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Cardiac amyloidosis: Innovations in diagnosis and treatment

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Cardiac amyloidosis (CA) is a progressive, underdiagnosed condition caused by the deposition of misfolded proteins in the myocardium, forming amyloid fibrils that impair cardiac structure and function. This review highlights recent advances in the diagnosis and treatment of amyloid light-chain (AL) and transthyretin (ATTR) CA, which globally account for most cases of CA. Novel diagnostic tools, including artificial intelligence-enhanced analysis and advanced imaging modalities like positron emission tomography with amyloid-specific tracers, might improve detection rates and diagnostic accuracy to enable non-invasive subtype differentiation. Furthermore, many innovative treatments are being investigated. For AL-CA, anti-fibril therapies are showing promising results, complementing traditional chemotherapy and autologous stem cell transplantation. In ATTR-CA, gene silencing and anti-fibril therapies are being tested in clinical trials and hold promise of halting disease progression and reducing amyloid deposits, respectively.

Cardiac amyloidosis (CA) is a progressive condition resulting from the deposition of misfolded proteins in the heart as amyloid fibrils, leading to structural and functional impairment. The two main subtypes are light-chain (AL) amyloidosis, caused by the accumulation of immunoglobulin light chains, and transthyretin (ATTR) amyloidosis, involving either wild-type (wt) or mutated (variant, v) transthyretin (TTR). Early diagnosis is crucial for effective management due to the irreversible damage caused by amyloid deposits.[1] This review summarizes the recent advances in diagnostic tools, including imaging techniques such as positron emission tomography (PET) and novel applications of artificial intelligence (AI), as well as innovations in treatments, including use of monoclonal antibodies and gene silencing therapies.

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Diagnosis of CA

Current diagnostic algorithm

The diagnostic algorithm of CA begins with a suspicion triggered by specific 'red flags'. Cardiac-related red flags include low QRS voltages relative to left ventricular (LV) mass, pseudonecrosis Q waves, atrioventricular conduction system disorders on electrocardiogram (ECG), disproportionate LV wall thickening without a clearly identifiable cause (pseudohypertrophy), sustained plasma elevation of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and troponin I or T levels.[2] Signs such as unexplained right heart failure or pericardial effusion may also raise suspicion. Extracardiac red flags, such as musculoskeletal alterations (e.g. carpal tunnel syndrome, spontaneous tendon rupture, lumbar spinal stenosis), are often early indicators of CA, especially in ATTR amyloidosis. Although proteinuria, macroglossia, and arterial hypotension and other symptoms of autonomic dysfunction may hint at AL-CA, they often occur when the disease is already at an advanced stage.[2]

The diagnostic work-up aims at differentiating the two main subtypes of AL-CA and ATTR-CA because treatment differs. This goal is achieved through the use of scintigraphy using bone tracers like technetium-labeled pyrophosphate or diphosphonates, which help detect ATTR deposits in the heart.[3,4] Serum and urine protein immunofixation and serum free light chain (FLC) assays are performed to check for the presence of monoclonal proteins, which may indicate AL amyloidosis.[5,6] Different guidelines from various medical societies (e.g. European Society of Cardiology, American Heart Association) emphasize the need for early diagnosis since patient outcomes depend largely on early initiation of therapy, especially in AL-CA.[2,7-11] They agree on the use of scintigraphy and monoclonal protein tests but differ slightly in the sequence of tests. Based on these tests, one of four scenarios may arise:

(1) If scintigraphy shows no cardiac uptake and no monoclonal protein is detected, CA is considered unlikely. However, if clinical suspicion persists, further testing, such as cardiac magnetic resonance (CMR) imaging or a biopsy, may be warranted, as some rare forms of CA may yield negative scintigraphy results.
(2) If cardiac uptake is detected on scintigraphy but no monoclonal protein is found, and the uptake is strong (grade 2 or 3 on the Perugini scale), ATTR-CA can be diagnosed without a biopsy. Genetic testing is crucial at this stage to differentiate between the wt and v forms of ATTR. In cases of weak uptake (grade 1), histological confirmation through biopsy, possibly including also an extracardiac site, is required.
(3) In the case of no cardiac uptake but a positive monoclonal protein test, AL amyloidosis is suspected. CMR may assist in determining whether cardiac involvement exists. If imaging suggests amyloidosis or results are inconclusive, a tissue biopsy from the heart or another affected organ, such as the kidneys, liver, or gastrointestinal tract, is needed.
(4) If both cardiac uptake and monoclonal protein are found, a combination of ATTR amyloidosis with monoclonal gammopathy of unknown significance, AL amyloidosis, or the coexistence of both amyloidosis forms is considered. In these cases, endomyocardial biopsy for histological amyloid typing is essential.[2]

Biomarkers, echocardiography, and CMR: new applications of old diagnostic tools

Elevated levels of natriuretic peptides and troponin are commonly employed as generic 'red flags' for suspecting CA. However, these biomarkers may hold a precise diagnostic value.[12] In a cohort of 343 patients with clinical suspicion of CA, NT-proBNP, and high-sensitivity troponin T (hs-TnT), either alone or combined, achieved high diagnostic accuracy [area under the curve (AUC) 0.721–0.821] for CA, which was confirmed in an external validation cohort of 806 patients with suspected CA (AUC 0.830–0.843). NT-proBNP <180 ng/L and hs-TnT <14 ng/L emerged as reliable thresholds to rule out CA, and hs-TnT ≥86 ng/L as an effective rule-in cut-off. These cut-offs performed well across various subgroups, supporting their broader clinical application.[13]

Speckle tracking echocardiography (STE) allows for quantitative analysis of myocardial function. It is particularly valuable for detecting CA in the initial stages, where longitudinal function is impaired while radial thickening remains preserved. STE can identify specific patterns, such as apical sparing (where basal myocardial segments show hypokinesis and apical segments retain contractility), typical of CA, distinguishing it from other causes of cardiac hypertrophy, such as hypertrophic cardiomyopathy and aortic stenosis. The longitudinal strain (LS) and global LS (GLS, i.e. the average of segmental strain values) measures are key parameters, with GLS values > −15% indicating subclinical disease. Other parameters such as the relative regional strain ratio and the septal apical-to-basal ratio further differentiate CA from other hypertrophic diseases. LS and septal apical-to-basal ratio have been included in multiparametric echocardiography scores for the diagnosis of CA. Specifically, the AL score and the IWT scores have been proposed to assess patients referred by hematologists or with unexplained LV hypertrophy, respectively. These scores are composed of four or five variables, respectively, including strain data.[14] The AMYLoidosis Index (AMYLI) is a simplified version, consisting only of relative wall thickness and E/e' ratio, that can be applied when STE imaging is not available.[15] Additionally, the HFA-PEFF score has shown diagnostic utility in patients with CA-caused heart failure with preserved ejection fraction.[16] Recently, the Mayo ATTR-CM score has been specifically devised to aid the identification of patients with heart failure and preserved ejection fraction requiring a screening for ATTR-CA. Score variables included age, male sex, hypertension, relative wall thickness >0.57, posterior wall thickness ≥12 mm, and ejection fraction <60%.[17] The Mayo ATTR-CM score shows a better discrimination compared with the IWT score, AMYLI score, and hs-TnT rule-in cut-off of 86 ng/L to distinguish ATTR-CA from AL-CA or no CA.[18] STE may also help guide the differential diagnosis between amyloidosis subtypes.[19] LV strain values are usually significantly worse in AL-CA, except for apical LV strain, which is usually more reduced in ATTR-CA. Right ventricular free-wall LS (particularly in its basal and mid-segments) is usually more impaired in AL-CA, while left atrium reservoir and pump functions are more reduced in wt ATTR-CA.[19-23]

CMR is usually employed to suspect CA in case of cardiac hypertrophy or to detect cardiac involvement in patients with an already diagnosed systemic amyloidosis.[24] Multiple CMR modalities such as late gadolinium enhancement, T1 and T2 mapping, and myocardial extracellular volume quantification are commonly used in clinical practice.[1] CMR also allows precise assessment of myocardial strain thanks to the improved image quality compared to echocardiography.[25] In addition, diffusion tensor imaging (DTI) is a promising contrast-free method that examines myocardial microstructure, enabling the detection of amyloid infiltration and distinguishing CA from other heart diseases. DTI has also revealed differences in myocardial mechanics between AL and ATTR amyloidosis.[26]

PET: a novel tool for etiological diagnosis

The validation of bone tracer scintigraphy as a diagnostic tool for CA has allowed to reach a definitive non-invasive diagnosis of ATTR-CA in a considerable number of patients.[4,24,27] In contrast, the diagnosis of AL-CA still requires histologic demonstration of amyloid deposits, often achievable only through an endomyocardial biopsy,

with intrinsic procedural risks.[2] Nonetheless, some PET radiotracers are emerging as novel tools for non-invasive detection of amyloid deposits in the heart, providing valuable information about the type and extent of amyloid involvement.[28,29] Several PET radiotracers, including ^{11}C-Pittsburgh Compound B (^{11}C-PiB), ^{18}F-flutemetamol, ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-sodium fluoride (^{18}F-NaF), have demonstrated a diagnostic potential in differentiating amyloid subtypes, quantifying amyloid burden, and monitoring disease progression. Additionally, the integration of PET with cardiac computed tomography or magnetic resonance imaging may further enhance the detection and localization of amyloid deposits (*Figure 1*).

^{11}C-PiB, originally developed for Alzheimer's disease, is one of the earliest PET radiotracers applied for CA detection. Studies have shown that it can identify both AL and ATTR amyloidosis and differentiate them based on the degree of uptake.[30] However, due to its short half-life, the need for an on-site cyclotron limits its clinical applicability.[31]

^{18}F-Flutemetamol, with a longer half-life of 110 min, has emerged as a promising alternative to ^{11}C-PiB.[32] It offers greater logistical flexibility and has demonstrated high sensitivity and specificity for detecting ATTR-CA. It correlates with key cardiac structural markers, such as LV wall thickness and mass, making it useful for quantifying disease burden.[33] Additionally, ^{18}F-flutemetamol might be valuable in monitoring treatment response, although more studies are required to confirm this assumption.[34]

^{18}F-Florbetapir has been approved by the Food and Drug Administration (FDA) for amyloid imaging in Alzheimer's disease[35] and has been adapted for CA. It offers the advantage of a longer scan window,[36] and studies have shown its ability to differentiate between amyloidosis patients and controls, particularly in AL amyloidosis.[37] In a pilot study, higher retention index values were observed in AL patients compared to ATTR, indicating its possible role in subtype differentiation.[38] ^{18}F-Florbetapir has also shown potential as a prognostic tool in AL-CA, predicting cardiovascular events,[39] and can even detect early right ventricular amyloid deposition before structural changes occur, making it a promising tool for early diagnosis.[40]

^{18}F-Florbetaben is another FDA-approved PET radiotracer that has shown significant promise in differentiating AL and ATTR amyloidosis. In a pivotal study by Genovesi *et al.*, ^{18}F-florbetaben PET/computed tomography effectively distinguished between AL-CA and ATTR-CA based on myocardial tracer retention at delayed acquisitions. Both early and delayed standardized uptake values (SUVs) were significantly higher in AL-CA compared to ATTR-CA (5.55 vs. 2.55 and 3.50 vs. 1.25, respectively) or LV hypertrophy (early SUV 3.50; delayed SUV 1.40), offering a clear diagnostic distinction between the two subtypes. Furthermore, the study demonstrated a correlation between ^{18}F-florbetaben uptake and echocardiographic markers such as LV wall thickness and LS, providing a comprehensive assessment of disease burden and cardiac function.[41] The ongoing phase III trials PETAL and CARdiag are investigating the diagnostic performance of ^{18}F-florbetaben for visualizing and quantifying amyloid in patients with suspected AL-CA, with the ambition to potentially eliminating the need for tissue biopsy.[42,43]

^{18}F-NaF, originally developed for bone imaging, has been repurposed for CA. It has shown promise in differentiating ATTR-CA from AL-CA based on calcium metabolism differences.[38,44] However, its diagnostic sensitivity is lower than scintigraphic ^{99m}Tc-labeled tracers.[45]

One of the newest additions to PET imaging for amyloidosis is ^{124}I-evuzamitide, a pan-amyloid-reactive peptide. Early studies have shown that it correlates well with cardiac structural parameters measured by echocardiography and CMR, suggesting its potential as both a diagnostic and a monitoring tool for amyloidosis patients.[46]

AI: is there a role for CA diagnosis?

AI can process large volumes of data, including clinical variables, ECG, and imaging techniques like echocardiography and CMR, to enhance diagnostic sensitivity and specificity beyond human capabilities. Several studies underscore AI's potential in improving the diagnosis of CA. For instance, Grogan *et al.* developed an AI-enhanced ECG model using data from 2541 CA patients at the Mayo Clinic, which demonstrated an AUC of 0.91, significantly improving CA detection. Their model successfully identified CA up to 6 months before clinical diagnosis in 59% of cases, outperforming traditional diagnostic methods.[47] Another study by Zhang *et al.* used echocardiography data from 14 035 patients to train convolutional neural networks, achieving C-statistics of 0.93 for hypertrophic cardiomyopathy and 0.87 for CA. These convolutional neural networks automated tasks like chamber segmentation and disease classification with high accuracy, matching, or surpassing human performance.[48]

In addition to ECG and echocardiography, AI has also been applied to advanced imaging techniques. Antonopoulos *et al.* used machine learning to analyse T1 mapping radiomics in CMR, differentiating CA from other forms of LV hypertrophy with an AUC of 0.84.[49] AI tools have also shown promise in PET, with early studies demonstrating high sensitivity and specificity in detecting CA.[50]

Despite recent advancements, AI applications in CA face limitations due to the disease's rarity, which results in small datasets that hinder the development of robust models. Additionally, these AI tools require refinement to reliably screen asymptomatic populations, where sensitivity tends to decrease. To address these challenges, larger, diverse datasets, and standardized protocols are essential. Identifying the optimal application of AI is also crucial, whether for broad population screening, patients undergoing specific diagnostic tests (ECG, echocardiography, CMR), or individuals with certain conditions (e.g. cardiac hypertrophy, monoclonal gammopathy of unknown significance, severe aortic stenosis). Furthermore, selecting the appropriate analytical approach is critical, whether utilizing a single method (such as deep learning or machine learning) or integrating multiple techniques, potentially alongside clinical features. As AI models continue to evolve, they hold the potential to revolutionize CA diagnosis by facilitating earlier detection, minimizing misdiagnoses, and guiding precision medicine (*Figure 1*).

Treatment of CA

Treatment of amyloid light-chain amyloidosis: from standard chemotherapy to monoclonal antibodies and anti-fibril therapies

Therapeutic success in AL amyloidosis is gauged by hematologic and organ responses. Hematologic responses

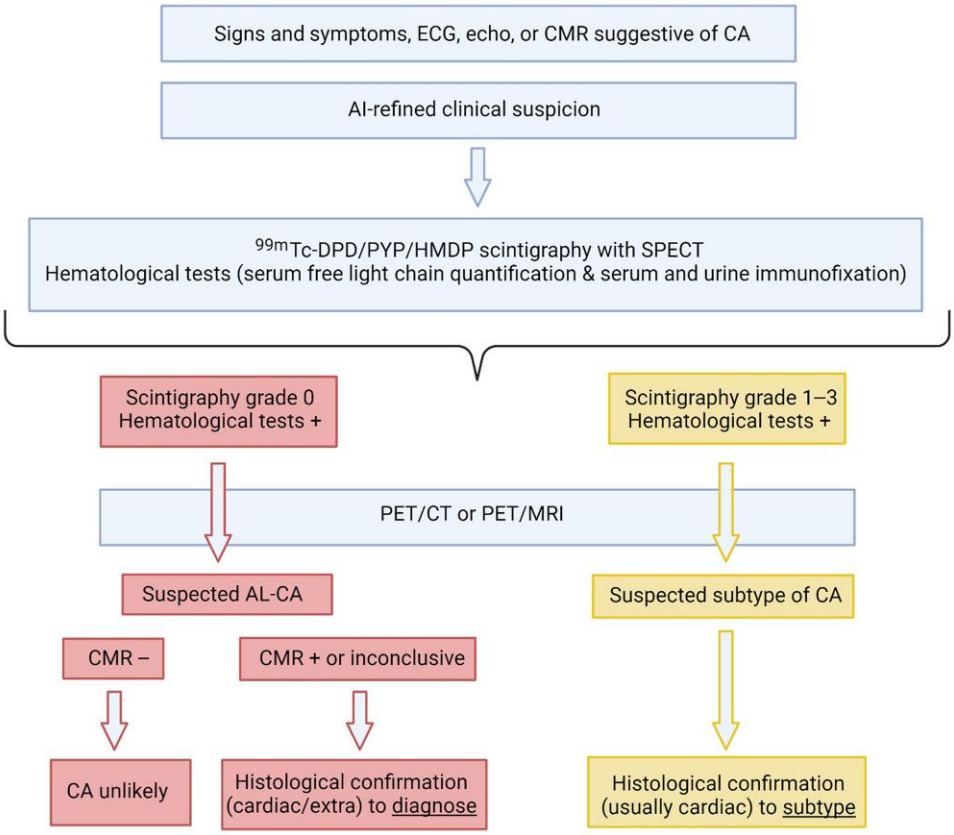

Figure 1 Possible integration of artificial intelligence tools and positron emission tomography in the diagnostic algorithm for light-chain cardiac amyloidosis. Artificial intelligence tools may refine clinical suspicion of cardiac amyloidosis. Positron emission tomography computed tomography or magnetic resonance imaging might allow the non-invasive diagnosis of amyloid light-chain-cardiac amyloidosis, thus limiting the need for histological confirmation. ECG, electrocardiogram; CMR, cardiac magnetic resonance; ^{99m}Tc-DPD, technetium-99m-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid; PYP, pyrophosphate; HMDP, hydroxymethylenediphosphonate; SPECT, single-photon emission computed tomography.

focus on reducing cytotoxic amyloidogenic FLC levels, with a complete hematological response defined as normalized FLCs and negative serum and urine tests.[51-53] Achieving a complete response is associated with improved outcomes.[52,53] However, even partial responses can prolong survival.[52,53] Organ responses are defined by improvements in their function,[51] such as reductions in NT-proBNP for cardiac involvement[54] and decreased proteinuria for renal disease.[55,56] Regular monitoring of response to treatment is essential, with adjustments made when responses are inadequate.[52] *Figure 2* highlights current and future treatment options for AL amyloidosis.

Autologous stem cell transplantation (ASCT) is an option for 20–25% of newly diagnosed patients, with the best results seen in those with minimal cardiac involvement and favourable cytogenetics.[57] However, ASCT carries risks, including transplant-related mortality, particularly in patients with significant cardiac disease, so patient selection is critical.[58,59] If a delay in transplantation is anticipated and the patient has multiple myeloma or a plasma cell burden above 10%, two to four cycles of induction therapy are recommended.[60] Traditionally, cyclophosphamide-bortezomib-dexamethasone (CyBorD) and bortezomib-melphalan-dexamethasone were common induction regimens.[60] Recently, daratumumab, an anti-CD38 monoclonal antibody, has been added to standard therapy, particularly for relapsed or refractory AL amyloidosis.[60]

For patients ineligible for transplantation, chemotherapy treatments targeting plasma cells are the mainstay.[61,62] The combination of daratumumab and CyBorD has become the standard of care for these patients, offering high response rates.[63] In cases of advanced cardiac involvement, dose modifications are essential, and single-agent therapies are considered.[64] In relapsed or refractory cases, treatment options expand to second-generation proteasome inhibitors like carfilzomib and ixazomib, and immunomodulatory drugs like pomalidomide.[61,63] A second ASCT may also be considered in selected patients who initially responded well to the procedure.[65]

Monoclonal antibodies that target the plasma cell clone, such as daratumumab, have emerged as a powerful adjunct in treating AL amyloidosis.[66] Daratumumab is a human anti-CD38 IgG1κ monoclonal antibody, initially approved for the treatment of multiple myeloma, which has shown substantial efficacy in AL amyloidosis.[67] It works by inducing direct apoptosis of plasma cells through antibody-dependent cellular cytotoxicity, targeting the underlying plasma cell clone responsible for producing amyloidogenic light chains.[68] In the phase III ANDROMEDA trial, daratumumab, combined with CyBorD, demonstrated a hematologic response rate of 92%, significantly higher

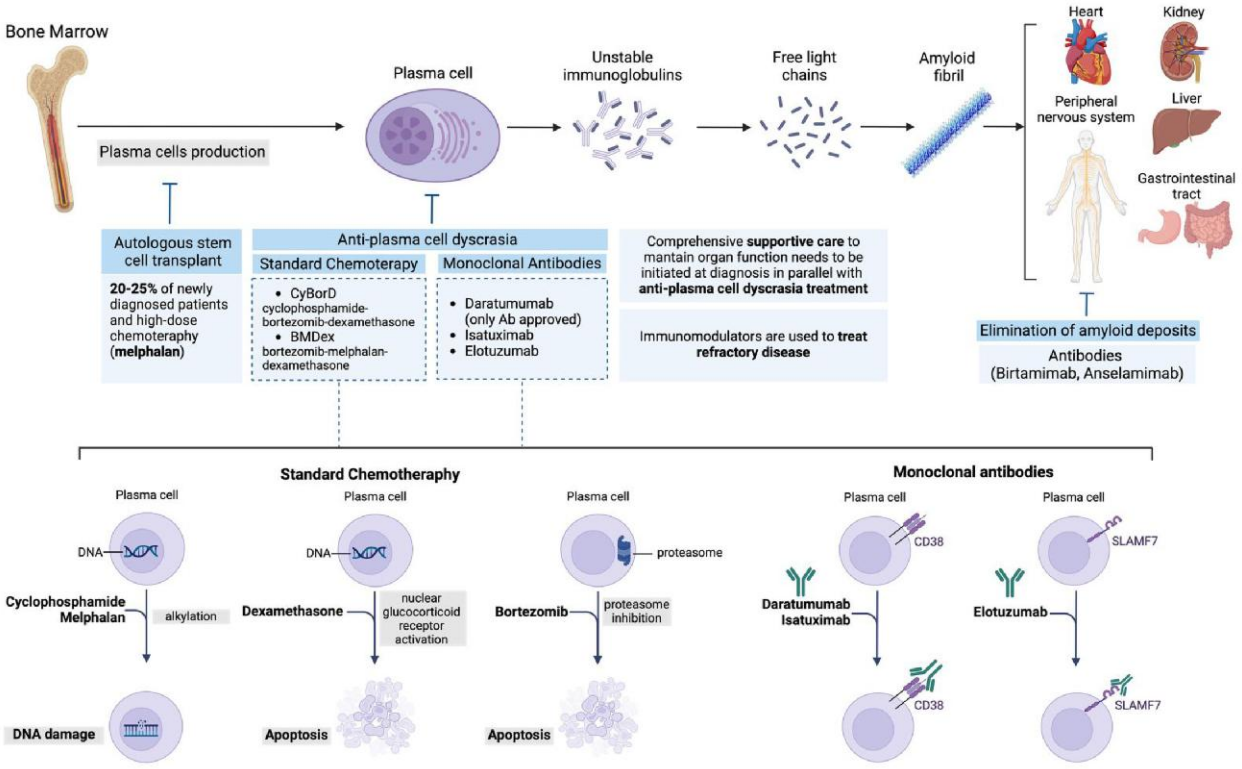

Figure 2 Treatment of light-chain amyloidosis. The current regimens for light-chain amyloidosis focus on anti-plasma cell dyscrasia strategies, which involve standard chemotherapy and monoclonal antibodies such as daratumumab, as well as autologous stem cell transplant for a small percentage of patients. Recently, antibodies eliminating amyloid deposits have emerged as a promising option. BMDex, bortezomib and dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; CD, cluster of differentiation; SLAMF7, signalling lymphocytic activation molecule F7.

than the 77% achieved with CyBorD alone.[69] Moreover, it produces a cardiac response in 42% of patients, compared to 22% in the control group.[69] These results led to the FDA's accelerated approval of daratumumab in combination with CyBorD for newly diagnosed AL amyloidosis patients in 2021.[68] Other monoclonal antibodies, such as isatuximab and elotuzumab, have also been explored for treating AL amyloidosis.[70-72] Isatuximab, like daratumumab, targets CD38 on plasma cells and has shown efficacy in relapsed and refractory AL amyloidosis.[70] In a phase II study, isatuximab achieved a 77% overall hematologic response rate, with 54% of patients reaching a very good partial response.[70] Elotuzumab targets SLAMF7, a glycoprotein expressed on plasma cells and has been investigated as part of combination therapies for relapsed patients.[72] Early studies suggest that it may enhance the efficacy of standard chemotherapy regimens when used in combination with agents like lenalidomide or bortezomib.[73]

Anti-fibril therapies offer a unique approach to AL amyloidosis by directly targeting the amyloid deposits themselves, which contribute to organ dysfunction, rather than solely focusing on the clonal plasma cells responsible for producing the amyloidogenic light chains.[67] These therapies are primarily based on monoclonal antibodies designed to recognize and facilitate the clearance of amyloid deposits.[67] Birtamimab is a humanized IgG1 monoclonal antibody that binds to misfolded amyloid fibrils and promotes their clearance by recruiting the immune system's phagocytic cells.[74] Birtamimab has been tested in several clinical trials, showing varying degrees of efficacy depending on patient subgroups. In early-phase studies, it was found to be safe and well-tolerated.[75] However, the phase III VITAL trial, which aimed to evaluate its effectiveness in newly diagnosed patients with cardiac involvement, was terminated early due to futility based on *interim* analyses.[76,77] Despite this setback, *post-hoc* analyses revealed a survival benefit in patients with advanced disease, particularly those classified as Mayo stage IV.[76] This prompted the initiation of the AFFIRM-AL trial, a phase III study focusing on patients with advanced CA.[78] Another promising agent in this class is anselamimab, a monoclonal antibody targeting a neo-epitope on misfolded light chains, thereby facilitating the removal of amyloid fibrils by macrophages.[79] Anselamimab has shown encouraging results in early-phase studies, particularly in patients with cardiac involvement.[66] In a phase I/II trial, anselamimab demonstrated a good safety profile and a significant cardiac response, with 67% of patients experiencing an early and sustained organ response, as evidenced by improvements in GLS.[80,81] Based on these promising results, two phase III trials are currently underway, focusing on patients with advanced CA. These trials will further assess the efficacy of anselamimab in combination with standard chemotherapy regimens.[82,83]

Treatment of ATTR amyloidosis: from stabilizers to gene editing

ATTR amyloidosis was previously treated only through liver transplantation,[84,85] whereas recent advancements have

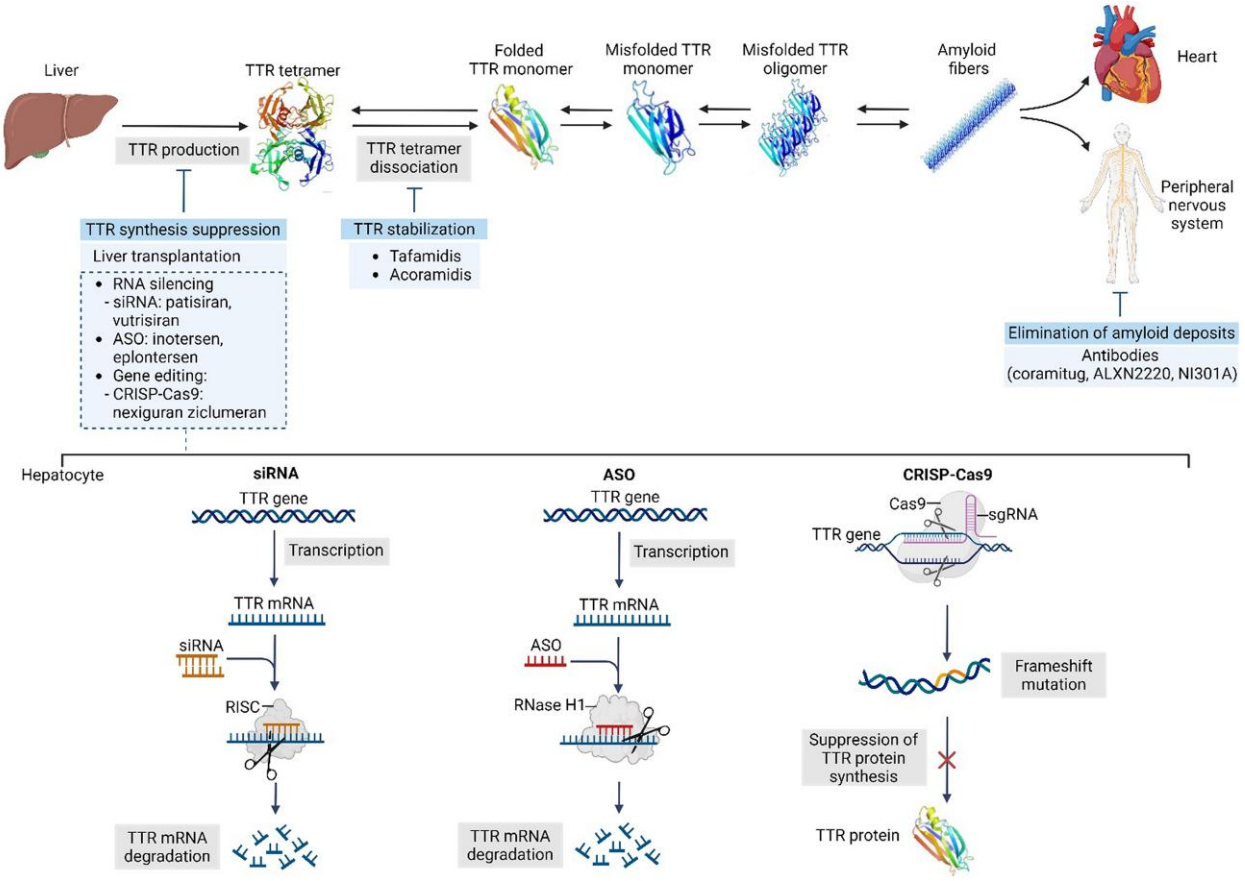

Figure 3 Treatment of transthyretin amyloidosis. Modified from Aimo *et al.*[103] The actual treatment of transthyretin amyloidosis is mainly based on transthyretin stabilization, with tafamidis being the only commercially available option for patients with cardiac involvement without polyneuropathy. However, new approaches such as transthyretin synthesis suppression through RNA silencing, antisense oligonucleotide and gene editing, and elimination of amyloid deposits with monoclonal antibodies are emerging as valuable alternatives. ASO, antisense oligonucleotide; RISC, RNA-induced silencing complex; sgRNA, single-guide RNA; siRNA, small interfering RNA.

introduced a variety of pharmacological therapies targeting different stages of the amyloidogenic process, from TTR stabilization to gene editing (*Figure 3*).

Tafamidis prevents TTR tetramer dissociation into amyloidogenic monomers.[86] In the ATTR-ACT trial, 441 patients with ATTR-CA (75% ATTRwt) were randomized to receive tafamidis (80 or 20 mg) or placebo.[87] Tafamidis demonstrated a significant reduction in all-cause mortality [hazard ratio (HR) 0.70, 95% CI 0.51–0.96] and cardiovascular hospitalizations (HR 0.68, 95% CI 0.56–0.81). Furthermore, it slowed the decline in 6-minute walk distance (6MWD) and improved quality of life (Kansas City Cardiomyopathy Questionnaire-Overall Summary, KCCQ-OS).[86] However, subgroup analysis revealed higher hospitalization rates among New York Heart Association (NYHA) class III patients, possibly due to the drug prolonging survival in advanced disease stages.[88] Tafamidis is currently the only approved disease-modifying drug approved for ATTR-CA in Europe (NYHA I–II) and the United States (NYHA I–III).[2] Acoramidis is another promising TTR stabilizer.[89,90] Unlike tafamidis, acoramidis binds TTR with greater selectivity, mimicking the protective T119M variant, which prevents amyloid deposition. The phase III ATTRibute-CM trial, involving 632 patients followed for 30 months, demonstrated that acoramidis resulted in a significantly better four-step primary hierarchical outcome, which included death from any cause, cardiovascular-related hospitalization, change from baseline in NT-proBNP levels and 6MWD. This yielded a win ratio of 1.8 (95% CI 1.4–2.2) compared to placebo.[91]

While TTR stabilizers aim to prevent the progression of amyloid formation, gene silencing therapies target the underlying cause by reducing the production of TTR protein by hepatocytes. Patisiran, the first small interfering RNA approved for ATTRv polyneuropathy in 2018, showed remarkable efficacy in the phase III APOLLO trial.[92] Patisiran reduced serum TTR levels by 80%, improved neuropathy (mNIS + 7), and quality of life (Norfolk Quality of Life-Diabetic Neuropathy), as well as reduced NT-proBNP levels in patients with cardiac involvement.[92] In the phase III APOLLO-B trial, enrolling patients with ATTRv polyneuropathy with or without cardiac involvement, patisiran suppressed circulating TTR levels by $86 \pm 13.6\%$ and improved quality of life, as displayed by 6MWD and the KCCQ-OS score, after 12 months of treatment. However, common side effects of patisiran are infusion-related reactions, requiring premedication and vitamin A supplementation due to reduced circulating TTR levels.[86]

Vutrisiran, a second-generation small interfering RNA, offers the same therapeutic effect as patisiran but with less frequent dosing (every 3 months, subcutaneously).[93] In the HELIOS-A trial, enrolling patients with ATTRv polyneuropathy, vutrisiran achieved an 88% reduction in TTR and improved neuropathy and quality of life.[93] It demonstrated non-inferiority to patisiran and was well-tolerated without the need for premedication, though patients still required vitamin A supplementation.[94] Subsequently, HELIOS-B was conducted to analyse the ATTR-CA population, focusing on cardiovascular outcomes. The study showed that vutrisiran reduced all-cause mortality and recurrent cardiovascular events more effectively than placebo, either when administered with tafamidis (0.72; 95% CI 0.56–0.93; $P = 0.01$) or as monotherapy (0.67; 95% CI 0.49–0.93; $P = 0.02$). Additionally, this drug preserved functional capacity and quality of life in ATTR-CA patients compared to placebo.[95]

Antisense oligonucleotides (ASO) represent another approach to silencing TTR gene expression. Inotersen, the first ASO approved for ATTRv polyneuropathy in 2018, showed positive results in the phase 3 NEURO-TTR trial.[96] It reduced TTR levels by 84%, improved neuropathy (mNIS + 7), and quality of life (Norfolk Quality of Life-Diabetic Neuropathy) scores. However, adverse effects such as thrombocytopenia and glomerulonephritis were reported, requiring regular platelet and renal monitoring. To address these safety concerns, eplontersen, a GalNAc-conjugated ASO, was developed.[97] Eplontersen is 50 times more potent than inotersen in reducing TTR expression, with fewer side effects. The ongoing CARDIO-TTRansform trial is evaluating its efficacy in ATTR-CA, with an expected enrolment of 1500 patients.[98]

One of the most groundbreaking developments in the field of ATTR amyloidosis treatment is gene editing using CRISPR-Cas9 technology.[99] Nexiguran ziclumeran (NTLA-2001), a CRISPR-Cas9-based therapy, is designed to permanently edit the *TTR* gene in hepatocytes, thus stopping the production of both wt and mutant TTR.[99] Early animal studies showed that a single dose of nexiguran ziclumeran reduced serum TTR levels by up to 96%, with similar results in early human trials.[99] In a phase I study, patients treated with nexiguran ziclumeran experienced significant TTR knockdown, with no severe adverse effects reported.[99] The potential for this therapy to offer a one-time, permanent solution makes it a revolutionary approach in the treatment landscape of TTR amyloidosis. However, long-term monitoring is required to assess the risks of off-target gene editing and other potential complications. The phase III MAGNITUDE trial is currently evaluating the efficacy and safety of intravenous infusion single dose of nexiguran ziclumeran in ATTR-CA patients compared to placebo.[100]

Anti-TTR antibodies represent another promising approach to the treatment of ATTR amyloidosis, specifically targeting the removal of amyloid deposits that have already accumulated in tissues. These antibodies work by stimulating the immune system to recognize and clear amyloid fibrils, potentially reversing the damage caused by the disease. Several antibodies are currently under development and have shown early success in clinical trials. One of the most advanced candidates is ALXN2220 (formerly NI006), a humanized monoclonal antibody that has been evaluated in a phase I clinical trial for both hereditary and wt ATTR-CA.[101] The trial aimed to assess the safety and preliminary efficacy of ALXN2220, with patients receiving infusions every 4 weeks for 4 months, followed by an open-label extension. The results were encouraging, as demonstrated a favourable safety drug profile with no serious treatment-related adverse events. Moreover, imaging studies, including bone scintigraphy and CMR, revealed a reduction in amyloid burden, as indicated by decreased radiotracer uptake and lower extracellular volume. Additionally, there were significant improvements in key biomarkers such as NT-proBNP and troponin T, suggesting that the antibody not only facilitates amyloid clearance but also positively impacts cardiac function.[101] The phase III trial DepleTTR-CM is currently investigating whether ALXN2220 reduces the total occurrence of all-cause mortality and total cardiovascular events after 48 months of therapy, along with changes in quality of life (evaluated through KCCQ-OS and 6MWD).[102] Another noteworthy candidate treatment is coramitug (formerly PRX004), a monoclonal antibody designed specifically for ATTR amyloidosis. Coramitug was evaluated in a phase I trial, where patients received escalating doses to assess the drug's safety and effectiveness.[103] Although the trial was cut short due to the COVID-19 pandemic, the initial findings were positive.[104] Among the seven patients with available data, coramitug improved GLS and did not lead to any serious treatment-related adverse events.[105] Coramitug is currently under evaluation in a phase II trial.[106] NI301A, another monoclonal antibody under development, targets a specific linear epitope on misfolded TTR proteins and ATTR deposits.[107] This epitope, known as WEPFA, is exposed only on misfolded TTR, making NI301A highly specific for amyloid aggregates.[107] NI301A is currently being evaluated in a phase I clinical trial in patients with ATTR-related cardiomyopathy, focusing on both safety and efficacy.[108] Preclinical research has also introduced Ab-A, a human IgG1 monoclonal antibody with high affinity for aggregated TTR. Ab-A has demonstrated the ability to significantly reduce ATTR aggregates through antibody-dependent phagocytosis in murine models of ATTRwt amyloidosis. Additionally, it has shown similar amyloid-clearing effects in human heart tissue samples from patients with ATTRwt.[109]

Conclusions

Recent advances in the diagnosis and treatment of CA have significantly improved patient outcomes, offering new hope in managing this once-challenging disease. Diagnostic innovations, particularly the development of advanced imaging modalities like PET with radiotracers targeting amyloid deposits and the application of AI, might prompt an early and non-invasive identification of both AL and ATTR subtypes of amyloidosis. This early detection is critical for guiding timely and appropriate therapy, which can slow disease progression and improve survival. Moreover, emerging therapies for both AL and ATTR amyloidosis, ranging from monoclonal antibodies to gene silencing and gene editing technologies, represent a paradigm shift in treatment strategies. These therapies not only target the underlying causes of amyloid deposition but also show promise in reversing existing organ damage.

Besides disease-modifying therapies, for decades, it has been advocated that traditional neurohormonal

antagonism therapies for heart failure should be discontinued or avoided in CA due to presumed intolerance and lack of efficacy.[2] However, recent studies have shown that these treatments are not only tolerated by most CA patients[110] but also have a pathophysiological rationale for their use,[111] as well as clear prognostic benefits,[112] at least in subsets of CA patients.[113] Furthermore, observational studies indicate that sodium-glucose cotransporter-2 inhibitors, now a standard of care for heart failure patients across the entire ejection fraction spectrum, may also offer prognostic benefits in CA patients, despite their exclusion from trials in heart failure.[114]

Ongoing research and clinical trials will be crucial in refining the best therapeutic approaches for CA, integrating both disease-modifying therapies and heart failure treatments. Ultimately, improving the prognosis for individuals affected by this life-threatening condition.

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