Aktuelle Entwicklungen bei Transthyretin-Amyloidose mit Kardiomyopathie (ATTR-CM)

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PATHOPHYSIOLOGIE, KLINISCHE PHENOTYPEN & BIOMARKER

Transthyretin serum levels and clinical outcomes in patients with transthyretin amyloid cardiomyopathy

Minervini A, Barge-Caballero G, López-López A. et al.; *European Journal of Internal Medicine* (29. July 2025)

Purpose: To study the prognostic value of serum transthyretin levels in patients with transthyretin amyloid cardiomyopathy (ATTR-CM).

Methods: We analysed the clinical information collected in a prospective registry of consecutive patients with ATTR-CM treated in 7 Spanish hospitals from January 1st, 2018 to October 31st, 2024. Baseline serum transthyretin was correlated by means of multivariable Cox´s regression with long-term clinical outcomes death from any cause and the combined endpoint death from any cause or heart failure (HF) hospitalization.

Results: We studied 216 patients with ATTR-CM who were followed over a median period of 835 days. Baseline transthyretin serum levels correlated with older age and with several markers of more advanced cardiac disease, including higher NYHA class and UK-NAC stage, as well as with poorer nutritional status, according to CONUT score. Multivariable Cox´s regression revealed a statistically significant, independent association between increasing values of serum transthyretin and lower risk of death from any cause (adjusted HR per 1 mg/dl = 0.954; 95 % CI 0.921–0.989) and lower risk of the combined endpoint death from any cause or HF hospitalization (adjusted HR per 1 mg/dl = 0.967; 95 % CI 0.936–0.999). Serum transthyretin showed incremental predictive value for both study outcomes in addition to the UK-NAC staging system.

Conclusions: Our study suggests that serum transthyretin is an independent prognostic factor in patients with ATTR-CM.

Zur Publikation

Unravelling the myriad physiologic roles of transthyretin: critical considerations for treating transthyretin amyloidosis

Gertz MA, Aras MA, Bart N, et al.; *Ann Med.* (27. July 2025)

Background: Transthyretin (TTR) is a highly conserved protein with crucial and broadly protective physiologic roles across organ systems and diseases. Evidence shows that TTR contributes to neuroprotection, cognition, glucose regulation, pregnancy, muscle development, and bone mineralization. In several disease states, including diabetes, Alzheimer's disease, Lewy body dementia, cerebrovascular disease, and osteoporosis, higher TTR levels may be protective. Numerous studies have shown that low levels of TTR are associated with increased mortality overall and in relation to cardiovascular disease and several malignancies.

Zur Übersicht

Purpose: There is a growing portfolio of approved and investigational transthyretin amyloidosis (ATTR) treatments that differ in their mechanisms and effects on circulating TTR. When selecting an ATTR therapy, clinicians must decide whether to stabilize and preserve TTR and its functions or knockdown and drastically reduce TTR. This review summarizes the vital physiologic roles of TTR in health and disease. We consider the potential effects on normal biologic pathways that may occur while therapeutically suppressing TTR and discuss clinical decisions concerning ATTR therapies in the context of the summarized literature.

Discussion: TTR is essential for a broad range of physiologic processes and may confer clinically protective effects in neurologic and other organ systems. While a link between low TTR and severe disease and mortality is well established, it remains unclear whether long-term TTR suppression via ATTR therapies increases risk of disease. Clinical decisions in ATTR, however, should reflect the current understanding of the roles of TTR and the patient's clinical history.

Conclusion: TTR serves vital physiologic roles across organ systems. Given its clinically protective properties, continued investigation into the potential long-term impact of TTR suppression via knockdown or gene editing therapies is prudent. ATTR treatment selection should reflect an awareness of the physiologic importance of TTR, as well as consideration of the potential long-term impact of chronic TTR suppression.

Zur Publikation

Gamma-glutamyltransferase independently predicts mortality and heart failure hospitalization in cardiac transthyretin amyloidosis

Aimo A, Castiglione V, Tomasoni D, et al. *Eur J Intern Med.*
(11. June 2025)

Background: Transthyretin cardiac amyloidosis (ATTR-CA) is a leading cause of heart failure (HF). Although transthyretin is synthesized in the liver, overt liver disease is uncommon in ATTR-CA. We characterized hepatic involvement in patients with ATTR-CA, and identified the correlates and prognostic value of elevated gamma-glutamyl transferase (GGT), the most prominently deranged biomarker.

Methods: We examined 528 patients from four centers, using scintigraphy, cardiovascular magnetic resonance, and circulating biomarkers to assess liver function. The primary endpoint was all-cause mortality; secondary endpoints included HF hospitalization alone or combined with all-cause mortality.

Zur Übersicht

Results: The cohort comprised predominantly older men (86 % male; median age 81 years). Scintigraphy showed no abnormal hepatic uptake, but liver extracellular volume was elevated (median 0.69; clinically significant cutoff 0.40). Median GGT was 49 U/L, with 48 % exceeding sex-specific upper reference limits. By comparison, elevated aspartate and alanine transaminases, total bilirubin, and alkaline phosphatase were observed in 26 %, 9 %, 33 %, and 1 % of patients, respectively. Patients with GGT ≥82 U/L displayed indicators of more advanced cardiac disease, hepatic injury, and venous congestion. During a median follow-up of 2.6 years, 39 % died and 33 % were hospitalized for HF. In multivariable analysis, GGT remained predictive of all-cause mortality and HF hospitalization beyond the National Amyloidosis Centre score (hazard ratio [HR] 1.15, 95 % confidence interval [CI] 1.01–1.31; p = 0.045, and HR 1.17, 95 % CI 1.03–1.32; p = 0.016, respectively).

Conclusions: Elevated GGT is associated with greater disease severity and predicts worse outcomes in ATTR-CA. GGT measurement may improve risk stratification and guide treatment decision-making

Zur Publikation

Zur Übersicht

IMAGING & DIAGNOSTIK

Cardiac magnetic resonance imaging and cardiac scintigraphy in the diagnosis of cardiac amyloidosis: A meta-analysis of 4866 patients

Balata M, M Attia A, Gbreel MI, et al.; *J Mol Cell Cardiol Plus.*
(17. October 2025)

Introduction: Cardiac amyloidosis (CA) impacts about 20 % of elderly heart failure patients, leading to myocardial dysfunction and life-threatening risks. However, it often remains undetected due to the significant risks associated with invasive biopsies. This highlights the critical need for safer and accurate non-invasive diagnostic techniques.

Aim: To compare the diagnostic value of Cardiac Magnetic Resonance (CMR) imaging and Cardiac Scintigraphy Imaging in the diagnosis of CA.

Methods: A comprehensive literature search across PubMed, Scopus, Web of Science, and Cochrane databases yielded studies that utilized CMR or cardiac scintigraphy for diagnosing CA. QUADAS-2 was employed for quality assessment.

Results: From 7117 records, 35 studies involving 4866 patients were analyzed. Cardiac scintigraphy demonstrated higher sensitivity and specificity across different radiotracers, with 99mTc-HMDP showing the highest specificity (1.00, 95 % CI: 0.93–1.00) and 99mTc-DPD the highest sensitivity (0.93, 95 % CI: 0.89–0.95). CMR imaging showed variable diagnostic accuracy with a sensitivity of 0.83 (95 % CI: 0.81–0.85) and a lower specificity of only 0.53 (95 % CI: 0.50–0.56).

Conclusion: Cardiac scintigraphy, particularly with 99mTc-HMDP, offers superior diagnostic accuracy for CA compared to CMR imaging. Controlled, randomized, prospective studies directly comparing these non-invasive techniques are essential to validate these findings.

Zur Publikation

Prediction of Cardiac Transthyretin Amyloidosis: Electrocardiographic Parameters and the Ratio of Posterior Wall Thickness to the Minimum QRS Complex Voltage in Limb Leads

Gawor-Prokopczyk M, Lipowska M, Sioma A, et al.; *Biomedicines.*
(13. October 2025)

Background/Objectives: Several predictive models have been proposed to estimate the probability of cardiac transthyretin amyloidosis (ATTR-CA). The aim of our study was to evaluate the usefulness of electrocardiographic parameters, as well as parameters consisting of a combination of myocardial thickness and QRS voltage, as potential predictors of ATTR-CA.

Zur Übersicht

Methods: In 2018–2025, 285 consecutive patients with suspected cardiac amyloidosis were evaluated, including blood tests, standard 12-lead electrocardiography, transthoracic echocardiography, and [99mTc]Tc-DPD scintigraphy.

Results: The ratio of posterior wall thickness to minimum QRS voltage in limb leads (PWT/minQRS ratio) as well as several ECG-derived parameters were independent predictors of ATTR-CA. In a comparison of ROC curves, PWT/minQRS ratio exceeded both the minimum and maximum voltage of QRS complexes in limb leads, demonstrated similar predictive value to TCAS and T-amylo scores, and had similar or superior predictive characteristics to posterior wall thickness. A cut-off of >3.3 for PWT/minQRS ratio was as accurate as the published cut-offs for TCAS score ≥6, T-amylo score ≥7, and posterior wall thickness ≥14 mm. In the subgroup of patients with myocardial thickness of at least 15 mm, PWT/minQRS ratio >3.3 was superior to posterior wall thickness ≥14 mm and T-amylo score ≥7 and had similar predictive value for ATTR-CA as TCAS score ≥6.

Conclusions: In a cohort of undifferentiated patients referred for [99mTc]Tc-DPD scintigraphy due to suspected cardiac amyloidosis, PWT/minQRS ratio showed strong predictive value for ATTR-CA, which was even more pronounced in the subgroup of patients with increased myocardial thickness.

Zur Publikation

Zur Übersicht

THERAPIE – Leitlinien, Metaanalysen & systematische Reviews

Transthyretin Cardiac Amyloidosis Evaluation and Management: 2025 ACC Concise Clinical Guidance

Kittleson M, Ambardekar A. et al.; *JACC* (31. October 2025)

Transthyretin amyloid cardiomyopathy has emerged as an increasingly recognized cause of heart failure, particularly in older individuals. There is now greater awareness of transthyretin amyloid cardiomyopathy as an underlying etiology of heart failure, particularly in individuals with musculoskeletal manifestations such as bilateral carpal tunnel syndrome or spinal stenosis. There have also been substantial advances in diagnosis, including the ability to perform accurate noninvasive diagnosis using radionuclide scintigraphy in individuals with a negative monoclonal protein screen. Finally, individuals with transthyretin amyloid cardiomyopathy have benefitted from advances in broadly effective heart failure therapies, namely mineralocorticoid receptor antagonists and sodium glucose-cotransporter 2 inhibitors, as well as specific disease-modifying therapies with transthyretin stabilizers, tafamidis and acoramidis, and the transthyretin silencer vutrisiran. The purpose of this Concise Clinical Guidance is to offer updated strategies to clinicians, reflecting the expanding therapeutic landscape, and reinforcing best practices for the diagnosis and management of transthyretin amyloid cardiomyopathy with a focus on choice of disease-modifying therapies, heart failure therapies, and future directions.

Zur Publikation

Monitoring Disease Progression in Patients With Transthyretin Amyloid Cardiomyopathy

García-Pavía, P, Witteles, R, Damy, T. et al. *J Am Coll Cardiol HF*.(2. December 2025)

Recognizing the lack of disease monitoring recommendations in transthyretin amyloid cardiomyopathy (ATTR-CM), international experts convened in 2021 to propose criteria for monitoring disease progression. Data have since been published demonstrating the prognostic value of certain parameters in ATTR-CM. Additionally, increased awareness and advances in diagnostic methods have led to a shift toward diagnosis at earlier stages of disease. In light of these developments, international experts with experience in treating ATTR-CM reviewed the available data, considered the feasibility of implementing evaluations in clinical practice, and proposed an update to the 2021 criteria. The criteria, with meaningful thresholds and monitoring frequency recommendations, are specifically designed to measure disease progression in patients with ATTR-CM, rather than to define progression of amyloid deposition. It remains unknown whether disease progression is an indicator for modifications to ATTR-CM treatment. Future studies should investigate whether changes in ATTR-CM disease-modifying treatment improve outcomes in patients demonstrating disease progression.

Zur Publikation

Zur Übersicht

Contextualizing the results of HELIOS-B in the broader landscape of clinical trials for the treatment of transthyretin cardiac amyloidosis

Girard AA, Sperry BW. *Heart Fail Rev.* (1. October 2025)

This focused review will highlight the results of HELIOS-B, the first randomized outcomes trial evaluating a gene silencing treatment for transthyretin cardiac amyloidosis (ATTR-CM). In HELIOS-B, vutrisiran was tested against placebo and demonstrated a 28% reduction in the composite of all-cause mortality and recurrent cardiovascular events. Additionally, there were clinically significant benefits on the 6-min walk test, Kansas City Cardiomyopathy Questionnaire, and NYHA class. Discontinuation rates and adverse events were similar between treatment and control arms, suggesting that vutrisiran is well tolerated. In this review, these promising results are explored and compared with other treatment trials in ATTR-CM.

Zur Publikation

Advances in Cardiovascular Pharmacotherapy. V. Molecular Targets in Transthyretin Amyloid Cardiomyopathy

Pagel PS, Hang D, Freed JK, Crystal GJ. *J Cardiothorac Vasc Anesth* (06. August 2025)

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an infiltrative disease that occurs when the tetrameric transthyretin complex dissociates into its constituent monomers, which then misfold, aggregate, and accumulate as amyloid fibrils in the myocardial extracellular matrix. The amyloid deposits thicken and stiffen the myocardium, interfering with cardiac function and leading to the development of heart failure. Chronic exposure to cytotoxic circulating amyloid precursors contributes to further myocardial damage. Once considered rare, ATTR-CM is now recognized as the most common form of cardiac amyloidosis, occurring in variant and wild types. Amyloid formation in variant ATTR-CM results from an inherited, defective transthyretin gene that causes an amino acid substitution, which renders the protein more vulnerable to instability, dissociation, and monomer misfolding. Wild type ATTR-CM originates from a normal gene and occurs primarily in the elderly. A comprehensive understanding of the molecular basis of ATTR-CM has led to the development of 3 new classes of drugs that stabilize transthyretin, silence its genetic expression, or act to degrade amyloid fibrils within the myocardium. These groundbreaking advances are transforming ATTR-CM from debilitating, uniformly fatal disease to a manageable chronic condition with extended life-expectancy and preserved quality of life. This review discusses the pathophysiology of ATTR-CM, reviews the clinical trials demonstrating the efficacy of drugs that stabilize transthyretin or silence its expression, describes the preliminary use of monoclonal antibodies to degrade amyloid fibrils and reverse the disease's structural and functional consequences, and lastly, comments on the potential anesthetic implications of these new disease-modifying therapies.

Zur Publikation

Zur Übersicht

THERAPIE – STABILIZER

Differential Binding Affinities and Kinetics of Transthyretin Stabilizers

Ji AX, Betz A, Sinha U. *J Cardiovasc Pharmacol*. (5. June 2025)

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, fatal disease. Dissociation of tetrameric transthyretin (TTR) is the triggering event in the pathogenic mechanism; destabilizing TTR mutations accelerate the process. The TTR stabilizers, tafamidis and acoramidis, are the only United States Food and Drug Administration (FDA) approved treatments for patients with ATTR-CM. By mimicking the stabilizing characteristics of the super-stabilizing, disease-protecting variant T119M, we hypothesize that acoramidis displays differential TTR binding, kinetic stability, and tetramer stabilization compared with other TTR stabilizers, such as tafamidis and diflunisal. The TTR binding affinity and thermodynamic stability of TTR interaction of acoramidis and tafamidis were assessed by surface plasmon resonance and microscale thermophoresis (MST). Tetrameric TTR stabilization by acoramidis, tafamidis, and diflunisal in the presence of plasma proteins against acidic denaturation was measured by immune blots. In kinetic studies, surface plasmon resonance demonstrated 4 times longer residence time for acoramidis bound to TTR than tafamidis. The dissociation constants were consistent with those determined by equilibrium measurements in MST. The affinity of acoramidis for purified TTR, as measured by MST, was 4 times higher than that of tafamidis. When tested at clinically relevant plasma concentrations, acoramidis stabilized TTR against acidic denaturation to a much higher extent (≥90%) than tafamidis or diflunisal. Of note, both tafamidis and diflunisal demonstrated partial stabilization of tetrameric TTR. Relative to other stabilizers, acoramidis is more potent as independently assessed by TTR binding affinity, kinetic stability, and acid-mediated denaturation. These properties may contribute to the ability of acoramidis to achieve near-complete stabilization of TTR in plasma samples.

Zur Publikation

Zur Übersicht

THERAPIE – STABILIZER
Acoramidis

Efficacy of Acoramidis in Wild-Type and Variant Transthyretin Amyloid Cardiomyopathy: Results From ATTRibute-CM and Its Open-Label Extension

Alexander KM, Davis MK, Akinbobye O. et al.; *JAMA Cardiol.* (08. November 2025)

Importance: Transthyretin amyloid cardiomyopathy (ATTR-CM), a progressive disease caused by misfolded transthyretin (TTR), occurs as wild-type (ATTRwt-CM) or variant (ATTRv-CM) forms. p.Val142Ile is the most common variant in the US, linked to rapid progression and increased mortality. Acoramidis achieves near-complete (90%) TTR stabilization and showed clinical benefit in the 30-month ATTRibute-CM trial and through month 42 in the ongoing open-label extension (OLE). OBJECTIVE To evaluate the efficacy of acoramidis in ATTRwt-CM, ATTRv-CM, and variant subgroups (p.Val142Ile and non-p.Val142Ile).

Design, Setting and Participants: This international, multicenter, phase 3, randomized placebo-controlled study took place from April 2019 to May 2023 with ongoing OLE (month 42). ATTRibute-CM enrolled 632 participants with ATTR-CM; 611 of 632 were included in the modified intention-to-treat (mITT) population. There were 380 participants who continued into the OLE. These data were analyzed from January 2025 to July 2025.

Interventions: Oral acoramidis, 712 mg, or placebo twice daily for 30 months, followed by 12 months of open-label treatment.

Main outcomes and measures: All-cause mortality (ACM), cardiovascular-related hospitalizations (CVH), serum TTR, 6-minute walk distance, Kansas City Cardiomyopathy Questionnaire Overall Summary score, and N-terminal pro B-type natriuretic peptide in participants with ATTRwt-CM and ATTRv-CM. Post-hoc analyses were conducted in variant subgroups, including p.Val142Ile.

Results: Overall, 552 participants with wild-type ATTR-CM (mean [SD] age, 78 [6.3] years; 92.0% male and 8.0% female) and 59 participants with variant ATTR-CM (mean [SD] age, 73 [7.7] years; 77.3% male and 22.7% female) were randomized (mITT population), including 35 with p.Val142Ile. Consistent efficacy was observed in wild-type and variant subgroups for ACM/CVH through month 30 and ACM through month 42. At month 30, acoramidis reduced the risk of ACM/first CVH vs placebo by 31% in ATTRwt-CM (hazard ratio [HR], 0.69; 95% CI, 0.52-0.90; P = .007) and by 59% in ATTRv-CM (HR, 0.41; 95% CI, 0.21-0.81; P = .01). ACM was reduced through month 42 with HRs of 0.70 (95% CI, 0.50-0.98; P = .04) and 0.41 (95% CI, 0.19-0.93; P = .03) in the ATTRwt-CM and ATTRv-CM groups, respectively. Consistent treatment benefit was observed in participants with ATTRwt-CM and ATTRv-CM for secondary end points. Within variant subgroups (p.Val142Ile vs non-p.Val142Ile), consistent treatment benefits were observed for ACM/CVH through month 30 and ACM through month 42.

Zur Übersicht

Conclusion and relevance: The beneficial effect of acoramidis was observed consistently in ATTRwt-CM and ATTRv-CM groups. These hypothesis-generating results indicate that further studies are warranted to better characterize the therapeutic benefit of acoramidis in variant subgroups.

Zur Publikation

Effect of Acoramidis on Recurrent and Cumulative Cardiovascular Outcomes in ATTR-CM: Exploratory Analysis From ATTRibute-CM

Masri A, Judge D, Ruberg F. et al. *JACC*. (28. October 2025)

Background: Transthyretin (TTR) amyloid cardiomyopathy (ATTR-CM) is a progressive disease with a significant burden of recurrent cardiovascular (CV) events. Acoramidis, an approved oral therapy for ATTR-CM, achieves early, nearcomplete (90%) TTR stabilization. In the phase 3 ATTRibute-CM (Efficacy and Safety of Acoramidis in Participants with Transthyretin Amyloid Cardiomyopathy) study, acoramidis significantly reduced the composite of all-cause mortality or first CV-related hospitalization (CVH), with an effect observed at month 3*. Its efficacy on the burden of cumulative CV outcome events has not been reported.

Objectives: This study was a post hoc exploratory recurrent-event analysis of the efficacy of acoramidis on the cumulative incidence of CV outcomes from ATTRibute-CM and its open-label extension.

Methods: Cumulative incidences of centrally adjudicated CV-related mortality (CVM) or recurrent CVH (first and, if applicable, subsequent CVH), recurrent CVH alone (month 30), and CVM (month 42) were measured in the modified intention-to-treat population (acoramidis, n = 409; placebo, n = 202). Mean cumulative events by treatment, and the difference between treatment groups were estimated by using a modified Andersen-Gill model.

Results: Acoramidis significantly reduced the cumulative risk of CVM or recurrent CVH through month 30 vs placebo (HR: 0.51; 95% CI: 0.43-0.62; P < 0.0001). A notable proportion of CV outcome events (19% of CVM or recurrent CVH events, 22% of CVH) occurred within the first 6 months. Numerically fewer cumulative events were observed with acoramidis compared with placebo at month 1, and the difference increased progressively, resulting at month 30 in 53 events avoided per 100 treated participants (95% CI: 29-79). At month 42, CVM was reduced with continuous acoramidis vs placebo-to-acoramidis (HR: 0.55; 95% CI: 0.39-0.79; P = 0.0011). The annualized frequency of recurrent CVH was significantly decreased through month 30 (relative risk ratio: 0.50; 95% CI: 0.35-0.69; P < 0.0001).

*"Das Ergebnis war hauptsächlich auf die ersten kardiovaskulären Hospitalisierungen zurückzuführen. Nach Monat 3 gingen die Kurven weiter auseinander und wiesen zu Monat 30 einen signifikanten Unterschied zwischen Acoramidis und Placebo auf."

Zur Übersicht

Conclusions: Acoramidis significantly reduced the cumulative burden of CV outcomes in ATTR-CM over 30 months. Numerically fewer eventswere observed with acoramidis vs placebo by month 1, and the difference increased progressively over time, resulting in 53 events avoided per 100 treated patients at month 30. Almost one-fourth of the cumulative CV events occurred within the first 6 months. These exploratory findings suggest that cumulative event burden may occur early, highlighting the importance of timely evaluation, diagnosis and treatment in ATTR-CM.

Zur Publikation

Zur Übersicht

THERAPIE – STABILIZER
Tafamidis

CMR-based assessment of long-term effects of tafamidis in patients with cardiac transthyretin amyloidosis

Zlibut A, Bietenbeck M, Akyol N. et al.; *Clin Res Cardiol* (27. October 2025)

Objectives and background: The aim of the study was to evaluate the long-term effects of tafamidis on cardiac disease progression beyond 12 months of treatment by performing (among others) serial multi-parametric cardiovascular magnetic resonance (CMR) studies in patients with transthyretin (ATTR) cardiac amyloidosis (CA) cardiomyopathy (ATTR-CM).

Methods: Patients with confirmed ATTR-CM (N=56) were divided into two groups: in the larger group A (N=39; 95% male), treatment with tafamidis 61 mg once daily was initiated after the first CMR study, whereas group B (N=17; 76% male) comprised ATTR-CM patients who did not receive tafamidis. The observational follow-up period lasted 27±6 months. During this period, patients underwent two multi-parametric CMR studies at our institution as part of a routine clinical observation pipeline.

Results: Clinical symptoms assessed by the NYHA class showed a slight, however, significant increase in both groups. NT-proBNP levels substantially increased in both groups at follow-up, however, with a significantly higher increase in the tafamidis-naïve group B ($p=0.014$). LV systolic function, defined by LV-EF and 3D global longitudinal peak strain, significantly worsened in both groups at follow-up (54% to 48% $p<0.001$ vs 56% to 46%, $p<0.001$; −7.4 to −5.3, $p<0.001$ vs −8.8 to −4.8, $p<0.001$). However, the tafamidis-naïve group B experienced a substantially higher impairment of both parameters when compared to group A ($\Delta p=0.008$ and $\Delta p=0.003$, respectively). LV wall thickness considerably increased in both groups at follow-up, however, with a significantly higher increase in the tafamidis-naïve group B (from 18.2 mm to 21.1 mm at follow-up, $p<0.001$) compared to the tafamidis-treated group A (from 18.5 mm to 19.2 mm, $p=0.012$; $\Delta p<0.001$). Both global native T1 and global ECV values were significantly elevated in both groups—at baseline and at follow-up—with a significant increase in both groups during follow-up. However, a substantially higher increase in global ECV was observed in the tafamidis-naïve group B compared to the tafamidis-treated group A (group A: 51% to 57%, $p<0.001$; group B: 50% to 67%, $p<0.001$; $\Delta p<0.001$).

Conclusion: Substantial worsening of clinical symptoms, serum biomarkers, and imaging parameters occurred in both tafamidis-treated and tafamidis-naïve ATTR-CM patients within a follow-up period of approximately 2 years. However, the “extent of worsening” is significantly lower in the tafamidis-treated compared to the tafamidis-naïve patients.

Zur Publikation

Zur Übersicht

THERAPIE – RNA-Interferenz (RNAi)-basierte Therapie Vutisiran

Efficacy and safety of vutrisiran in transthyretin amyloid cardiomyopathy across the age spectrum: The HELIOS-B trial

Sheikh A, Miao ZM, Claggett B, et al.; *Eur J Heart Fail* (29. October 2025)

Aims: Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive condition primarily affecting older adults, who are at increased risk of morbidity and mortality. In HELIOS-B, vutrisiran reduced all-cause mortality and recurrent cardiovascular events versus placebo in patients with ATTR-CM. This prespecified analysis evaluated efficacy and safety outcomes by age category (<75, 75 to <80, and ≥80 years) and across age as a continuous measure.

Methods and results: HELIOS-B randomized patients with ATTR-CM in a 1:1 ratio to vutrisiran 25 mg or placebo every 12 weeks for up to 36 months. Eligible patients were aged 18–85 years. We assessed the primary composite of all-cause mortality and recurrent cardiovascular events, changes in 6-min walk test (6MWT) and Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OSS), and safety outcomes across age groups. Among 654 patients (aged 45–85 years; mean 75.3 ± 6.7), 257 (39.3%) were <75, 201 (30.7%) 75 to <80, and 196 (30.0%) ≥80 years. Vutrisiran reduced the risk of the primary composite outcome in all age categories (pinteraction = 0.56) and across the age spectrum as a continuous function (pinteraction = 0.50). Consistent benefits were seen for individual outcome components, with no significant interaction between treatment and age. Functional capacity and quality of life were preserved across age groups (pinteraction = 0.35 and = 1.00 for KCCQ-OSS and 6MWT, respectively). Safety was comparable across groups, with no increase in adverse events in older patients.

Conclusions: Vutrisiran reduced all-cause mortality and cardiovascular events and maintained function and quality of life in patients with ATTR-CM across the age spectrum, including those ≥80 years.

Zur Publikation

Zur Übersicht

THERAPIE – RNA-Interferenz (RNAi)-basierte Therapie Patisiran

Impact of patisiran on polyneuropathy of hereditary transthyretin amyloidosis in patients with a V122I or T60A variant: a phase IV multicenter study

Hussain Y, Malhotra S, Sperry BW, et al.; *Ann Med*. (20. September 2025)

Background: This study assessed the effectiveness and safety of patisiran in patients with V122I/T60A variant transthyretin (ATTRv) amyloidosis with polyneuropathy. These variants have been under-represented in previous trials of gene-silencing agents.

Methods: This was a multicenter, phase IV study conducted at 27 sites in the USA. Patients were ≥ 18 years, diagnosed with ATTRv amyloidosis with polyneuropathy and a documented V122I or T60A variant. Patisiran-treated patients were enrolled prospectively, ambispectively, and retrospectively. The primary endpoint was the proportion of patients with a stable or improved polyneuropathy disability (PND) score at 12 months vs. baseline. Safety was monitored throughout the trial.

Results: Sixty-seven patients were enrolled, of whom 58 received ≥ 1 dose of patisiran. In the efficacy population, 42/45 (93.3%) patients demonstrated stable or improved PND scores from baseline to Month 12. Patients also showed stable or improved quality of life, health status, autonomic symptoms, and cardiac function vs. baseline. Adverse events occurred in 13/42 (31.0%) patients in the prospective and ambispective cohorts; most were mild or moderate. No deaths or cardiac hospitalizations were considered related to patisiran.

Conclusions: Patisiran demonstrated a consistent positive effect across multiple endpoints in patients with V122I/T60A ATTRv amyloidosis, including polyneuropathy manifestations.

Zur Publikation

Zur Übersicht

KOMORBIDITÄTEN & UNSPEZIFISCHE THERAPIE
Arrhthmien & Elektrophysiologie

Atrial Fibrillation in Transthyretin Amyloid Cardiac Atrial Cardiomyopathy: Mechanisms, Prevalence, and Clinical Implications

Kantharia BK, Hulsurkar MM, Heijman J et. al.; *Am J Cardiol.*
(15. November 2025)

Cardiac amyloidosis, characterized by myocardial deposition of amyloid fibrils, is a significant cause of restrictive cardiomyopathy, leading to heart failure and a spectrum of cardiac arrhythmias including premature ventricular complexes (PVCs), ventricular tachycardia/fibrillation (VT/VF), atrial tachycardia (AT), atrial flutter/fibrillation (AFL/AF) and atrioventricular (AV) conduction blocks.

Zur Publikation

Atrial Fibrillation Burden, Risk Factors, and Prognosis in Wild-type Transthyretin Amyloidosis Cardiomyopathy

Skov JK, Ladefoged B, Pedersen ALD et. al.; *Am J Cardiol.*
(01. November 2025)

Atrial fibrillation (AF) is common in patients with wild-type transthyretin amyloidosis (ATTRwt), yet data on incident AF following diagnosis, associated risk factors, and its prognostic impact remain limited. In this single-centre cohort study conducted at Aarhus University Hospital, we examined the incidence of new-onset AF, identified clinical predictors, and explored the association between AF and all-cause mortality in patients with ATTRwt diagnosed between 2016 and 2022. Among 208 patients, AF was present at diagnosis in 56%, and the cumulative incidence of new-onset AF in the remaining patients reached 45% (95% CI: 32% to 56%) at three years after diagnosis. Multivariable Cox regression identified body mass index (HR 1.13, 95% CI 1.04 to 1.23), higher National Amyloidosis Centre stage (HR 1.93, 95% CI 1.14 to 3.27), and left ventricular mass index per 10-unit increase (HR 1.06, 95% CI 1.01 to 1.12) as significant risk factors of new-onset AF. A clinical history of AF at the time of ATTRwt diagnosis seemed to be associated with increased all-cause mortality, but did not reach statistical significance (HR 1.74, 95% CI 0.96 to 3.16, p = 0.07). In conclusion, AF is highly prevalent at diagnosis and frequently develops after diagnosis in patients with ATTRwt, with body mass index, National Amyloidosis Centre stage, and increasing left ventricular mass index emerging as risk factors for new-onset AF. Having AF is likely associated with adverse prognostic implications warranting further investigation.

Zur Publikation

Zur Übersicht

KOMORBIDITÄTEN & UNSPEZIFISCHE THERAPIE
Zentrales Nervensystem

Central nervous system involvement in cardiac amyloidosis: Redefining the heart-brain axis

Giamundo DM, Cassataro G, Ministrini S, Stämpfli SF.; *Eur J Clin Invest.* (23. September 2025)

Background: Amyloidosis is characterised by the extracellular accumulation of misfolded proteins forming amorphous aggregates called amyloid. Cardiac amyloidosis results from myocardial involvement in systemic amyloidosis, leading to impaired heart function. Besides myocardial involvement, cardiac amyloidosis may also directly and indirectly affect the central nervous system.

Methods: This narrative review summarises current evidence about on central nervous system involvement in cardiac amyloidosis and the pathophysiological mechanisms linking heart and brain in the context of this systemic disease.

Results: Although the pathophysiological relationship between cardiac amyloidosis and cognitive decline remains poorly understood, central nervous system involvement likely results from the complex interplay of direct amyloid deposition, cerebrovascular changes, and cardiac dysfunction.

Conclusion: The growing awareness of cognitive impairment in patients with cardiac amyloidosis highlights the need for further research and supports a multidisciplinary approach in the assessment and management of affected individuals.

Zur Publikation

Peripheral Neuropathy in p.Val142Ile (Val122Ile) Variant Hereditary Transthyretin-Mediated Amyloidosis

Zhang VJW, O'Donnell LF, Skorupinska M, et al.; *Neurol Genet.* (23. September 2025)

Background and Objectives: p.Val142Ile (p.V142I) is one of the most common pathogenic transthyretin (TTR) variants typically presents as transthyretin amyloid cardiomyopathy (ATTRv-CM), although frequent concurrent peripheral nerve involvement has been reported (94%). We aimed to characterize the polyneuropathy in p.V142I ATTR amyloidosis (ATTRv-PN) from the UK amyloidosis cohort.

Methods: We performed a retrospective cohort study of all confirmed p.V142I Variant Transthyretin Amyloidosis (ATTRv) individuals in the National Hospital for Neurology and Neurosurgery Inherited Neuropathy Clinic between January 2019 and October 2024. Because presence of ATTRv-PN was required to access disease-modifying therapy for amyloidosis during this time, all individuals with p.V142I ATTRv were evaluated for neuropathy, providing an unselected cohort.

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Results: We identified 52 individuals with p.V142I ATTRv among whom the clinical presentation was cardiac in 47 (90%) and neuropathic in 5 (10%). Age at diagnosis was 71.3 ± 12.2 years. Twenty of the 52 individuals (38%) had symptoms suggestive of neuropathy with an average duration of symptoms of 4.9 ± 3.5 years 20/52 (38%) had signs suggestive of neuropathy with average Neuropathy Impairment Score being 9.0 ± 10.5. After investigations, 21/52 (40%) individuals had clinical features, neurophysiology, and/or skin biopsies consistent with ATTRv-PN (8 large-fiber/13 small-fiber). Six of the 52 individuals (12%) had neuropathies because of alternative etiologies (e.g., diabetes).

Discussion: Real-world experience from the UK national cohort of p.V142I ATTRv indicates that peripheral neuropathy is of a mild severity and less frequent than previously reported.

Zur Publikation

KOMORBIDITÄTEN & UNSPEZIFISCHE THERAPIE
SGLT2-Inhibitoren

Impact of sodium- glucose co-transporter 2 inhibitors in mortality and Decongestion in cardiac amyloidosis: A systematic review and meta-analysis

Santo C, Romero C, Vaz Kerges Bueno B, et al.; *Curr Probl Cardiol.* (18. June 2025)

Background:While Sodium glucose Co-transporter 2 inhibitors (SGLT2i) show proven benefits in heart failure with preserved ejection fraction (HFpEF), their role in transthyretin cardiac amyloidosis (ATTR-CA) remains uncertain. This meta-analysis evaluates SGLT2i efficacy and safety specifically in ATTR-CA patients, a population excluded from pivotal trials.

Materials and Methods: Following PRISMA guidelines, we systematically searched PubMed/Embase/Cochrane through December 2024 for studies assessing SGLT2i in cardiac amyloidosis. Primary outcomes included all-cause mortality, cardiovascular mortality, NT-proBNP levels, and hospitalizations. Risk Ratios (RR) and Hazard Ratios (HR) with 95 % confidence intervals (CIs) were used to compare treatment effects for categorical endpoints. Continuous outcomes were compared with mean differences (MD).

Results: Five observational studies (5101 patients; 2528 SGLT2i vs 2573 controls) met inclusion criteria. SGLT2i use was associated with significantly lower all-cause mortality (RR 0.37, 95 % CI 0.28-0.49, $p < 0.00001$, I^2=12 %) and cardiovascular mortality (RR 0.30, 0.16-0.55, $p < 0.00001$, I^2=25 %). NT-proBNP levels were significantly reduced (MD -299.66 pg/mL, -493.24 to -106.08, $p = 0.002$, I^2=0 %) and hospitalization rates were significantly lower (HR 0,59, 95 %CI 0,38-0,90; $p = 0,01$, I2=0 %). Most studies had moderate bias risk, primarily from retrospective designs and selection bias.

Conclusions: In ATTR-CA patients, SGLT2i were associated with 63-70 % relative risk reduction in mortality and improved cardiac biomarkers and hospitalization rates. While promising, these observational findings require confirmation in randomized trials to address potential confounding factors.

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