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Diastolic Heart Failure and Cardiac Amyloidosis

-The Forgotten Piece of the Heart Failure Story

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November 14, 2019

Disclosures

- Research funding
  - Ionis
  - Eidos

- I will discuss about novel and investigational treatments for transthyretin cardiac amyloidosis

Amyloidosis

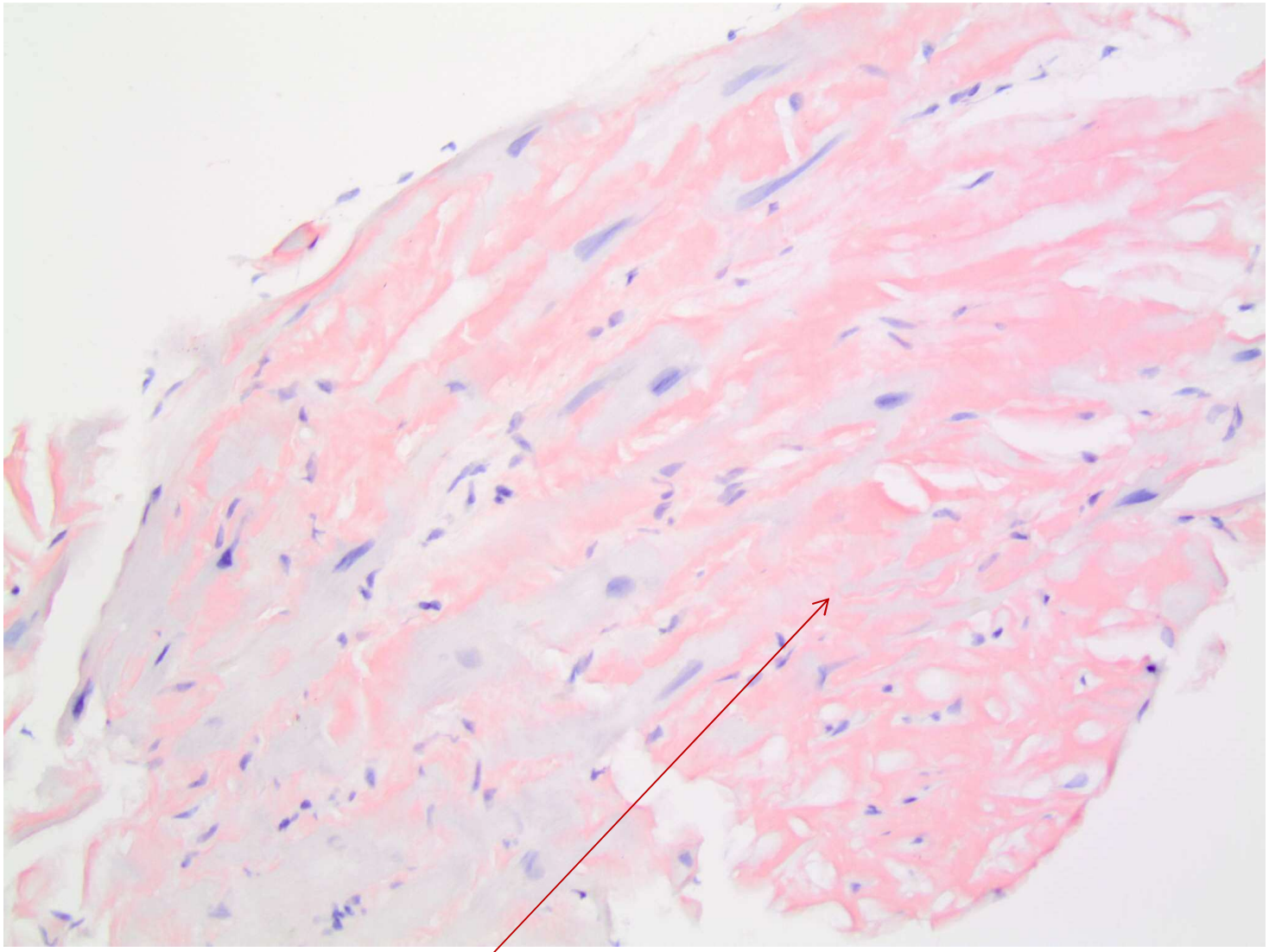
- Group of protein-folding disorders in which ≥1 organ is infiltrated by proteinaceous deposits known as amyloid

- More than 30 different precursor proteins have the propensity to form amyloid fibrils.

- Common precursor proteins that deposit in the heart are
  - Immunoglobulin light chain proteins
  - Immunoglobulin heavy chain proteins
  - Transthyretin
  - Serum amyloid A
  - Apolipoprotein A I

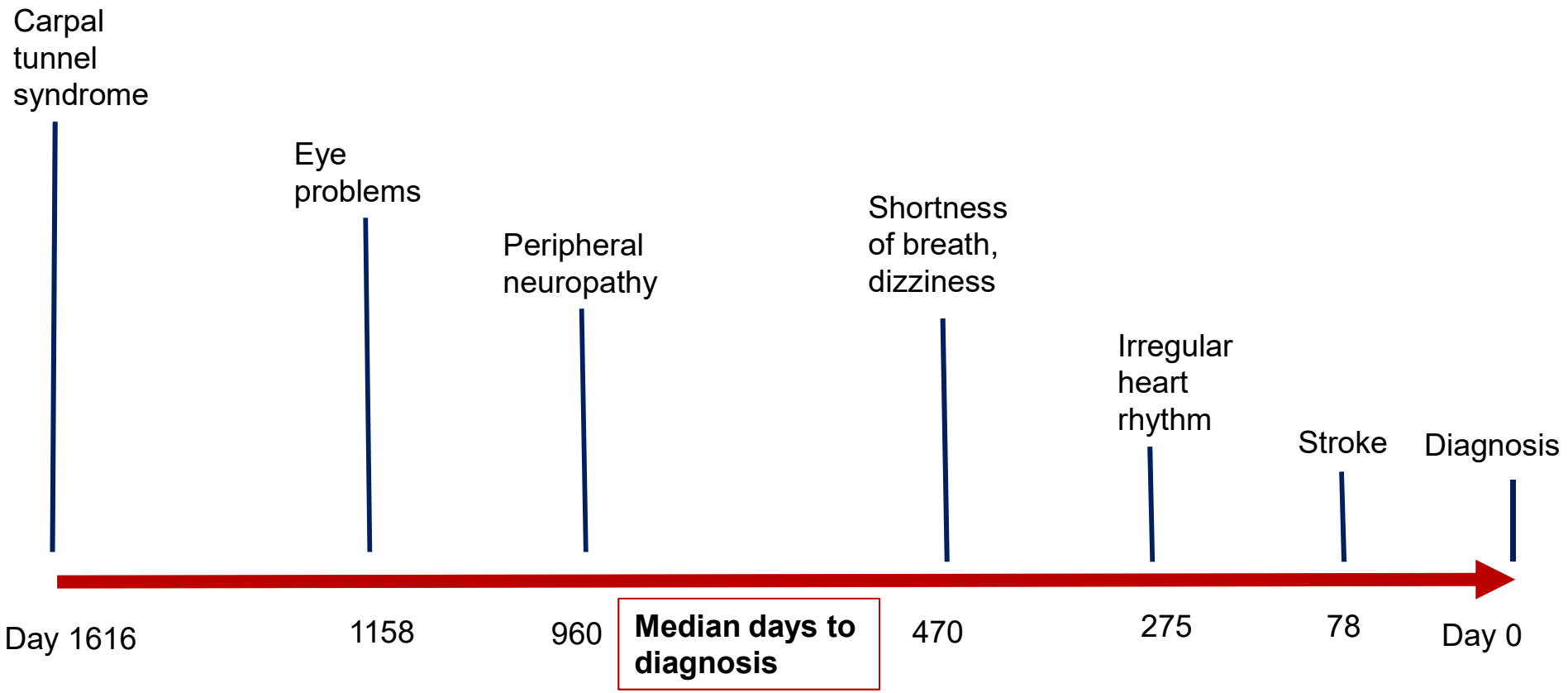
Rodney H. Falk Circulation. 2005;112:2047-2060
Papotsidakis N et al. J Card Fail. 2018; 24(2):131-133

Congo Red Stain

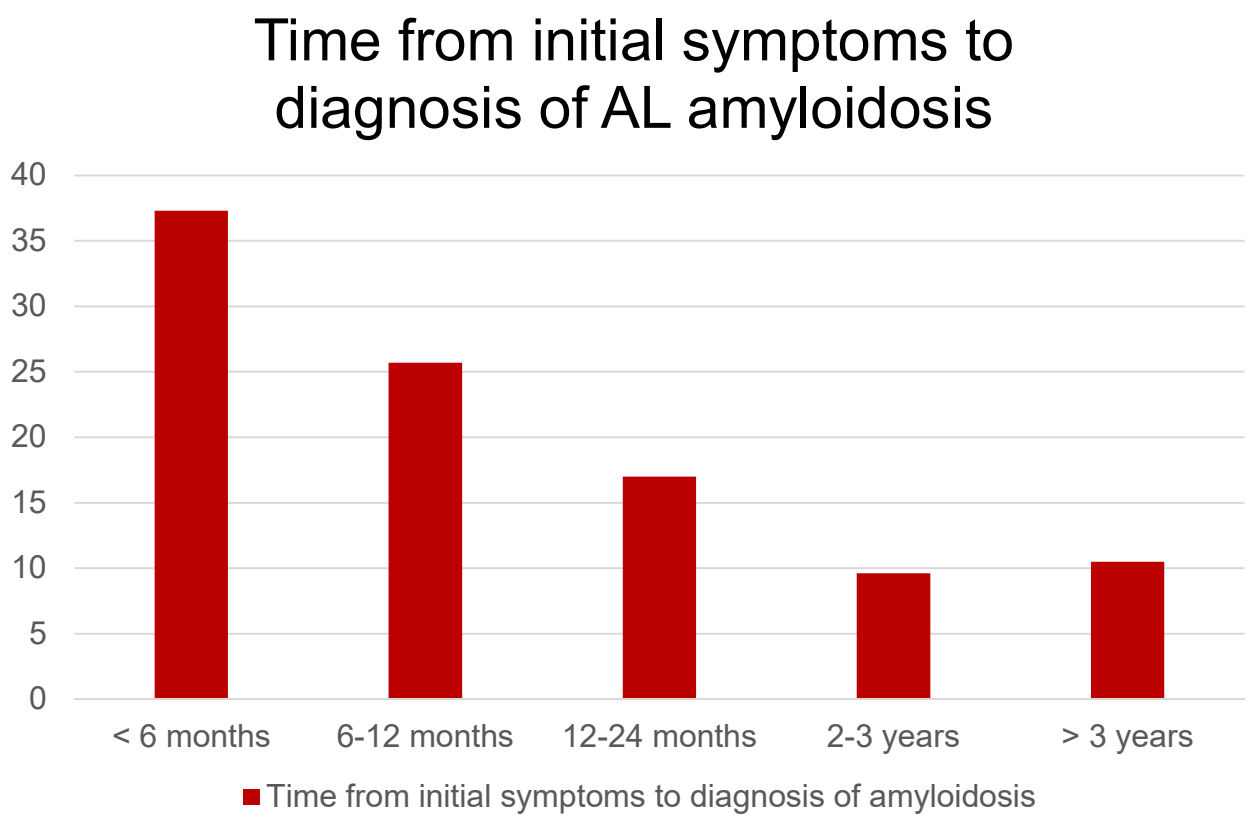


Amorphous, eosinophilic deposits are congophilic

Amyloidosis – Great pretender

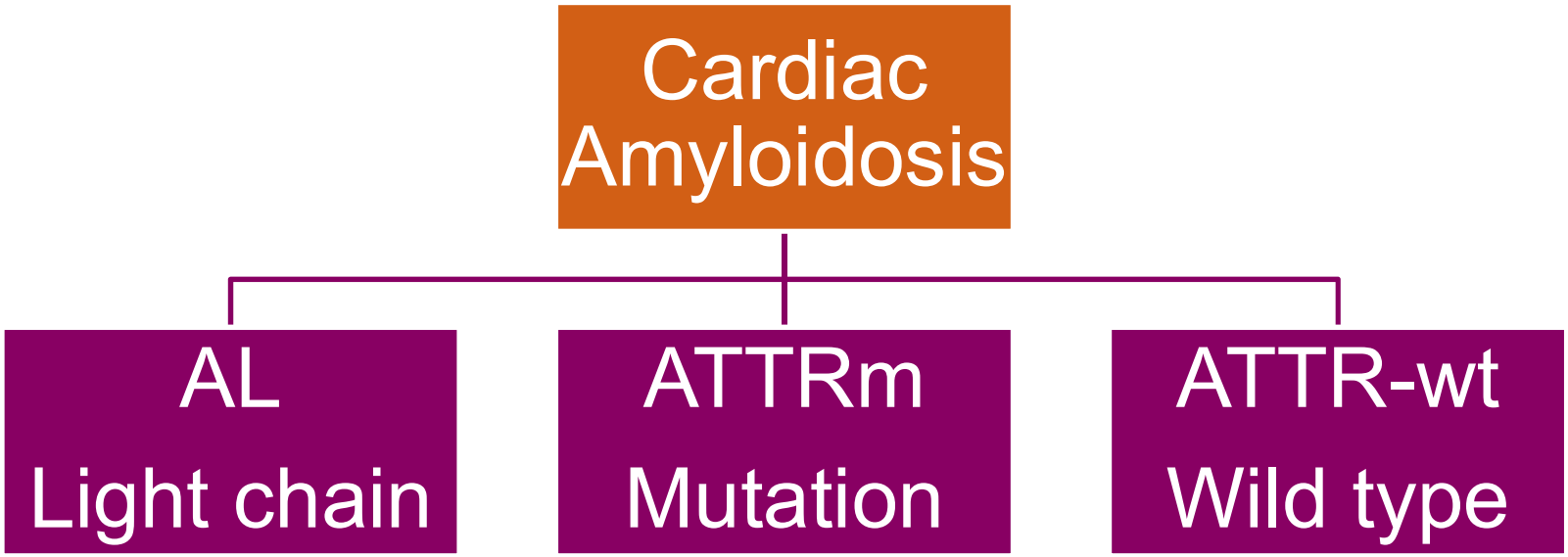


Amyloidosis – Delayed diagnosis



Lousada et al. Advances in Therapy. 2015; 32(10): 920-928

Nomenclature – precursor protein



Others:
AFib
AA

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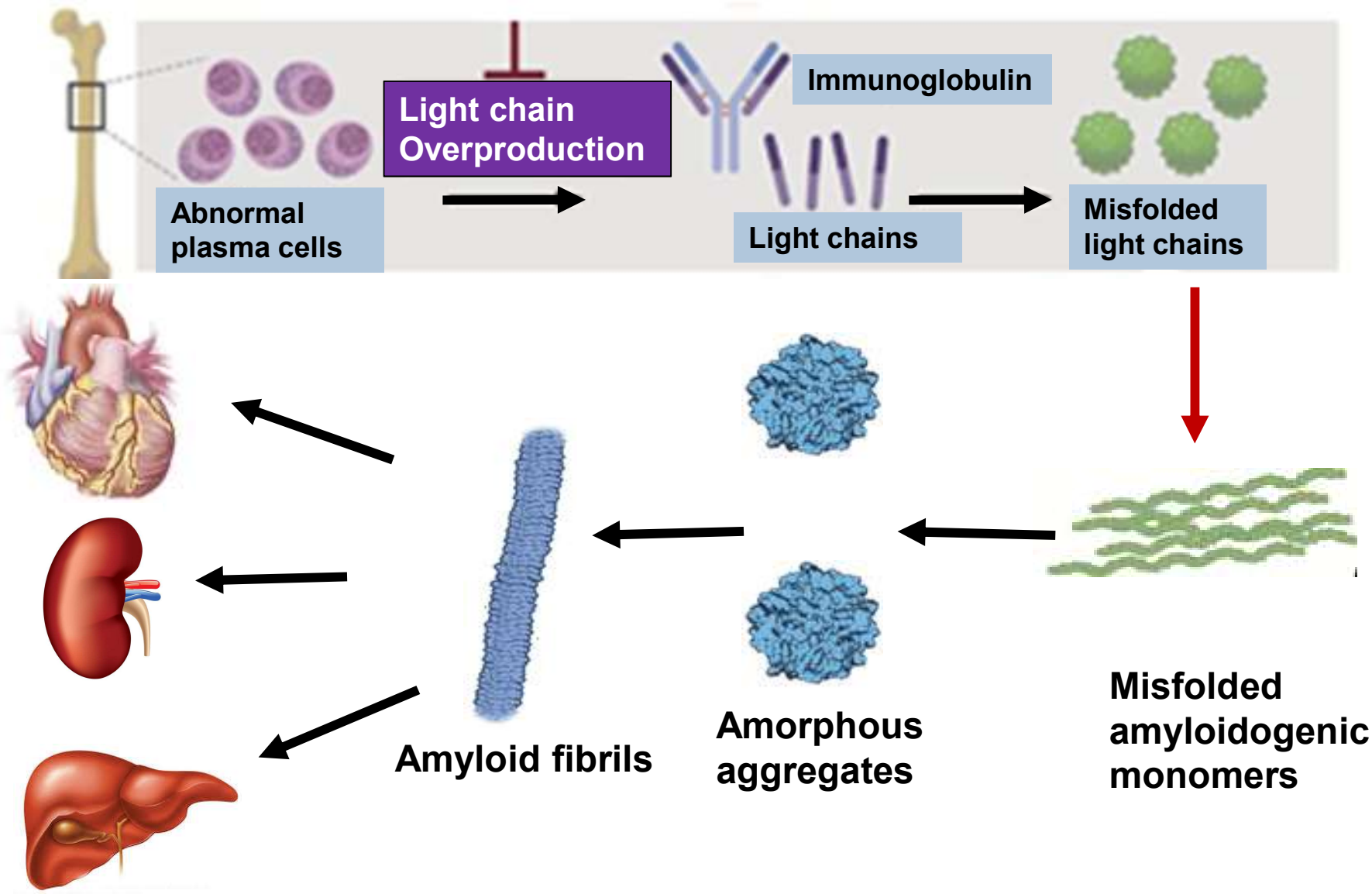
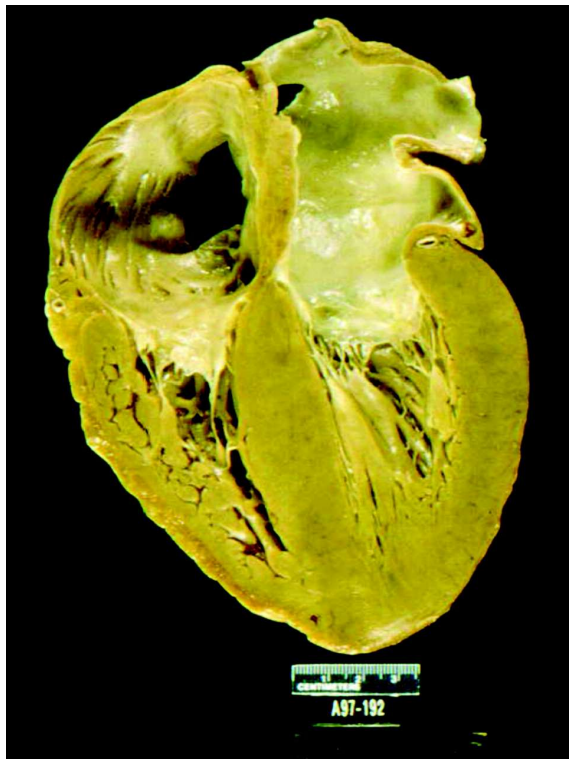
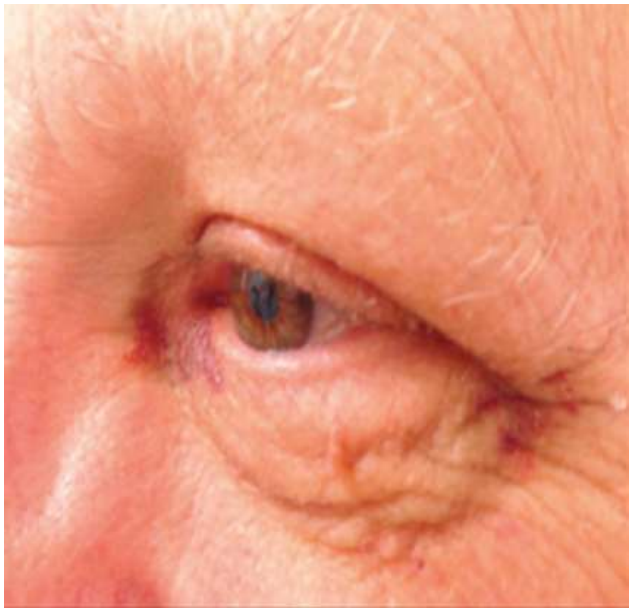
Rodney H. Falk Circulation. 2005;112:2047-2060

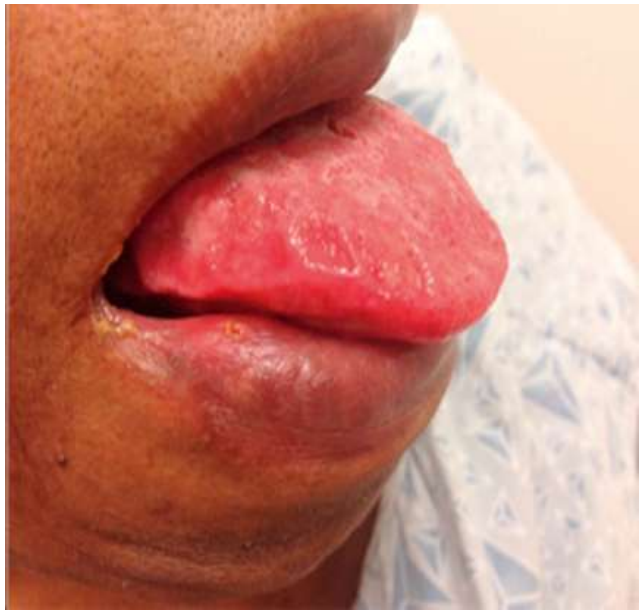
Protein Deposition in AL- Amyloidosis



AL Amyloidosis

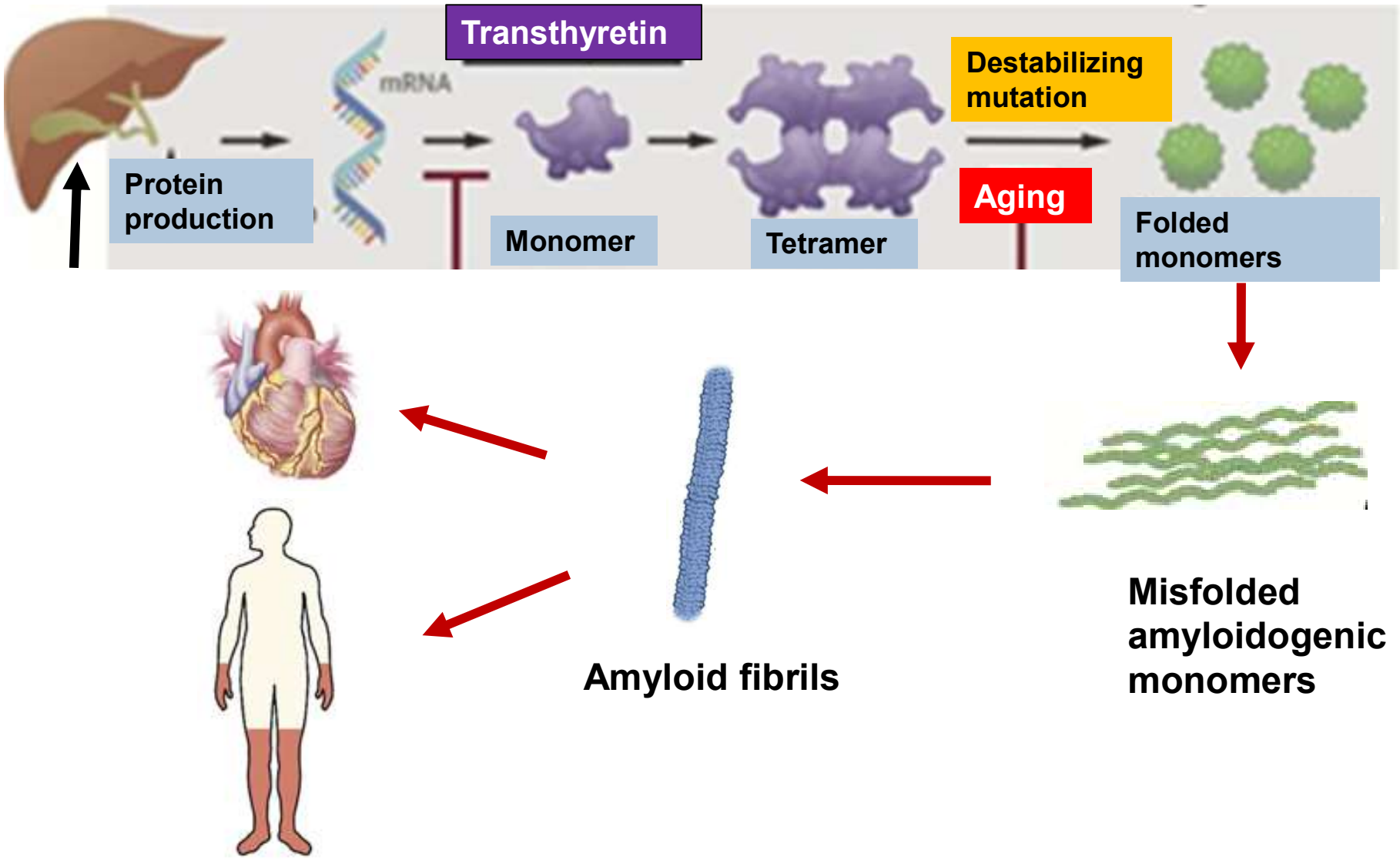






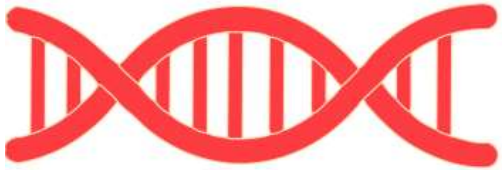
Rodney H. Falk Circulation. 2005;112:2047-2060

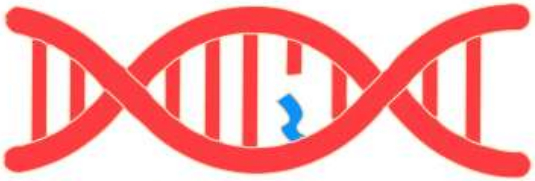
Protein Deposition in Transthyretin Amyloid



Transthyretin Mutation

Normal gene



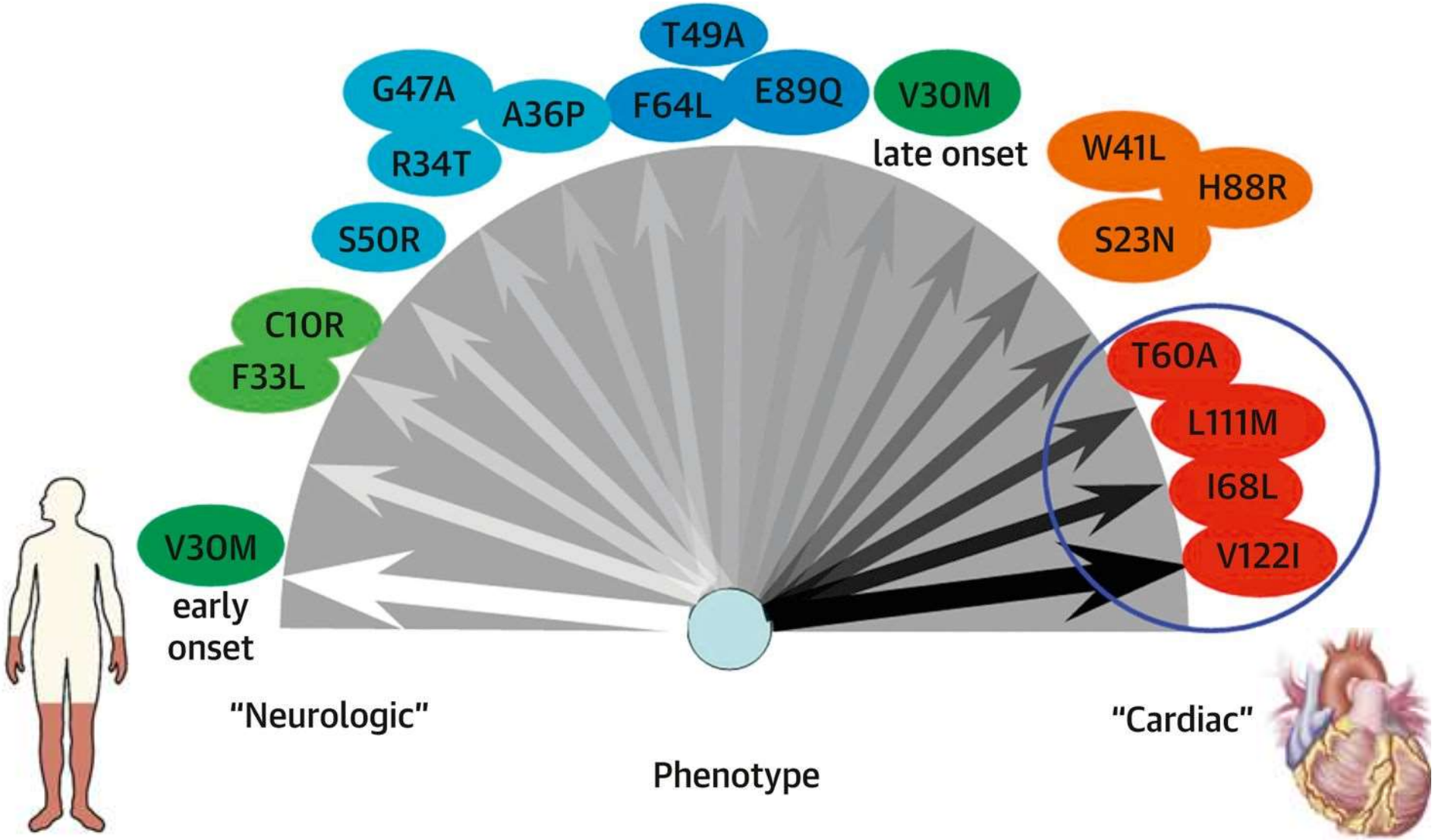


Gene Mutation

Protective Mutation
- **T119M**

Destabilizing Mutation
- **V122I**
- **V30M**
- **T60A**

Hereditary/mutant TTR Amyloidosis



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Marc J. Semigran JACC 2016;68:173-175

Wild Type TTR Amyloidosis

Other names

- Senile cardiac amyloidosis
- Senile systemic amyloidosis
- Age-related cardiac amyloidosis

- Abbreviation: ATTR-wt

- Carpal tunnel syndrome
- Biceps tendon rupture (Pop-eye sign)
- Spinal stenosis

2 – 10 years before heart failure symptoms

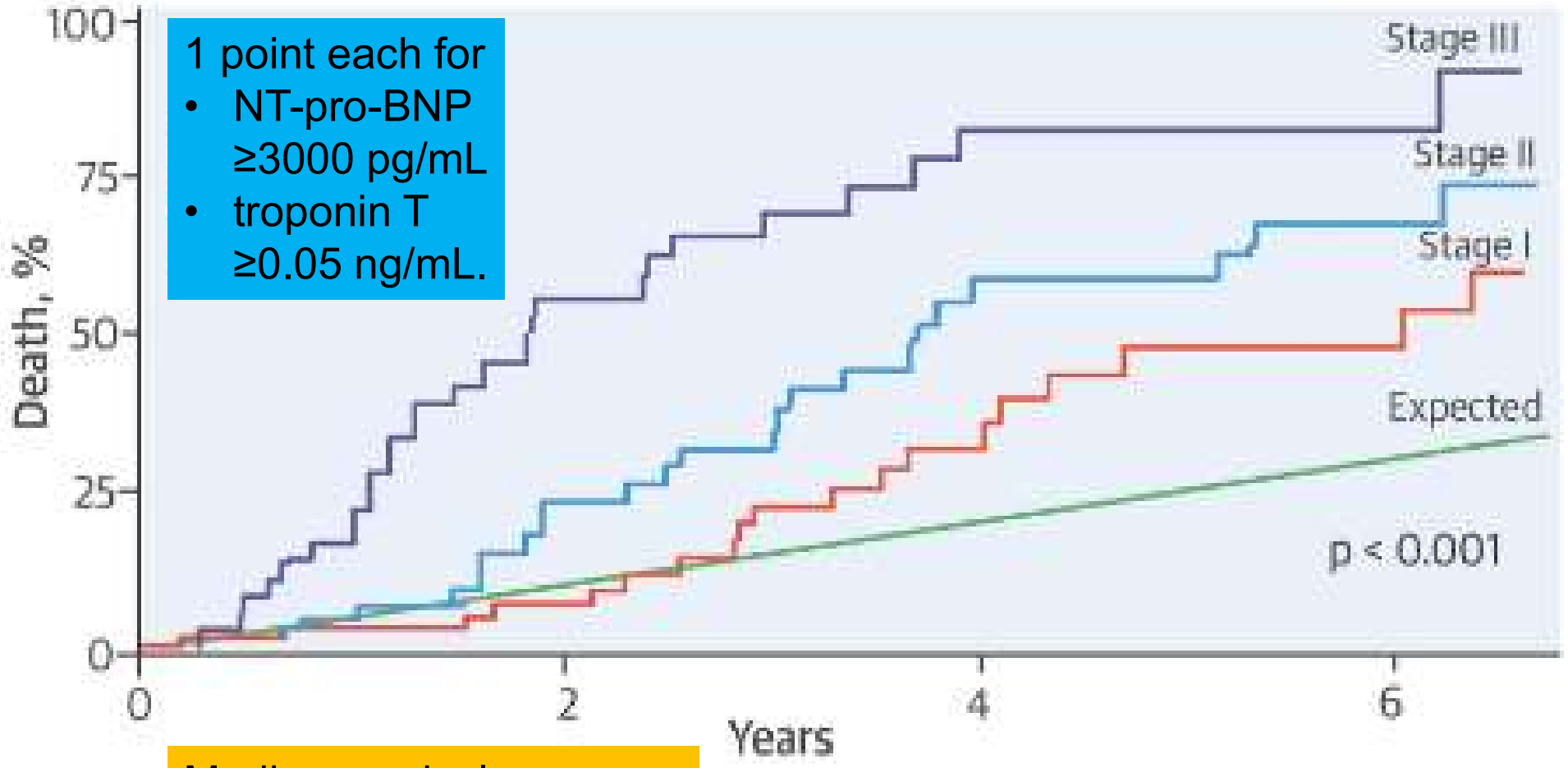
	Hereditary ATTRm	Wild-type ATTR-WT
Age of onset	• Variable (depends on mutation)	• Average 75 yrs.
Gender (M/F)	• 50%/50%	• 95%/5%
Affected organs	• Nerves • Heart • Eyes, GI tract	• Heart
Median survival after diagnosis without treatment	• ~ 2.5 years (Val122Ile)	• ~ 3.5 years

Rudberg FL et al. *JACC 2019; 73(22):2872-2891.*

Cardiac Amyloidosis – Is it rare?

AL-Amyloid	• 10 people per million • ~ 3000 cases per year • 40-50% cardiac involvement
Hereditary ATTRm	• Val122Ile: 3.4% of African Americans • Thr60Ala : ~ 1% Northern Ireland • 25,000 – 120,000 patients in US
Wild type ATTR-wt	• ~ 25% of adults > 85 yrs • 13% heart failure patients > 60 yrs • ~ 1 million patients in US

Survival in TTR amyloidosis

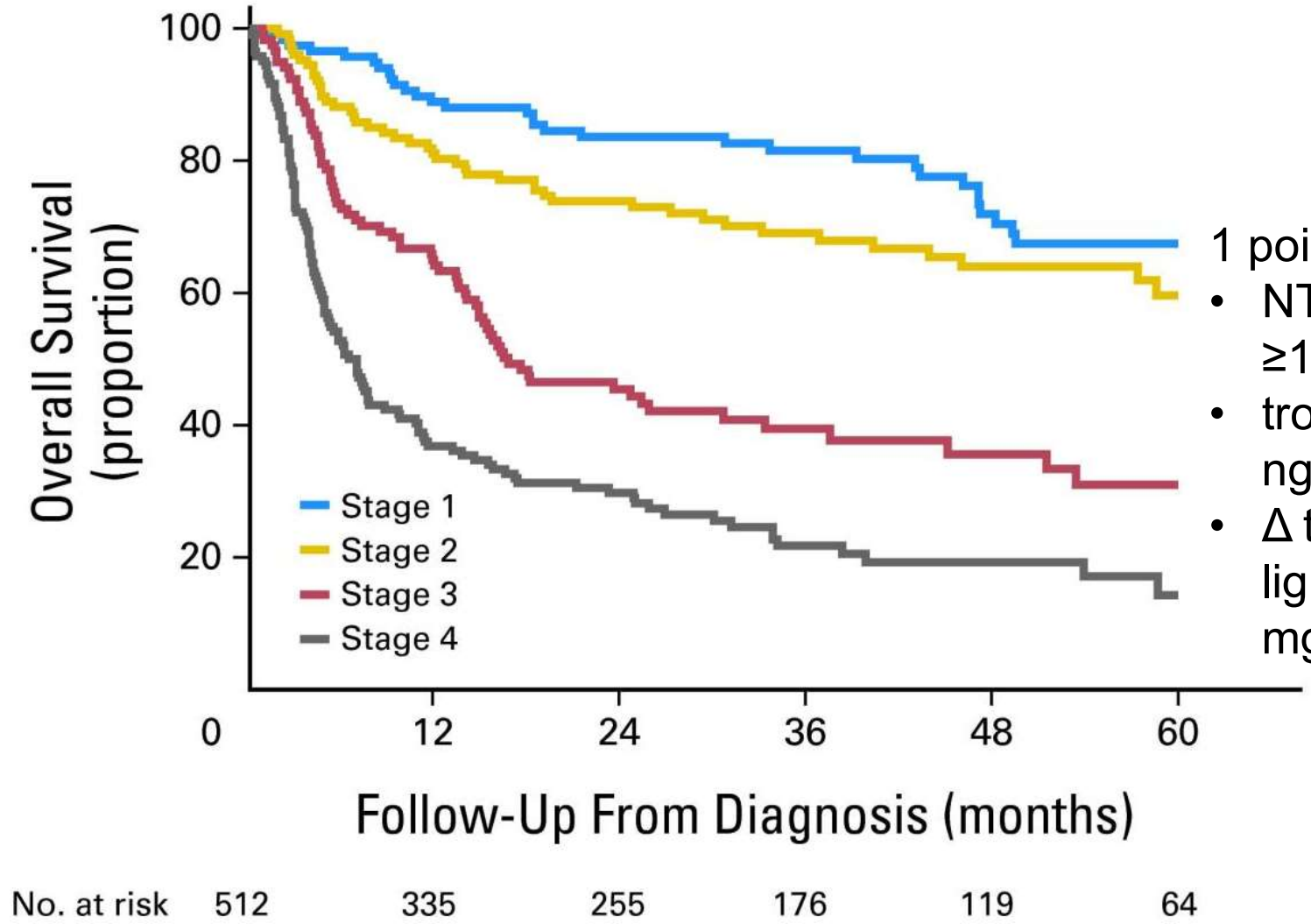


1 point each for
- NT-pro-BNP ≥3000 pg/mL
- troponin T ≥0.05 ng/mL.

Median survival
Stage 1 – 66 months
Stage 2 – 42 months
Stage 3 – 20 months

Grogran M et al. JACC 2016;68: 1014-20

Survival in AL- amyloidosis



1 point each for

- NT-pro-BNP ≥1800 pg/mL
- troponin T ≥0.025 ng/mL
- Δ the κ and λ free light chains ≥18 mg/dL.

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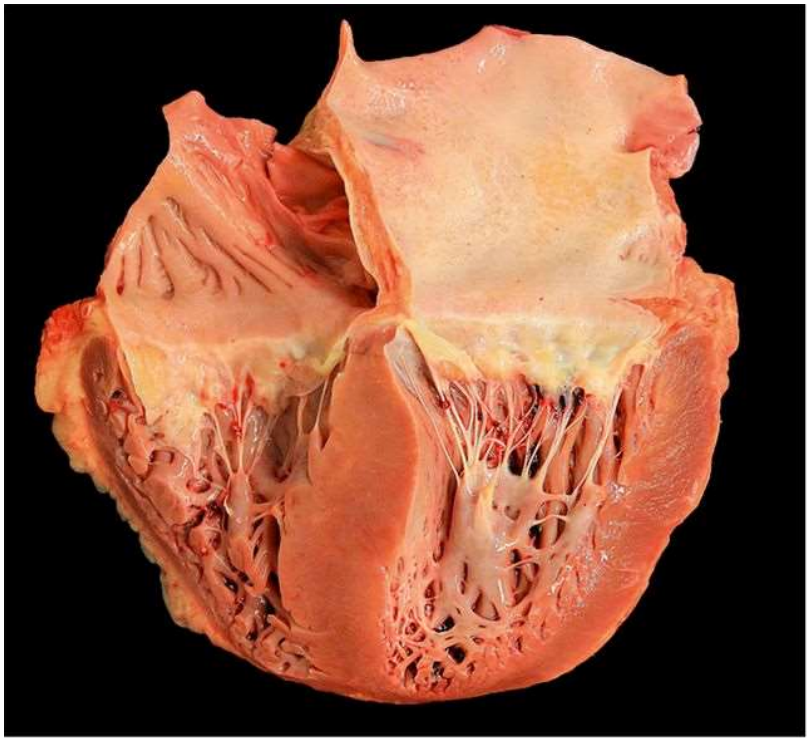
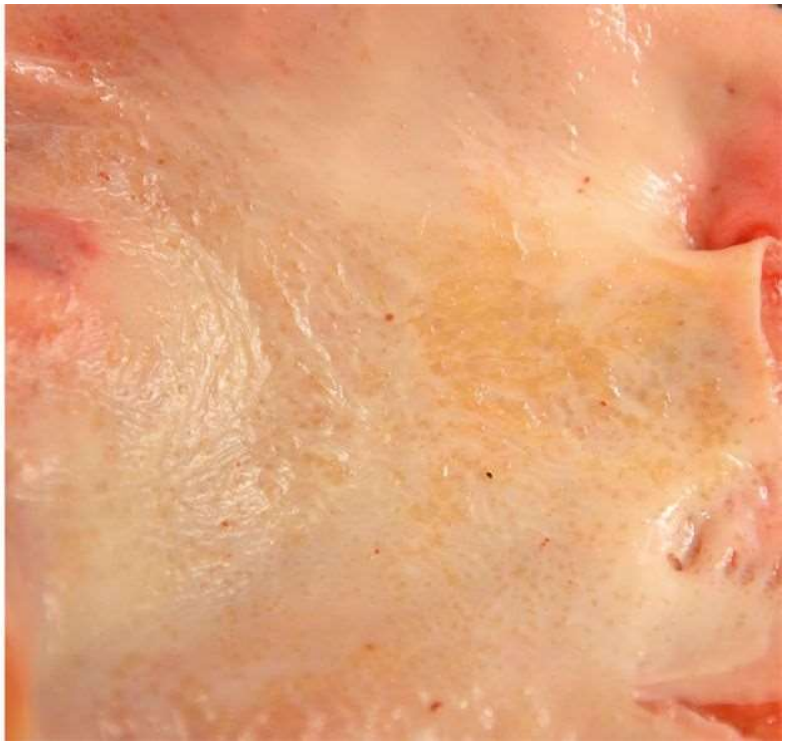
Kumar S et al.J Clin Oncol.2012;30:989–995.

Cardiac Amyloidosis





Falk RH, et al. JACC 2016;68:1323-1341

Clinical features

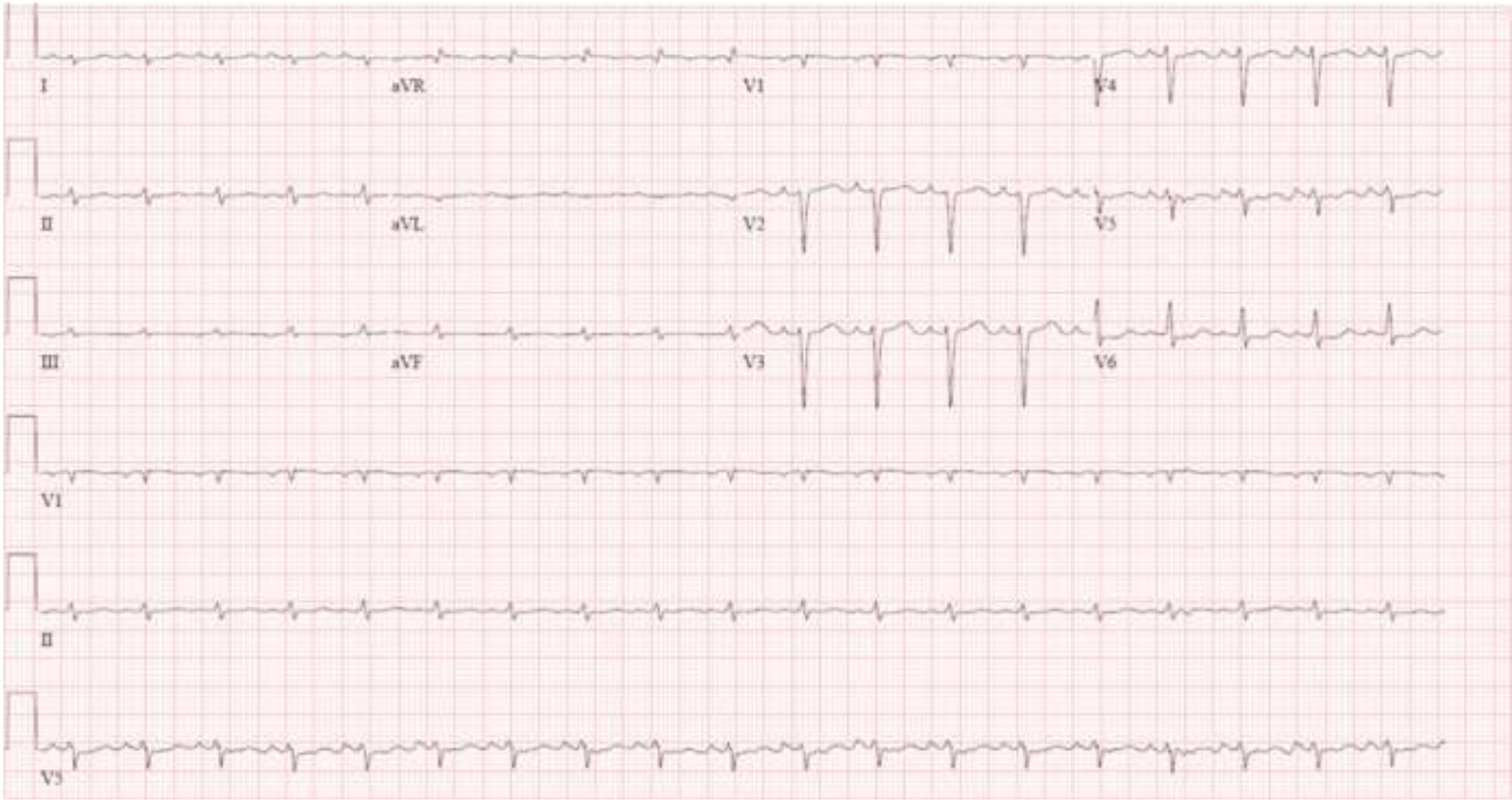
- Common symptoms
  - ❑ exercise intolerance
  - ❑ peripheral edema / leg swelling
  - ❑ Ascites / abdominal bloating
  - ❑ Chest pain / chest fullness
- Exertional syncope / passing out – due to low and fixed cardiac output
- Trouble sleeping
  - ❑ Orthopnea – sleeping with pillows
  - ❑ PND – waking up after 3-4 hours due to shortness of breath
- Dizziness / lightheadedness

Maurer et al. *Circulation 2017;135:1357-1377.*

When to suspect cardiac amyloidosis

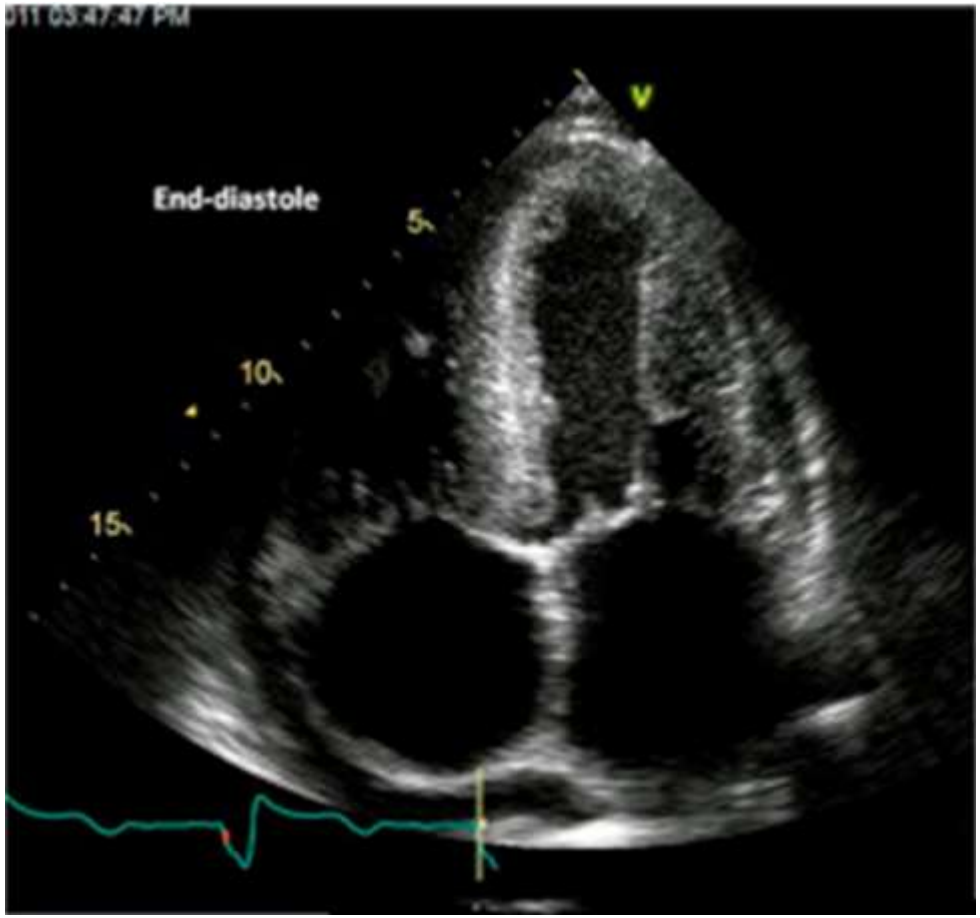
- In any patient with heart failure, unexplained increased thickness of heart muscle and small chambers
- Abnormal ratio between heart thickness and ECG
- Bilateral carpal tunnel syndrome, lumbar spinal stenosis, or spontaneous biceps tendon rupture
- Diffuse late gadolinium enhancement on cardiac MRI
  Apical sparing on echocardiogram
- Unexplained neuropathic pain, orthostatic hypotension, and a diagnosis of hypertrophic cardiomyopathy after 60 years
- Intolerance to routine heart failure medications

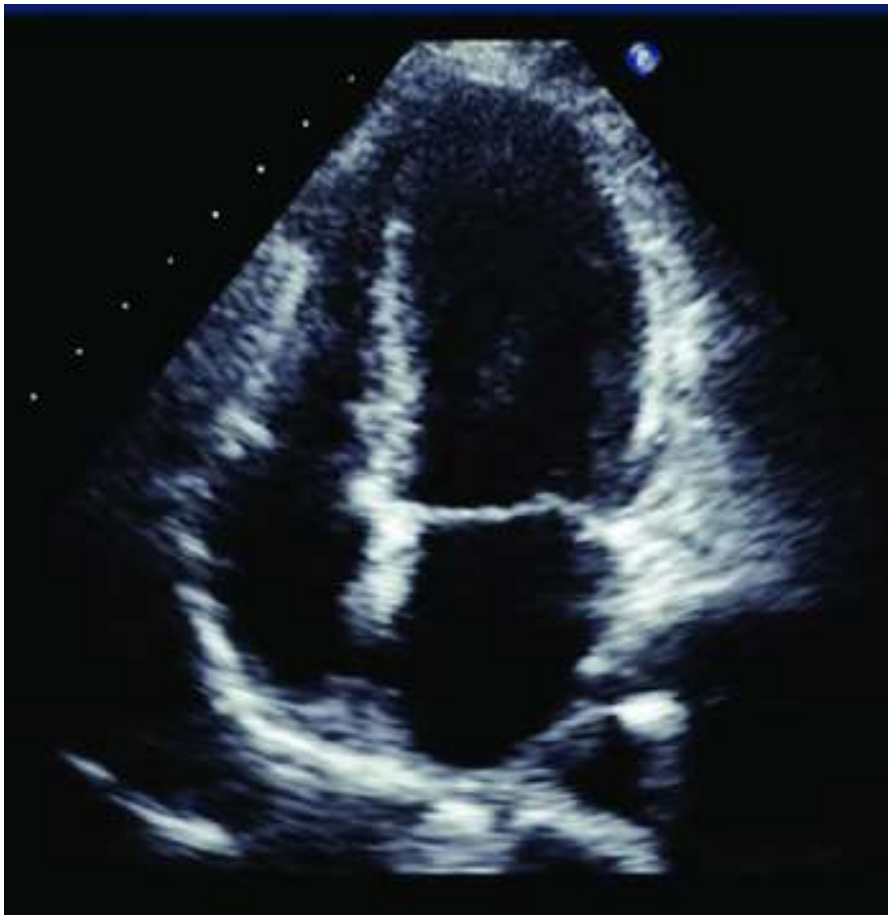
ECG – Cardiac Amyloidosis



Cyrille NB et al. Am J Cardiol. 2014;114:1089–1093
Mussinelli R et al. Ann Noninvasive Electrocardiol. 2013;18:271–280

Echocardiogram





Amyloidosis

Normal

Falk, R.H. et al. JACC. 2016;68(12):1323-41

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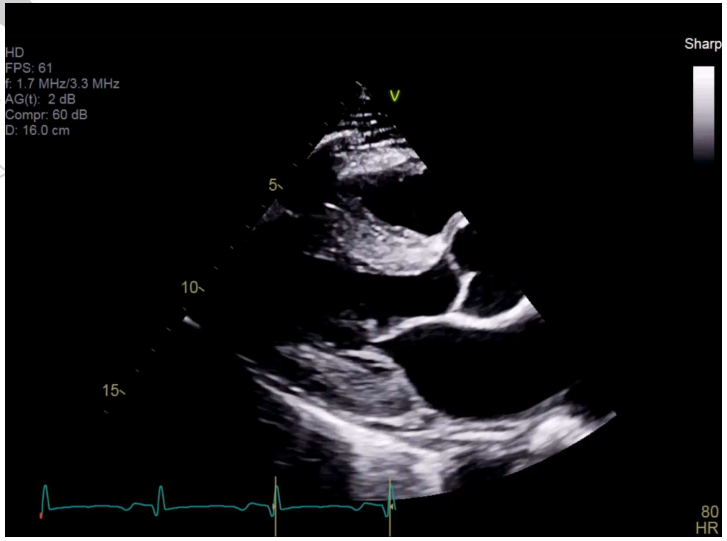
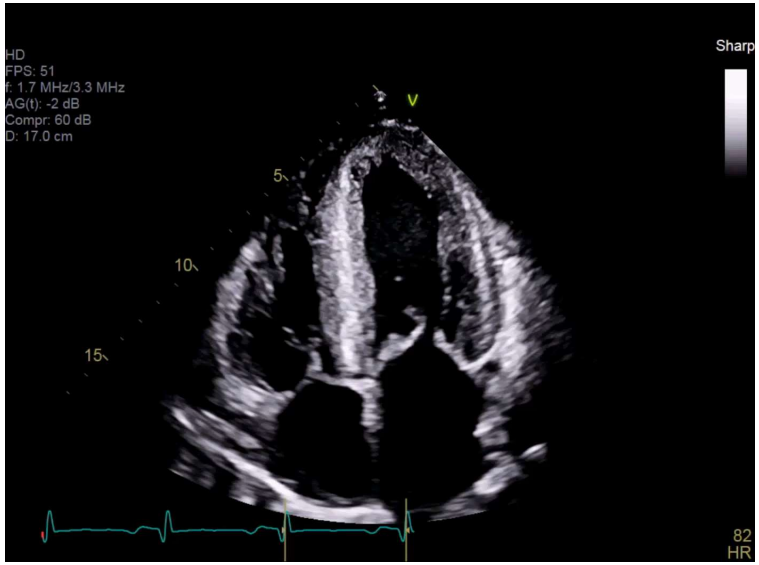
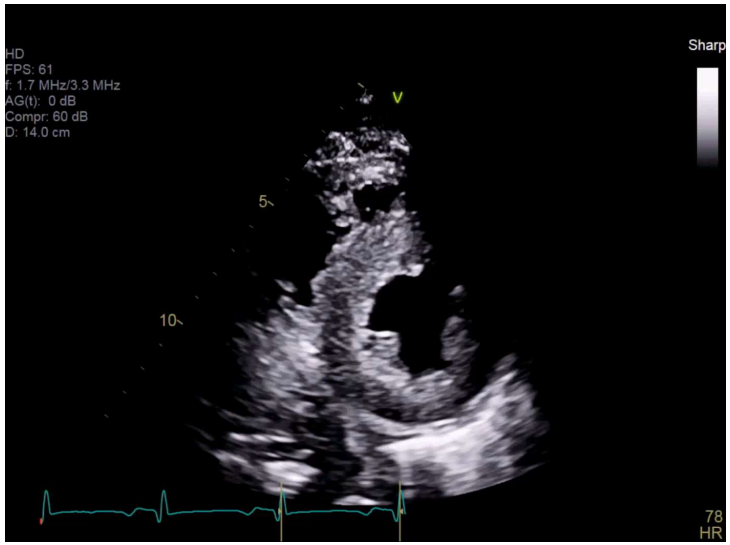
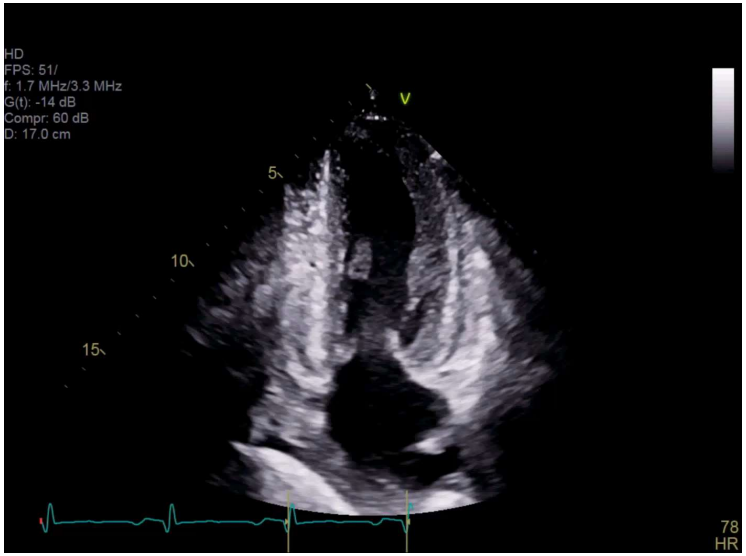
Echocardiogram

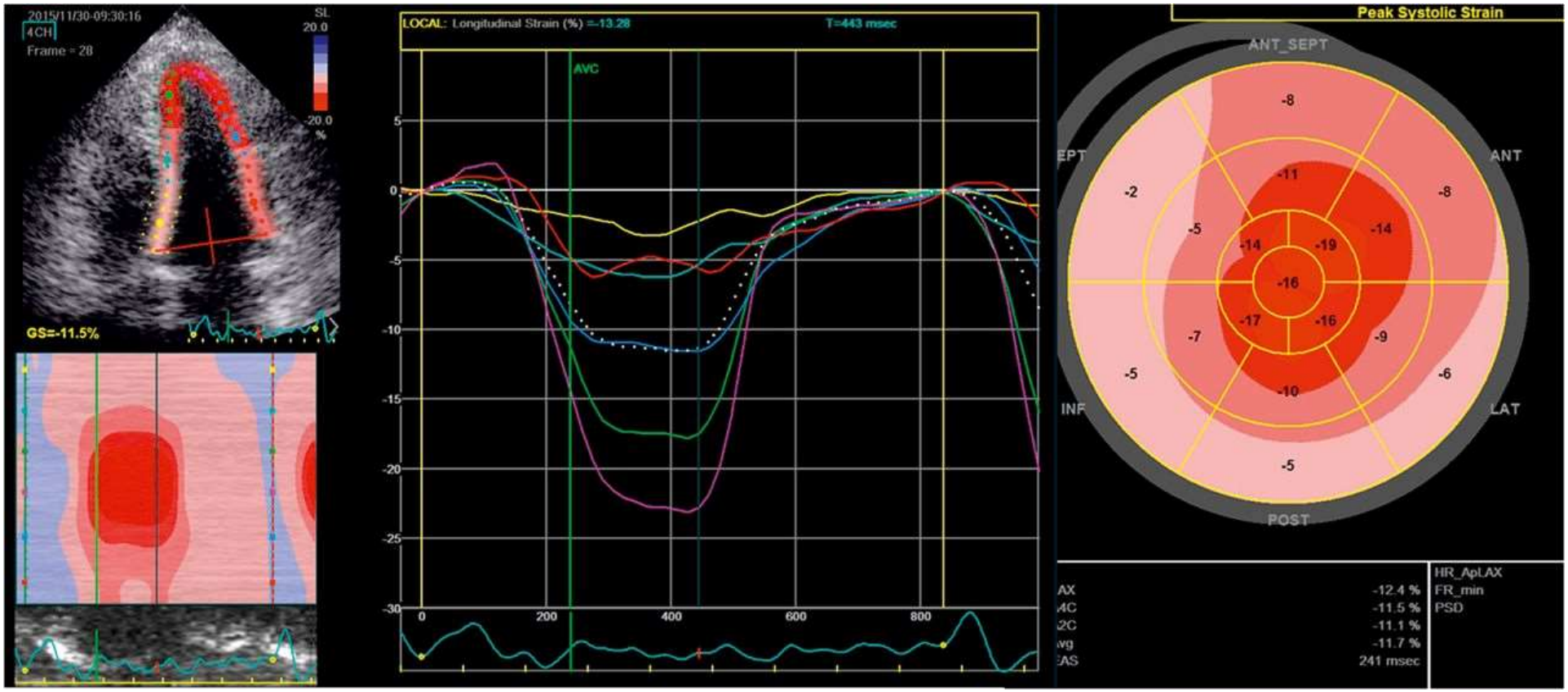






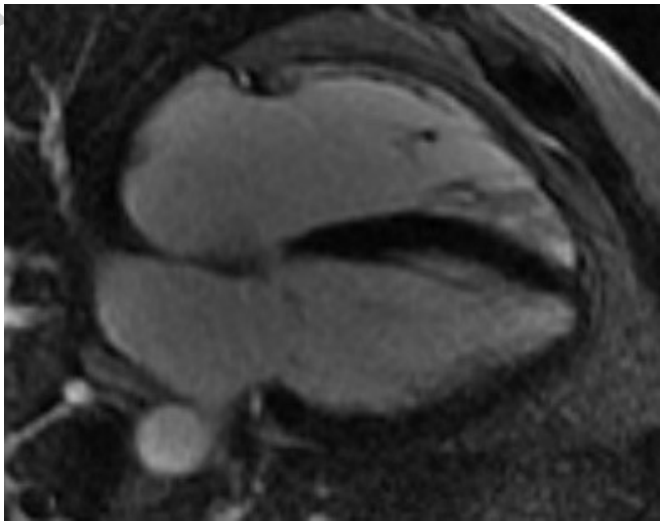


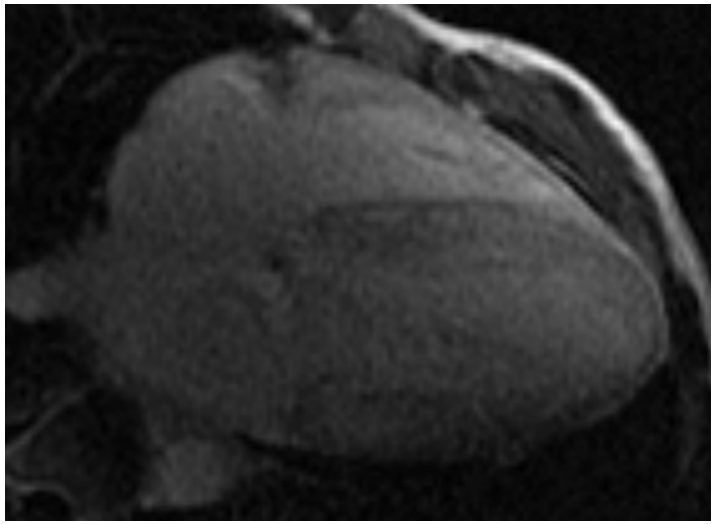
Preserved Apical Strain
“Cherry on Top”

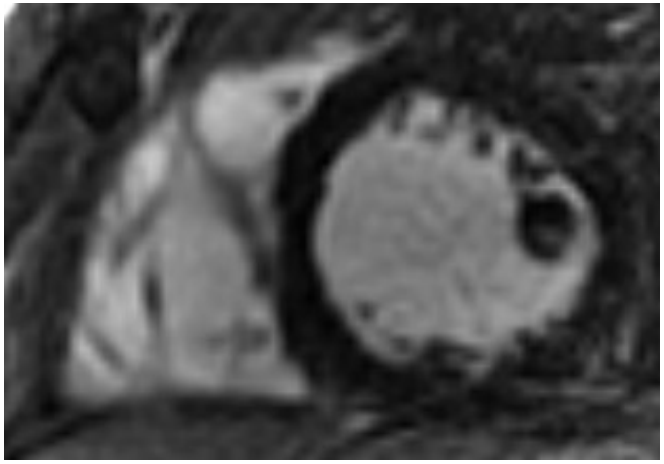


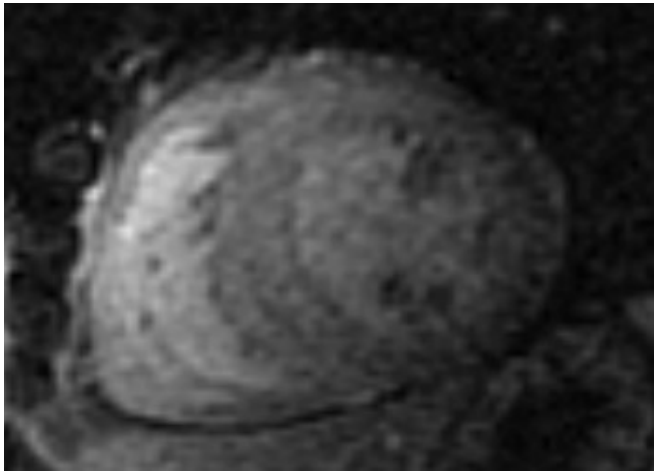
Falk, R.H. et al. JACC. 2016;68(12):1323-41

Cardiac MRI









Normal

Amyloidosis

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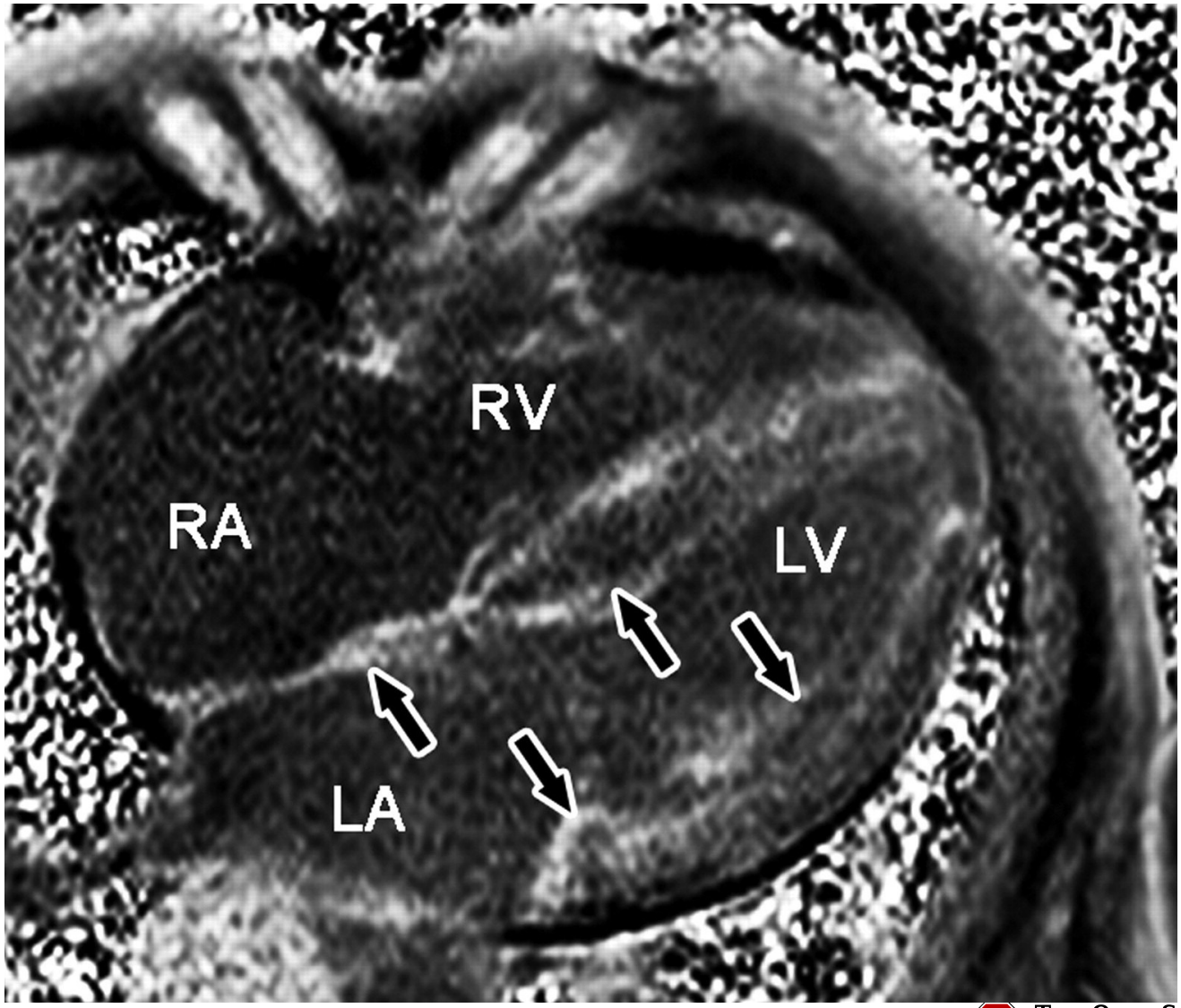
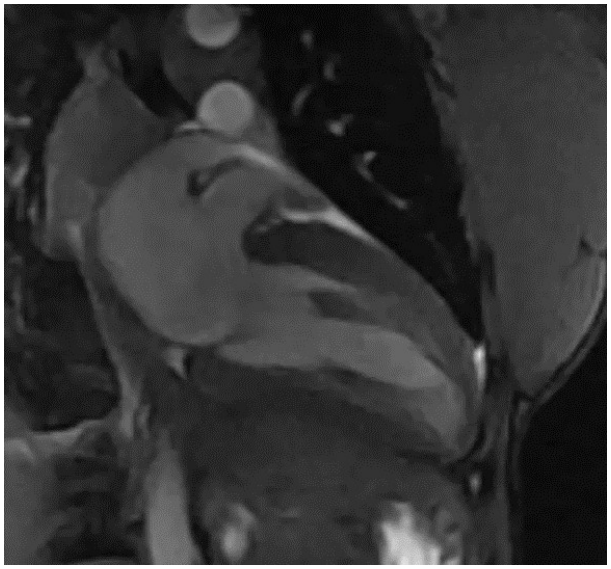
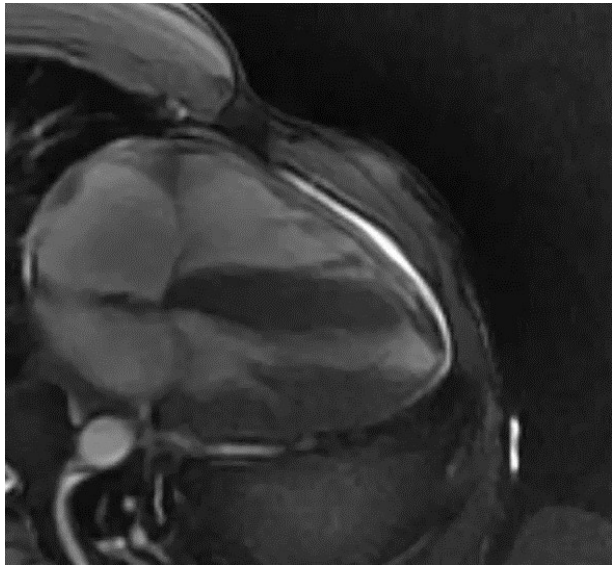
Cardiac MRI
Diffuse Late Gadolinium Enhancement

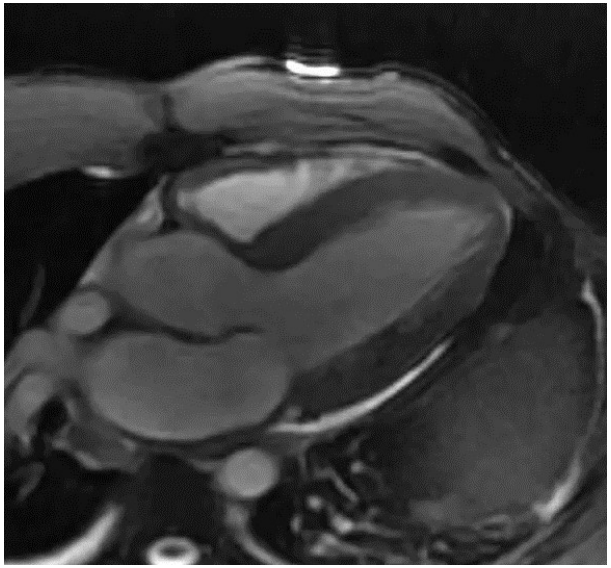


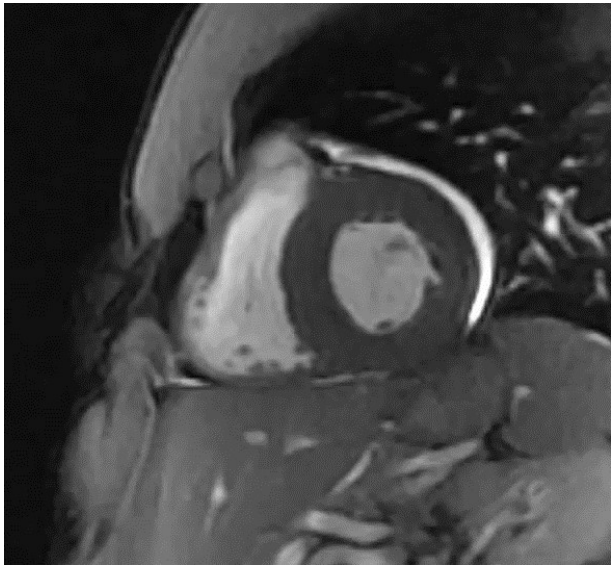
Rodney H. Falk Circulation. 2011;124:1079-1085.

Cardiac MRI

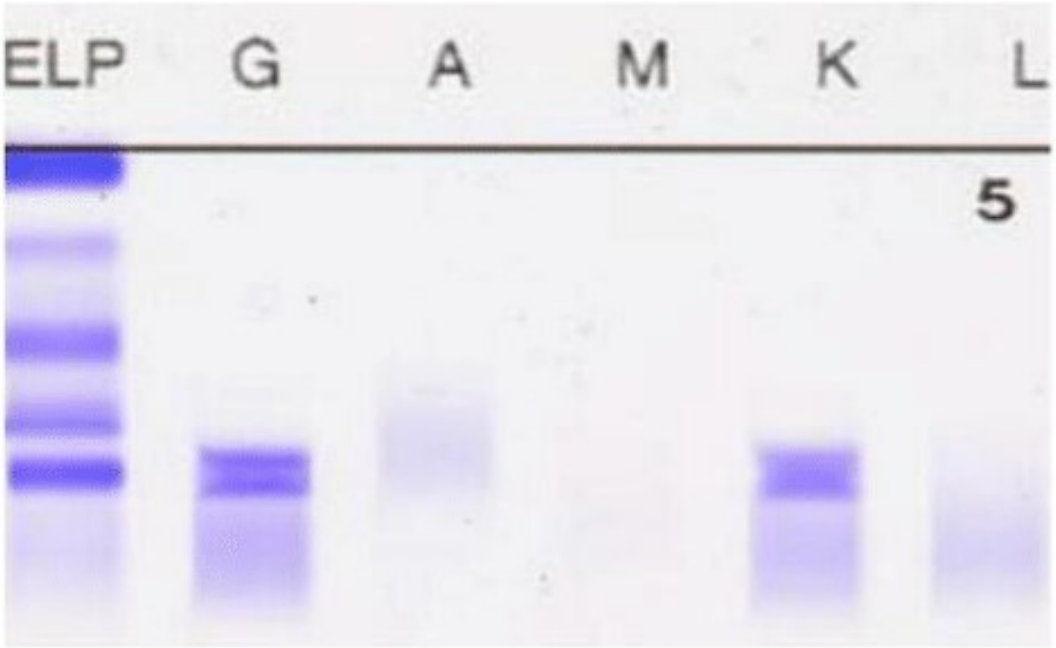






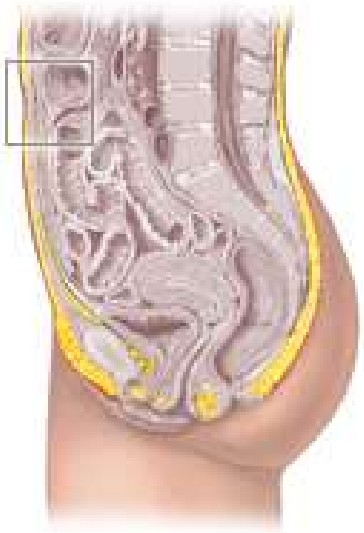


Immunofixation electrophoresis to assess for monoclonal protein



Protein	Results	Reference
Ig-G	19.8	7-16g/L
Ig-A	0.86	0.7-4.0g/L
Ig-M	0.18	0.5-2.2g/L
κ-light chain	5.91	1.7-3.7g/L
λ-lignt chain	1.15	0.9-2.1g/L

Fat pad biopsy for AL-amyloidosis

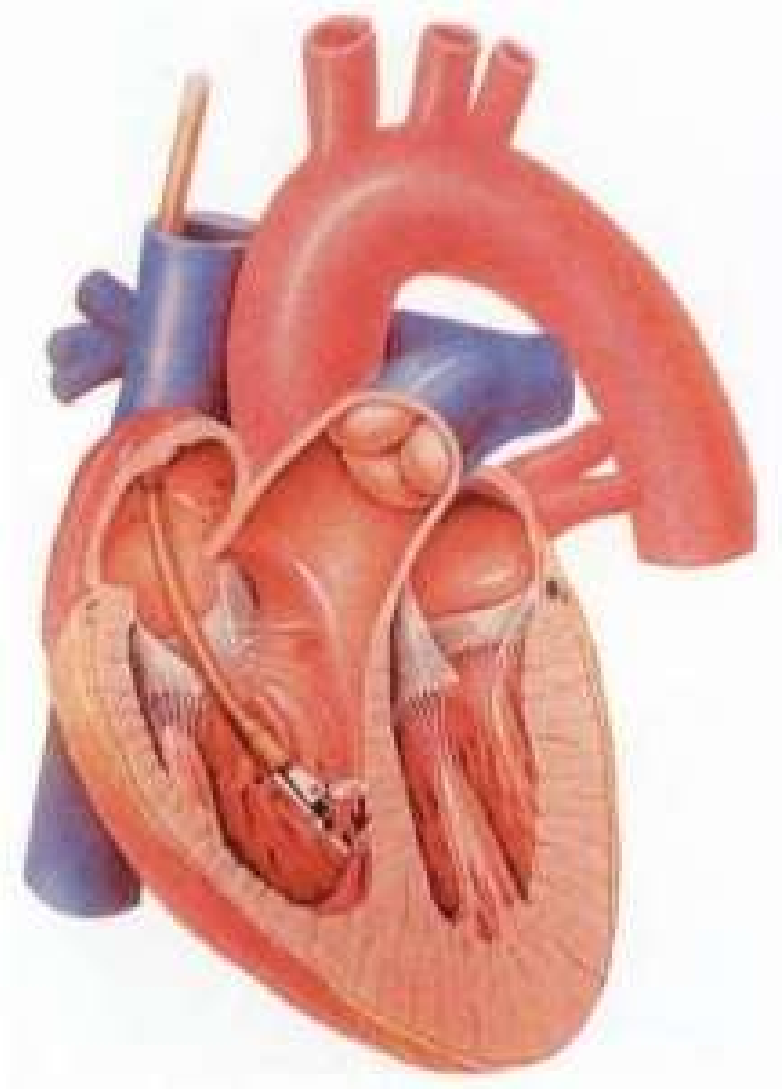


Small core of fat tissue is removed for biopsy

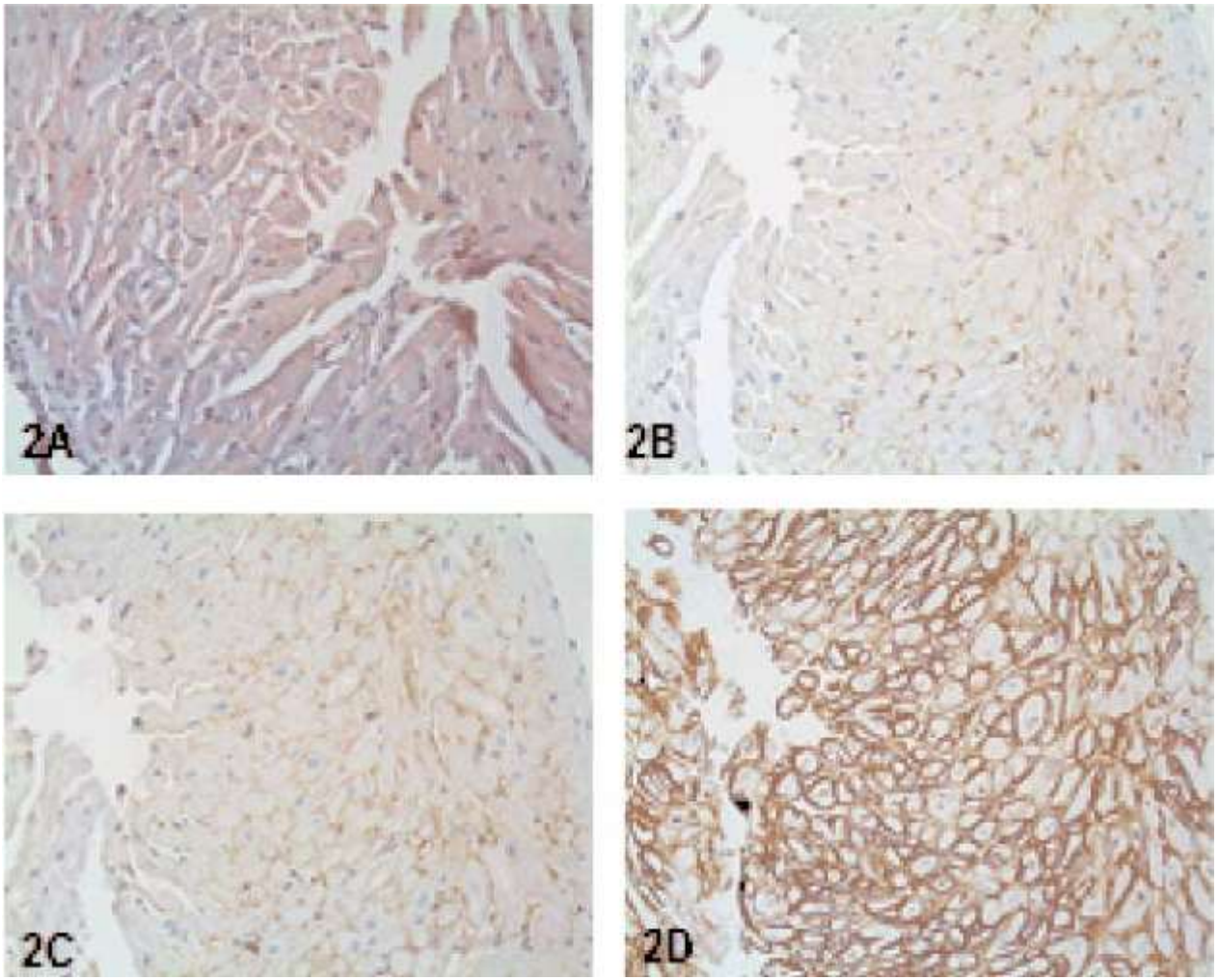
Positive in

- > 70% AL
- ~ 60% - ATTRm
- ~ 10% - ATTR-wt

Endomyocardial biopsy



Immunohistochemistry / Mass spectrometry



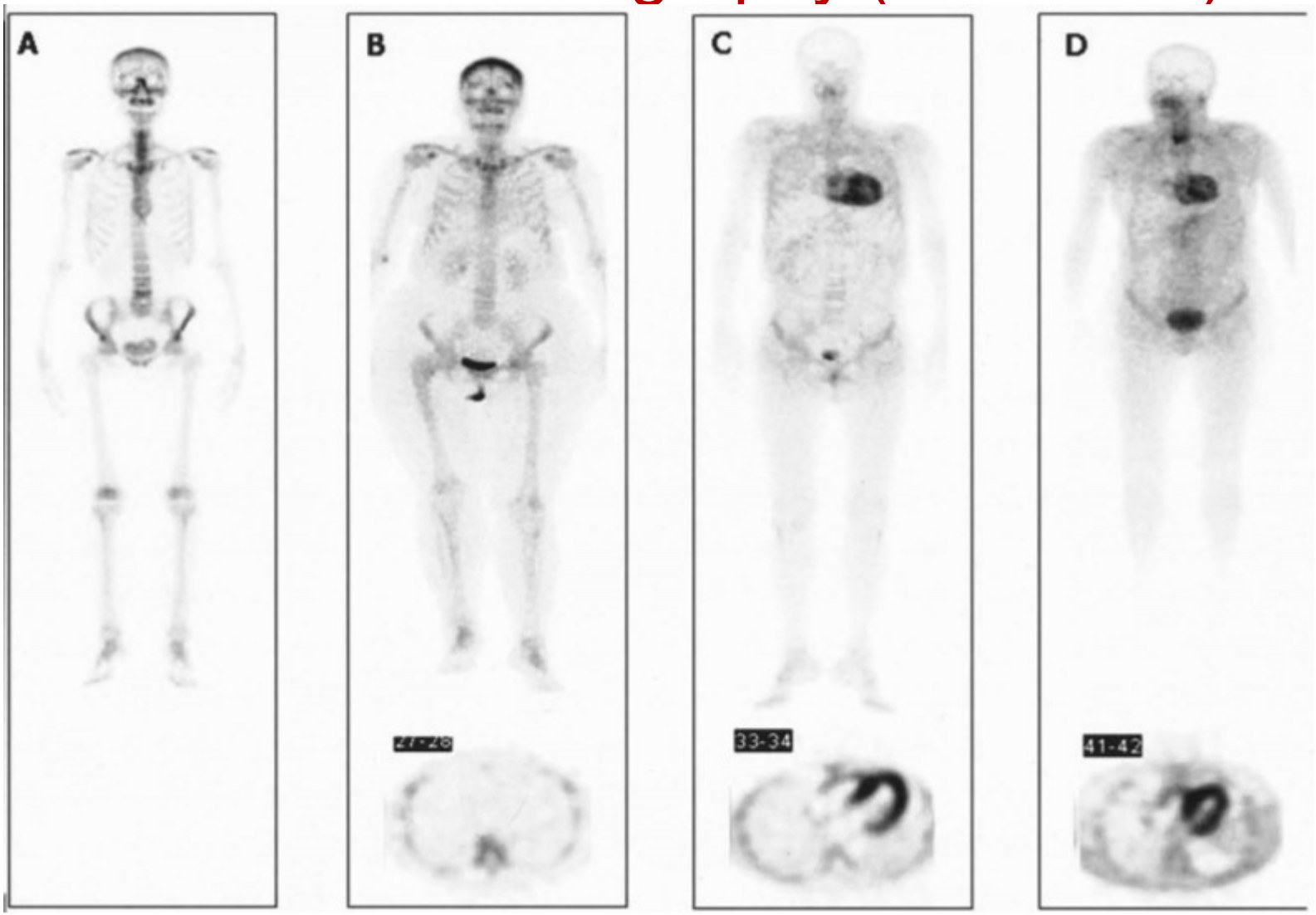
Lambda

Kappa

Transthyretin

Vrana JA et al. Blood. 2009;114:4957–4959.
Satoskar AA et al. Am J Surg Pathol 35:1685–1690.

Diagnosis of TTR cardiac amyloidosis with bone scintigraphy (PYP scan)



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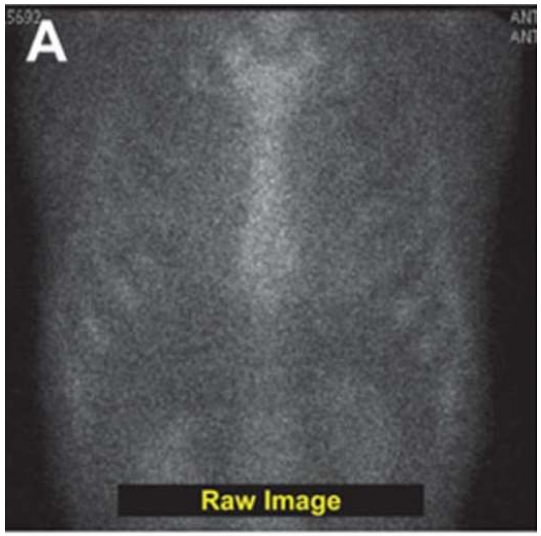
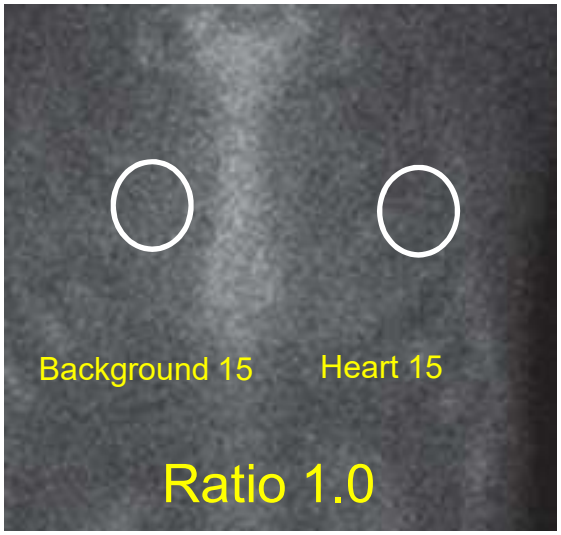
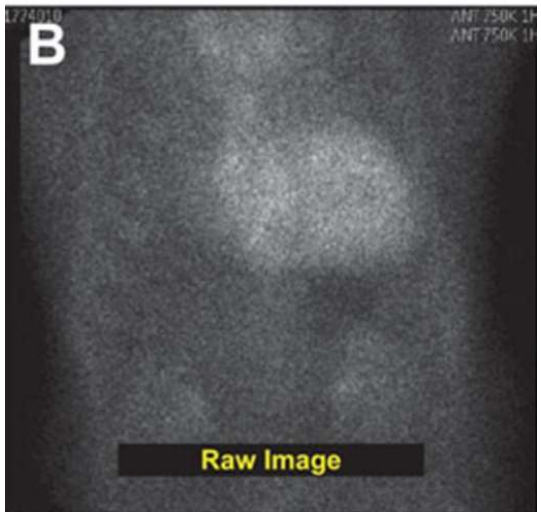
Perugini E et al. *JACC 2005;46:1076-84.*

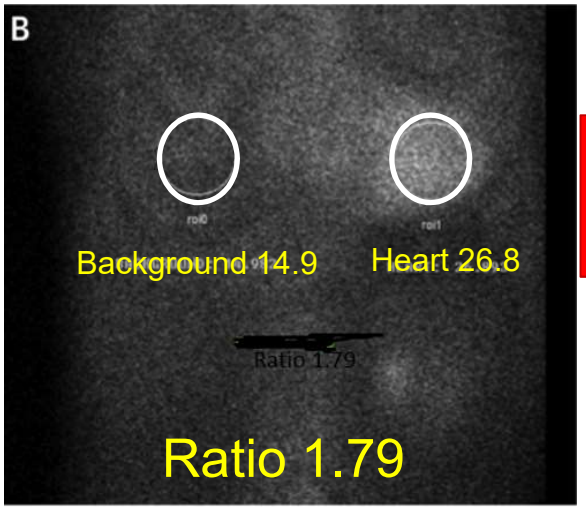
Bone scintigraphy - PYP Scan





Negative uptake





Positive uptake

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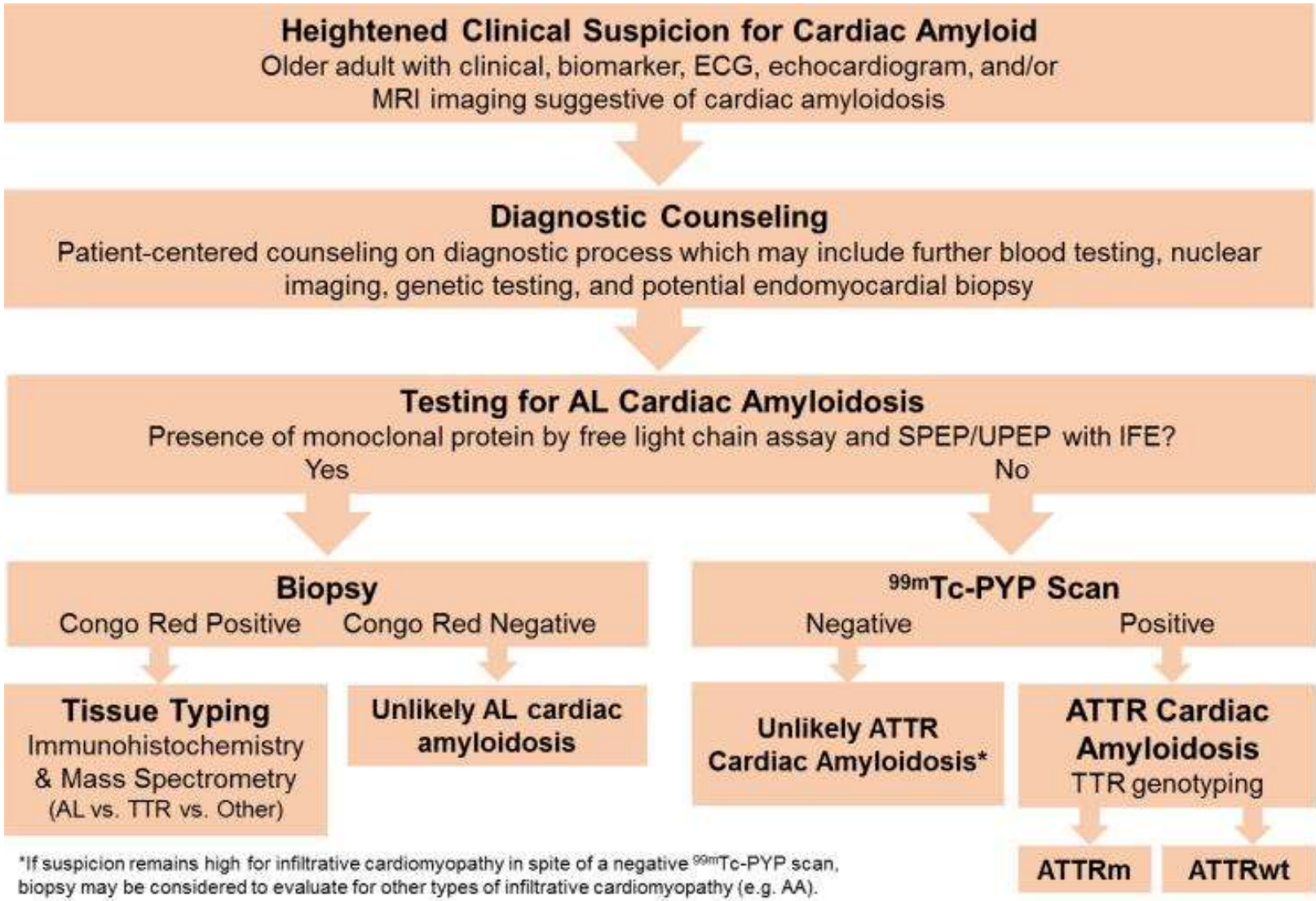
Rudberg FL et al. *JACC 2019; 73(22):2872-2891*

Algorithm – Cardiac Amyloidosis



Brunjes DL et al. *JCF 2016; 22(12):996-1003.*

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Treatment

- Diuretics + salt restriction – Mainstay of therapy.
  - Aldosterone antagonists & loop diuretics
- Calcium channel blockers & digoxin contraindicated
- ACEi/ARBs poorly tolerated
- Beta-blockers – often intolerant
- Hypotension – compression stockings & midodrine
- Pacemaker – (25% develop heart block)

Grogan M., Dispenzieri A. Heart Fail Rev. 2015. 20:155–162
Rubinow A., Skinner M., Cohen A.S. Circulation. 1981.63:1285–1288

Treatment for AL Cardiac Amyloidosis

- Stem cell transplant
- Cytotoxic chemotherapy
  - CyBorD
  - Oral Melphalan/Dexamethasone
  - Daratumumab
- Cytotoxic chemotherapy followed by stem cell transplant
- Stem cell transplant + heart transplant

Falk, R.H. et al. JACC. 2016;68(12):1323-41
Jaccard A et al. Haematologica. 2014;99(9):1479-85.
Maurer et al. *Circulation 2017;135:1357-1377.*

Therapies for TTR Cardiac Amyloidosis

Amyloidogenic TTR Cascade

Suppression of TTR synthesis
- Liver Transplantation
- RNA interference agents
- Antisense Oligonucleotides

Rate limiting TTR dissociation

TTR Stabilization
- Tafamidis
- Diflunisal
- AG10

Monomer misfolding

Aggregation

Amyloid Fibrils

Fibril reabsorption & degradation
- Doxycycline
- TUDCA

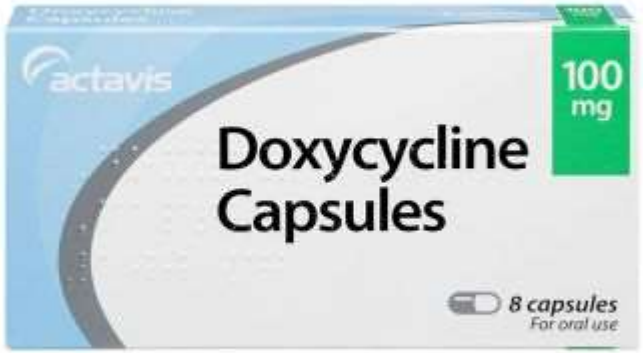
Maurer et al. *Circulation 2017;135:1357-1377.*

Therapies for TTR Cardiac Amyloidosis

Green tea

- No change in wall thickness
- Decrease in LV muscle mass

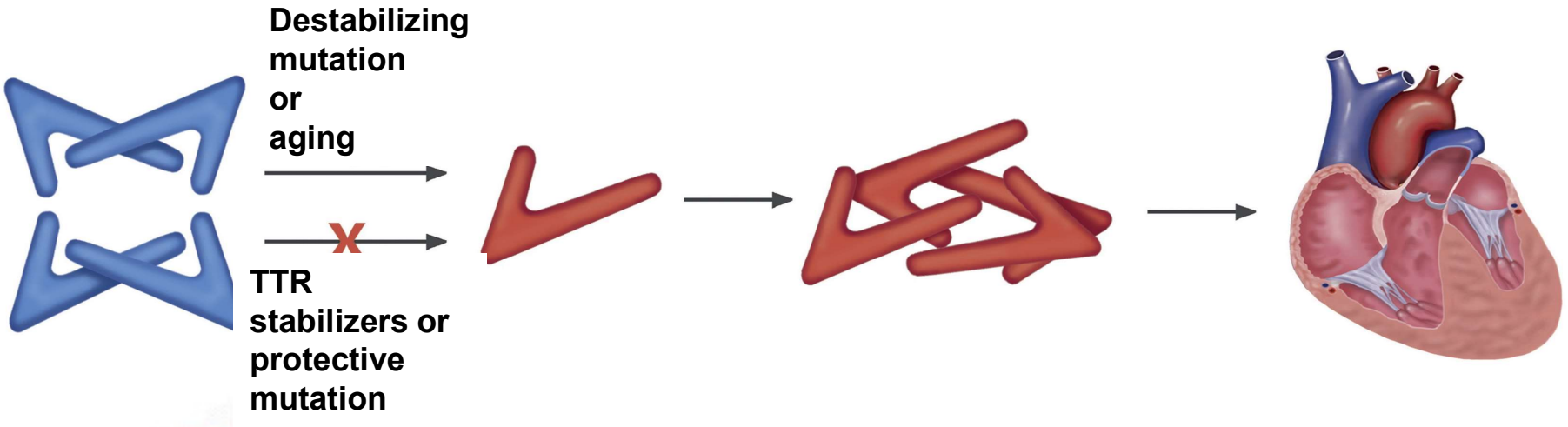
Therapies for TTR Cardiac Amyloidosis

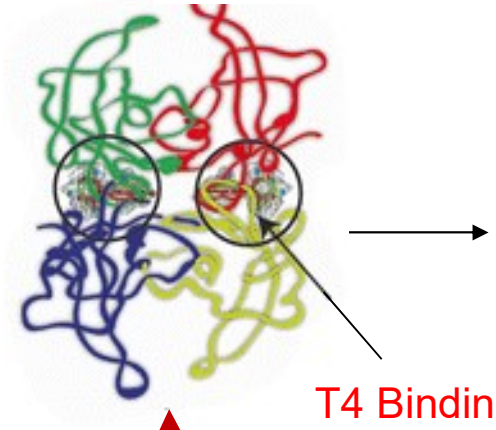


Doxycycline & TUDCA (bile salt)

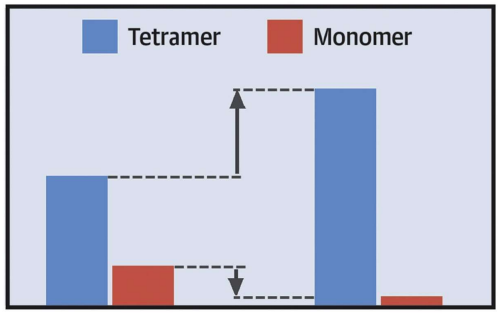
- Enhances fibril degradation
- Stabilize heart disease
- Skin complications (60%), discontinuation (30%)

Transthyretin Stabilizers

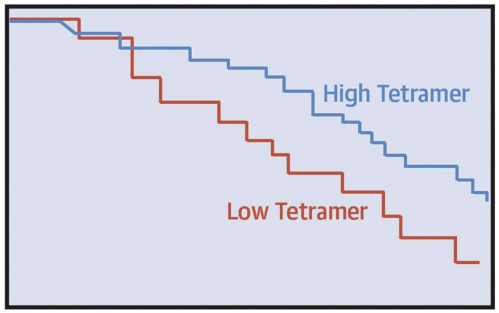




Tafamidis
Diflunisal
AG 10



Decrease monomers
Increase tetramers



Prolong survival

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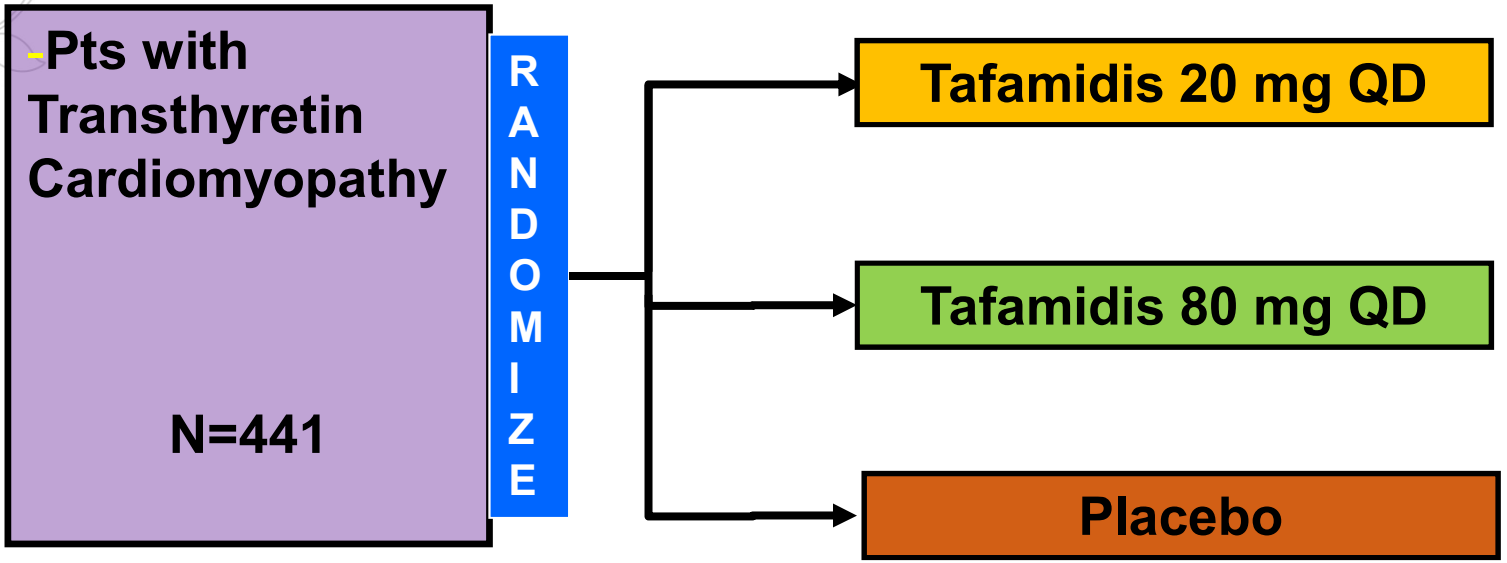
TTR Stabilizer – Tafamidis (Vyndaqel)

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Maurer MS et al. NEJM. 2018 Sep 13; 379(11):1007-16

Tafamidis for Transthyretin Amyloid Cardiomyopathy

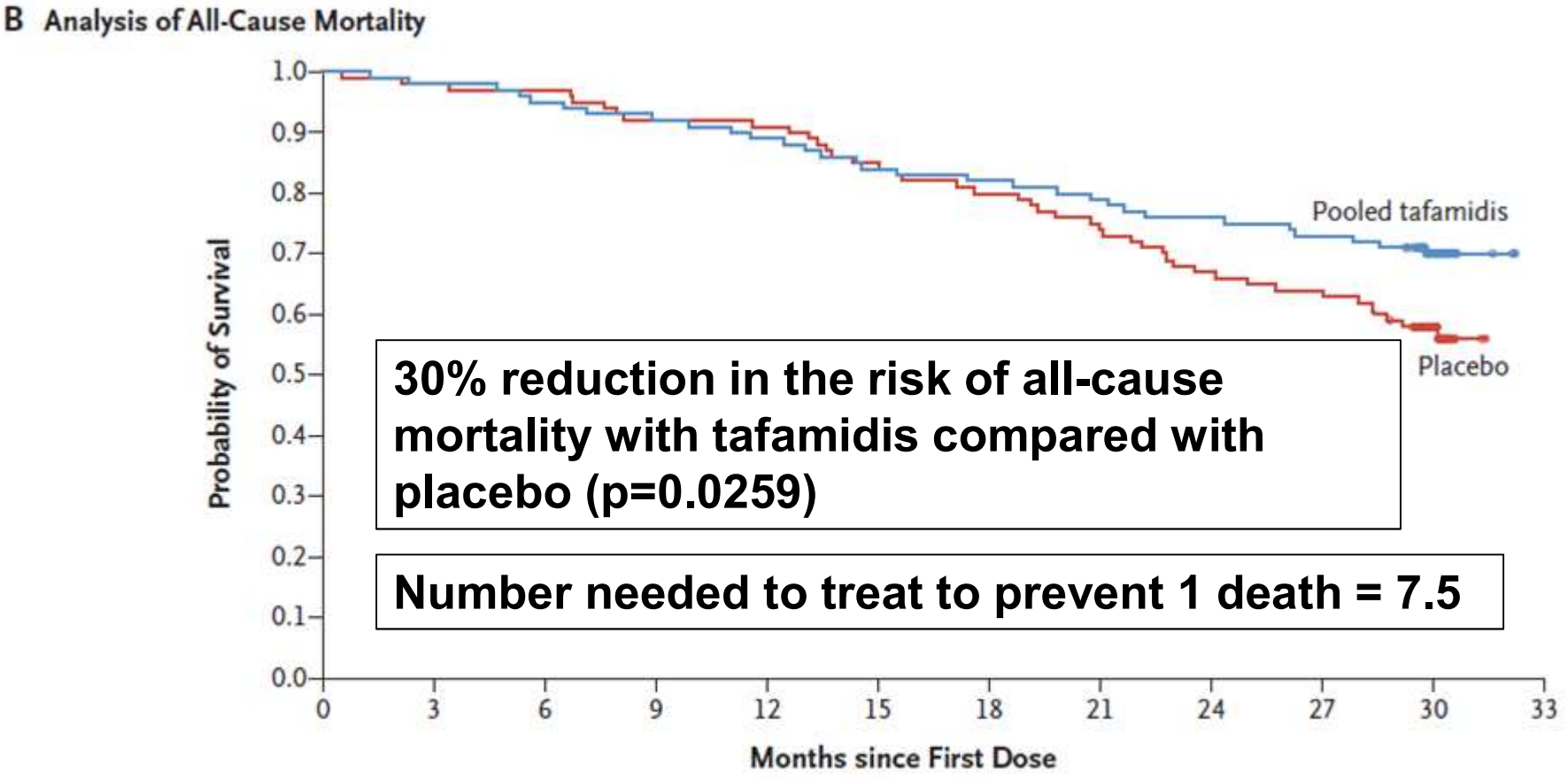


Treatment for 30 months

Primary endpoints: **All-cause mortality & frequency of CV-related hospitalizations**

Maurer MS et al. NEJM. 2018 Sep 13; 379(11):1007-16

Tafamidis (Vyndaqel)



30% reduction in the risk of all-cause mortality with tafamidis compared with placebo (p=0.0259)

Number needed to treat to prevent 1 death = 7.5

No. at Risk (cumulative no. of events)

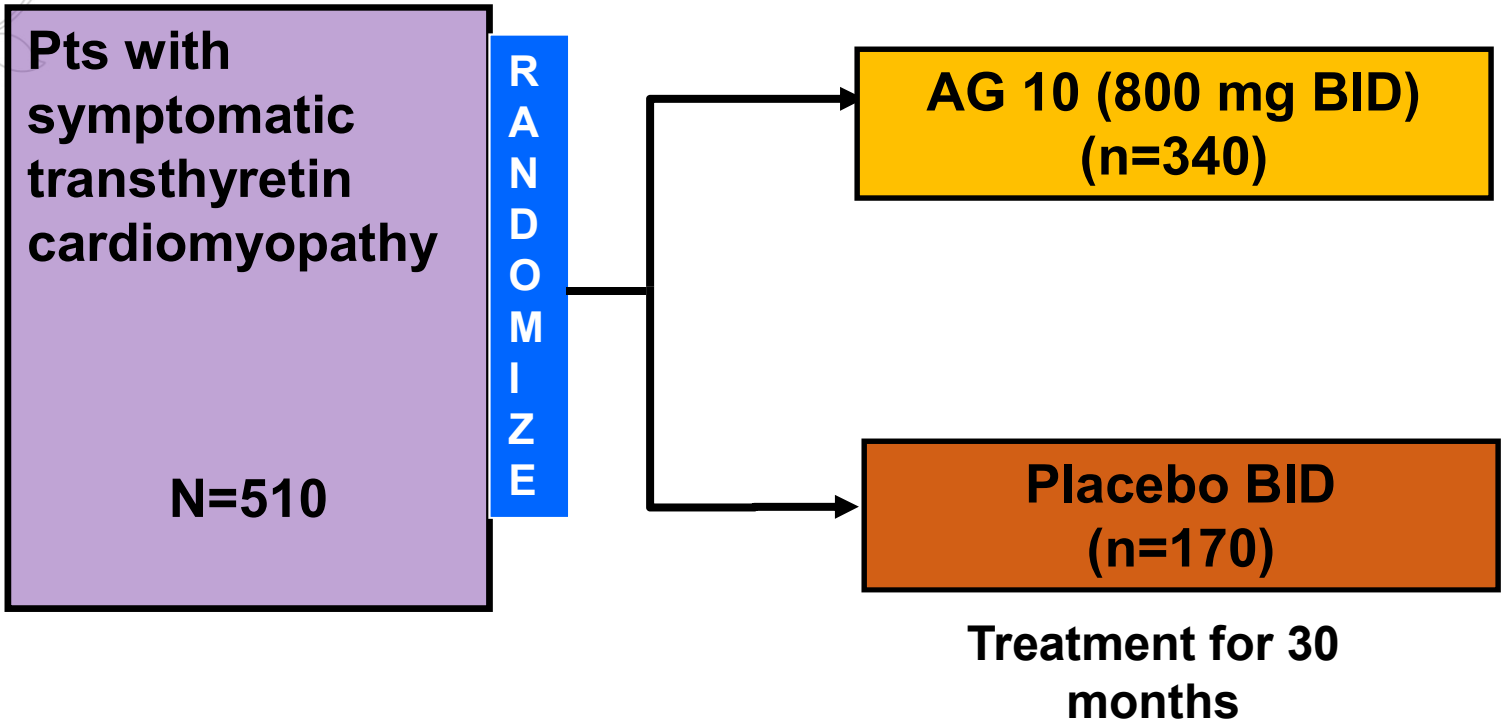
Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

Maurer MS et al. NEJM. 2018 Sep 13; 379(11):1007-16

TTR Stabilizers

- Stabilized progression of neuropathy
- Patients with no bleeding issues, not retaining water and normal kidney function
- Not FDA-approved

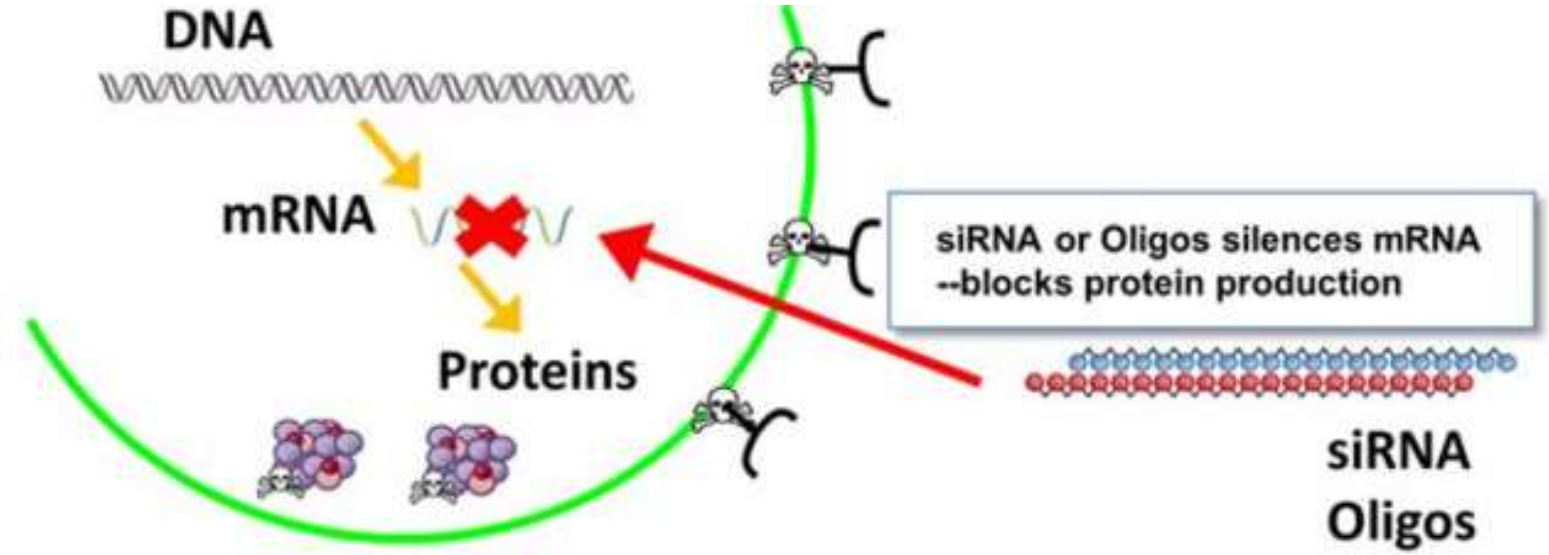
Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (ATTRIBUTE-CM Trial)



AG10 mimics the stabilizing effects of the super-stabilized TTR mutation T119M

https://clinicaltrials.gov/ct2/show/NCT03860935?cond=AG+10&rank=3

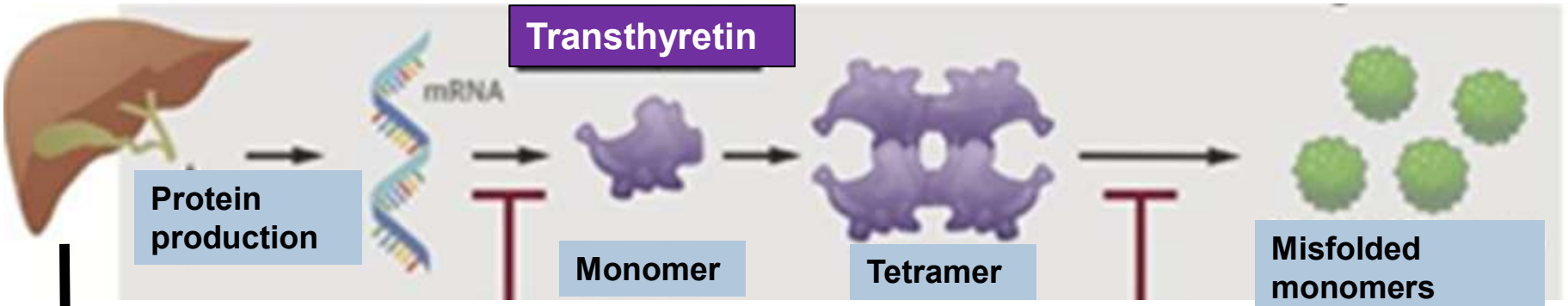
Suppression of TTR production



- **Patisiran – RNA interference (RNAi) agent**
- **Inotersen – Antisense Oligonucleotide (ASO)**

Niemietz C et al. Molecules. 2015;**20**:17944–17975.
Coelho T et al. N Engl J Med. 2013;**369**:819–829.
Ackermann EJ et al. Amyloid. 2012;**19**(suppl 1):43–44

Suppression of TTR production



Patisiran
Inotersen

Knock down production of mutant and wild type TTR by > 90%

→

Decrease unstable circulating TTR tetramers

→

Decrease deposition of monomers

Patisiran - Onpattro

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

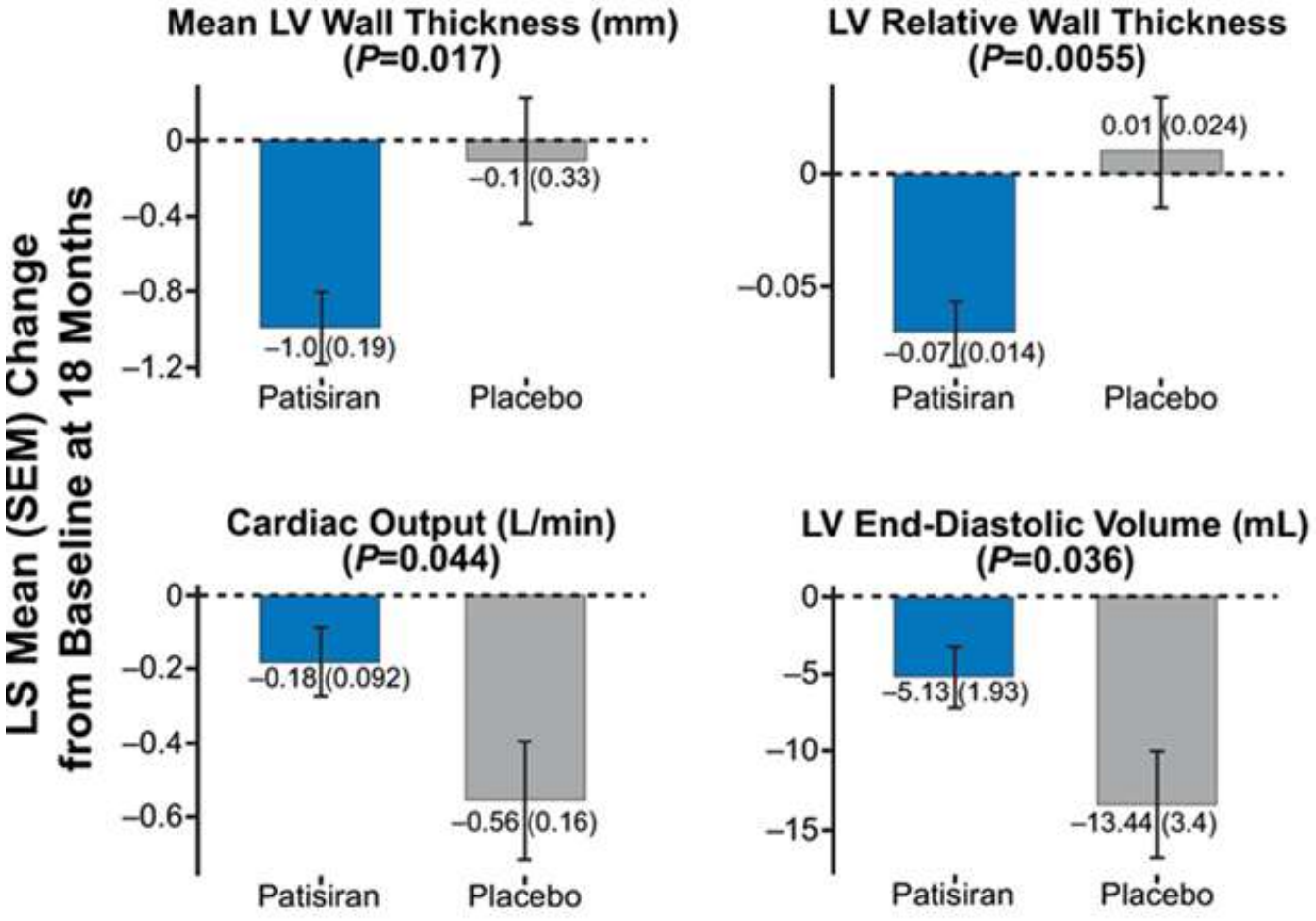
Adams D et al. NEJM. 2018 Jul 5; 379(1): 11-21

Patisiran – Onpattro

Approved indication	Neuropathy
Administration	IV, every 3 weeks
Common side effects	Infusion related reactions Vitamin A deficiency
Concomitant Therapy	IV corticosteroid, Acetaminophen, IV H1 blocker, IV H2 blocker Daily Vitamin A supplements
Monitoring	None

Adams D et al. NEJM. 2018 Jul 5; 379(1): 11-21

Patisiran - Onpattro



- Echocardiogram changes at 18 months
- ↓ NT- pro BNP by 9 months

Solomon S et al. Circulation. 2019;10(6). 139: 431-443

Inotersen – Tegsedi

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

M.D. Benson, M. Waddington-Cruz, J.L. Berk, M. Polydefkis, P.J. Dyck, A.K. Wang, V. Planté-Bordeneuve, F.A. Barroso, G. Merlini, L. Obici, M. Scheinberg, T.H. Brannagan III, W.J. Litchy, C. Whelan, B.M. Drachman, D. Adams, S.B. Heitner, I. Conceição, H.H. Schmidt, G. Vita, J.M. Campistol, J. Gamez, P.D. Gorevic, E. Gane, A.M. Shah, S.D. Solomon, B.P. Monia, S.G. Hughes, T.J. Kwoh, B.W. McEvoy, S.W. Jung, B.F. Baker, E.J. Ackermann, M.A. Gertz, and T. Coelho

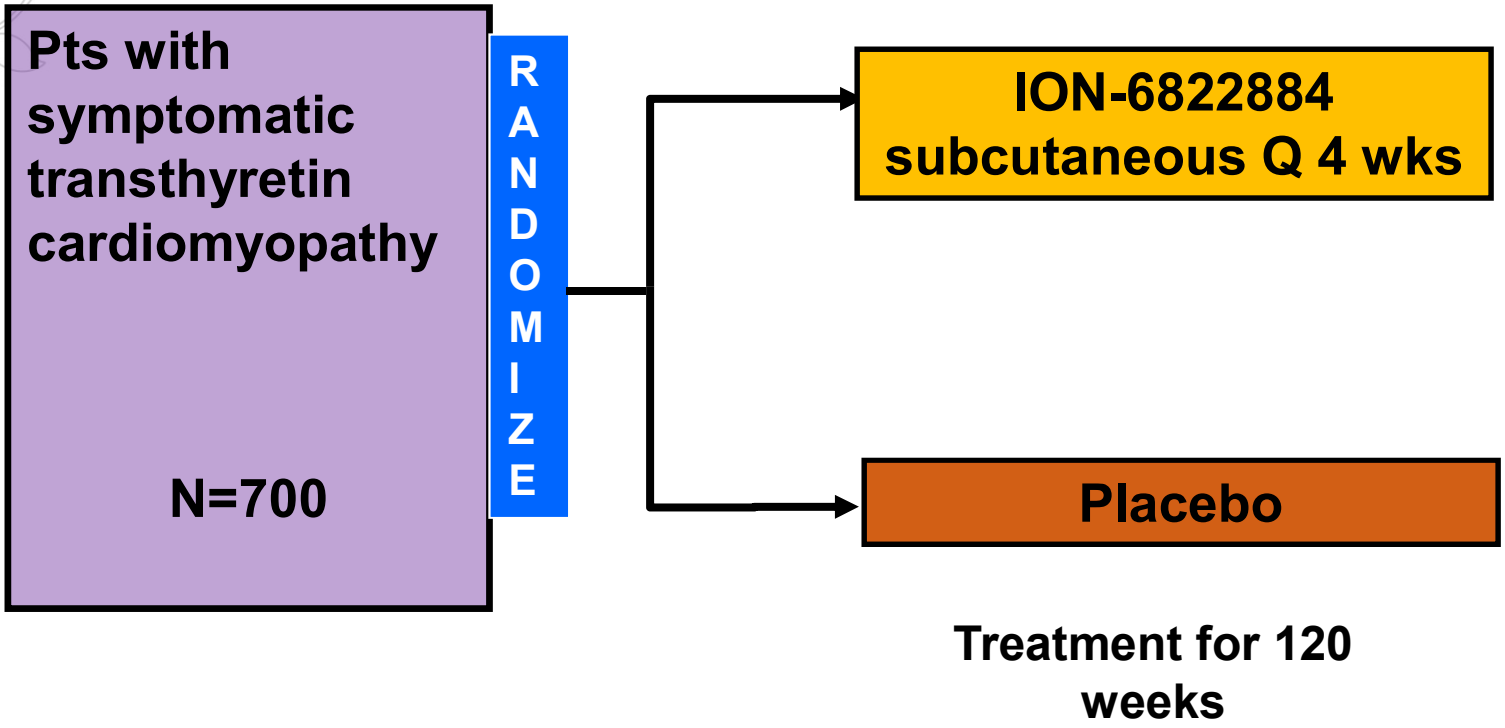
Benson MD et al. NEJM. 2018 Jul 5; 379(1): 22-31

Inotersen – Tegsedi

Approved indication	Neuropathy
Administration	Subcutaneous, every week
Common side effects	Thrombocytopenia Glomerulonephritis Vitamin A deficiency
Concomitant Therapy	Daily Vitamin A supplements
Monitoring	Platelet function, weekly Renal function, every 2 weeks

Benson MD et al. NEJM. 2018 Jul 5; 379(1): 22-31

Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM)

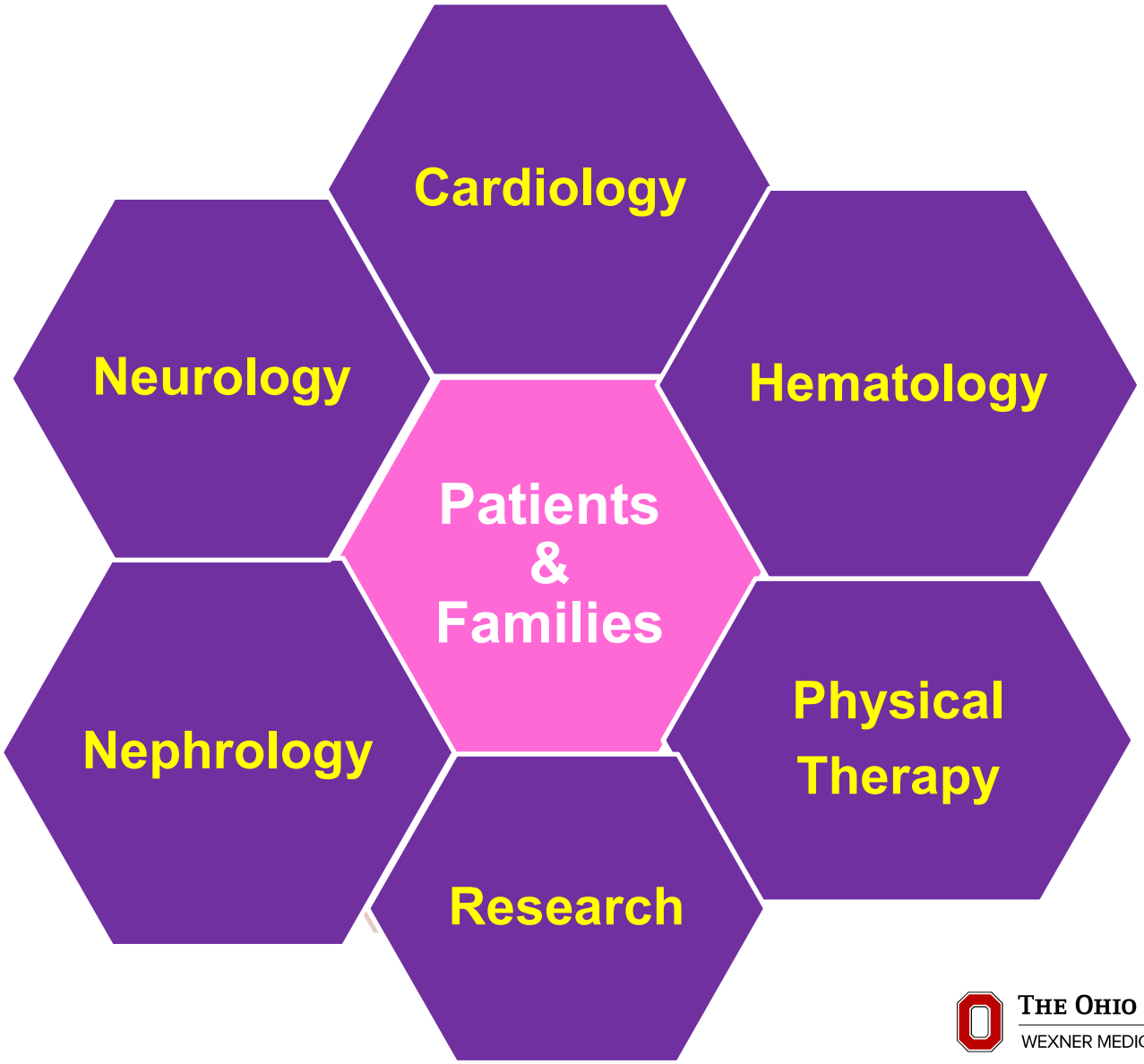


Primary endpoints:

1. Change in 6 min walk distance (60 weeks)
2. All-cause mortality & frequency of CV-related hospitalizations

Courtesy: Ionis /Akcea ION-682884 TTR-L program.

Comprehensive Amyloidosis Clinic



Comprehensive Amyloidosis Clinic

Hematology

Yvonne Efebera

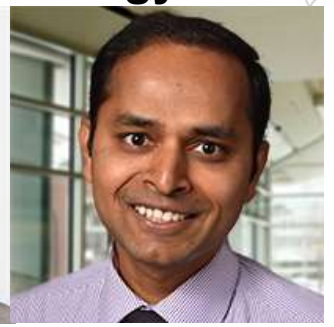
Naresh Bumma

Physical Therapy

Elyse Redder

Cardiology

Rami Kahwash



Ajay Vallakati

Neurology

Samantha LoRusso

Miriam Freimer

Nephrology

Samir Parikh

Jason Prosek

Salem Almaani

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Thank you

Therapies for TTR Amyloidosis

Drug	Patient Population	Design	Efficacy	Safety
Green tea (Epigallocatechin-3-gallate)	TTR wTTR	2 Phase II trials	No echo Δ in LV wall thickness ↓ LV mass by Cardiac MRI	No subjects discontinued green tea
Doxycycline +TUDCA	TTRm, wTTr, CA- AL	3 Phase II trials	Stable cardiac disease Controls ↓ in strain	60 % skin complications 30% stopped taking
Diflunisal (250 mg BID)	TTRm All TTR	Phase III Phase II	No change in LVEF, LV mass or strain	No significant ↑ GI bleed or volume overload

Coelho T, et al. Neurology. 2012;79(8):785-92.
Kristen AV, et al. Clinical research in cardiology. 2012;101(10):805-13.
Obici L. et al. Amyloid. 2012;19 Suppl 1:34-6.
Sekijima Y, et al. Amyloid. 2006;13(4):236-49.