TREATMENT OVERVIEW

HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

Cece has hATTR amyloidosis.

Amyloidosis Research Consortium

ARCI.ORG

KNOWLEDGE IS POWER

ABOUT THE AMYLOIDOSIS RESEARCH CONSORTIUM

The Amyloidosis Research Consortium (ARC) is a nonprofit organization dedicated to driving advances in awareness, science, and treatment of amyloid diseases. ARC's mission is to improve and extend the lives of those with amyloidosis. ARC is committed to collaborative efforts that accelerate the pace of discovery, expand patient access to the most effective care, and improve short- and long-term outcomes. Working with partners in industry, government, and academia, ARC seeks to spark innovation and to bring promising treatments from labs to clinics. Our outreach and educational efforts inform and empower patients, families, caregivers, physicians, and researchers.

To learn more about ARC, visit **www.arci.org** or call **(617) 467-5170**.

Amyloidosis Research Consortium

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This booklet is not intended to provide medical advice. It is merely an educational tool. Patients should speak with their care team when making any treatment decisions.

INTRODUCTION

We live in a time of rapid advances in genetic knowledge and pharmacological technologies. The pace of discovery in Amyloidosis care is accelerating, increasing awareness and driving the development of new treatment options.. The exact course of hATTR varies with each patient, but the outlook holds promise for all. This booklet is designed as a comprehensive guide to help you and your family navigate treatment resources and options that would be most effective for you.

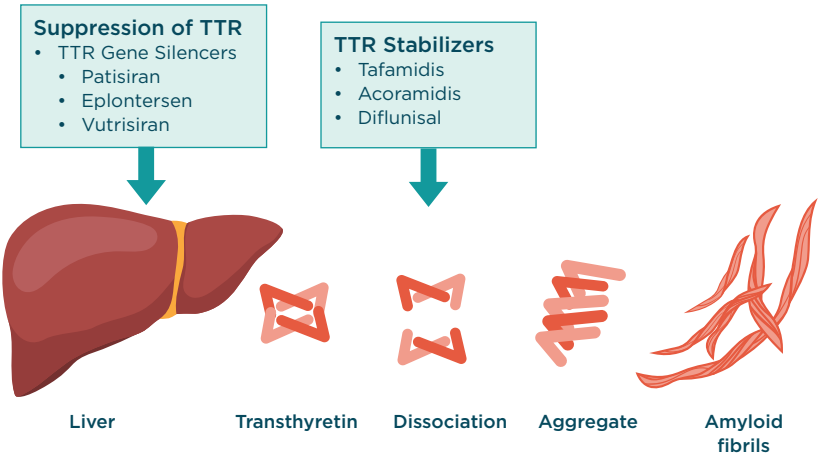
HOW IS hATTR TREATED?

While no current therapies can reverse damage caused by amyloid deposits, new drugs can prevent or slow the progression of the disease. Your care will depend on which tissues and organs are affected and how far the disease has advanced.

GOALS OF TREATMENT: AN OVERVIEW

There are several ways that therapies approach treating the disease, but ultimately, they have the same goal: to reduce the amount of circulating misfolded transthyretin (TTR) protein. Since TTR is produced in the liver, some treatments target production at the source using a drug classified as a Gene Silencer, which aims to slow the creation of TTR proteins. TTR Stabilizers are another classification of drugs used to treat hATTR. TTR Stabilizers work to prevent the TTR proteins from misfolding and forming amyloid deposits or fibrils. Another option, not as frequently used today, is to perform a liver transplant. Lastly, there is research being conducted on anti-fibril agents, which medications that work to destroy the amyloid fibrils that have already accumulated. Unfortunately, there are no approved treatments for fibril degradation at this time, but some drugs that were originally designed for other uses are thought to provide this therapeutic benefit in amyloidosis patients. However, more studies are needed to confirm this.

TREATMENTS THROUGHOUT THE hATTR DISEASE PROCESS



IMPORTANCE OF EARLY TREATMENT

Treatment should start at the first signs of symptom development and once an official diagnosis is made. Early care is essential to slow or prevent progression. For asymptomatic carriers, or those that have had genetic testing and are confirmed to carry a TTR genetic mutation but do not have any symptoms, the goal is to detect the disease and treat it as soon as symptoms appear. This requires systematic and regular monitoring. Currently, there are no approved treatments for asymptomatic carriers.

If you are a carrier, it is recommended that you are evaluated at an Amyloidosis Treatment Center to create a baseline analysis and discuss the results with a specialist.

Early diagnosis and treatment initiation are essential for the best possible outcomes.

STAGING

Staging relies on tests of your peripheral and autonomic nervous systems and imaging to identify amyloid in your heart or other organs. These test results establish if disease is present, progression

of the disease, as well as the suitability of various drugs and procedures to treat it. The four stages of hATTR range from asymptomatic to severe impairment and are shown in Table 1.

TABLE 1. STAGES OF hATTR NERVE INVOLVEMENT	
Stage 0	No symptoms: TTR gene mutation detected.
Stage I	Unimpaired walking: mostly mild sensory, motor, and autonomic neuropathy in the lower limbs.
Stage II	Assistance required for walking: moderate impairment with progression to lower limbs, upper limbs, and trunk.
Stage III	Wheelchair-bound or bedridden: severe sensory, motor, and autonomic involvement of all limbs.

POLYNEUROPATHY VS. CARDIOMYOPATHY

hATTR is defined by dominant symptoms which are outlined in detail in our first booklet, *Hereditary Transthyretin Amyloidosis: Disease Overview*. Patients can experience polyneuropathy (PN) or cardiomyopathy (CM), or a mix of both. Although new drugs are tested and approved for either polyneuropathy or cardiomyopathy, it's not unusual for patients to experience both symptoms. Your health care team will work with you to develop a treatment strategy that addresses your specific needs.

TREATMENT OPTIONS

DISEASE-MODIFYING THERAPIES

While therapeutic support strategies relieve symptoms and manage affected organs (Table 2 on page 11), disease-modifying treatments attack the disease itself. From liver transplants to the frontiers of molecular and genetic medicine, there are many new treatment options to help hATTR patients control their disease.

AVAILABLE APPROVED TREATMENTS

TTR Stabilizers

ATTRUBY™ (acoramidis)
Acoramidis is a TTR stabilizer approved for use in the U.S. treating patients with transthyretin amyloidosis (ATTR) who have heart involvement (cardiomyopathy). The drug works by binding to the TTR protein and helping to stabilize that protein structure, preventing it from breaking down, misfolding, and forming fibrils.

In the randomized, double-blind, **placebo-controlled** Phase III ATTRibute-CM clinical trial, acoramidis resulted in a statistically significant better combined outcome that took into account death, hospitalization, biomarker, and function.

Acoramidis is a 712mg tablet taken by mouth twice a day and is generally well tolerated. The most commonly observed side effects were diarrhea and stomach-area (abdominal) pain. These are not all of the possible side effects of Attruby.

BridgeBio (Palo Alto, CA, USA) www.bridgebio.com.

VYNDAMAX® (tafamidis)
Tafamidis is a selective TTR stabilizer approved for use in the U.S. and Canada to treat cardiomyopathy in adults with hereditary TTR amyloidosis (hATTR) and approved for use in Europe, Mexico, Japan, Argentina and other countries to slow the disease progression of polyneuropathy in early stage hereditary TTR amyloidosis (stage I-III). The drug works by binding to TTR protein to prevent misfolding that leads to amyloid fibrils.

In the randomized, phase III ATTR-ACT clinical trial in patients with hATTR-CM, tafamidis significantly reduced all-cause death and heart disease related hospitalizations in patients with early disease. It also slowed loss of function and helped maintain quality of life.

Tafamidis is a 61mg capsule taken by mouth once a day and has very few reported side effects in patients with cardiomyopathy.

Pfizer (New York, NY USA) www.pfizer.com.

Gene Silencers

AMVUTTRA® (vutrisiran)

Amvuttra (vutrisiran) is a gene silencer approved for use in the U.S., Canada, Europe and several other countries, for treating patients with hereditary transthyretin amyloidosis (hATTR) who have peripheral nerve involvement (polyneuropathy). and/or cardiomyopathy (heart damage). This is another drug using **RNA interference (RNAi)** to inhibit the production of TTR protein in the liver, reducing TTR levels in the body and preventing amyloid build-up and organ damage.

In the phase III HELIOS-B clinical trial, patients with cardiomyopathy who received Amvuttra had a lower risk of death and heart-related hospital visits compared to those who received the placebo. Patients also maintained better physical function and quality of life. In the phase III HELIOS-A clinical trial, it significantly improved neuropathy symptoms, as well as walking, quality of life, nutritional status, and activities of daily living when compared to those who received placebo.

Amvuttra is a subcutaneous (under the skin) injection administered by a health care professional in a hospital or clinic setting once every three months.

Alnylam Pharmaceuticals (Cambridge, MA, USA)
www.amvuttra.com.

ONPATTRO® (patisiran)

Patisiran is gene silencer approved for use in the U.S. and Europe, treating patients with stage I or II hereditary transthyretin amyloidosis (hATTR) who have peripheral nerve involvement (polyneuropathy). The drug works using RNA interference (RNAi) to prevent the production of TTR protein in the liver and reduce levels in the blood.

In the phase III APOLLO clinical trial, patisiran significantly improved symptoms of polyneuropathy as well as walking, quality of life, and activities of daily living. Some patients also experienced improved cardiac function.

Patisiran is an 80-minute intravenous (IV) infusion, usually administered in a clinic, once every three weeks. Reported side effects include mild or moderate infusion-related reactions and vitamin A deficiency. It is important to note that “pre-drugs” are also prescribed, which include corticosteroids, acetaminophen, and antihistamines, to prepare for the infusion.

Alnylam Pharmaceuticals (Cambridge, MA, USA)
www.alnylam.com

WAINUA™ (eplontersen)

Eplontersen is a gene silencer approved for use in the U.S. treating patients with stage I or II hereditary transthyretin amyloidosis (hATTR) who have peripheral nerve involvement (polyneuropathy). The drug works by binding to **messenger RNA (mRNA)** to prevent the production of TTR proteins in the liver.

In the NEUROTTR phase III randomized, controlled trial, participants receiving eplontersen experienced a sustained decrease in transthyretin levels, which significantly slowed disease progression. Participants receiving eplontersen also demonstrated significantly improved quality of life and neuropathic symptoms.

Eplontersen is a monthly self-administered subcutaneous (under the skin) injection. The recommended dose is 45 mg, which comes in a pre-filled autoinjector containing 0.8 mL of solution. Reported side effects include decreased vitamin A levels, vomiting, and an increase in protein levels in the urine. Injection site reactions included erythema, pain, and itching. About 6% of participants in the study also experienced cataract or blurred vision.

AstraZeneca and Ionis Pharmaceuticals. (Gaithersburg, MD and Carlsbad, CA). www.astrazeneca.com

Organ transplants

Depending on damage to the heart or other organs, a heart or other organ transplant may also be considered Transplantation, though well-established, is costly and high-risk. Post-transplant complications are common. Outcomes depend on age of onset and type of mutation. Other factors include age at the time of

transplant and nutritional status. Transplant slows the disease but does not stop it.

Off-label treatments are prescribed by physicians based on expert opinion, small study outcomes, or clinical experience. Because the claims can often be misleading, you should discuss them with your health care provider to find out if they might be right for you.

OFF-LABEL AND OVER THE COUNTER (OTC) TREATMENTS

Off-label drugs means they are used for indications other than what is approved by the FDA. Physicians prescribe them based on expert opinion, small study outcomes, or clinical experience. Some have been on the market for many years but have yet to go through the rigorous testing needed to gain FDA approval for a new use. We recommend that you discuss off-label drugs with your physician to see if they might be right for you.

OTC drugs and supplements are available online or in retail outlets without a prescription. Claims of health benefits may be misleading, so check with your physician before you start taking them.

OFF-LABEL TREATMENTS

DOLOBID® (diflunisal)

Diflunisal is an NSAID (non-steroidal anti-inflammatory drug) that also works as a TTR stabilizer. NSAIDs are common medications to reduce inflammation and diflunisal is also used in patients to decrease arthritis pain. It may be prescribed off-label for treating ATTR polyneuropathy, with limited data in ATTR cardiomyopathy usage.

In a 24-month randomized clinical trial in patients with hATTR-PN, diflunisal slowed progression and preserved quality of life. It also led to a two-to-threefold improvement in neuropathy impairment scores. In a nonrandomized single-center study in patients with hATTR-CM, it delivered a significant survival benefit.

Diflunisal is a 250mg tablet taken by mouth twice a day and is widely available at low cost. Side effects are kidney disease, gastrointestinal upset or bleeding, and worsening fluid retention thus, it is not suitable for all patients.

Merck and Co., Inc. (Whitehouse Station, NJ USA)
www.merck.com

TASMAR® (tolcopone)

Tolcapone is an FDA-approved drug used to treat Parkinson's disease. It inhibits the catechol-O-methyltransferase enzyme. A proof-of-concept clinical trial in 17 asymptomatic carriers and patients showed significant increases in TTR stabilization without serious side effects. Tolcapone is approved to treat Parkinson's disease in the U.S. and is being investigated for treatment of ATTR amyloidosis.

Bausch Health (formerly Valeant Pharmaceuticals; Laval, Quebec, Canada) www.bauschhealth.com.

OVER THE COUNTER (OTC) TREATMENTS

GREEN TEA (EGCG)

Green tea contains Epigallocatechin-3-gallate (EGCG), a well-known major polyphenol which may inhibit formation of TTR amyloid fibrils and help break down amyloid deposits. Preliminary clinical data of patients consuming approximately 550 mg EGCG daily for 12 months, showed significant reductions in heart wall thickness and left ventricular myocardial mass. This early evidence suggests that green tea can slow the progression of ATTR cardiomyopathy. The extract from green tea is available in a capsule. More research is needed to confirm the benefits.

SYMPTOM MANAGEMENT

SUPPORTIVE CARE

hATTR has wide-ranging effects on body tissues and systems. Supportive care involves the treatment of symptoms and the management of disease in the heart and other organs (Table 2). Other therapies may include replacement of the liquid part of the eye (**vitrectomy**) and carpal tunnel surgery. While a well-planned treatment strategy can substantially improve quality of life, a multidisciplinary approach is essential for the best possible outcome.

For more symptom management options to explore, please see our companion booklets - Neuropathy and Amyloidosis, and Gastrointestinal Amyloidosis Symptoms and Management, or contact an ARC Patient Support Specialist.

TABLE 2. SUPPORTIVE CARE FOR hATTR

Signs and Symptoms	Treatment
Arrhythmias/ palpitations	Pacemaker/ ICD implantation, medications.
Heart failure (leg swelling, abdominal swelling)	Diuretics, salt and fluid restriction, cardiac rehab.
Orthostatic hypotension	Medications to increase blood pressure (droxidopa, midodrine, florinef), thigh-high compression stockings, stopping medications that lower blood pressure, standing up slowly
Diarrhea	Loperamide, tincture of opium, lomotil, avoid fatty foods, avoid medications that cause diarrhea
Constipation	Laxatives, fiber supplements, avoid medications that are constipating.

TABLE 2. SUPPORTIVE CARE FOR hATTR, CONT.	
Signs and Symptoms	**Treatment**
Slow motility (delayed stomach emptying)	Metoclopramide, eat small frequent meals.
Neuropathic pain	Pregabalin, gabapentin, amitriptyline, duloxetine. Topical lidocaine (OTC). Avoid alcohol.
Carpal tunnel syndrome	Surgery or wrist splints.
Dry mouth	Potassium dihydrogen phosphate, cevimeline.
Hypoglycemia	Glucose loading, monitor glucose at home.
Urinary incontinence	Medications (Distigmine, Detrol), voiding schedule.
Hypothyroidism	Medications, determine underlying cause.
Ocular amyloidosis (floaters)	Vitrectomy, trabeculectomy.

CARDIAC CARE

Commonly prescribed drugs for cardiac conditions are under new scrutiny as we learn more about their effects on patients with hATTR. Many need to be used with caution, started at low doses, and closely monitored.

Digoxin strengthens heartbeat but can bind to amyloid fibrils. This could cause the amount of **digoxin** in the body to rise to toxic levels, resulting in problems with your nervous system, heart rate, and electrolytes.

Hypertension medications—**beta-blockers, angiotensin-converting enzyme (ACE)** inhibitors, and **angiotensin receptor blockers (ARBs)**—may be poorly tolerated in patients with amyloidosis, especially in those with low blood pressure. One class of **calcium**

channel blockers, non-dihydropyridine, is **contraindicated** in patients with hATTR-CM, and typically should be avoided. Your physician may have good reason to prescribe these medications to you, but amyloidosis patients should be very closely monitored while taking them.

CLINICAL TRIALS

Clinical trials are investigational studies that aim to prove the efficacy and safety of new treatments. Any drug or therapy for any disease that is approved today is made available because of clinical trials and the participation of patients in those trials.

Trials may test whether new drugs or new combinations of current treatments are better than the currently available standard care. Those who enroll in clinical trials could be the first to benefit from advances in care, but there could also be some unexpected side effects or risks. It's important you talk to your healthcare team about what's involved in a clinical trial so you can make an informed decision about your participation.

Some benefits to participating in a clinical trial may include:

- Benefitting from the latest advances in research and new treatments.
- More frequent testing and monitoring from disease specialists.
- Helping researchers learn and improve upon treatments for years to come.

Some potential risks associated with clinical trial participation may include:

- Unexpected side effects.
- New treatment might not work as expected.
- You may be in a "control" group that gets the standard care and not the new treatment.

ARC PATIENT SUPPORT AND RESOURCES

The Amyloidosis Research Consortium (ARC) is a nonprofit organization with a mission to advance scientific discovery, improve access to state-of-the-art care, and empower patients with innovative educational tools and support. Please see the companion booklet in the hATTR series, **Disease Overview for Hereditary Transthyretin Amyloidosis**, for more information on hATTR, or check out our free online tool, My Amyloidosis Pathfinder, to learn about treatment centers and set up personalized notifications for clinical trials.

MAP | My Amyloidosis Pathfinder

New trials are always in development to help expand treatment options and improve quality of life. Join MAP to receive notifications as new clinical trials and treatment centers are posted.

Treatment Center Selector

Clinical Trial Finder

www.myamyloidosispathfinder.org

KEY QUESTIONS TO ASK YOUR HEALTH CARE TEAM

Therapeutic education and genetic counseling can answer many questions. Research in medical journals and information from advocacy groups like ARC may answer others. Some common questions about treatment are listed below.

1. Where is the closest specialized amyloidosis treatment center and will you provide a referral?
2. What tests are required before I can begin treatment?
3. What will these tests show and how reliable are they?
4. How will I know if I've had all the necessary testing completed?
5. How will my treatment strategy be determined?
6. Who is on my care team?
    a. What specialists will be involved in my care and why?
    b. Who will be my main point of contact for treatment and care navigation and how do I get in touch with them?
    c. Who will coordinate care and arrange for regular monitoring and follow-up?
7. Am I eligible for treatment with new drugs?
8. Will my treatment be covered under insurance?
    a. Who can I talk to if I have questions about my insurance coverage?
9. What can I expect as we move forward with my treatment plan?
10. What emotional support is available for me and my caregiver(s) as we navigate this diagnosis?

GLOSSARY

Amyloid. A starch-like substance caused by the misfolding of proteins. Amyloid binds together into rigid, linear structures (fibrils) that accumulate in tissues and organs.

Amyloid fibril: A rigid stack of amyloid proteins that builds up in the body.

Amyloidosis. A disease caused by the accumulation of abnormally shaped proteins (amyloid proteins) in tissues and organs.

Angiotensin-converting enzyme (ACE) inhibitors. A class of drugs prescribed to control high blood pressure, prevent kidney disease, and treat and prevent heart attacks and heart failure.

Angiotensin receptor blockers (ARBs). A class of drugs prescribed to control blood pressure, treat heart failure, and prevent kidney failure in people with diabetes or high blood pressure.

Antisense oligodeoxynucleotides (ASOs). Short, chemically modified oligonucleotides that bind to TTR mRNA to prevent production of TTR protein.

Arrhythmia. An irregular heart rhythm.

Beta-blockers. A class of drugs prescribed after a heart attack or to treat abnormal heart rhythms (arrhythmias); widely used to treat high blood pressure but are no longer first line therapy for most patients.

Calcium channel blockers. Medications that cause blood vessels to relax and widen (vasodilate) to improve oxygen supply to the heart and lower blood pressure; some also slow the heart rate.

Contraindication. A specific situation in which a drug, procedure, or surgery should not be used because it may be harmful.

CRISPR/Cas9. A tool developed by scientists to edit genes by cutting DNA.

Digoxin. A drug used to treat congestive heart failure and slow the heart rate in patients with atrial fibrillation.

Diuretics. Medications that help flush excess fluid and sodium from the body; used to treat congestive heart failure, liver disease, and kidney disease.

Hereditary transthyretin amyloidosis (hATTR). A rare, progressive form of systemic amyloidosis caused by an inherited genetic mutation that causes a buildup of amyloid in multiple organs and tissues.

hATTR-CM. Hereditary transthyretin amyloidosis with cardiomyopathy.

hATTR-PN. Hereditary transthyretin amyloidosis with polyneuropathy.

Hypoglycemia. Low blood sugar.

Messenger RNA (mRNA). A large family of RNA molecules that convey genetic information from DNA to the ribosome, where they specify the amino acid sequence of the protein products of gene expression.

Monoclonal antibodies (MABs). A type of protein made in a laboratory that can bind to substances in the body, including cancer cells.

Orthostatic hypotension. A condition that causes blood pressure to fall when standing up or sitting.

Placebo-controlled. A clinical trial in which the drug being tested is compared to a placebo (a substance containing no medicine).

RNA interference (RNAi) therapeutics. Double-stranded, small interfering RNAs (siRNA) that bind to TTR messenger RNA (mRNA) to preventing production of TTR protein.

Staging. Exams and tests to learn the extent of disease progression.

Trabeculectomy. A surgical procedure to treat glaucoma.

Transthyretin. A protein mainly produced in the liver that transports vitamin A (retinol) and a hormone called thyroxine throughout the body.

Vitrectomy. A surgical procedure where the vitreous humor gel that fills the eye cavity is removed to provide better access to the retina for vision correction.

Wild-type transthyretin amyloidosis (ATTRwt). Acquired amyloidosis with a normal (nonmutated) transthyretin protein; typically causes cardiac dysfunction and is seen in men 60 years or older.

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» *Pfizer*
» *Protego Biopharma*
» *Prothena Biosciences*
» *Ultromics*

You are not alone — ARC is here to support you every step of the way.

To receive one-on-one guidance, learn more about ARC, or support our mission, contact us:

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Learn more at **ARCI.ORG**

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