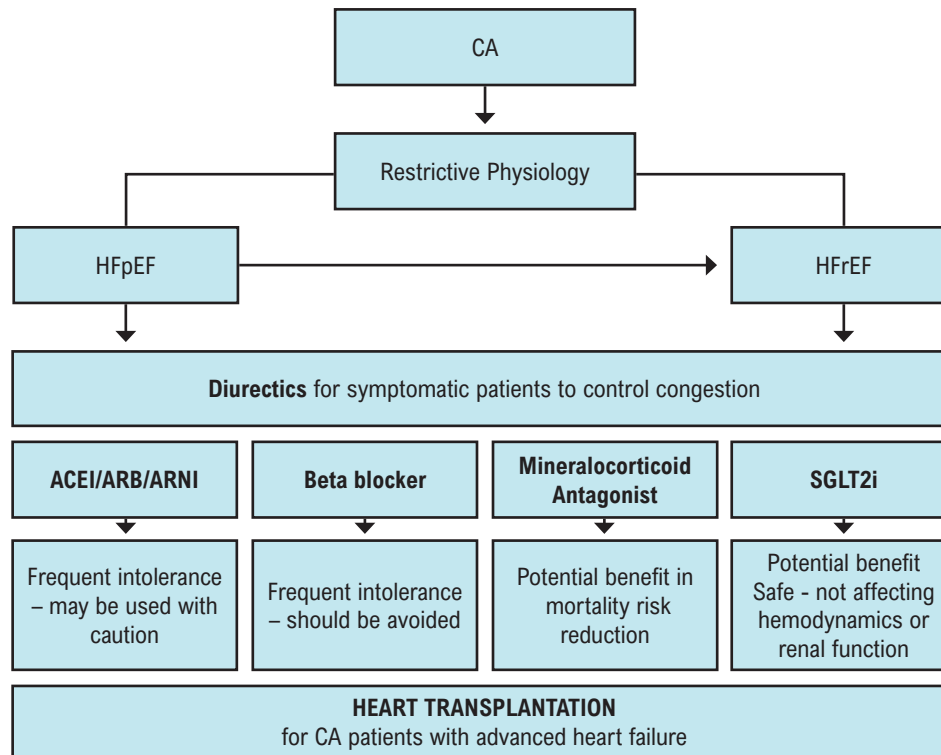




**Central Illustration: Heart Failure Management of Patients with Amyloid Cardiomyopathy**

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CA has a restrictive physiology, characterized by elevated filling pressures and low stroke volumes. Initially, patients present with preserved ejection fraction, which may decrease in late stages of disease. The use of diuretics is crucial in the treatment of patients with CA. The evidence of GDMT in the treatment of patients with CA is not very robust and is based on retrospective cohort analysis. Heart transplantation may be considered for patients with advanced HF. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; SGLT2i: sodium-glucose transport protein 2 inhibitors; CA: cardiac amyloidosis.

of ATTRwt,<sup>4,5</sup> with a higher incidence observed in individuals over 70 years old, primarily among men.

The AL form represents a clonal and neoplastic hematologic disorder, which inflicts structural harm on the heart, resulting in vascular rigidity, impaired contraction and relaxation, and conduction disturbances. Additionally, the AL may exert toxicity on myocardial cells.<sup>6</sup> This form constitutes the primary cause of CA, with an annual incidence of 6 to 10 million people diagnosed. It is linked with a quicker progression of heart failure (HF) and a poorer prognosis compared to ATTR.<sup>7</sup>

By means of screening with bone scintigraphy, a notable prevalence of ATTR has been identified in certain populations: 12% in HF with preserved ejection fraction (HFpEF) accompanied by left ventricular hypertrophy (LVH), 8% in severe aortic

stenosis, 7% in LVH associated with hypertrophic cardiomyopathy (HCM), and 7% in individuals with carpal tunnel syndrome.<sup>8</sup>

CA warrants consideration in patients exhibiting LVH alongside cardiac or extracardiac red flags, especially in specific clinical scenarios, notably among individuals aged over 65 years.<sup>9</sup>

Depending on the organs affected and the extent of dysfunction, a broad range of clinical presentations may be evident. The primary organs impacted include the heart, kidneys, central and peripheral nervous system, and liver. Common nonspecific clinical features often include fatigue, weight loss, peripheral edema, and orthostatic hypotension.

In cases of ATTRv, the clinical presentation is largely determined by the specific mutation, with

neuropathy or heart disease predominating. Conversely, in ATTRwt, heart disease emerges as the primary clinical manifestation, typically affecting elderly men who develop HFpEF without prior identifiable risk factors. Certain extracardiac manifestations may precede CA by several years, notably bilateral carpal tunnel syndrome and spontaneous rupture of the biceps tendon. Recognizing these signs as integral components of the clinical presentation of amyloidosis is crucial, as they can facilitate earlier diagnosis and enable the implementation of targeted treatments aimed at halting the progression of heart disease.<sup>10</sup>

CA can be diagnosed using both invasive and non-invasive diagnostic criteria, with the latter being accepted only for ATTR. Invasive criteria involve demonstrating amyloid fibrils within cardiac tissue or, alternatively, detecting amyloid deposits in an extracardiac biopsy along with characteristic features of CA observed on echocardiography or cardiac magnetic resonance imaging (CMR).<sup>9</sup> Non-invasive criteria include typical echocardiographic/CMR findings combined with planar and single-photon emission computed tomography (SPECT) showing grade 2 or 3 myocardial radiotracer uptake on <sup>99m</sup>technetium-pyrophosphate (<sup>99m</sup>Tc-PYP) scintigraphy, alongside exclusion of clonal dyscrasia through serum free light-chain assay, and serum and urine protein electrophoresis with immunofixation.<sup>11</sup>

To sum up, planar and SPECT scintigraphy, combined with monoclonal protein assessment, followed by CMR and/or cardiac/extracardiac biopsy, if necessary, enable accurate diagnosis in patients exhibiting suggestive signs or symptoms.

Distinguishing between wild-type and mutated ATTR relies on TTR genetic testing. Therefore, TTR genetic testing is advised for all patients with ATTR, regardless of age, as approximately 5% of patients aged 70 years or older exhibit ATTRv.<sup>9</sup>

CA is a progressive condition with unfavorable outcomes in the absence of intervention. AL amyloidosis is linked to a poorer prognosis compared to ATTR, characterized by a swift advancement of HF.<sup>7</sup> Prognosis in ATTR is influenced by the specific variant, extent of cardiac involvement, and neurological phenotype. Treatment for CA involves addressing and preventing complications while halting or slowing amyloid deposition through specific interventions.<sup>12</sup> Additionally, general measures are necessary to manage HF and cardiac rhythm disturbances.

AL amyloidosis arises from abnormal production of immunoglobulin AL, necessitating specific treatment aimed at eliminating this production through chemotherapy or autologous stem-cell transplant.<sup>13</sup>

In the case of ATTR, there are several potential therapeutic targets within the pathophysiological process of amyloid fibril formation and deposition in cardiac tissue. These include liver transplantation, TTR tetramer stabilizers, hepatic TTR synthesis inhibitors, and interventions aimed at degrading and resorbing deposited amyloid fibrils.<sup>12</sup>

Tafamidis is the only medication demonstrated to offer prognostic benefits in ATTR. This highly specific drug targets the circulating TTR protein, stabilizing the TTR tetramer to prevent its dissociation into amyloidogenic monomers, which then deposit in the myocardium, leading to restrictive cardiomyopathy. Evidence from a phase 3 trial (ATTR-ACT)<sup>14</sup> indicates that tafamidis reduces all-cause mortality and cardiovascular hospitalizations in ATTR. The most significant effects were observed in patients classified as New York Heart Association (NYHA) functional class I and II. This prospective, randomized, placebo-controlled trial included 441 patients (18 to 90 years of age) diagnosed with hereditary or wild-type ATTR cardiomyopathy who were characterized by a history of HF, interventricular septal thickness > 12 mm on echocardiography, TTR amyloid deposits (confirmed by biopsy or positive bone marker scintigraphy), NT-pro-BNP > 600 pg/mL, and > 100 meters walked in the 6-minute walk test. The main exclusion criteria were NYHA functional class IV, AL CA, and Glomerular filtration rate (GFR) < 25 mL/min/1.73 m<sup>2</sup>.

More recently, an open-label extension study of ATTR-ACT revealed that a daily dosage of 80 mg of tafamidis led to notably higher survival rates compared to a dosage of 20 mg/day (RR = 0.70 [95% CI: 0.50 to 0.979], p = 0.0374).<sup>15</sup>

Based on this, tafamidis 80 mg/day is recommended for patients with ATTRv or ATTRwt, in NYHA I to III, without severe renal dysfunction, who are beginning therapy at the earliest stages of the disease,<sup>16</sup> and it is currently approved in Brazil by the Brazilian Health Regulatory Agency. New therapies specifically for ATTR are under investigation.

### Treatment of HF

CA deserves special consideration regarding HF management. CA initially presents as HFpEF and

a restrictive pattern of left ventricular (LV) filling, which could lead to disease progression and reduced ejection fraction (EF).<sup>16</sup> Fluid control is crucial, but achieving euvolemia can be challenging, as excessive diuretic dosages may lead to decreased preload and subsequent reduction in cardiac output in hearts with already compromised stroke volume. Additionally, in patients with autonomic polyneuropathy, hypotension may hinder diuretic utilization due to unstable preload conditions.<sup>17</sup> Within the framework of restricted physiology leading to a fixed stroke volume, a higher heart rate might be necessary to uphold cardiac output, explaining why patients with CA poorly tolerate beta blockers. In fact, beta blockers and neurohormonal antagonists, such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and angiotensin receptor-neprilysin inhibitors (ARNI) pose a risk of hypotension and may exacerbate autonomic dysfunction. Additionally, the inability to enhance stroke volume in response to vasodilation could also contribute to the intolerance of ACEI and ARB. Often, discontinuation of vasodilators results in symptom improvement and should be considered. Moreover, non-dihydropyridine calcium channel blockers should be avoided in patients with AL amyloidosis, as they tend to bind to amyloid fibrils, potentially resulting in advanced blocks and cardiogenic shock.

For all these reasons, conventional HF medications are poorly tolerated in patients with CA, and expert consensus documents<sup>9,16,18</sup> recommend caution against their use. The cornerstone of the treatment remains the judicious use of loop diuretics and mineralocorticoid receptor antagonists (MRA) to control volume overload. In addition to the poor tolerance, it is still unknown whether HF disease modifying medications may also improve prognosis in patients with CA, because they were not included in previous HF trials. Due to the lack of dedicated randomized clinical trials evaluating HF medications in CA, available evidence is based on observational studies.

In a recent retrospective study including patients with ATTR-CA (n = 2371, mean age 77.5 years, 90% men, 77.6% ATTRwt and 22.4% ATTRv), roughly 50% of patients received beta blockers (64% with LV ejection fraction [LVEF] < 40%), and 50% received ACEI or ARB (60% with LVEF ≤ 40%). MRAs were prescribed to 40% of patients (47% with LVEF ≤ 40%).<sup>19</sup> Of those patients treated with beta blockers, over half (63%) received lower than 25% of the target dose recommended for HF. The

most commonly prescribed beta blocker was bisoprolol (88%), and 61% of these patients received less than 2.5 mg/day. Only 5.7% had the target beta blocker dose. Of those patients treated with ACEI/ARB, 53% received lower than 50% of the target dose for HF. The most frequently prescribed ACEI/ARB was ramipril (51%), and 50% of these patients received less than 2.5 mg/day. Only 11.6% had the target ACEI/ARB dose. Of those patients treated with MRA, 80% were taking spironolactone, and 20% were taking eplerenone. Discontinuation rates were around 20% for beta blockers, 30% for ACEI/ARB, and only 8% for MRA. MRA were found to be independently linked to a reduced risk of mortality in the overall population (HR 0.82, 95% CI 0.71 to 0.94, p = 0.004), as well as in patients with a LVEF > 40%. Additionally, low-dose beta blockers were independently associated with a decreased risk of mortality in patients with an LVEF of 40% or lower.<sup>18</sup> This retrospective study excluded patients with concomitant polyneuropathy, which could, in part, explain the results, as this condition frequently leads to hypotension and intolerance of HF medications. These recent findings contrast with the results of some other small observational studies; thus, randomized controlled clinical trials (RCCTs) are needed.

Regarding MRA, a recent retrospective analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, focusing on a cohort enriched for amyloidosis based on echocardiographic features, revealed a positive outcome with spironolactone. This analysis showed a reduction in the combined endpoint of cardiovascular death, HF hospitalization, or aborted cardiac arrest in patients taking spironolactone (p = 0.024).<sup>20</sup>

In another retrospective single-center study involving 99 patients with CA (age 80 years, 33% AL and 67% ATTR), the use of ACEI or ARB and MRA was safe, and gradual dose adjustments were possible when no contraindications were present. However, beta blockers were less well tolerated in AL patients with either left or right ventricular dysfunction.<sup>21</sup>

Based on guideline-directed medical therapy (GDMT) for HF, it is crucial to analyze the role of sodium-glucose transport protein 2 inhibitors (SGLT2i) in patients with CA. Due to their safety profile, not adversely affecting hemodynamics or renal function, SGLT2i have aroused interest as a treatment for HF in patients with CA. Some small retrospective analyses have tested the safety and tolerability of this new class of drugs. In a retrospective pilot study involving stable ATTR patients treated with



tafamidis, the introduction of SGLT2i therapy using dapagliflozin was well tolerated.<sup>22</sup> However, evidence on efficacy in improving outcomes remains unknown.

The Central Figure depicts the management of HF in patients with CA, and Table 1 displays the recommendations according to the *Brazilian Position Statement on Amyloidosis*.

### Use of implantable cardioverter-defibrillators (ICDs) and anticoagulation

Given the arrhythmogenic potential and damage to the conduction system caused by amyloid deposition, implantable devices such as pacemakers or defibrillators are commonly utilized to reduce mortality and enhance survival in this patient population.<sup>9</sup> However, current available data do not support the use of ICDs in primary prevention.<sup>23</sup> ICDs may be beneficial for patients with unstable ventricular tachycardia or those who have survived cardiac arrest without a reversible cause and have a life expectancy of more than 1 year, with significant quality of life.<sup>24-25</sup>

The decreased contractility resulting from amyloid infiltration may contribute to thrombus formation, thereby increasing the risk of stroke. CA is associated with a heightened risk of stroke, and the annual incidence of stroke/transient ischemic attack is 3 times higher in this group of cardiomyopathy patients with atrial fibrillation (AF). Hence, anticoagulation should be considered for these patients with any type of

AF or flutter, according to the European Society of Cardiology guidelines (I-B).<sup>12</sup>

### Treatment of advanced HF

In cases of advanced HF associated with CA, implementation of advanced support strategies, such as mechanical circulatory assistance and transplantation, poses significant challenges, primarily due to the multisystem nature of the disease. Furthermore, the reduced size of the LV cavity and frequent involvement of the right ventricle may limit the use of long-term mechanical circulatory assist devices.<sup>26</sup> Historically, heart transplantation showed lower survival rates in CA.<sup>27</sup> However, recent studies suggest that outcomes may be comparable to those of other etiologies.<sup>28</sup> This improvement could be attributed to better strategies, such as double transplantation for patients with ATTRv and heart transplantation preceding bone marrow transplantation in AL amyloidosis. In recipients of heart transplantation with ATTR-CA, the use of disease modifying therapies, such as tafamidis, may be a possibility to improve outcomes, but it has not yet been studied in this population.

### Conclusion

Treatment of HF in patients with CA is a huge challenge. Due to the restrictive physiology of the disease, patients often present hypervolemia and cardiorenal syndrome, and these conditions require decongestion strategies. However, the use of diuretics may also lead to decreased preload

**Table 1 – Recommendations for HF treatment, based on the *Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis from the Brazilian Society of Cardiology and the III Brazilian Guideline of Heart Transplantation*.**

| Recommendation   | Class of recommendation | Level of evidence |
|--|-------------------------|-------------------|
| Loop diuretics to control congestion   | I                       | C                 |
| Avoid negative chronotropic drugs, except in special situations                    | I                       | C                 |
| Oral anticoagulation in AF, Regardless of calculated embolic risks                 | I                       | C                 |
| Double transplantation (cardiac and hepatic) in refractory ATTR-CA                 | II-A                    | B                 |
| Cardiac transplantation in AL amyloidosis followed by bone marrow transplantation* | II-A                    | B                 |
| Routine use of HF disease modifying drugs in CA                                    | III                     | C                 |

\* In patients with contraindication to specific therapy due to cardiac involvement and without significative extracardiac involvement. AF: atrial fibrillation; AL: light chain; ATTR: transthyretin amyloidosis; CA: cardiac amyloidosis; HF: heart failure.

and subsequent reduction of cardiac output in hearts with already compromised stroke volume. Autonomic dysfunction and hypotension are also very common.

In summary, not only is there insufficient evidence supporting GDMT use in patients with CA, but these medications are also frequently poorly tolerated. Accordingly, beta blockers should be avoided. In the presence of HF symptoms, loop diuretics are recommended, because the mainstay of symptom management has long been meticulous volume control. Aldosterone antagonists may have a synergistic effect when added to loop diuretics. SGLT2i have aroused interest as a treatment for CA, but their use still requires evaluation through RCCTs. Finally, heart transplantation may offer an opportunity for patients with advanced disease and may be considered in experienced centers.

## Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data,

writing of the manuscript and critical revision of the manuscript for intellectual content: Faria VS, Murad CM, Marcondes-Braga FG.

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No potential conflict of interest relevant to this article was reported.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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