutaneously once every 12 weeks), compared to placebo in patients with ATTR-CM (89% ATTRwt).[19]

Antisense oligonucleotides

Inotersen is an antisense oligonucleotide that targets hepatic synthesis of mRNA and is administered subcutaneously. It has shown benefit in echocardiographic parameters and 6mWD in patients with ATTR-CM in a single-arm observational study.[20] It requires Vitamin A supplementation (3000 IU daily) and can cause infusion site reactions, thrombocytopenia, and glomerulonephritis.[27] Eplontersen showed improvement in LV function in the cardiomyopathy subgroup of 144 patients with ATTRv polyneuropathy[28] and is being evaluated further in ATTR-CM (variant or wild type) in the CARDIO-TTRansform trial.[21]

Other Therapies

Another novel technology, CRISPR-CAS9 (*in vivo* gene editing), involves targeted DNA cleavage, which triggers endogenous repair mechanisms through non-homologous end joining, resulting in the introduction of indels into the TTR gene. This leads to frame shift mutations that prevent the formation of a functional protein. A recent phase 1 open-label trial evaluated nexiguran ziclumeran (CRISPR-CAS9 gene editing) in 36 patients, which led to a significant reduction in TTR levels (−90%, 95% CI: −93 to −87) at 12 months.[29] Clinical outcomes were not evaluated.

Since the liver is the site for TTR synthesis, orthotopic liver transplant (OLT) has been attempted to treat ATTR amyloidosis, with 5 year survival rates of around 100% in patients with the pV50M mutation and 59% for non pV50M patients.[30]

While limited retrospective data suggest safety and stabilization of echocardiographic progression with older therapies such as doxycycline with D-UDCA (D-Ursodeoxycholic acid) and green tea, they have no role in the era of tafamidis.[2,31]

Management of Cardiac Involvement in Amyloidosis

Heart failure

Volume management is the mainstay of management of heart failure in amyloidosis. These patients have a narrow euvolemic window. Loop diuretics and sequential blockade with mineralocorticoid antagonists are helpful. A retrospective analysis from the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist trial with a cohort of amyloidosis patients showed improvement in CV death, aborted cardiac arrest, or heart failure hospitalizations with spironolactone.[32] Thiazides should be used carefully due to a higher risk of hyponatremia, hypokalemia, and renal impairment. CA is characterized by pressure-volume alterations with ventricular-vascular uncoupling,[33] leading to reduced stroke volume, a greater dependence on heart rate for maintaining cardiac output, due to which beta blockers are poorly tolerated.[34] These patients often have autonomic dysfunction and are unable to augment cardiac output in response to vasodilation. Therefore, Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and Angiotensin receptor- neprilysin inhibitors (ARNIs) should be used with caution. An observational study demonstrated the safety of use of dapaglifozin in 34 patients with stable tafamidis-treated ATTR CM with a reduction in NTproBNP levels.[35] A small nonrandomized study evaluating cardiac resynchronization therapy in 30 patients with ATTR-CM compared to standard care ($n = 30$), with a mean QRS duration of 147 ms and LVEF of 33% showed an improvement in NYHA class and survival (hazard ratio: 0.39, 95% CI: 0.21–0.74; $P = 0.003$).[36] However, it remains controversial due to limited life expectancy, especially in patients with advanced amyloidosis. In patients with advanced/stage D heart failure, mechanical circulatory support (MCS) with LV assist devices is less likely to be tolerated due to the small LV cavity size (higher risk of suction events) and biventricular dysfunction.[37] Another concern may be the risk of infections in patients receiving plasma cell-directed therapies.[38] Temporary MCS, such as an intra-aortic balloon pump or a percutaneous micro-axial catheter-based pump, may be used as a bridge to transplantation in these patients.[39] The patients who should be considered for cardiac transplantation are those with:

- Repeated hospitalizations or emergency department visits for heart failure (HF) in the past 12 months
- Need for intravenous inotropes
- Persistent NYHA III-IV symptoms despite therapy

- Severely reduced exercise capacity (peak VO2 <14 ml/kg/min or <50% predicted, 6mWD <300 m, or inability to walk one block on level ground due to dyspnea or fatigue
- Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d or use of supplemental metolazone therapy
- Refractory clinical congestion
- Progressive deterioration in kidney or hepatic function
- Worsening right HF or secondary pulmonary hypertension
- Frequent SBP readings ≤90 mm Hg
- Cardiac cachexia
- Persistent hyponatremia (serum Na <134 mEq/l)
- Refractory or recurrent ventricular arrhythmias (VAs); frequent implantable cardiac defibrillator (ICD) shocks.[2]

There are multiple considerations in patients with CA before planning cardiac transplantation. If the projected survival from amyloidosis is <75% at 5 years and <50% at 10 years, the risk of cardiac transplantation is prohibitive. This would be especially true in cases of high-risk cytogenetic alterations such as t(11;14) associated with resistant plasma cell disease. In a study from Mayo Clinic, 23 AL-CM patients underwent cardiac transplantation and were followed up for a median of 3.5 years. Survival at 1 year was 77%, and at 5 years, 43% (lower than the 5-year survival for non-amyloid patients undergoing heart transplantation), and varied based on the degree of hematologic response.[40] Similar 1-year survival rates have been noted in a study from France, including 23 patients with amyloidosis (74% AL and 26% ATTRv), undergoing heart transplantation.[41] Among AL-CM patients, 5 had undergone heart–kidney transplants, whereas 5 ATTR-CM patients had undergone heart–liver transplants. Furthermore, the AL-CM patients who are being planned for a heart transplantation should be considered for a sequential heart transplant followed by a stem cell transplant. There are only a few case series reporting sequential transplantation in AL amyloidosis. In a series of five patients undergoing sequential heart transplant followed by SCT, followed up for a median of 95 months, three patients were well without evidence of intracardiac or extracardiac amyloid infiltration. Two patients died of disease progression at 33 and 90 months, following relapse of the underlying plasma cell dyscrasia.[42] Table 3 summarizes the extracardiac contraindications to a cardiac transplant.[2]

Table 3: Extracardiac contraindications to cardiac transplant in a patient with cardiac amyloidosis

Disease condition	Severity characteristics
Frailty	Fried frailty phenotype ≥3 criteria (weakness, slowness, exhaustion, low physical activity, unintentional weight loss)
Autonomic neuropathy	Severe symptomatic orthostasis requiring midodrine and/or droxidopa
Peripheral neuropathy	Symptoms are severe enough to limit ambulation
Pulmonary disease	Symptomatic pulmonary involvement (pleural effusion, parenchymal nodules)
GIT disease	Modified BMI <600 kg/m^2. g/L (BMI × serum albumin)
	GI bleed, malabsorption
Renal disease	Proteinuria ≥500 mg/dL
Hematologic disease	Light chains are not responsive to therapy
	High-risk cytogenetics
	Multiple myeloma

BMI: Body mass index, GI: Gastrointestinal

Arrhythmias

CA is characterized by various arrhythmias such as atrial fibrillation (AF)/atrial flutter, VAs, atrioventricular (AV) blocks, and rarely, sinus node dysfunction.

Atrial fibrillation

The most common arrhythmia in patients with amyloidosis is AF. It is seen in up to 56% patients with AL-CM and 79% patients with ATTR-CM.[43] These patients are very high risk of intracardiac thrombosis, up to 33%, even those on chronic anticoagulation. Therefore, oral anticoagulation is recommended in all amyloidosis patients with AF *irrespective of CHA2DS2VASc score*. Furthermore, transesophageal echocardiography is essential in all amyloidosis patients before cardioversion, irrespective of the duration of AF.[44] Direct oral anticoagulants are preferred in general, though there are no direct comparisons with warfarin in these patients. There are insufficient data for left atrial appendage occlusion in this group of patients. Rate control drugs, such as beta blockers, are generally poorly tolerated in these patients due to profound hypotension despite low doses. Calcium channel blockers and digoxin have been traditionally relatively contraindicated in CA due to their binding to amyloid fibrils, causing negative inotropic effects and rhythm disturbances.[45] However, digoxin has now been used safely in these patients with close monitoring in some observational studies.[46,47] Rhythm control should be considered if symptoms due to AF persist despite rate control. Amiodarone and dofetilide are the preferred drugs for rhythm control.[48] Catheter ablation is more likely to be successful if undertaken early in the disease course.[48] Extensive ablation beyond the pulmonary veins is often required due to the diffuse nature of amyloid infiltration. A retrospective study including 72 ATTR CM patients compared catheter ablation in 24 patients with medical therapy in 48 patients.[49] At a mean follow-up of 39 ± 26 months, 10 (42%) patients remained free of recurrent arrhythmia following ablation. Death occurred in 7 (29%) patients in the ablation group compared to 36 (75%) in the nonablation arm (P = 0.01). In patients with AF with tachycardia–bradycardia syndrome, AV junction ablation with permanent pacing can be considered.

Ventricular tachyarrhythmias

Sudden cardiac death in amyloidosis patients is more often caused by pulseless electrical activity (PEA) or asystole rather than VAs. Therefore, VAs may not have as significant an impact on mortality as expected in these patients. A study of AL-CM patients with presyncope or syncope with a loop recorder implanted showed that among 272 recordings, bradycardia followed by PEA was the

Table 4: Commonly used staging systems for amyloidosis

Staging system	Mayo 2012[52]	UK staging system[53]
Patient population	AL-CM	ATTR-CM (wild type and variant)
Parameters and thresholds	TnT ≥0.025 µg/L or hsTnT ≥40 ng/L BNP ≥400 ng/L or NT-proBNP ≥1800 ng/L dFLC ≥18 mg/dL	NT-proBNP ≤3000 pg/mL eGFR ≥45 mL/min
Median survival (months)		
Stage I: No parameters above threshold	94.1	69.2
Stage II: One parameter above threshold	40.3	46.7
Stage III: Two parameters above threshold	14	24.1
Stage IIIA: 2 parameters above threshold and NT proBNP <8500 pg/mL	NA	NA
Stage IIIB: 2 parameters above threshold and NT proBNP ≥8500 pg/mL	NA	NA
Stage IV: 3 parameters above threshold	5.8	NA

NA: Not available, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, eGFR: Estimated glomerular filtration rate, ATTR: Transthyretin amyloidosis, CM: Cardiomyopathy, AL: Amyloid light chain, dFLC: Difference between involved and uninvolved free light chain

terminal rhythm in 62% deaths compared to a single episode of nonsustained ventricular tachycardia.[50] The role of ICDs in these patients is controversial, and a survival benefit has not been proven so far. Survival of these patients is often less than a year, which would be a contraindication to ICD insertion. Furthermore, high defibrillation thresholds caused by amyloid infiltration within the myocardium may reduce the likelihood of success of attempted ICD therapy.

Atrioventricular blocks

First-degree AV block is seen in 49% ATTRwt, 43% ATTRv, and 18% AL-CM patients. In a single-center retrospective study, 369 patients with ATTR-CM, 9.5% had pacemakers implanted for high-grade AV block before being diagnosed as CA. At a follow-up of 28 months, another 11% patients developed a need for permanent pacing for high-grade AV block.[51] High burden of RV pacing is associated with deleterious consequences in these patients. It helps to aim for maintaining AV synchrony. Biventricular pacing may be considered in these patients.

Sinus node dysfunction

Although rarely reported in CA, SND may present as sinus arrest, sinus bradycardia, or sinus pauses. It was reported in 7% of 369 patients with ATTR CM in a single-center study.[51]

Prognosis of Cardiac Amyloidosis

Various staging systems have been described to estimate disease severity and survival [Table 4]. Importantly, most of these systems were developed before the advent of newer therapies (tafamidis for ATTR and daratumumab for AL amyloidosis).[2] These generally incorporate cardiac biomarkers-troponin and NT proBNP. Cardiac involvement is the most important prognostic factor in amyloidosis.

Conclusion

Amyloidosis is a multisystem disorder requiring coordination among the cardiologist, hematologist, neurologist, nephrologist, and gastroenterologist, depending on the manifestations. Patients with AL amyloidosis should be assessed for SCT, which may be contraindicated in patients with severe cardiac involvement. If deemed ineligible for SCT, these patients should receive plasma cell-directed therapies (preferably, Dara-CyBorD, a regimen which is less cardiotoxic also). The only FDA-approved therapy for ATTR amyloidosis at present is Tafamidis, a TTR stabilizer. This is a rapidly evolving field, as newer therapies such as TTR silencers and gene editing technologies are being tested in these patients. However, these treatment modalities are very expensive, and diflunisal is a more cost-effective alternative in resource-poor settings. The specific management of cardiac manifestations of the disease has been discussed in detail, with emphasis on caution in using heart failure therapies due to the risk of profound hypotension despite low doses.

Ethics clearance

Not applicable.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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