UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

Jessi Clark, PharmD
Saturday, November 14th

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Making cardiac amyloidosis drugs ta-famous-dis:

A review of cardiac amyloidosis therapies

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Disclosure

Relevant Financial Conflicts of Interest
- CE Presenter: Jessi Clark, PharmD:
  - No financial relationships
- CE Mentor: Irene Pan, PharmD:
  - No financial relationships

Off-Label Uses of Medications
- Diflunisal (Novo-Diflunisal)

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Pharmacist Learning Objectives

- **Describe** the clinical characteristics and manifestations of light chain, wild type, and variant type cardiac amyloidosis
- **Manage** disease modifying therapies for cardiac amyloidosis
- **Prepare** treatment plans for cardiac amyloidosis-associated comorbid conditions
- **Analyze** evidence for the use of newly FDA-approved disease-modifying therapies for cardiac amyloidosis

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Technician Learning Objectives

- **List** brand and generic names of agents used in the treatment of cardiac amyloidosis
- **Recall** the clinical manifestations of cardiac amyloidosis
- **Assess** the cost of a patient's cardiac amyloidosis medications

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01

Pathophysiology

Amyloid proteins and fibrils

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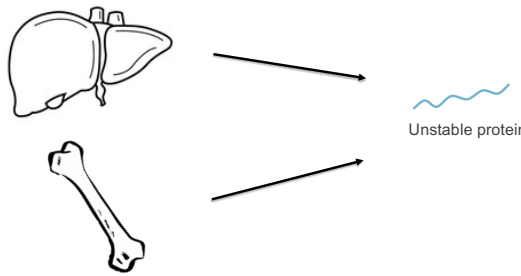
Unstable Proteins



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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22.

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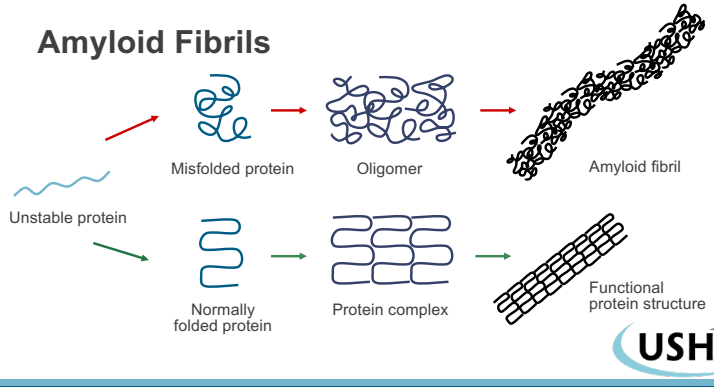
Amyloid Fibrils



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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22. 9

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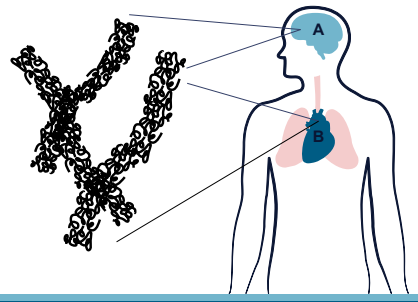
Amyloid Fibrils



A

Nervous System

Primarily the autonomic and peripheral nervous system affected

B

Heart

Restrictive cardiomyopathy, arrhythmias

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22. 10

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Restrictive Cardiomyopathy

Lower cardiac output

Dependent on changes in heart rate to maintain cardiac output

Restricted left ventricular filling

Amyloid fibrils make the ventricles not as compliant, causing a fixed stroke volume

CO = HR x SV

↓ ↑ ↓

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22. 11

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Proteins

Monoclonal Immunoglobulin Light Chain Proteins

Mutant/Variant Transthyretin (TTR) Proteins

Wild Type Transthyretin (TTR) Proteins

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22. 12

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Proteins

Monoclonal Immunoglobulin Light Chain Proteins

Abnormal clonal proliferation of plasma cells in the bone marrow

Transthyretin (TTR) Proteins

Liver-synthesized proteins that transport thyroxine and retinol-binding protein

Mutant/Variant Transthyretin (TTR) Proteins

Genetically inherited mutated variant of the TTR gene, autosomal dominant

Wild Type Transthyretin (TTR) Proteins

Native TTR proteins misfold, deposit, and aggregate randomly

Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22 | Grogan et al. *Heart* 2017;103:1065-1072. 13

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Types of Cardiac Amyloid

Monoclonal Immunoglobulin Light Chain Proteins

Monoclonal Immunoglobulin Light Chain Cardiomyopathy
AL - CM

Mutant/Variant Transthyretin (TTR) Proteins

Mutant/Variant Transthyretin Amyloid Cardiomyopathy
ATTRm/v - CM

Transthyretin (TTR) Proteins

Transthyretin Amyloid Cardiomyopathy
ATTR - CM

Wild Type Transthyretin (TTR) Proteins

Wild Type Transthyretin Amyloid Cardiomyopathy
ATTRwt - CM

Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22 | Grogan et al. *Heart* 2017;103:1065-1072. 14

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Cardiac Amyloid Summary

AL - CM

- Misfolded proteins from abnormal proliferation in bone marrow

ATTRm/v - CM

- Misfolded proteins due to genetically inherited mutated variant of TTR gene

ATTR - CM

ATTRwt - CM

- Misfolded proteins randomly form and deposit

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Relevance

Prognosis, new advances, and prevalence of cardiac amyloidosis

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Epidemiology

Cardiac Amyloidosis in Medicare beneficiaries

- Incidence and prevalence from the year 2000 to 2012
  - New cases: 18 → 55 patients per 100,000 person-years
  - Carry a diagnosis: 8 → 17 patients per 100,000 person-years
  - A total of 15,737 beneficiaries (~0.12%) carried a diagnosis in 2012
- Patient Populations
  - Prevalence greater in men: 70 vs 44 patients per 100,000 person-years
  - Highest prevalence was in black men: 174 patients per 100,000 person-years
  - Increased incidence in patients ≥ 75 years old

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Gilstrap LG, et al. *Circ Heart Fail*. 2019;12:e005407

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Mortality

AL-CM

8 years without cardiac involvement

6 months after development of cardiomyopathy

<6 months if untreated

ATTRm/v-CM

2-15 years after onset of neuropathy

2-5 years after onset of cardiomyopathy

2.5 years after diagnosis if untreated

ATTRwt-CM

5-6 years from onset of symptoms

3.6 years after diagnosis if untreated

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Nativi-Nicolau, et al. *Curr Opin Cardiol*. 2018;33(5):571-579 | Kittleson, et al. *Circulation*. 2020;142(1):e7-e22 | Grogan et al. *Heart* 2017;103:1065-1072 | Dungu JN. *Eur Cardiol*. 2015;10(2):113-117

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Delays in diagnosis

Cardiac amyloidosis is incurable! If there is nothing we can do to treat, why diagnose?

Cardiac amyloidosis, what are the symptoms of that? They don't teach that in depth in school

I don't want to put this poor patient through a cardiac biopsy

Cardiac amyloidosis is so rare, I'm sure that isn't the cause of my patient's heart failure!

My patient's symptoms are all over the place, the possible causes are endless

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Nativi-Nicolau, et al. *Curr Opin Cardiol*. 2018;33(5):571-579 | Kittleson, et al. *Circulation*. 2020;142(1):e7-e22.

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New Advances

Imaging

Bone scintigraphy for a non-invasive diagnosis

Medications

New disease-modifying therapies approved by the FDA

Prevalence

New observational studies indicating that cardiac amyloidosis may be greatly underdiagnosed

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Kittleson, et al. *Circulation*. 2020;142(1):e7-e22.

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Prevalence

16% of patients with degenerative aortic stenosis found to have ATTR deposits on autopsy

13-17% of patients with heart failure with preserved ejection fraction (HFpEF) were found to have ATTR-CM

5% of patients with presumed hypertrophic cardiomyopathy were found to have ATTRm/v-CM

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Kittleson, et al. *Circulation*. 2020;142(1):e7-e22.

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Cardiac Amyloid Summary

AL - CM
- Misfolded proteins from abnormal proliferation in bone marrow
- Mortality 6 mo after cardiomyopathy

ATTRm/v - CM
- Misfolded proteins due to genetically inherited mutated variant of TTR gene
- Mortality 2-5 years after cardiomyopathy

ATTR - CM

ATTRwt - CM
- Misfolded proteins randomly form and deposit
- Mortality 5-6 years after onset of symptoms

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Symptoms

Physical exam, raising suspicion, and early identification

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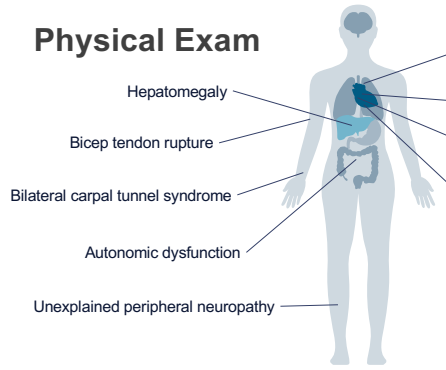
Physical Exam



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Nativi-Nicolau, et al. *Curr Opin Cardiol*. 2018;33(5):571-579 | Kittleson, et al. *Circulation*. 2020;142(1):e7-e22.

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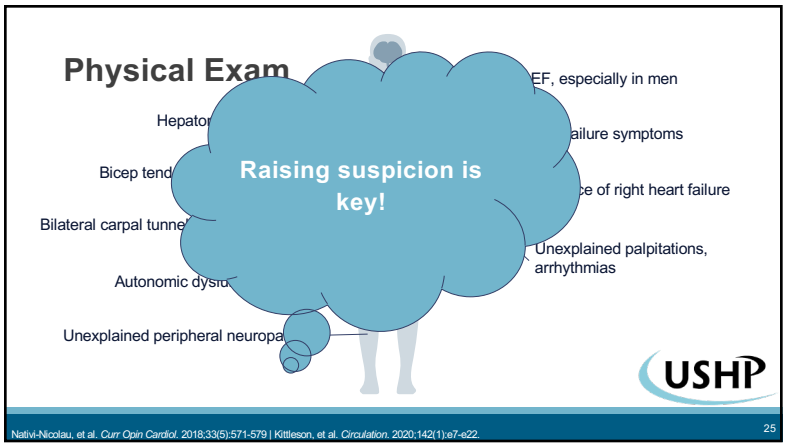
Physical Exam
EF, especially in men
Hepator
ailure symptoms
Bicep tend
Raising suspicion is key!
ce of right heart failure
Bilateral carpal tunne
Unexplained palpitations, arrhythmias
Autonomic dysfu
Unexplained peripheral neuropa
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Nativi-Nicolau, et al. Curr Opin Cardiol. 2018;33(5):571-579 | Kittleson, et al. Circulation. 2020;142(1):e7-e22.
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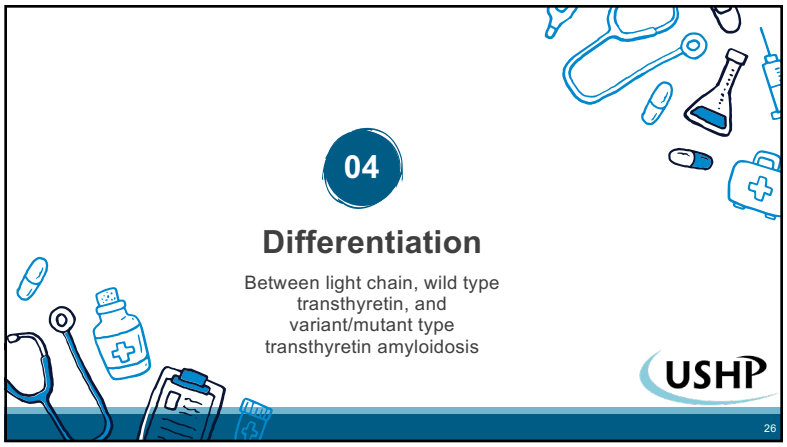
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Differentiation
Between light chain, wild type transthyretin, and variant/mutant type transthyretin amyloidosis
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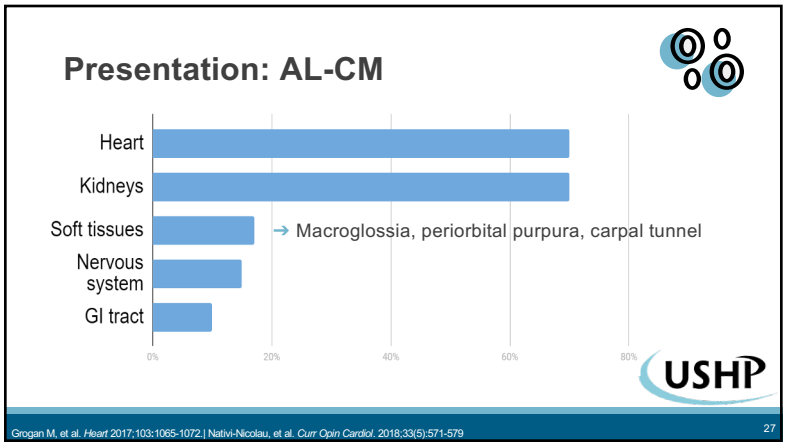
Presentation: AL-CM
Heart
Kidneys
Soft tissues
→ Macroglossia, periorbital purpura, carpal tunnel
Nervous system
GI tract
0%
20%
40%
60%
80%
USHP
Grogan M, et al. Heart 2017;103:1065-1072 | Nativi-Nicolau, et al. Curr Opin Cardiol. 2018;33(5):571-579
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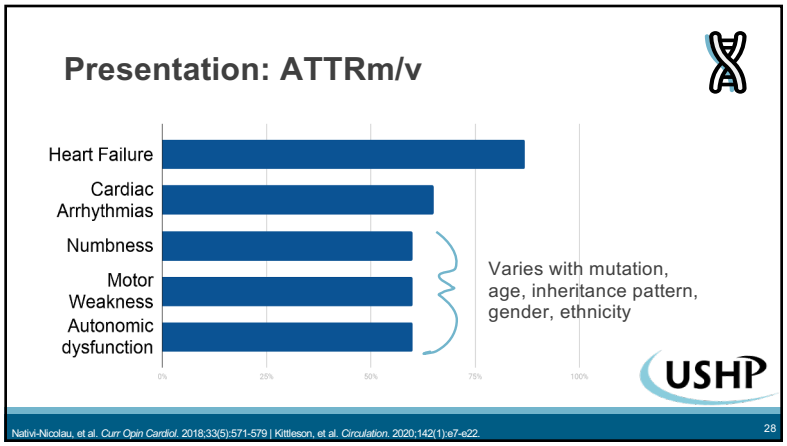
Presentation: ATTRm/v
Heart Failure
Cardiac Arrhythmias
Numbness
Motor Weakness
Autonomic dysfunction
Varies with mutation, age, inheritance pattern, gender, ethnicity
0%
25%
50%
75%
100%
USHP
Nativi-Nicolau, et al. Curr Opin Cardiol. 2018;33(5):571-579 | Kittleson, et al. Circulation. 2020;142(1):e7-e22.
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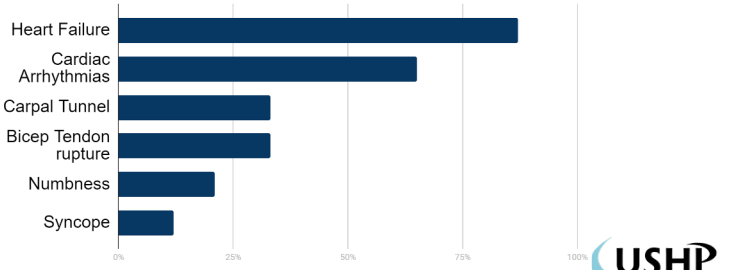
Presentation: ATTRwt



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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22.

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Cardiac Amyloid Summary

AL - CM	ATTRm/v - CM	ATTR - CM	ATTRwt - CM
→ Misfolded proteins from abnormal proliferation in bone marrow	→ Misfolded proteins due to genetically inherited mutated variant of TTR gene		→ Misfolded proteins randomly form and deposit
→ Mortality 6 mo after cardiomyopathy	→ Mortality 2-5 years after cardiomyopathy		→ Mortality 5-6 years after onset of symptoms
→ Symptoms: nonspecific, heart & kidneys	→ Symptoms: vary; neuropathy & cardiac		→ Symptoms: heart failure, arrhythmias, & carpal tunnel

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Testing and Diagnosis

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Lab Values

Immunofixation electrophoresis (IFE) testing

Characterizes monoclonal proteins, abnormal kappa to gamma light chain ratio can indicate possible AL-CM, reference range 0.26-1.65

Retinol binding protein 4

Low levels can discriminate patients with ATTRm/v from patients with other causes of HF

Misfolded TTR oligomers

Presence can discriminate patients with ATTRm/v from patients with other causes of HF

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22 | Grogan M, et al. *Heart* 2017;103:1065-1072

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Imaging

EKG

Low voltage in limb leads in <40% of patients, appears in late phase

Echo

Thickened valves, septum, or ventricles; atrial enlargement. Changes in LA volume index, LV strain, and global longitudinal strain

Cardiac MRI

Delayed gadolinium enhancement as amyloid infiltrates the myocardium

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22. 33

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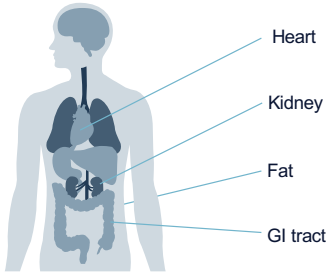
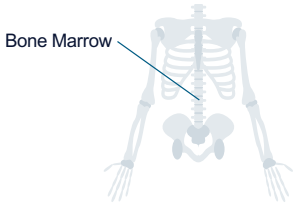
Tissue Biopsy





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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22. 34

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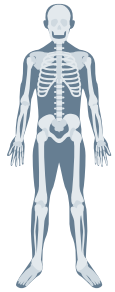
Bone Scintigraphy



- Conduct IFE testing prior to rule out AL-CM
- Pyrophosphate: radionucleotide that binds calcium in myocardial tissue
- Compare cardiac uptake to bone uptake on scan
- Heart:contralateral ratio > 1.5 is highly suggestive of ATTR
- 100% positive predictive value

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22. 35

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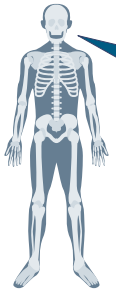
Bone Scintigraphy



- Conduct IFE testing prior to rule out AL-CM
- Pyrophosphate: radionucleotide that binds calcium in myocardial tissue
- Compare cardiac uptake to bone uptake on scan
- Heart:contralateral ratio > 1.5 is highly suggestive of ATTR
- 100% positive predictive value

All ATTR positive patients should undergo TTR gene sequencing to differentiate between ATTRwt and ATTRm/v

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22. 36

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Cardiac Amyloid Summary

AL - CM
- Misfolded proteins from abnormal proliferation in bone marrow
- Mortality 6 mo after cardiomyopathy
- Symptoms: nonspecific, heart & kidneys
- Diagnosis: bone marrow biopsy required

ATTRm/v - CM
- Misfolded proteins due to genetically inherited mutated variant of TTR gene
- Mortality 2-5 years after cardiomyopathy
- Symptoms: vary; neuropathy & cardiac

ATTR - CM
- Diagnosis: biopsy **or** bone scintigraphy + genetic testing

ATTRwt - CM
- Misfolded proteins randomly form and deposit
- Mortality 5-6 years after onset of symptoms
- Symptoms: heart failure, arrhythmias, & carpal tunnel

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Symptom and Comorbidity Management

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Heart Failure

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No data to support standard of therapy

BB, ACE/ARB/ARNI, and CCB poorly tolerated → patients rely on heart rate

May exacerbate hypotension from amyloid-associated autonomic dysfunction

✓

Loop diuretics to manage congestion

Aldosterone antagonists

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22.

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Arrhythmias

Atrial fibrillation

Anticoagulation (DOAC/VKA) in all patients

Amiodarone is rate/rhythm agent of choice

Heart Block

Common effect of amyloid, requires pacemaker +/- implantable cardioverter defibrillator (ICD)

Drugs

High doses of digoxin and non-dihydropyridines contraindicated, bind to amyloid fibrils

VT/aborted SVT

Implantable cardioverter defibrillator (ICD)

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22.

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Arrhythmias

Atrial fibrillation

Anticoagulation (DOAC/VKA) in all patients

Amiodarone is rate/rhythm agent of choice

Hea

amyl

pacer

implantable cardioverter defibrillator (ICD)

Intracardiac thrombi present in 27% of patients with cardiac amyloidosis

AL-CM had higher rates, 35%

Anticoagulation was associated with significantly decreased risk of intracardiac thrombus (p<0.006)

orted VT

ble ter or (ICD)

bind to amyloid fibrils

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Feng et al. *Circulation*. 2009 May 12;119(18):2490-7

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Arrhythmias

Atrial fibrillation

Anticoagulation (DOAC/VKA) in all patients

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Peripheral and Autonomic Nervous System

Neuropathy

Initial treatment typically with gabapentin or pregabalin

GI Effects

Nausea: ondansetron, prochlorperazine

Diarrhea: loperamide, atropine-diphenoxylate

Orthostatic Hypotension

Initial treatment typically with midodrine

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Nativi-Nicolau, et al. *Curr Opin Cardiol*. 2018;33(5):571-579 | Kittleson, et al. *Circulation*. 2020;142(1):e7-e22.

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Disease Modifying Therapies

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AL-CM Therapies

Chemotherapy

Melphalan + dexamethasone + stem cell transplant

Bortezomib + cyclophosphamide + dexamethasone (CyBorD)

Researching...

Monoclonal antibodies such as daratumumab

Doxycycline

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Grogan M, et al. *Heart* 2017;103:1065-1072 | Nativi-Nicolau, et al. *Curr Opin Cardiol*. 2018;33(5):571-579

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ATTR Disease-Modifying Therapies

Diflunisal (Novo-Diflunisal)

Diflunisal Trial Consortium
December 25th, 2013

Not FDA approved for this use

Inotersen (Tegsedi)

NEURO-TTR trial July 5, 2018

FDA approved October 5, 2018

Patisiran (Onpattro)

APOLLO trial July 5, 2018

FDA approved August 10, 2018

Tafamidis (Vyndamax, Vyndaqel)

ATTR-ACT trial Sept 13, 2018

FDA approved May 3, 2019

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before we dive into trials…

Neuropathy Impairment Score (NIH+7)

Assesses muscle weakness, sensory loss, muscle stretch, nerve conduction, vibratory detection, and heart rate variability.

Range 0-304; higher score is more impairment

Norfolk Quality of Life (QOL) Scale

Typically used for diabetic neuropathy. 47 questions that assess large, small, and autonomic nerve fiber symptoms and their impact on daily life activities.

Range -4 to 126; higher score is lower quality of life

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TTR Silencers

Diflunisal (Novo-Diflunisal)

Diflunisal Trial Consortium
December 25th, 2013

Not FDA approved for this use

Inotersen (Tegsedi)

NEURO-TTR trial July 5, 2018

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Tafamidis (Vyndamax, Vyndaqel)

ATTR-ACT trial Sept 13, 2018

FDA approved May 3, 2019

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Patisiran (Onpattro)

- Double stranded siRNA, cleaves TTR mRNA → reduced TTR protein production & deposits
- t ½ = 3.2 days, onset 10-14 days, Vd 0.25 L/kg, plasma protein binding <2%
- 0.3 mg/kg IV every 3 weeks, max dose 30 mg
- Not studied CrCl < 30 mL/min
- Not studied in moderate to severe hepatic impairment
- Infusion reactions (20%, premedicate), URI, AV block, nausea, muscle spasm/pain, dizziness, flushing
- Take with vitamin A

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Patisiran. In: Lexi-drugs online database. Hudson OH, Lexicomp Inc. 2020 Sept 17

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APOLLO Study

NEJM 2018: Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

Purpose	Phase III trial; patisiran has already shown a dose-dependent reduction of circulating TTR levels and potential to halt progression or improve disease control in phase II trials
Patients	225 patients ages 18-85 with ATTRm/v with polyneuropathy. Excluded liver transplant patients and NYHA III-IV. Average patient was a 62 year old white male
Interventions	Randomized 2:1 to patisiran 0.3mg/kg IV every 3 weeks or placebo
Outcomes	Primary: change from baseline modified neuropathy impairment score (mNIS+7) at 18 months Secondary: change in Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire, 10 meter walk test, and modified BMI to monitor nutritional status

Adams, et al. *N Engl J Med*. 2018;379(1):11-21.

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APOLLO Study

NEJM 2018: Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

Results	▪ mNIH+7: -34 points better with patisiran (95% CI -39.9 to -28.1, p<0.001) ▪ Norfolk QOL-DN: -21.1 points better with patisiran (95% CI -27.2 to -15.0, p<0.001) ▪ Safety: more infusion reactions (20% vs 10%). Severe ADR were reported more in placebo (36% vs 28%) Subgroup analysis of patients with cardiomyopathy: ▪ LV wall thickness (change from baseline -0.1mm ± 0.3mm vs -1.0mm ± 0.2mm, p=0.02) ▪ LV longitudinal strain (change from baseline 1.46% ± 0.48% vs 0.08% ± 0.28%, p=0.02) ▪ NT–proBNP (baseline to current ratio (pg/mL) 1.97:1 vs 0.89:1, p<0.001)
Conclusion	In patients with ATTRm/v with neuropathy, patisiran showed less progression of neuropathy and improved quality of life, as well as improved cardiac parameters in a subgroup analysis
Limitations	Primary outcomes focus on neuropathy, excluded NYHA III-IV, wasn't powered to look for significance in cardiac outcomes so these are hypothesis generating

Adams, et al. *N Engl J Med*. 2018;379(1):11-21.

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Inotersen (Tegsedi)

- Single stranded antisense oligonucleotide, binds and degrades TTR mRNA → ↓ TTR production
- t ½ = 32.3 days, Vd 293 L, plasma protein binding >94%
- 284 mg subcutaneously once weekly
- Not studied CrCl < 30 mL/min
- Not studied in moderate to severe hepatic impairment
- **Glomerulonephritis & thrombocytopenia** (BBW, REMS), stroke, hepatic impairment, hypersensitivity, inflammatory reactions
- Take with vitamin A

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Inotersen. In: Lexi-drugs online database. Hudson OH, Lexicomp Inc. 2020 Sept 22

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NEURO-TTR Trial

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

Purpose	Phase III trial; inotersen had previously shown reduction in circulating TTR levels
Patients	173 adults ages18 to 82 years old with stage 1 or stage 2 ATTRm/v proven by biopsy with polyneuropathy. Excluded other causes of polyneuropathy, NYHA III-IV, on other disease-modifying therapies. The average patient was a 59 year old white male
Interventions	2:1 inotersen 300mg subcutaneously weekly vs placebo, with vitamin A 3000 IU daily x 15 mo
Outcomes	Primary: change in modified neuropathy impairment score (mNIH+7), change in Norfolk quality of life score (QOL-DN)

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Benson, et al. *N Engl J Med.* 2018;379(1):22-31.

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NEURO-TTR Trial

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

Results	• NIH+7: –11.7 points better with inotersen (95% CI -26.4 to -13.0, p<0.001) with improvement in 50% • Norfolk QOL-DN: –19.7 points better with inotersen (95% CI -18.3 to -5.1, p<0.001) with improvement in 36% • Subgroup analysis of patients with cardiomyopathy: less of an improvement in QOL (p=0.04), same improvement NIH+7 • Safety: more thrombocytopenia (3%) and glomerulonephritis (3%), more nausea/vomiting and fever/chills
Conclusion	In patients with ATTRm/v with neuropathy, inotersen slowed neuropathy progression and improved QOL in patients with and without cardiomyopathy
Limitations	Primary outcomes focus on neuropathy, excluded NYHA III-IV, did not specifically look at cardiac function or improvement

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Benson, et al. *N Engl J Med.* 2018;379(1):22-31.

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ATTR Disease-Modifying Therapies

Diflunisal (Novo-Diflunisal)
Diflunisal Trial Consortium
December 25th, 2013
Not FDA approved for this use

Inotersen (Tegsedi)
NEURO-TTR trial July 5, 2018
FDA approved October 5, 2018

Patisiran (Onpattro)
APOLLO trial July 5, 2018
FDA approved August 10, 2018

Tafamidis (Vyndamax, Vyndaqel)
ATTR-ACT trial Sept 13, 2018
FDA approved May 3, 2019

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TTR Stabilizers

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Diflunisal (Novo-Diflunisal)

- Non-specific non-steroidal anti-inflammatory drug (NSAID); stabilizes TTR homotetramer (off label)
- t ½ = 8-12 hours, Vd 7.5 L, plasma protein binding >99%
- 250mg by mouth twice daily
- Decrease dose by 50% in CrCl < 50 mL/min
- No adjustment necessary for hepatic dysfunction
- **Contraindicated after CABG, increased risk of CVD/VTE, GI bleeding** (BBW) Increased risk of bleeding, hyperkalemia, renal dysfunction
- Take with a PPI

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Diflunisal. In: Lexi-drugs online database. Hudson OH, Lexicomp Inc. 2020 Sept 11

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Diflunisal Trial Consortium

JAMA 2013: Repurposing Diflunisal for Familial Amyloid Polyneuropathy

Purpose	In a phase I trial, diflunisal was found to stabilize TTR and prevent amyloid fibril formation. Goal to determine the effect on polyneuropathy progression in ATTRm/v
Patients	130 patients ages 18 to 75 years old with biopsy and genetically proven ATTRm/v with peripheral or autonomic neuropathy. Excluded patients with other causes of neuropathy, NYHA IV, on anticoagulation, CrCl <30. The average patient was a 59 year old white male
Interventions	1:1 diflunisal 250 mg oral BID or placebo for 2 years
Outcomes	Primary: difference in neuropathy impairment score (NIH+7) Secondary: quality of life questionnaire (36-item short-form health survey (SF-36)), modified BMI

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Berk et al. *JAMA*. 2013;310(24):2658-2667.

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Diflunisal Trial Consortium

JAMA 2013: Repurposing Diflunisal for Familial Amyloid Polyneuropathy

Results	▪ NIH+7 score declined by 16.3 points less with diflunisal (95% CI 8.1 - 24.5 points, p<0.001) ▪ SF-36 physical scores were 6.4 points higher with diflunisal (95% CI 2.9 - 9.8, p<0.001), SF-36 mental score were 4.9 points higher with diflunisal (95% CI 0.7 - 9.0, p=0.02) ▪ Safety: more musculoskeletal/connective tissue disorders (12.1% vs 29.7%) and more cardiac disorders (13.6% vs 23.4%)
Conclusion	Diflunisal for 2 years reduced rate of progression of neurological impairment and preserved quality of life in patients with ATTRm/v
Limitations	Primary outcomes focused on neuropathy, excluded NYHA IV, no mention of prevalence cardiac outcomes, does not specify what adverse events were, NSAIDs have known CV risks, no mention of comorbidities such as atrial fibrillation

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Berk et al. *JAMA*. 2013;310(24):2658-2667.

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Tafamidis (Vyndamax), tafamidis megumine (Vyndaquel)

- Binds TTR thyroxine binding site, stabilizes the TTR transport protein, slowing dissociation into monomers
- t ½ = 49 hours, Vd 18.5 L, plasma protein binding >99%
- Vyndamax: 61 mg by mouth daily
  Vyndaquel: 80 mg by mouth daily
  **doses not equivalent/substitutable
- Not studied CrCl < 30 mL/min
- Not studied in moderate to severe hepatic impairment
- Not well reported, do not use in pregnant or breastfeeding patients

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Tafamidis. In: Lexi-drugs online database. Hudson OH, Lexicomp Inc. 2020 Sept 17

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ATTR-ACT Trial

NEJM 2018: Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Purpose	Phase III trial; tafamidis showed stabilization of TTR in patients with ATTR-CM with acceptable safety profile and association between tafamidis and improved survival in phase II trials
Patients	441 patients aged 18-90 with ATTRwt or ATTRm/v confirmed with biopsy, cardiac involvement on echo, evidence of heart failure, NT-proBNP ≥ 600 pg/mL, 6 minute walk test distance >100 meters. Excluded NYHA IV, ICD, GFR <25, AST/ALT >2x ULN. The average patient was a 75 year old white male
Interventions	2:1:2 to tafamidis 80 mg, tafamidis 20 mg, or placebo for 30 months
Outcomes	Primary: all-cause mortality, frequency of CV hospitalizations Secondary: change from baseline 6 minute walk test and Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) at 30 months

Maurer, et al. *N Engl J Med*. 2018;379(11):1007-1016. 61

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ATTR-ACT Trial

NEJM 2018: Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Results	■ All-cause mortality 29.5% tafamidis vs 42.9% placebo (HR 0.7, 95% CI 0.51-0.96, p<0.001, NNT 8) beginning at 18 months ■ CV hospitalizations: 0.48 per year vs 0.70 per year (RR 0.68, 95% CI 0.56-0.81); in patients with NYHA III symptoms the tafamidis group had significantly more hospitalizations than placebo ■ Secondary: lower rate of decline in 6-minute walk test beginning at 6 months (p<0.001) and decline in KCCQ-OS score (p<0.001) ■ Safety: similar adverse events in both groups
Conclusion	Tafamidis reduced all-cause mortality, reduced decline in functional capacity, and improved quality of life across all ATTR-CM patients, and reduced CV hospitalizations in patients with less advanced HF symptoms
Limitations	Excluded NYHA IV, don't compare two dosing strategies, not diverse cohort and we know ATTRm/v-CM is prevalent in people of African descent

Maurer, et al. *N Engl J Med*. 2018;379(11):1007-1016. 62

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Other TTR Stabilizers

➔ **AG10**
- Binds the TTR tetramer and mimics co-inheritance of the TTR T119M mutation, stabilizing TTR to prevent fibril formation and deposition
- Phase III trial underway: ATTRIBUTE-CM

➔ **Epigallocatechin-3-gallate (EGCG)**
- Catechin in green tea, found to stabilize the TTR protein in preclinical studies, inhibiting amyloid fibril formation
- Little clinical benefit seen, uncertain use now that FDA approved agents exist

Nativi-Nicolau, et al. *Curr Opin Cardiol*. 2018;33(5):571-579 | Kittleson, et al. *Circulation*. 2020;142(1):e7-e22. | Judge, et al. *Cardiovasc Drugs Ther*. 2020;34(3):357-370. 63

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Cost to Patient

	Medicare Part D yearly cost & premium: University of Utah community pharmacy	Medicare Part D yearly cost & premium: Mail order	Average Wholesalers Pricing per year
Inotersen (Tegsedi)	$6,185	$2,750	$539,760
Patisiran (Onpattro)	Not on formulary	Not on formulary	$387,600 *
Tafamidis (Vyndamax) or tafamidis megumine (Vyndaqel	$4,614	$2,752	$270,000
Diflunisal (Novo-Diflunisal)	$159	$158	$724

* for a 70 kg patient

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Find a Medicare Plan: Drug Plan Part D. Medicare.gov | In: Micromedex Red Book online database. Truven Health Analytics, Inc. Ann Arbor, MI. 2020

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Advanced Heart Failure Therapies

Left Ventricular Assist Device (LVAD)

Stage D heart failure

Use is challenging due to small left ventricle cavity and right ventricular dysfunction is usually also present

Heart Transplant

May be considered in patients with stage D heart failure.

Often heart-liver transplant is performed in patients with ATTRm/v-CM at risk for neuropathy

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Nativi-Nicolau, et al. *Curr Opin Cardiol.* 2018;33(5):571-579 | Kittleson, et al. *Circulation.* 2020;142(1):e7-e22.

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Cardiac Amyloid Summary

AL - CM

- Misfolded proteins from abnormal proliferation in bone marrow
- Mortality 6 mo after cardiomyopathy
- Symptoms: nonspecific, heart & kidneys
- Diagnosis: bone marrow biopsy required
- Treatment: chemotherapy +/- stem cell transplant

ATTRm/v - CM

- Misfolded proteins due to genetically inherited mutated variant of TTR gene
- Mortality 2-5 years after cardiomyopathy
- Symptoms: vary; neuropathy & cardiac
- Treatment with TTR silencers (patisiran, inotersen) if have polyneuropathy

ATTR - CM

- Diagnosis: biopsy **or** bone scintigraphy + genetic testing
- Treatment with TTR stabilizers (tafamidis and/or diflunisal) if disease isn't advanced

ATTRwt - CM

- Misfolded proteins randomly form and deposit
- Mortality 5-6 years after onset of symptoms
- Symptoms: heart failure, arrhythmias, & carpal tunnel

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Looking Forward

Many trials underway!

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TTR Disruptors

→ **Doxycycline + Taurosodeoxycholic acid (TUDCA)**
- Synergistic effect of doxycycline, shown to remove amyloid deposits in animals, and TUDCA, a biliary acid that lowers non-fibrillar TTR deposits
- Conflicting preclinical trial results, concern for side effects

→ **Monoclonal antibodies**
- Many under study

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Detection in Minority Populations

→ **SCAN-MP trial**
- Working to help detect ATTR-CM in minority subjects with heart failure

→ **TEAM Amylose**
- Frequency of cardiac amyloidosis in Caribbean Islanders

→ **Large-scale biobank genotype studies**
- Determine prevalence of TTR mutations in different populations

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And many more

→ **APOLLO-B study**
- Evaluation of patisiran in participants with ATTR-CM

→ **HELIOS-B study**
- Evaluating vutrisiran in patients with ATTR-CM

→ **CARDIO-TTRansform study**
- Evaluating the efficacy and safety of AKCEA-TTR-LRx in patients with ATTR-CM

→ **Transthyretin Cardiac Amyloidosis in HFpEF**

→ **Screening for Transthyretin-Related Familial Amyloidotic Polyneuropathy**

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Takeaway

01 The Disease
Cardiac amyloidosis is an underdiagnosed cause of heart failure with high morbidity/mortality. Raising suspicion is key!

02 3 Types
Light chain (AL-CM), mutant/variant transthyretin (ATTRm/v-CM), and wild type transthyretin (ATTRwt-CM)

03 Heart Disease Management
Poor tolerance of BB, ACE/ARB/ARNI, CCB
Nondihydropyridines & high doses of digoxin contraindicated
AFib requires anticoagulation

04 TTR Silencers
Patisiran (Onpattro) and Inotersen (Tegsedi) can be used for ATTRm/v with neuropathy

05 TTR Stabilizers
Diflunisal (Novo-diflunisal) and tafamidis (Vyndamax, Vyndaqel) can be used in all ATTR-CM

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