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ORIGINAL ARTICLE

# Recommendations for treatment and follow-up in patients with transthyretin-mediated hereditary amyloidosis

## *Recomendaciones de tratamiento y seguimiento en pacientes con amiloidosis hereditaria mediada por transtirretina*

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## Abstract

**Introduction:** *Transthyretin-mediated hereditary amyloidosis is an autosomal dominant disease with progressive systemic involvement that affects the function of multiple organs and is associated with high morbidity and mortality. Patients present neurological, cardiac, autonomic, ophthalmological and renal involvement, among others, related to the patient's genotype. These alterations affect quality of life and are directly related to early mortality. Peripheral neuropathy is an early marker of the disease. Its identification allows early treatment with disease-modifying therapies aimed at stabilizing disease progression, which, along with adequate follow-up, has a positive impact on patients' quality of life and prolongs life expectancy.* **Objective:** *To structure a series of recommendations appropriate to the local setting on treatment and follow-up in patients with hereditary transthyretin-mediated amyloidosis.* **Materials and method:** *Delphi methodology was used, and a cut-off point of 75% favorability was established.* **Results and conclusions:** *A series of recommendations were presented based on the available evidence and international recommendations, applicable to the local setting, on diagnostic methods that facilitate early detection of the affected patient and the parameters for initiation of treatment and follow-up that improve the quality of life, decrease complications, and increase the life expectancy of these patients.*

***Keywords:*** *Hereditary amyloidosis. Transthyretin (TTR). Hypertrophic cardiomyopathy. Cardiology.*

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## Resumen

**Introducción:** *La amiloidosis hereditaria mediada por transtirretina es una enfermedad autosómica dominante, con compromiso sistémico y progresivo, que altera la función de múltiples órganos, y se asocia con una alta morbilidad y mortalidad. Se presenta compromiso neurológico, cardiaco, autonómico, oftalmológico y nefrológico, entre otros, que se relacionan con el genotipo del paciente. Estas alteraciones afectan la calidad de vida y tienen una relación directa con la mortalidad temprana en estos pacientes. La neuropatía periférica es un marcador temprano de la enfermedad. Su identificación permite un tratamiento temprano con terapias modificadoras de la enfermedad, en busca de la estabilización de la progresión de la enfermedad, lo cual, acompañado de un seguimiento adecuado, tiene un impacto positivo en la calidad de vida de los pacientes y una prolongación de la expectativa de vida.* **Objetivo:** *Estructurar una serie de recomendaciones adecuadas al entorno local sobre el tratamiento y seguimiento en pacientes con amiloidosis hereditaria mediada por transtirretina.* **Materiales y método:** *Se utilizó la metodología Delphi y se estableció como punto de corte un 75% de favorabilidad.* **Resultados y conclusiones:** *Se plantearon una serie de recomendaciones basadas en la evidencia disponible y las recomendaciones internacionales, aplicables al entorno local, sobre métodos diagnósticos que faciliten la detección temprana del paciente afectado y los parámetros de inicio del tratamiento y el seguimiento que mejoren la calidad de vida, disminuyan las complicaciones y aumenten la expectativa de vida de estos pacientes.*


***Palabras clave:*** *Amiloidosis hereditaria. Transtirretina (TTR). Miocardiopatía hipertrófica. Cardiología.*

## Introduction

Hereditary transthyretin-mediated (hATTR) amyloidosis is a rare, progressively debilitating and fatal disease caused by a pathogenic transthyretin (TTR) mutation[1-4]. It has a global prevalence of 5 to 10,000 cases worldwide, with endemic areas[5]. Approximately 150 TTR mutations or pathogenic deletions[6] have been reported to date, with genotype-phenotype variability and incomplete penetrance[7,8].

Genotypic characterization of the patients allows treatment and follow-up to be individualized, given its high phenotypic variability[9,10] and the association of certain mutations with specific phenotypes[11-13]. The most common mutation in the world is *p.Val50Met*, which occurs with endemic regional variations and is characterized by polyneuropathy with autonomic and ocular involvement[14,15]. On the other hand, patients with *p.Leu78His, p.Leu78Arg, p.Lys90Asn, p.Ile104Ser, p.Ile127Val* and *p.Tyr134His* variants have carpal tunnel syndrome as their first symptom[14], while those with *p.Asp38Asn, p.Val40Ile, p.Pro44Ser, p.Ala65Thr, p.Ala65Ser, p.His76Arg, p.Gly77Arg, p.Ile88Leu, p.Ala101Thr, p.Ala101Val, p.His108Arg, p.Glu112Lys, p.Arg123Ser, p.Leu131Met* and *p.Val142Ile* genotypes develop cardiomyopathy without peripheral neuropathy[14]. There is another subgroup of hATTR patients who present the following genotypic variations: *p.Leu32Pro, p.Asp38Gly, p.Ala45Thr, p.Val50Gly, p.Ala56Pro, p.Gly73Glu, p.Gly73Ala, p.Phe84Ser, p.Tyr89His* or *p.Tyr134Cys*[14], and these patients accumulate amyloid in the leptomeningeal membranes and blood vessels of the subarachnoid space.

Transthyretin is mainly synthesized in the liver, with less synthesis in the choroid plexuses and retinal pigment epithelium[8,16-18]. It circulates as a tetramer and is involved in vitamin A-retinol and thyroxin transport[19,20]. Transthyretin mutations result in an unstable protein which dissociates into monomers, misfolds and aggregates in amyloid fibrils[21,22] that accumulate in the extracellular space of organs and tissues[1,3]. Amyloid deposits cause organ damage with manifestations like bilateral sensory and motor polyneuropathy, autonomic dysfunction, infiltrative cardiomyopathy and cardiac dysautonomia[1,3,8,23-33].

The age of symptom onset varies; once instated, the disease progresses relatively rapidly in its neuropathic presentation[9], and, therefore, three to five years after symptoms begin, patients begin to need assistance for walking, and they can lose that function within five to ten years if not treated[9]. Death occurs approximately 4.7 years after diagnosis, and patients with heart disease have a life expectancy of 3.4 years[9].

Despite the genotypic-phenotypic variability reported in these patients, heart disease and polyneuropathy occur in most[12,34-36]. From a neurological perspective, patients with hATTR have mixed axonal polyneuropathy with sensory and motor symptoms[9], with peripheral neuropathy being an early marker of the disease. In some cases and genotypes, the neuropathy may be compressive, in which case carpal tunnel syndrome is the most common manifestation[9]. The symptoms derived from neurological complications include pain, paresthesia, difficulty walking, balance disorders and difficulty with fine motor movement in the hands. Some negative signs are related to loss of the sensory function, such as hypoalgesia and/or anesthesia to pain in the lower extremities, areflexia, apallesthesia in the feet and muscular weakness, such as bilateral foot drop[9]. From a cardiac perspective, the

patients have sympathetic and parasympathetic involvement with secondary cardiac dysautonomia[8,9], which manifests with orthostatic hypotension and heart rate variability (standard deviation of the R-R interval variability on a Holter monitor or electrocardiogram)[9,37,38]. Cardiomyopathy usually occurs in those over 50, with symptoms suggesting congestive heart failure, like dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, jugular distention, lower extremity edema, fatigue, abdominal distention, exertional tachycardia, syncope, low exercise tolerance or weight gain[9,39].

In addition, patients may develop intravitreal amyloid deposits with secondary eye problems, kidney dysfunction, weight loss, nausea and fatigue. All of these abnormalities secondary to amyloid deposits naturally have a negative impact on the quality of life[9].

Disease modifying therapies include TTR tetramer stabilizers, gene silencing therapies and antisense therapies[8,9,35,36,40-42]. There is evidence that these therapies halt disease progression and, in some cases, improve its clinical signs and symptoms[8,9]; therefore, early initiation of these therapies is vital, given the rapid progression associated with the disease.

Index case family testing is important, as it can identify presymptomatic patients, and thus provide them with adequate management and follow-up[43]. In addition, a multidisciplinary approach to these patients is essential for correct data interpretation, genetic counseling and specific disease management[43].

Likewise, patients should be followed after diagnosis to determine the course of the disease and response to treatment[8].

In summary, in light of the available evidence, multidisciplinary management of patients with amyloidosis, preceded by a prompt diagnosis with early treatment and adequate follow-up, are vitally important aspects.

This article proposes a series of locally adapted recommendations regarding diagnostic methods, parameters for beginning treatment, and follow-up in different areas of amyloidosis patient treatment, such as genetics, neurology, cardiology, ophthalmology and nephrology. Their implementation is expected to have a positive effect on the quality of life of these patients and reduce their morbidity and mortality.

## Materials and method

### Panel creation

A multidisciplinary panel of experts was selected, composed of 41 specialists in different fields of medicine (cardiology, pulmonology, physiatry, genetics, nephrology, ophthalmology, neurology and imaging). The experts were selected based on their knowledge and experience in managing hereditary transthyretin-mediated amyloidosis.

### Method description

Once the available evidence was reviewed by the experts in the previously mentioned specialties, they gathered to develop their proposed recommendations in each of these areas. All participants in the Position Statement meeting received the available bibliography on the disease and its treatment, including clinical practice guidelines.

An on-site meeting was held during which one or two experts from each area presented a summary of the concepts derived from the review of the literature on the disease, its diagnosis, treatment and follow-up. Then they presented the recommendations drafted for each area, and these were voted on. The Delphi method was used, with 75% favorability established as the cut-off. If this favorability threshold was not reached, the arguments in favor and against were presented by the panel of experts, the recommendation was restructured according to the discussion, and it was presented for a second vote. Once the recommendations were accepted, minor adjustments were made in their wording and content, based on the participants' opinions.

## Recommendations

### 1. The role of genetics in hATTR

#### Recommendation 1

The following studies are recommended for diagnosing hATTR[3,34]:

- Complete sequencing of the TTR gene to diagnose the index case
- Point mutation in the pedigree study

#### Recommendation 2

Molecular studies[8,44] are recommended for:

- Symptomatic patients
- Immediate relatives of the index case
  - Over the age of 18
  - Patients who state that they wish to have the test

  This point should be individualized for each case.

#### Recommendation 3

All patients should be referred to genetics for a family study and genetic counseling[44].

## 2. Neurological follow-up in symptomatic patients

### Recommendation 4

Treatment for hATTR[45,46] should be started when there is evidence of:

- Objective clinical and/or neurophysiological symptoms of polyneuropathy and/or pathological evidence of amyloid deposits
- Patients in stage I or II of the Polyneuropathy Disability (PND) scale[47]

### Recommendation 5

The following scales and clinical criteria are recommended to be included in patient follow-up[1,48-52]:

- The neuropathy scale in diabetic polyneuropathy (PND) to stage the disease. It should be applied every three to six months.
- These follow up scales are recommended: a) Neuropathy Impairment Score (NIS), b) Neuropathy Impairment Score in the Lower Limbs (NIS-LL), c) Neuropathy Impairment Score plus seven components (NIS+7) and d) the Norfolk Quality of Life (Norfolk-QOL) questionnaire, as follows:
  - Asymptomatic patients: every year
  - Symptomatic patients: every three to six months

Follow-up should be done by neurology and/or physiatry and/or a specialist with appropriate training in the disease.

### Recommendation 6

Neurophysiological follow-up is recommended[8]:

- With the following frequency:
  - Every 12 months for asymptomatic carriers
  - Every six to twelve months for symptomatic patients
- Including bilateral nerve conduction tests:
  - Motor (median, ulnar, peroneal and tibial)
  - Sensory (median, ulnar, sural and superficial peroneal)
  - F waves of the lower extremities
  - Sympathetic skin response (SSR) in the foot and hand.

### Recommendation 7

Disease progression should be considered in light of any of the following findings[48,49]:

- Worsening by at least one stage, measured qualitatively
- A more than 10-point increase on the NIS scale
- An increased PND score
- A decrease of more than 50% from the baseline amplitude of the composite motor and sensory score
- Absent sympathetic skin response in the foot and hand score, when it was previously present

## 3. Complementary tests in patients with hATTR and carpal tunnel syndrome

### Recommendation 8

In patients with hATTR and mild carpal tunnel syndrome, the following is recommended:

- Begin conservative treatment immediately, keeping in mind the clinical and paraclinical findings[23,24,53]
- Consider surgical management in severe or moderate cases that do not respond to conservative management

### Recommendation 9

In patients with hereditary transthyretin-mediated amyloidosis with carpal tunnel syndrome, the following are recommended:

- Electromyography and nerve conduction tests of the upper extremities[23,24,53] at baseline and every 6 to 12 months
- Clinical follow-up every 6 to 12 months, using questionnaires such as the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and Boston Questionnaire
- Neurophysiological follow-up every 6 to 12 months with electromyography and nerve conduction tests of the upper extremities

## 4. Complementary autonomic nervous system assessments in patients with hATTR

### Recommendation 10

We recommend:

- Clinical follow-up of autonomic symptoms using the Composite Autonomic Symptom Score-31 (COMPASS-31) at diagnosis and every six months[54,55]
- Paraclinical follow up with a tilt-table test and RR interval every 12 months, according to clinical judgement[9]

### Recommendation 11

Clinical follow-up of neuropathic symptoms is recommended with the Norfolk-QOL scale at diagnosis and every six months[9,56,57]

## Complementary tests

### Recommendation 12

– Quantitative sensory testing (QST) is recommended (when the technology is available) at the time of diagnosis[27,58-60]
– To evaluate progression (the onset of new sensory impairment), QST is recommended every 12 months (when the technology is available) for patients with hATTR with no previously documented sensory impairment[27,58,60]

## 5. Cardiology assessment in patients with hATTR

### Recommendation 13

The following clinical, paraclinical and imaging tests are recommended for cardiological assessment of patients with transthyretin-mediated amyloidosis to determine the disease's stage and prognosis[13] (every 6 to 12 months, depending on the tool used[61]):

– Clinical parameters: hospitalizations for heart failure, functional class (based on the New York Heart Association [NYHA] classification), six-minute walk test, functional tests, and quality of life (EQ-5D)
– Paraclinical tests: N-terminal pro-brain natriuretic peptide (NT-proBNP), electrocardiogram, troponin, NAC scale
– Imaging: transthoracic echocardiogram with global longitudinal strain

### Recommendation 14

Disease progression should be determined when any of the following parameters are present[62,63]:

– From a clinical or functional perspective:
  • The need to be hospitalized for heart failure
  • Functional class deterioration
  • Decreased scores on quality of life questionnaires (KCCQ/EQ-5D)
  • A 30 to 40-meter reduction in the six-minute walk
– From a biomarker perspective:
  • A 30% increase in natriuretic peptide, starting from the NT-proBNP cut-off point of 300 pg/ml
  • A 30% increase in troponin I
  • An advanced NAC stage
– From a cardiovascular imaging perspective[62,64-66]:
  • A 2 mm increase in wall thickness
  • Increased degree of diastolic dysfunction
  • A change in some of the echocardiographic parameters (> 5% reduction in LVEF, > 5% reduction in stroke volume, > 1% increase in global longitudinal strain)
  • EKG: onset of a new conduction disorder

## 6. Nephrological follow-up in patients with hATTR

### Recommendation 15

The following paraclinical tests should be ordered for the nephrological assessment of patients with or without transplant[67-70]:

– Baseline tests and at the beginning of treatment and for follow up (every 6 to 12 months):
  • Creatinine
  • Urinalysis
  • Albumin/creatinine ratio (if > 300 mg/g, order 24-hour protein)

### Recommendation 16

A nephrology assessment is recommended in patients with amyloidosis[9]:

– Before beginning treatment, to establish their baseline kidney status
– The frequency of the assessment should be based on the grade of renal involvement:
  • Grades 1 and 2: every 12 months
  • Grades 3A and 3B: every 3 to 6 months, depending on the stability
  • Grades 4 and 5: these patients have a high degree of progression to end stage renal disease, and therefore must adhere to the high-cost care coverage policies in Colombia, in the nephroprotection program, for follow-up and the paraclinical test panel stipulated by nephrology at a national level

### Recommendation 17

A kidney biopsy is recommended if the patient is a candidate for liver transplant, to determine if he/she requires a kidney transplant[67,71].

## 7. Ophthalmological treatment of patients with hATTR

### Recommendation 18

An ophthalmological exam is recommended at the following times[70,71]:

– When making the genetic diagnosis
– A biannual exam in asymptomatic carriers

– An annual exam in symptomatic patients

In addition, quarterly follow-up of retinal microangiopathy is recommended, along with biannual follow up of:

– Amyloid deposits in the iris
– Irregular pupils
– Chronic glaucoma
– Treated or monitored vitreous opacities

### *Recommendation 19*

Regarding patients' ophthalmological management, this should be divided according to symptomatology:

– Asymptomatic patients
  • Biannual follow-up
  • Look for symptoms
– Symptomatic patients
  • Monitor glaucoma
  • Use lubricants for dry eyes
  • Pay close attention to the onset of opacities and retinal changes
  • Use tacrolimus/cyclosporine

## Conclusions

Hereditary transthyretin-mediated amyloidosis is a rare, progressive and fatal disease that requires early diagnosis, appropriate treatment and close follow-up to improve patients' quality of life and reduce their morbidity and mortality. It is important to emphasize that patients with hATTR may have neurological involvement from the initial stages, although not always with the typical symptoms; therefore, it must be diagnosed promptly and treated appropriately.

The above recommendations are intended to be a guide for clinicians in diagnosing and following patients with hATTR, and they help monitor the disease and determine when to begin treatment and the follow-up needed by the different specialties to provide patients with comprehensive management.

## Glossary

– NAC Scale (United Kingdom National Amyloidosis Centre Staging System): An easily applied scale that requires knowing the level of NT-proBNP and glomerular filtration rate (GFR), with which patients are classified in three stages, and helps determine the mortality prognosis. Patients in NAC stage I (NT-proBNP less than 3,000 ng/L and GFR greater than 45 ml/min) have an average survival of 69.2 months; patients in NAC stage III (NT-proBNP greater than 3,000 ng/L and GFR less than 45 ml/min) have an average survival of 24.1 months, and patients in stage II (those who do not meet the criteria for stages I and III) have a survival of 46.7 months[72].
– NT-proBNP: N-terminal pro-brain natriuretic peptide.
– PND: polyneuropathy disability.

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## Conflicts of interest

Dr. Jennifer Garay has been a scientific advisor for PTC Therapeutics. Dr. Juan D. López-Ponce de León has been a scientific advisor for PTC Therapeutics, Pfizer and Sanofi. Dr. Maria Juliana Rodríguez has been a scientific advisor for PTC Therapeutics, Boehringer Ingelheim, Abbot, Pfizer, Sanofi and Novartis. The rest of the authors report no conflicts of interest.

## Ethical disclosures

**Human and animal protection.** The authors declare that no experiments were performed on humans or animals for this study.

**Data confidentiality.** The authors declare that no patient data appear in this article.

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## References

1. Adams D, Coelho T, Obici L, Merlini G, Mincheva Z, Suanprasert N, et al. Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. Neurology. 2015;85(8):675-82. doi:10.1212/WNL.0000000000001870.
2. Hanna M. Novel drugs targeting transthyretin amyloidosis. Curr Heart Fail Rep. 2014;11(1):50-7. doi:10.1007/s11897-013-0182-4.
3. Hawkins PN, Ando Y, Dispenzeri A, González-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. Ann Med. 2015;47(8):625-38. doi:10.3109/07853890.2015.1068949.
4. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. Nat Rev Neurol. 2019;15(7):387-404. doi:10.1038/s41582-019-0210-4.
5. Obi CA, Mostertz WC, Griffin JM, Judge DP. ATTR epidemiology, genetics, and prognostic factors. Methodist Debakey Cardiovasc J. 2022;18(2):17-26. doi:10.14797/mdcvj.1066.
6. Rowczenio DM, Noor I, Gillmore JD, Lachmann HJ, Whelan C, Hawkins PN, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat. 2014;35(9):E2403-12. https://onlinelibrary.wiley.com/doi/full/10.1002/humu.22619.
7. Rowczenio DM, Noor I, Gillmore JD, Lachmann HJ, Whelan C, Hawkins PN, et al. Online registry for mutations in hereditary amyloidosis including nomenclature recommendations. Hum Mutat. 2014;35(9). doi:10.1002/humu.22619.
8. Ando Y, Adams D, Benson MD, Berk J, Planté-Bordeneuve V, Coelho T, et al. Guidelines and new directions in the therapy and monitoring of ATTRv amyloidosis. Amyloid. 2022;0(0):1-13. https://doi.org/10.1080/13506129.2022.2052838.

9. Adams D, Algalarrondo V, Polydefkis M, Sarswat N, Slama MS, Nativi-Nicolau J. Expert opinion on monitoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. Orphanet J Rare Dis. 2021;16(1):411. https://doi.org/10.1186/s13023-021-01960-9.
10. Conceição I, Coelho T, Rapezzi C, Parman Y, Obici L, Galán L, et al. Assessment of patients with hereditary transthyretin amyloidosis – understanding the impact of management and disease progression. Amyloid. 2019;26(3):103-11. doi:10.1080/13506129.2019.1627312.
11. Conceição I, Coelho T, Rapezzi C, Parman Y, Obici L, Galán L, et al. Assessment of patients with hereditary transthyretin amyloidosis – understanding the impact of management and disease progression. Amyloid. 2019;26(3):103-11. https://doi.org/10.1080/13506129.2019.1627312.
12. Rapezzi C, Quarta CC, Obici L, Perfetto F, Longhi S, Salvi F, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an italian perspective. Eur Heart J. 2013;34(7):520-8. doi:10.1093/eurheartj/ehs123.
13. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM. Fontan M, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075. doi:10.1161/CIRCHEARTFAILURE.119.006075.
14. Sekijima Y. Hereditary transthyretin amyloidosis summary genetic counseling gene review scope suggestive findings. Gene Rev. 2021;(2):1-28.
15. Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and treatment of hereditary transthyretin amyloidosis (HATTR) polyneuropathy: current perspectives on improving patient care. Therapeutics and Clinical Risk Management. 2020;16:109-23. http://doi.org/10.2147/TCRM.S219979.
16. Soprano DR, Herbert J, Soprano KJ, Schon EA, Goodman DS. Demonstration of Transthyretin mRNA in the Brain and other Extrahepatic Tissues in the Rat. J Biol Chem. 1985;260(21):11793-8. doi:10.1016/s0021-9258(17)39100-7.
17. Cavallaro T, Martone RL, Dwork AJ, Schon EA y Herbert J. The retinal pigment epithelium is the unique site of transthyretin synthesis in the rat eye. Investig Ophthalmol Vis Sci. 1990;31(3):497-501.
18. Holmgren G, Steen L, Ekstedt J, Groth CG, Ericzon B□G, Eriksson S, et al. Biochemical effect of liver transplantation in two swedish patients with familial amyloidotic polyneuropathy (FAP□met30). Clin Genet. 1991;40(3):242-6. doi:10.1111/j.1399-0004.1991.tb03085.x.
19. Monaco HL, Rizzi M, Coda A. Structure of a complex of two plasma proteins: transthyretin and retinol-binding protein. Science. 1995;268(5213):1039-41. doi:10.1126/science.7754382.
20. Sekijima Y. Recent Progress in the Understanding and Treatment of Transthyretin Amyloidosis. J Clin Pharm Ther. 2014; 39(3): 225-233. doi:10.1111/jcpt.12145.
21. Hammarström P, Jiang X, Hurshman AR, Powers ET, Kelly JW. Sequence-dependent denaturation energetics: a major determinant in amyloid disease diversity. Proc Natl Acad Sci USA. 2002;99 Suppl 4:16427-32. doi:10.1073/pnas.202495199.
22. Kelly JW. Amyloid fibril formation and protein misassembly: a structural quest for insights into amyloid and priori diseases. Structure. 1997;5(5):595-600. doi:10.1016/S0969-2126(97)00215-3.
23. Nakagawa M, Sekijima Y, Yazaki M, Tojo K, Yoshinaga T, Doden T, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) Amyloidosis. Amyloid. 2016;23(1):58-63. doi:10.3109/13506129.2015.1135792.
24. Sperry BW, Reyes BA, Ikram A, Donnelly JP, Phelan D, Jaber WA. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. J Am Coll Cardiol. 2018;72(17):2040-50.
25. Sekijima Y, Yazaki M, Ueda M, Koike H, Yamada M, Ando Y. First nationwide survey on systemic wild-type ATTR Amyloidosis in Japan. Amyloid. 2018;25(1):8-10. doi:10.1080/13506129.2017.1409706.
26. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Hear Fail. 2019;7(8):709-16.
27. Shin SC, Robinson-Papp J. Amyloid neuropathies. Mt Sinai J Med. 2012;79(6):733-48. doi:10.1002/msj.21352.
28. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation. 2012;126(10):1286-300.
29. Dungu JN, Anderson LJ, Whelan CJ, Hawkins PN. Cardiac transthyretin amyloidosis. Heart. 2012;98(21):1546-54. doi:10.1136/heartjnl-2012-301924.
30. Algalarrondo V, Dinanian S, Juin C, Chemla D, Bennani SL, Sebag C, et al. Prophylactic pacemaker implantation in familial amyloid polyneuropathy. Heart Rhythm. 2012;9(7):1069-75. doi:10.1016/j.hrthm.2012.02.033.
31. Van den Berg MP, Mulder BA, Klaassen SHC, Maass AH, Van Veldhuisen DJ, Van der Meer P, et al. Heart failure with preserved ejection fraction, atrial fibrillation, and the role of senile amyloidosis. Eur Heart J. 2019;40(16):1287-93. doi:10.1093/eurheartj/ehz057.
32. Minutoli F, Sindoni A, Baldari S. Reduced myocardial 123-iodine meta-iodobenzylguanidine uptake: a prognostic marker in familial amyloid polyneuropathy. Circ Cardiovasc Imaging. 2013;6(6):627-36. doi:10.1161/CIRCIMAGING.113.001038.
33. Algalarrondo V, Antonini T, Théaudin M, Chemla D, Benmalek A, Lacroix C, et al. Cardiac dysautonomia predicts long-term survival in hereditary transthyretin amyloidosis after liver transplantation. JACC Cardiovasc Imaging. 2016;9(12):1432-41. doi:10.1016/j.jcmg.2016.07.008.
34. Coelho T, Maurer MS, Suhr OB. THAOS-The Transthyretin amyloidosis outcomes survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin. 2013;29(1):63-76. doi:10.1185/03007995.2012.754348.
35. Adams D, Gonzalez-Duarte A, O'Riordan W, Chih-Chao Y, Ueda M, Kristen AV, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2015;379(1):11-21.
36. Doğan FU, Kürtüncü M. Inotersen Treatment for patients with hereditary transthyretin amyloidosis. Turk Noroloji Derg. 2019;25(1):52-3. doi:10.4274/tnd.galenos.2019.57224.
37. Shields JW. Heart rate variability with deep breathing as a clinical test of cardiovagal function. Cleve Clin J Med. 2009;76 Supl 2. doi:10.3949/ccjm.76.s2.08.
38. Koike H, Nakamura T, Hashizume A, Nishi R, Ikeda S, Kawagashira Y, et al. Cardiac and peripheral vasomotor autonomic functions in late-onset transthyretin val30met familial amyloid polyneuropathy. J Neurol. 2017;264(11):2293-302. doi:10.1007/s00415-017-8629-2.
39. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural History of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol. 2016;68(10):1014-20. doi:10.1016/j.jacc.2016.06.033.
40. Merkies ISJ. Tafamidis for Transthyretin Familial Amyloid Polyneuropathy: A Randomized, Controlled Trial. Neurology. 2013;80(15):1444-45. doi:10.1212/01.wnl.0000429338.33391.87.
41. Berk JL, Suhr OB, Obici L, Sekijima Y, Zeldenrust SR, Yamashita T, et al. Repurposing Diflunisal for Familial Amyloid Polyneuropathy: A Randomized Clinical Trial. JAMA. 2013;310(24):2658-67. doi:10.1001/jama.2013.283815.
42. Judge DP, Heitner SB, Falk RH, Maurer MS, Shah SJ, Witteles RM, et al. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. J Am Coll Cardiol. 2019;74(3):285-95. doi:10.1016/j.jacc.2019.03.012.
43. Grandis M, Obici L, Luigetti M, Briani C, Benedicenti F, Bisogni G, et al. Recommendations for pre-symptomatic genetic testing for hereditary transthyretin amyloidosis in the era of effective therapy: a multicenter italian consensus. Orphanet J Rare Dis. 2020;15(1):1-7. https://doi.org/10.1186/s13023-020-01633-z.
44. González-López E, López-Sainz Á, García-Pavia P. Diagnóstico y tratamiento de la amiloidosis cardiaca por transtirretina. Progreso y esperanza. Rev Esp Cardiol. 2017;70(11):991-1004. http://www.revespcardiol.org/es-diagnostico-tratamiento-amiloidosis-cardiaca-por-artículo-S0300893217303500.
45. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2019;73(22):2872-91. doi:10.1016/j.jacc.2019.04.003.
46. Conceição I, González-Duarte A, Obici L, Schmidt HHJ, Simoneau D, Ong ML, et al. Red-flag symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21(1):5-9. doi:10.1111/jns.12153.
47. Adams D, Ando Y, Beirão JM, Coelho T, Gertz MA, Gillmore JD, et al. Expert consensus recommendations to improve diagnosis of ATTR Amyloidosis with polyneuropathy. J Neurol. 2021;268(6):2109-22. doi:10.1007/s00415-019-09688-0.
48. Dyck PJ, Boes CJ, Mulder D, Millikan C, Windebank AJ, Dyck PJB, et al. History of standard scoring, notation, and summation of neuromuscular signs. A current survey and recommendation. J Peripher Nerv Syst. 2005;10(2):158-73. doi:10.1111/j.1085-9489.2005.0010206.x.
49. Dyck PJB, González-Duarte A, Obici L, Polydefkis M, Wiesman JF, Antonino I, et al. Development of measures of polyneuropathy impairment in hATTR amyloidosis: from NIS to mNIS + 7. J Neurol Sci. 2019;405:116424. doi:10.1016/j.jns.2019.116424.
50. Dyck PJ, Kincaid JC, Dyck PJB, Chaudhry V, Goyal NA, Alves C. Assessing mNIS+7|ONIS and International Neurologists' Proficiency in a Familial Amyloidotic Polyneuropathy Trial. Muscle Nerve. 2017;56(5):901-11.
51. Cortese A, Vita G, Luigetti M, Russo M, Bisogni G, Sabatelli M, et al. Monitoring Effectiveness and safety of tafamidis in transthyretin amyloidosis in italy: a longitudinal multicenter study in a non-endemic area. J Neurol. 2016;263(5):916-24. doi:10.1007/s00415-016-8064-9.
52. Obici L, Berk JL, González-Duarte A, Coelho T, Gillmore J, Schmidt HHJ, et al. Quality of life outcomes in APOLLO, the phase 3 trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis. Amyloid. 2020;27(3):153-62. doi:10.1080/13506129.2020.1730790.
53. Sood RF, Kamenko S, McCreary E, Sather BK, Schmitt M, Peterson SL, et al. Diagnosing systemic amyloidosis presenting as carpal tunnel syndrome: a risk nomogram to guide biopsy at time of carpal tunnel release. J Bone Joint Surg Am. 2021;103(14):1284-94. https://journals.lww.com/jbjsjournal/Fulltext/2021/07210/Diagnosing_Systemic_Amyloidosis_Presenting_as.5.aspx.

54. Sletten DM, Suárez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated composite autonomic symptom score. Mayo Clin Proc. 2012;87(12):1196-201. doi:10.1016/j.mayocp.2012.10.013.
55. Conceição I, de Castro I, Castro J. Correlation between Sudoscan and COMPASS 31: assessment of autonomic dysfunction on hATTR V30M Patients. Amyloid. 2019;26 Supl 1:23. doi:10.1080/13506129.2019.1582494.
56. Vinik EJ, Hayes RP, Oglesby A, Bastyr E, Barlow P, Ford-Molvik SL, et al. The Development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. Diabetes Technol Ther. 2005;7(3):497-508. doi:10.1089/dia.2005.7.497.
57. Vinik EJ, Vinik AI., Paulson JF, Merkies ISJ, Packman J, Grogan DR, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2014;19(2):104-14. doi:10.1111/jns5.12059.
58. Díaz-Campos A, Castro J, Conceição E. Uso del test de cuantificación sensitiva. Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario; 2013.
59. Pinto MV, Dyck PJB, Gove LE, McCauley BM, Ackermann EJ, Hughes SG, et al. Kind and distribution of cutaneous sensation loss in hereditary transthyretin amyloidosis with polyneuropathy. J Neurol Sci. 2018;394:78-83. doi:10.1016/j.jns.2018.08.031.
60. Georgopoulos V, Akin-Akinyosoye K, Zhang W, McWilliams DF, Hendrick P, Walsh DA. Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability, and negative affect: a systematic review and meta-analysis. Pain. 2019;160(9):1920-32. doi:10.1097/j.pain.0000000000001590.
61. Rapezzi C, Aimo A, Serenelli M, Barison A, Vergaro G, Passino C, et al. Critical comparison of documents from scientific societies on cardiac amyloidosis: JACC state-of-the-art review. J Am Coll Cardiol. 2022;79(13):1288-1303. doi:10.1016/j.jacc.2022.01.036.
62. García-Pavia P, Bengel F, Brito D, Damy T, Duca F, Dorbala S, et al. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. Eur J Heart Fail. 2021;23(6):895-905. doi:10.1002/ejhf.2198.
63. Perfetto F, Zampieri M, Fumagalli C, Allinovi M, Cappelli F. Circulating biomarkers in diagnosis and management of cardiac amyloidosis: a review for internist. Intern Emerg Med. 2022;17(4):957-69. doi:10.1007/s11739-022-02958-2.
64. García-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working group on myocardial and pericardial diseases. Eur Heart J. 2021;42(16):1554-68. doi:10.1093/eurheartj/ehab072.
65. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Heart Fail. 2019;7(8):709-16. doi:10.1016/j.jchf.2019.04.010.
66. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. Cleve Clin J Med. 2017;84(12 Supl 3):12-26. doi:10.3949/ccjm.84.s3.02.
67. Rocha A, Lobato L. Liver Transplantation in transthyretin amyloidosis: characteristics and management related to kidney disease. Transplant Rev. 2017;31(2):115-20. doi:10.1016/j.trre.2016.09.002.
68. Lobato L, Beirão I, Silva M, Bravo F, Silvestre F, Guimarães S, et al. Familial ATTR amyloidosis: microalbuminuria as a predictor of symptomatic disease and clinical nephropathy. Nephrol Dial Transplant. 2003;18(3):532-8. doi:10.1093/ndt/18.3.532.
69. Wixner J, Mundayat R, Karayal ON, Anan I, Karling P, Suhr OB. THAOS: gastrointestinal manifestations of transthyretin amyloidosis - common complications of a rare disease. Orphanet J Rare Dis. 2014;9:61. doi:10.1186/1750-1172-9-61.
70. Rocha A, Bravo F, Beirão I, Vizcaíno J, Oliveira JC, Lobato L. Urinary biomarkers for kidney disease in ATTR amyloidosis. J Nephrol Ther. 2014;04(05):1-5. doi:10.4172/2161-0959.1000181.
71. Oguchi K, Takei YI, Ikeda SI. Value of renal biopsy in the prognosis of liver transplantation in familial amyloid polyneuropathy ATTR Val30Met patients. Amyloid. 2006;13(2):99-107. doi:10.1080/13506120600722662.
72. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018;39(30):2799-806. doi: 10.1093/eurheartj/ehx589. PMID: 29048471.