

REVIEW ARTICLE

Not so rare after all: Rethinking hereditary transthyretin amyloidosis

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Abstract

Introduction: Hereditary transthyretin amyloidosis (ATTRv) is a progressive multi-systemic disorder caused by extracellular deposits of misfolded transthyretin (TTR) protein. Presenting as cardiomyopathy, polyneuropathy, or mixed phenotypes, ATTRv exhibits high clinical heterogeneity, often causing diagnostic delays.

Objective: This narrative review provides an updated overview of emerging epidemiological and registry insights, genotype–phenotype correlations, current diagnostic modalities, and evolving individualized therapies for ATTRv, emphasizing the clinical relevance of early identification.

Methods: A literature search was conducted across medical databases to identify recent studies evaluating the clinical characteristics, diagnostic approaches, and therapeutic outcomes of ATTRv. Data from multinational registries, including the Transthyretin Amyloidosis Outcomes Survey, were examined to assess phenotypic variability across geographical regions and genotypes.

Results: ATTRv presents with early- or late-onset phenotypes, the latter often showing advanced neurological and cardiac involvement at diagnosis, with Val30Met remaining the most prevalent global variant. Early recognition of clinical “red flags” and the use of bone scintigraphy facilitate prompt diagnosis, which is crucial for the timely initiation of disease-modifying therapies—including TTR stabilizers (e.g., tafamidis) and second-generation gene silencers—to suppress disease progression, improve survival, and reduce adverse cardiovascular events.

Conclusion: Therapeutic strategies for ATTRv have advanced remarkably, rendering a historically fatal condition increasingly manageable. Emerging studies demonstrate that this condition is not as rare as commonly believed. Given its systemic nature, a coordinated, multidisciplinary approach remains crucial for screening and long-term patient care.

Keywords: Transthyretin amyloidosis; Hereditary transthyretin amyloidosis cardiomyopathy; Hereditary amyloidosis; Tafamidis; Gene silencers; Early diagnosis; Disease-modifying therapy

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1. Introduction

Hereditary transthyretin amyloidosis (ATTRv) is an autosomal dominant inherited disorder caused by pathogenic variants in the *TTR* gene. These variants destabilize the

native homotetrameric TTR protein synthesized by the liver, accelerating its dissociation into misfolded monomers that aggregate into insoluble extracellular amyloid fibrils.¹ These fibrils progressively deposit in various organs, predominantly affecting the peripheral nervous system, myocardium, gastrointestinal tract, kidneys, and eyes. To date, more than 140 pathogenic mutations have been reported, with the Val30Met (p.Val50Met) substitution being the most widespread genotype globally.²⁻⁴

Historically, ATTRv was considered an extremely rare disease isolated to traditional endemic pockets in Portugal, Sweden, and Japan.^{5,6} In these regions, a positive family history and classic clinical signs facilitated early suspicion. Conversely, in non-endemic areas, the absence of a known family history and overlapping presentations with other cardiovascular or neurological conditions frequently led to prolonged diagnostic delays or misdiagnoses. Over the last decade, the clinical paradigm has evolved. The implementation of non-invasive diagnostic tools and expanding genetic screening have revealed that ATTRv is more distributed than previously recognized, prompting a re-evaluation of its true prevalence and phenotypic diversity.⁷

This review synthesizes recent registry data and clinical cohorts to contrast ATTRv and wild-type ATTR (ATTRwt) profiles, analyze shifting epidemiological trends, evaluate the utility of genetic testing across clinical contexts, and outline contemporary diagnostic and therapeutic algorithms.

2. Methodology

A literature search was conducted to identify relevant peer-reviewed articles, systematic reviews, and registry analyses focusing on ATTRv published between January 2020 and April 2026. Search terms included: hereditary transthyretin amyloidosis, ATTRv, transthyretin (*TTR*) gene mutations, genetic testing, epidemiology, and prevalence.

To ensure high-quality evidence, the selection prioritized original research and multi-center registry data, specifically from the Transthyretin Amyloidosis Outcomes Survey (THAOS), the Healthcare European Amyloidosis Registry (HEAR), and the Transthyretin Cardiac Amyloidosis Registry of São Paulo (REACT-SP).

Exclusion criteria were applied to mitigate bias and limit lower-tier evidence: case reports involving single patients, editorials, non-English publications, studies restricted to pediatric cohorts, and *in vitro* or animal models were excluded. Crucially, when evaluating prevalence and clinical recommendations, we interpreted data from preliminary conference abstracts or registry-based reports

with appropriate caution, distinguishing them from full, peer-reviewed clinical trials. A final selection of 57 publications informed this review.

3. Comparative clinical profiles: Hereditary transthyretin amyloidosis vs. wild-type transthyretin amyloidosis

3.1. Demographic disparities and diagnostic delay

Hereditary transthyretin amyloidosis exhibits distinct demographic patterns compared to ATTRwt. While ATTRwt is almost exclusively a disease of elderly males, ATTRv often presents earlier, though its onset is highly dependent on the specific mutation and geographical region. Data from the Brazilian REACT-SP registry highlight that many ATTRv patients present at a younger age but experience a protracted delay from symptom onset to definitive diagnosis.⁸ Similarly, the global THAOS registry reports a mean age of symptom onset of 56.6 years among symptomatic ATTRv carriers, illustrating a younger demographic profile than typically seen in ATTRwt.² However, in certain cohorts, such as those evaluated in the HEAR registry, specific variants like Val122Ile present much later in life, mimicking ATTRwt demographics, though ATTRv patients still tend to be diagnosed slightly younger (78 ± 9 years vs. 83 ± 7 years, $p < 0.001$).^{9,10} Clinical characteristics and phenotypic differences between ATTRv and ATTRwt are presented in [Figure 1](#).

3.2. Phenotypic diversity and organ involvement

The clinical spectrum of ATTRv is remarkably heterogeneous, characterized by neurological, cardiac, or mixed phenotypes. This contrasts sharply with ATTRwt, which presents predominantly as an isolated cardiomyopathy. Registry data underline these differences: in the REACT-SP cohort, cardiac involvement was documented in 43.9% of ATTRv patients compared to 89.9% of ATTRwt patients ($p < 0.001$), whereas a neurological phenotype was significantly more prevalent in the hereditary cohort (56.8% vs. 31.7%, $p < 0.001$). A mixed phenotype involving both systems was observed in approximately one-fourth (25.6%) of ATTRv individuals.^{8,11}

Genotype plays a dominant role in steering this phenotype.¹² For instance, the Val30Met mutation exhibits geographical divergence: in classic endemic regions, it presents as an early-onset, severe polyneuropathy, whereas in non-endemic areas, it often manifests as a late-onset form where conduction abnormalities predominate, and cardiac involvement can affect over 20% of patients.^{13,14}

3.3. Genotype-specific manifestations

Certain mutations are strongly linked to specific organ

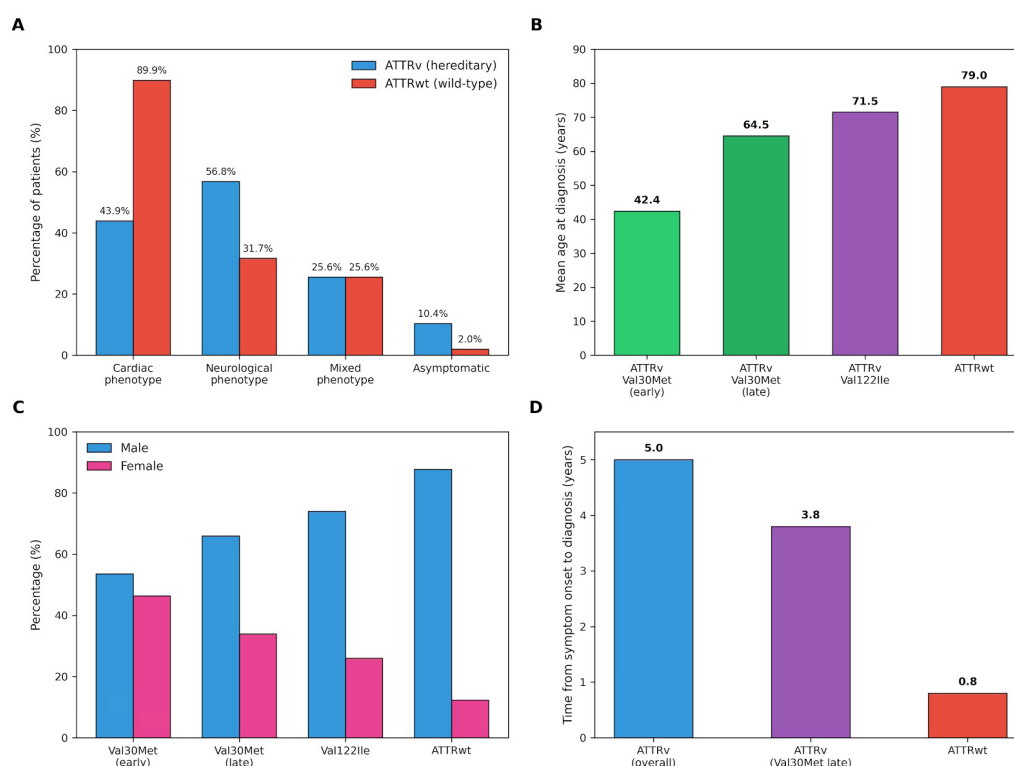


Figure 1. Comparison of clinical characteristics between hereditary (ATTRv) and wild-type (ATTRwt) transthyretin amyloidosis. (A) Phenotype distribution in ATTRv and ATTRwt. The majority of patients with ATTRv show neurological involvement, whereas patients with ATTRwt show predominantly cardiac involvement. (B) Age at diagnosis by genotype. Val30Met patients have the earliest symptom onset, whereas later onset is observed in other genotypes and in ATTRwt. (C) Gender distribution by genotype. The majority of patients are males, and the gender imbalance is more pronounced in later onset and in ATTRwt. (D) Diagnostic delay by genotype. Delay to diagnosis is longer in hereditary than in ATTRwt. Data derived from the Transthyretin Cardiac Amyloidosis Registry of São Paulo, Transthyretin Amyloidosis Outcomes Survey, and the Healthcare European Amyloidosis Registry. Data derived from previous studies.⁸⁻¹²

damage, though pure phenotypes are rare:

- (i) Val122Ile (p.Val142Ile): Primarily recognized as a cardiotropic variant associated with significant interventricular septal thickness and markedly elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. However, emerging registry data suggest that neurological assessments can reveal concurrent neuropathy in a substantial proportion of these patients, challenging the assumption of isolated cardiac disease.^{15,16}
- (ii) Late-onset Val30Met and L58H (p.Leu78His): Often display severe neurological impairment at presentation. In a THAOS analysis, late-onset Val30Met patients exhibited higher median neuropathy impairment scores in the lower limbs (DNS_IL of 25.0) than early-onset patients (DNS_IL of 8.0), frequently accompanied by atypical electrophysiological features that complicate early-stage diagnosis.^{10,17}
- (iii) Extracardiac red flags: Carpal tunnel syndrome (frequently bilateral) is a common early manifestation

across multiple genotypes, appearing in 58% to 97% of certain cohorts, alongside autonomic dysfunction (e.g., gastrointestinal disturbances, orthostatic hypotension).¹⁵

Red flags aiding in the clinical suspicion of ATTRv and the diagnostic delays following their onset are illustrated in Figure 2.

4. Epidemiology and global distribution

4.1. Endemic foci and founder effects

While ATTRv is distributed globally, localized founder effects maintain exceptionally high prevalence rates in specific regions:

- (i) The Balearic Islands (Spain): Mallorca and Menorca represent major global foci for the Val30Met variant, with estimated genetic prevalences of 1 in 2,900 and 1 in 4,700, respectively. Screenings indicate that a significant majority of these carriers also harbor a baseline G6S polymorphism on the same

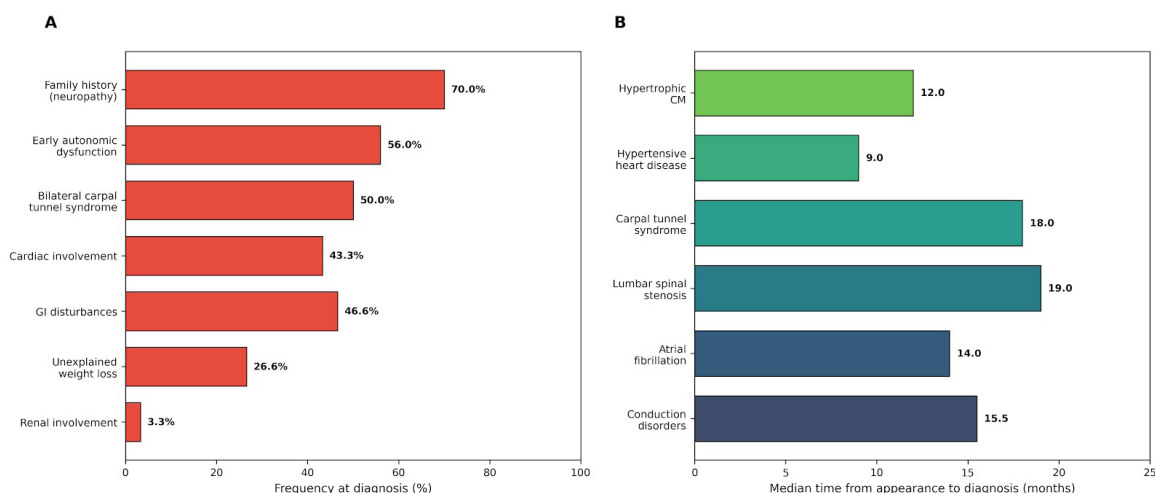


Figure 2. Red flags for hereditary transthyretin amyloidosis (ATTRv) diagnosis and diagnostic delays. The figure shows data from patients with adult-onset symptoms from non-endemic areas of Spain (A) and from Japan (B). Delay in diagnosis, especially for those extracardiac manifestations. Data derived from previous studies.^{2,16,18-23}

chromosome, confirming a distinct regional founder effect.¹⁸

- (ii) Bulgaria: Targeted screening programs over a seven-year period identified a clustering of the Glu89Gln mutation, which represents over 78% of detected carriers in the country.^{24,25}
- (iii) Spain (Mainland): A large nationwide retrospective study identified distinct high-prevalence clusters for pathogenic variants in regions such as Cádiz, Castellón, Ciudad Real, Huelva, Valencia, and Zamora.^{19,20}

- (iv) China: The Ala97Ser (p.Ala117Ser) variant exhibits a prominent founder effect in Southern Mainland China, typically presenting as a late-onset polyneuropathy.²¹ The Gly103Arg mutation is similarly unique to populations of Chinese ancestry.²²

Worldwide genetic variability and estimated prevalence of ATTRv—including the global predominance of Val30Met and the distinct clustering of Val142Ile in African Americans—are illustrated in Figure 3.

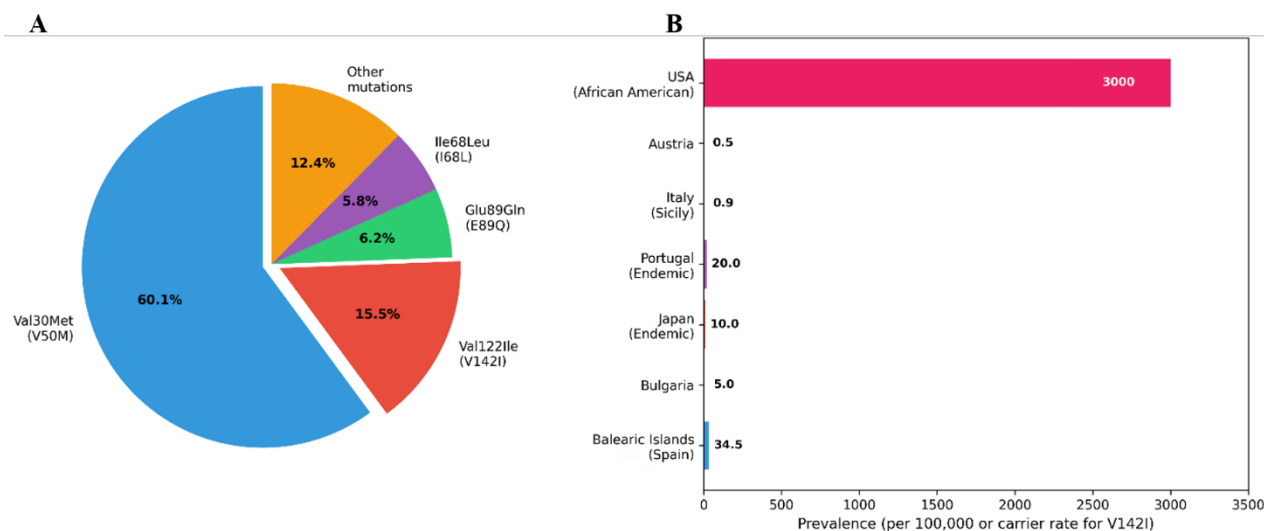


Figure 3. Global distribution of *TTR* mutations and prevalence estimates. (A) Distribution of major *TTR* mutations in hereditary transthyretin amyloidosis worldwide (THAOS registry). The most common mutation worldwide remains Val30Met. (B) Estimated prevalence and carrier frequency by geographic region. Variability between populations is considerable. The exceptionally high carrier frequency for Val142Ile in the African American population is noteworthy. Data derived from previous studies.^{6,26-28}

4.2. Interpretation of prevalence and screening data

Recent large-scale genomic sequencing and population health surveys suggest that the carrier frequency of certain *TTR* variants may be higher than historical clinical diagnoses implied. However, these data require cautious interpretation: the presence of a genetic variant does not automatically equate to clinical disease, as the penetrance of many mutations remains incomplete or age-dependent.

For example, a comprehensive genomic screen of over 134,000 individuals identified pathogenic or likely pathogenic *TTR* variants in 0.12% of the cohort, yet only a minimal fraction had a formal clinical diagnosis of amyloidosis recorded in their electronic health files.²⁹ Among carriers over the age of 60 within this genomic cohort, approximately 14% exhibited structural heart disease (septal thickness >12 mm), though most remained

undiagnosed with amyloidosis.²⁹

Similarly, in the United States, the Val122Ile variant is found in 3% to 4% of individuals of African ancestry, making it a key genetic consideration in African American patients presenting with unexplained cardiomyopathy.^{30,31}

Despite these high carrier frequencies, systematic or unselected general screening remains unsupported. For instance, the CATCH study, which screened an unselected elderly population, identified wild-type ATTR cardiomyopathy in 0.34–0.46% of subjects but found no *TTR* mutations, indicating that routine genetic screening is inefficient outside of clinically suspicious or high-risk populations.²⁶

As detailed in [Table 1](#), epidemiological data across diverse cohorts indicate a higher prevalence of ATTRv than previously estimated in historical literature.

Table 1. Prevalence of hereditary transthyretin amyloidosis in various screening studies and populations

Population/Study	Ref.	Sample size	Hereditary transthyretin amyloidosis prevalence/detection	Most common mutation
Japanese (Biobank Japan)	6	7,949	0.75% carriers	Asp119Asn
Greek left ventricular hypertrophy population	9	294	8.5% of hereditary transthyretin amyloidosis cardiomyopathy	Various
Hispanic/Latino (Hispanic Community Health Study/Study of Latinos)	16	12,687	0.8% carriers	Val122Ile
TRAM study (Germany/Austria/Switzerland)	23	5,141	1.1%	Various (21 variants)
African American bilateral carpal tunnel syndrome	28	16	12.5%	Val122Ile
Italian elderly cardiac hereditary transthyretin amyloidosis (>70 years)	32	52	19%	Val30Met, Ile68Leu, Val142Ile, Phe84Leu
DISCOVERY (US cardiac amyloidosis suspects)	33	1,001	7.4%	Val122Ile

5. Genetic testing strategies and cascade screening

5.1. Late-onset presentations and the elderly

A key clinical misconception is that ATTR in patients over 70 or 80 years of age is invariably the wild-type form. Although ATTRwt is far more prevalent in this demographic, small cohort studies have revealed that a meaningful proportion of elderly individuals diagnosed

with ATTR cardiomyopathy actually harbor pathogenic *TTR* mutations.^{23,27,30–32,34} Consequently, current guidelines recommend genetic sequencing for all patients diagnosed with ATTR, regardless of age at presentation. Identifying a hereditary variant in an elderly patient is clinically consequential, as it alters the therapeutic options and carries profound implications for younger relatives. The clinical yield of genetic testing across diverse populations and age groups is presented in [Figure 4](#).

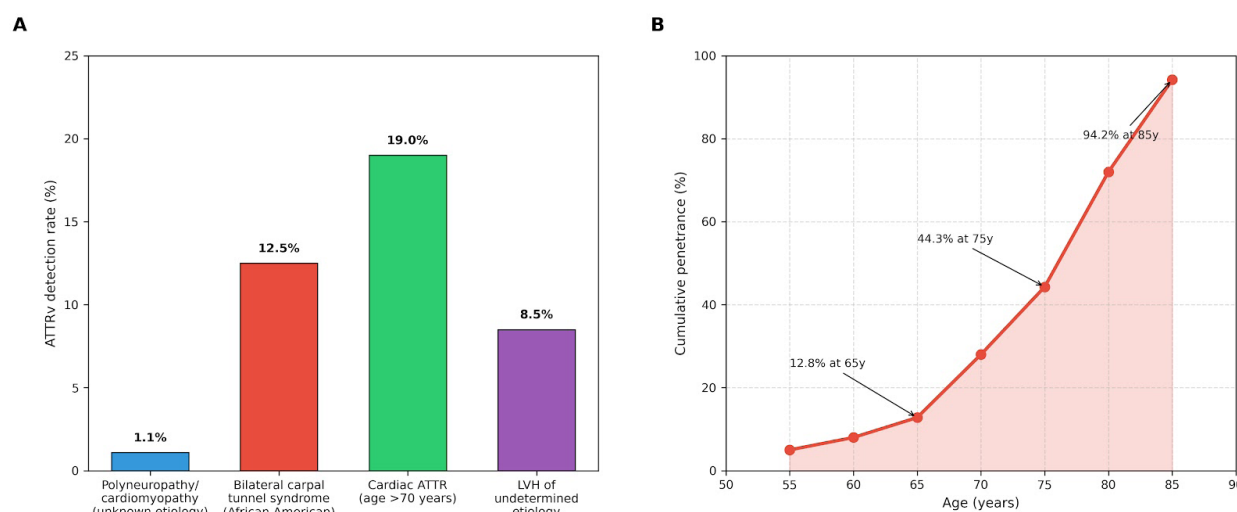


Figure 4. Importance of genetic testing across ages and populations. (A) Hereditary transthyretin amyloidosis (ATTRv) detection rates in various high-risk populations, demonstrating that genetic testing reveals substantial hereditary disease even in elderly cardiac amyloidosis patients. (B) Age-related penetrance of the Val142Ile variant in a Spanish cohort, showing a progressive increase with age that supports screening at any age to identify at-risk individuals before symptom onset. Data derived from previous studies.^{4,35-40}

5.2. Family counseling and presymptomatic monitoring

Once an index case (proband) is identified with a pathogenic *TTR* variant, family cascade screening should be initiated in conjunction with genetic counseling.⁴¹ Asymptomatic gene carriers possess a prognosis identical to the general population until amyloid deposition begins.¹² Therefore, early identification aims to establish a structured monitoring protocol to detect the earliest transition from asymptomatic carrier status to subclinical or clinical disease.

Longitudinal tracking of asymptomatic carriers indicates that clinical manifestations develop progressively over time.⁴² Monitoring strategies require a multifaceted approach, as isolated tests may lack sensitivity:

- Neurological assessment:** While nerve conduction studies are standard, they can remain completely normal in the early phases of small-fiber neuropathy. Advanced subclinical tracking may necessitate quantitative sensory testing or autonomic evaluations.⁴²
- Cardiac evaluation:** Serial electrocardiograms, biomarker monitoring (NT-proBNP, troponins), and advanced echocardiography (including longitudinal strain imaging) are employed to detect early myocardial changes before overt heart failure develops.^{42,43}

5.3. Screening within high-risk cohorts

Targeted genetic testing within specific symptomatic

populations has demonstrated variable but notable detection rates:

- Unexplained neuropathy/cardiomyopathy:** The TRAM study, which screened over 5,100 patients with neuropathy or cardiomyopathy of unknown etiology, identified pathogenic *TTR* variants in 1.1% of cases.⁷
- Suspected cardiac amyloidosis:** In the United States-based DISCOVERY study, which evaluated patients undergoing clinical workups for suspected cardiac amyloidosis, a pathogenic mutation was found in 8% of the cohort, with Val122Ile being highly prevalent among Black patients.³³
- Bilateral carpal tunnel syndrome:** Preliminary pilot data in specific demographic cohorts (e.g., African Americans with bilateral carpal tunnel syndrome) reported carrier frequencies up to 12.5%, though these small sample sizes require validation in larger peer-reviewed cohorts before broad screening recommendations can be formulated.²⁸

6. Contemporary diagnostic and therapeutic advances

6.1. Diagnostic algorithm

The diagnostic framework for ATTR cardiomyopathy has been transformed by non-invasive pathways, primarily driven by technetium-labeled bone scintigraphy. When combined with the rigorous exclusion of monoclonal gammopathies (via serum/urine immunofixation and free light chain assays), a Grade 2 or 3 myocardial

radiotracer uptake provides a definitive diagnosis of ATTR cardiomyopathy without requiring an endomyocardial biopsy.

Once ATTR amyloidosis is confirmed via imaging or histology, genetic sequencing of the *TTR* gene is mandatory to definitively differentiate between ATTRwt and ATTRv. Complementary imaging modalities, such as cardiac magnetic resonance utilizing T1 mapping and extracellular volume quantification, offer high diagnostic accuracy and help characterize the total myocardial amyloid burden.^{44–46}

6.2. Disease-modifying therapies

The management of ATTRv has transitioned from supportive care to target-specific, disease-modifying interventions that interrupt the amyloid cascade at different stages.

6.2.1. Transthyretin stabilizers

Tafamidis binds to the thyroxine-binding sites of the TTR tetramer, preventing its dissociation into amyloidogenic monomers. Real-world registry data and clinical trials have demonstrated that tafamidis significantly reduces all-cause mortality and heart failure-related hospitalizations in patients with ATTR cardiomyopathy, including hereditary variants such as Val122Ile.^{35,36,47} Long-term tracking shows a clear correlation between earlier drug initiation and enhanced survival outcomes.

In symptomatic ATTRv Val122Ile patients ($n = 513$), tafamidis treatment was associated with improved survival at 48 months, with women treated with tafamidis demonstrating significantly better survival than men (hazard ratio for all-cause mortality 0.452 [95% confidence interval (CI): 0.332–0.614] vs. 0.767 [95% CI: 0.356–0.877], $p = 0.02$).⁴⁸ In the ATTR-ACT trial, tafamidis (80 mg or 20 mg pooled) significantly shifted health status toward improvement; among 441 patients, more patients taking tafamidis were alive and not worse at month 30 (37% vs. 15%), with improvements in Kansas City Cardiomyopathy Questionnaire Overall Summary scores (odds ratio for 10-point improvement 2.4; 95% CI: 1.6–3.4; $p < 0.001$).³⁷

6.2.2. Gene silencers (RNA interference and antisense oligonucleotides)

These agents target hepatic TTR synthesis by degrading *TTR* mRNA, thereby lowering circulating serum TTR levels:

- (i) Patisiran and vutrisiran: RNA interference therapeutics. In the multi-center “PatisiranItaly” observational study, approximately 70% of

ATTRv patients with polyneuropathy experienced stabilization or improvement in neurologic impairment, demonstrating efficacy across varying degrees of baseline severity.³⁶ Second-generation agents like vutrisiran offer comparable therapeutic suppression with less frequent subcutaneous dosing.

- (ii) Inotersen and eplontersen: Antisense oligonucleotides that similarly suppress TTR production and have demonstrated efficacy in halting the progression of hereditary polyneuropathy.³⁸

In a meta-analysis of patisiran for ATTRv polyneuropathy including 11 studies with 503 patients, the pooled responsiveness rate was 88% (95% CI: 81%–94%), with standardized mean differences in modified Neuropathy Impairment Score plus 7 tests of -0.18 (95% CI: -0.32 to -0.03 , $p = 0.018$) and Norfolk Quality of Life–Diabetic Neuropathy of -0.21 (95% CI: -0.35 to -0.08 , $p = 0.002$); adverse events occurred in 84.8% of patients (mostly mild to moderate), serious adverse events in 32.4%, and 7.6% mortality, with no deaths attributed to patisiran.³⁹ In a real-world French study of 50 ATTRv patients with cardiomyopathy who switched from or added RNA interference therapy to tafamidis monotherapy, 76% were stable on tafamidis alone, while after adding/switching to RNA interference (patisiran or vutrisiran), 90% remained stable, none worsened, and 10% improved over a mean follow-up of 3.8 ± 2.7 years on tafamidis and 2.5 ± 1.9 years on RNA interference.⁴⁰ For diphosphono-1,2-propanodicarboxylic acid scintigraphy in ATTRv Val30M mutation carriers ($n = 288$), the test presented suboptimal sensitivity (56.1%) and specificity (95.6%) with positive predictive value of 67.7% and negative predictive value of 92.9% for detecting amyloid cardiomyopathy; however, patients with abnormal cardiac diphosphono-1,2-propanodicarboxylic acid uptake had a 13-fold higher mortality risk (hazard ratio: 12.59; 95% CI: 4.56–34.72; $p < 0.001$), and prognostic value was additive with ventricular thickness, with 5-year mortality ranging from 39.9% to 53.3% in patients with septal thickening and/or abnormal diphosphono-1,2-propanodicarboxylic acid retention.⁴⁹

6.2.3. Gene silencing and CRISPR-Cas9 breakthroughs in hereditary transthyretin amyloidosis

Recent therapeutic developments in ATTRv have shifted the treatment paradigm from limited options—historically consisting of liver transplantation and TTR-stabilizers—to effective small interfering RNA and antisense oligonucleotide treatments targeting liver TTR mRNA, with patisiran (small interfering RNA) and inotersen (antisense oligonucleotide) now commercially

available and significantly improving ATTRv neurological outcomes, while ongoing clinical trials evaluate vutrisiran (small interfering RNA) and eplontersen (antisense oligonucleotide formulation), alongside a CRISPR-Cas9-based *TTR* gene editing treatment currently under evaluation with encouraging preliminary results.⁵⁰ NTLA-2001, an intravenous CRISPR-Cas9-based therapy delivered via lipid nanoparticle containing a guide RNA targeting *TTR* and mRNA encoding Cas9 protein, achieved greater than 97% knockdown of mouse *TTR* in preclinical studies, and in an early human trial of six participants, achieved 52% *TTR* reduction at a 0.1 mg/kg dose and 87% reduction at the lowest 0.3 mg/kg dose by day 28, with minimal adverse effects (50% reported transient adverse events, 83% showed transient elevated D-dimer levels that normalized within seven days, and liver function remained normal).⁵¹ In the first-in-human *in vivo* CRISPR/Cas9 trial (NTLA-2001) in patients with ATTR cardiomyopathy, 12 subjects received NTLA-2001 at doses of 0.7 or 1.0 mg/kg, achieving mean serum *TTR* reductions of >90% by day 28 and sustained through 4–6 months (New York Heart Association [NYHA] I/II at 0.7 mg/kg = 92%, at 1.0 mg/kg = 92%, and NYHA III at 0.7 mg/kg = 94%), with only two patients (16.7%) reporting transient infusion reactions and one grade 3 infusion-related reaction that resolved without sequelae.⁵²

6.2.4. Advanced gene editing and clinical trial outcomes in hereditary transthyretin amyloidosis polyneuropathy and cardiomyopathy

A phase 1 open-label study of nexiguran ziclumeran (nex-z), a CRISPR-Cas9-based *in vivo* therapy for ATTRv with polyneuropathy, administered as a single intravenous infusion to 36 patients with mean 27-month follow-up, achieved mean serum *TTR* reductions of ~90% at day 28 sustained through month 24 (~92%), with treatment-related adverse events including transient infusion-related reactions (in 21 patients), decreased thyroxine level without hypothyroidism (in 8), and headache (in 4). At month 24, familial amyloid polyneuropathy stage and polyneuropathy disability score remained stable in 29 and 27 patients, respectively, improved in 2 and 5 patients, respectively, and worsened in 2 and 2 patients, respectively, with a mean change in serum neurofilament light chain of -9.0 pg/mL and a mean modified Neuropathy Impairment Score + 7 change of -8.5.⁵³ In a phase 1 trial of nex-z for ATTR cardiomyopathy involving 36 patients (50% NYHA class III, 31% variant ATTR cardiomyopathy) with 12-month follow-up, mean serum *TTR* reduction was -89% (95% CI: -92 to -87) at 28 days and -90% (95% CI: -93 to -87)

at 12 months, with NT-proBNP geometric mean factor change of 1.02 (95% CI: 0.88 to 1.17) and high-sensitivity cardiac troponin T change of 0.95 (95% CI: 0.89 to 1.01) from baseline to month 12. Median 6-minute walk distance change was 5 m (interquartile range, -33 to 49), and 92% of patients had either improvement or no change in NYHA class, with transient infusion-related reactions in 5 patients and transient liver-enzyme elevations in 2 assessed as treatment-related.⁵⁴ The expanding therapeutic landscape for ATTR now includes first-generation therapies such as tafamidis with demonstrated survival benefits in ATTR cardiomyopathy, second-generation agents including the *TTR* stabilizer acoramidis, and RNA silencers such as vutrisiran and eplontersen showing promising efficacy in clinical trials. Additional strategies under investigation include gene editing and monoclonal antibodies targeting *TTR* amyloid deposits, with emphasis on the need for early detection and individualized treatment approaches to optimize clinical outcomes.⁵⁵

6.2.5. Combined and surgical approaches

Historically, orthotopic liver transplantation was the primary intervention to eliminate mutant *TTR* production in early-onset Val30Met patients. However, its utility is limited by donor availability and the ongoing risk of post-transplant wild-type *TTR* deposition on pre-existing cardiac amyloid templates. Recent systematic reviews suggest that post-orthotopic liver transplantation patients who exhibit disease progression may derive clinical benefit from the introduction of adjuvant disease-modifying therapies like *TTR* stabilizers or silencers.⁵⁶

6.3. Prognosis and survival outcomes

The integration of target therapies has shifted the natural history of ATTRv. In large observational cohorts, patients receiving disease-specific treatments (stabilizers, silencers, or transplantation) exhibited significantly superior survival compared to untreated historical controls.

Poorer prognostic indicators across all genotypes include an advanced NYHA functional class (II–IV), a reduced left ventricular ejection fraction, markedly elevated baseline NT-proBNP, and severe concurrent neurological deficits. Achieving an early, accurate diagnosis before these markers of advanced organ damage manifest remains the single most important factor in maximizing the therapeutic efficacy of modern disease-modifying agents.⁵⁷ Treatment outcomes and therapeutic efficacy in hereditary transthyretin amyloidosis, based on clinical trial and real-world registry data, are summarized in [Figure 5](#).

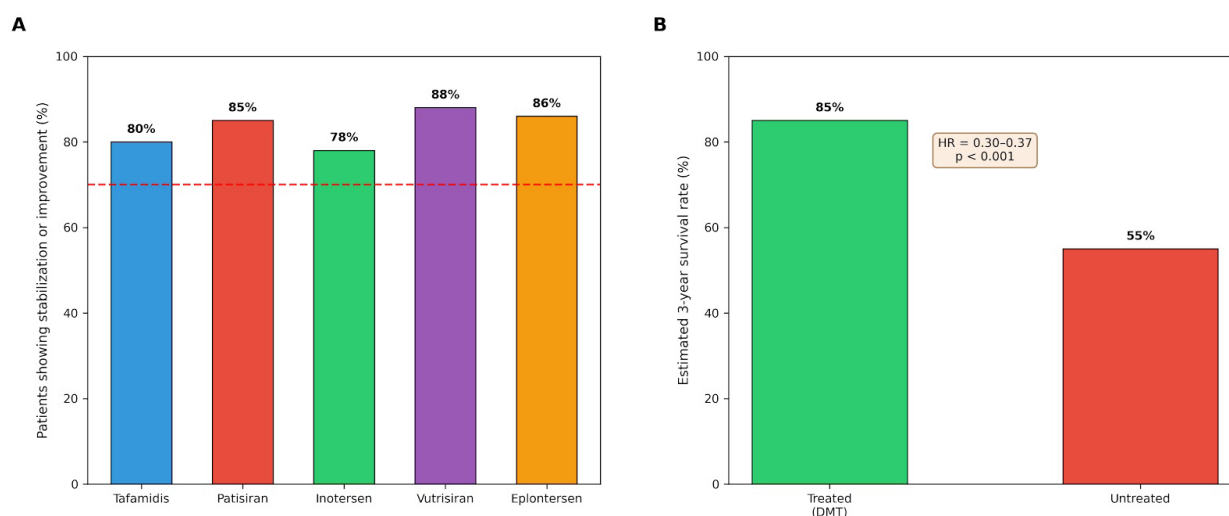


Figure 5. Treatment outcomes in hereditary transthyretin amyloidosis. (A) Disease-modifying therapy efficacy across different agents showing high rates of stabilization or improvement. (B) Impact of disease-modifying therapy on survival in patients with hereditary transthyretin amyloidosis cardiomyopathy, demonstrating substantial survival benefit with treatment. Data derived from clinical trials and real-world registry analyses. Data derived from previous studies.^{7,24,29,31,33,34}

7. Conclusion

Hereditary transthyretin amyloidosis has undergone a fundamental clinical paradigm shift over the past decade. Once considered a rare, untreatable, and invariably fatal geographical entity restricted to endemic pockets, emerging epidemiological data and multi-center registry insights demonstrate that ATTRv is far more prevalent and phenotypically diverse than previously recognized. Integrating non-invasive imaging algorithms with routine genetic sequencing has significantly improved diagnostic accuracy, uncovering substantial disease burdens even among elderly populations where wild-type ATTR was historically assumed. Heightened clinical awareness of systemic “red flags” (e.g., bilateral carpal tunnel syndrome, autonomic dysfunction, unexplained polyneuropathy, or hypertrophic cardiomyopathy) remains paramount to overcoming diagnostic delays and identifying affected patients at subclinical or early symptomatic stages.

Therapeutically, ATTRv management has evolved from purely palliative measures or orthotopic liver transplantation to a highly effective, target-specific armamentarium. TTR tetramer stabilizers (e.g., tafamidis) and second-generation gene silencers (RNA interference agents and antisense oligonucleotides) have established clear survival benefits, significantly slowing clinical progression and improving quality of life. Furthermore, groundbreaking advances in *in vivo* CRISPR-Cas9 gene editing offer the promising prospect of single-dose, lifelong disease suppression. Ultimately, because ATTRv

is a complex multisystemic condition, maximizing the efficacy of these novel disease-modifying therapies depends on early intervention. Achieving this goal requires a multidisciplinary collaborative network, widespread genetic cascade screening for at-risk family members, and structured longitudinal monitoring protocols to optimize long-term patient outcomes.

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Conflict of interest

The authors declare they have no competing interests.

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