

Hot Topic in Cardiology: Evolving Strategies for Diagnosis and Management of Cardiac Amyloidosis

Sarah AM Cuddy, MB BCh BAO, MD, MPH
Director, MGB Amyloidosis Program
Division of Cardiovascular Medicine,
Department of Medicine
Brigham and Women's Hospital
Assistant Professor of Medicine
Harvard Medical School

Sarah Cuddy, MD



University College Dublin

Medicine Residency @ Mater Misericordiae

University Hospital/Royal College of Physicians
Ireland (RCPI)

Cardiovascular Medicine Fellowship @RCPI

Non-invasive CV Imaging Fellowship @BWH

Cardiac Amyloidosis Fellowship @BWH

Asst. Prof of Medicine@ HMS

Director Amyloidosis Program @ MGB

- Clinical focus: Cardiac Amyloidosis, MRI, Echo
- Research focus: Cardiac Amyloidosis

Disclosures

Other Financial Benefit: Site PI for trials sponsored by Alnylam, Ionis, Astra Zeneca, Alexion, Intellia
Honoraria: Pfizer, BridgeBio, Astra Zeneca, Alexion, Novo Nordisk
Advisory Board: Astra Zeneca, Novo Nordisk, Alexion, BridgeBio, Intellia, Pfizer
Grant support from NIH 1K23HL166686-01 and AHA 23CDA857664;



Key Learning Objectives

- Comprehensive understanding of the diagnostic work up
- Review treatment advances



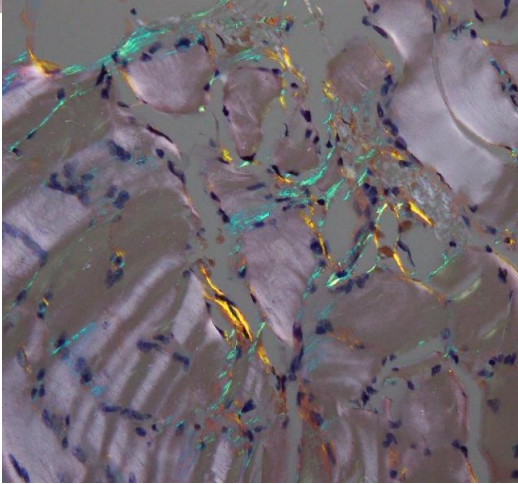
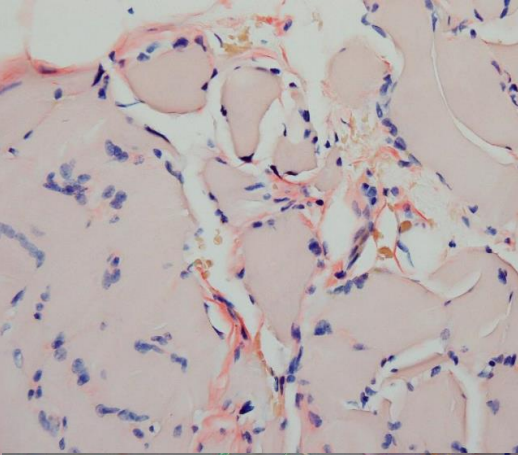
Question

The following tests are required to make a diagnosis of ATTR cardiac amyloidosis

1. FDG PET and serum protein electrophoresis.
2. Echo and Cardiac MRI and Serum protein electrophoresis (SPEP).
3. Echo or Cardiac MRI, and PYP/HMDP scan and serum and urine protein electrophoresis with immunofixation, and serum free light chains
4. Cardiac MRI and FDG PET and serum and urine protein electrophoresis with immunofixation, and serum free light chains



Amyloid and Amyloidosis



- Group of complex diseases caused by **protein misfolding** and aggregation into highly ordered **amyloid fibrils**
- Deposit in tissues, resulting in **progressive organ damage**
- **Localized** deposition
- **Systemic** amyloidosis- at least 17 proteins identified
 - Transthyretin (ATTR) (a.k.a. Senile Systemic)
 - Light Chain (AL)
 - Reactive systemic amyloidosis – serum amyloid A protein (AA)

Cardiac Amyloidosis



Transthyretin
ATTR

Wild-type

Variant
(Mutant/hereditary)

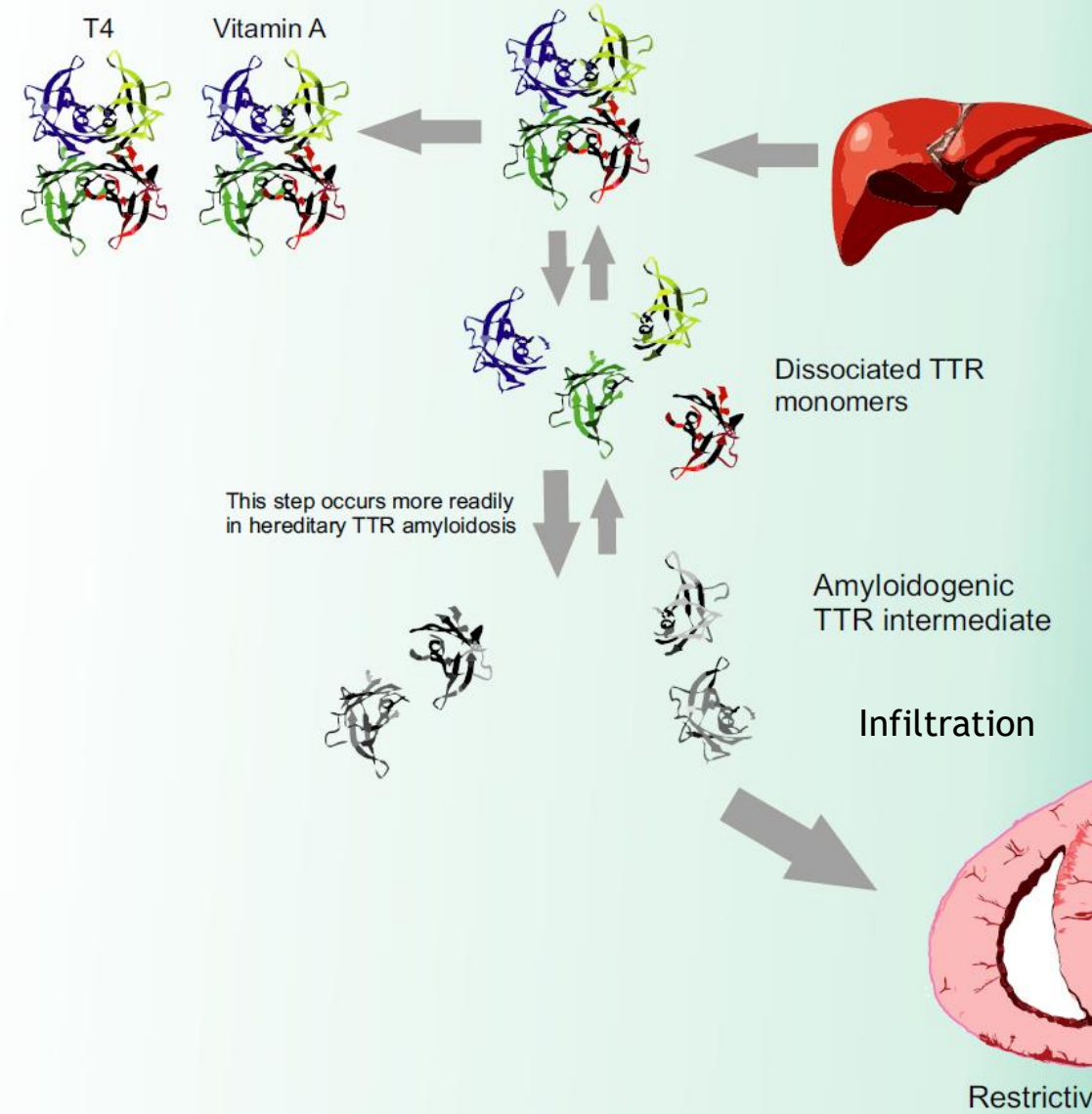
Light Chain
AL

AA,
Apolipoprotein AI-4,
B2Microglobulin

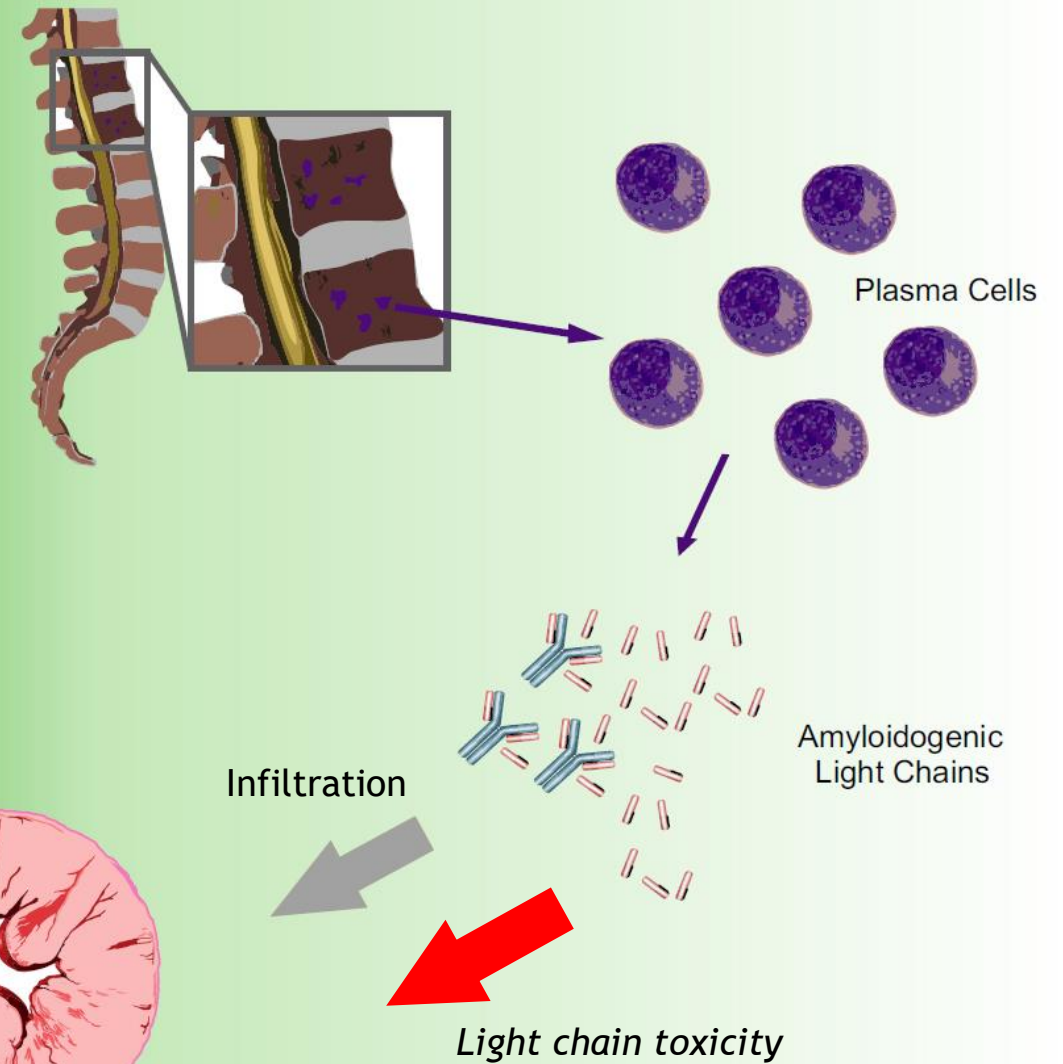
Transthyretin Cardiac Amyloidosis

Normal function to transport

TTR composed of 4 identical subunits

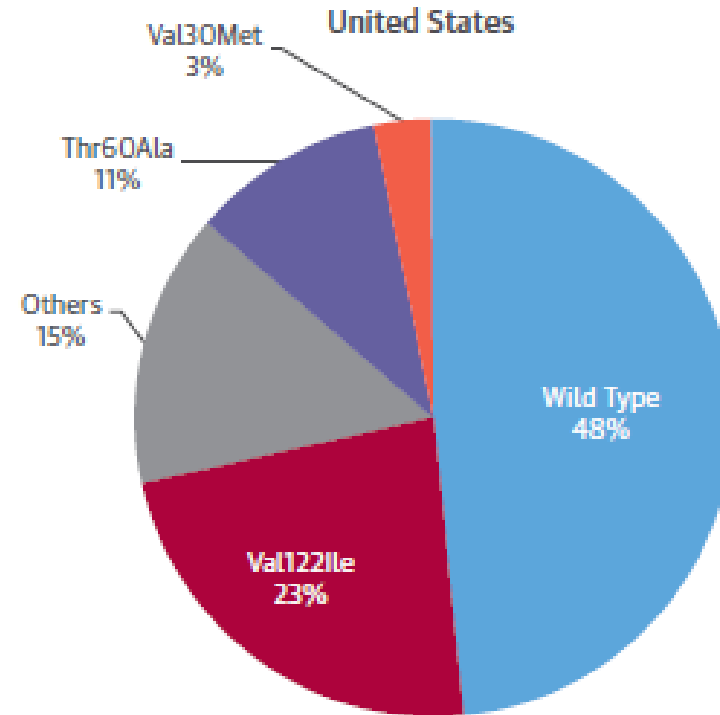
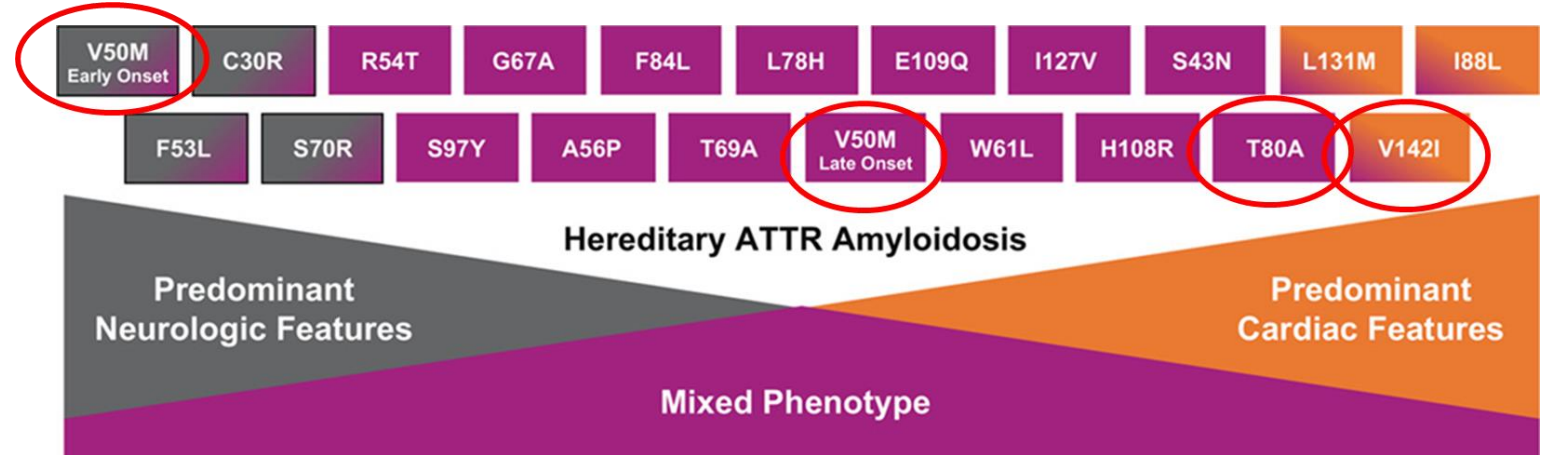


Cardiac AL Amyloidosis



Epidemiology ATTR: Hereditary and Wild Type

- Single point mutations can increase the likelihood of TTR misfolding
- Autosomal dominant pattern
- **Incomplete penetrance**
- Change in nomenclature:
add 20 amino acids



Buxbaum & Ruberg Genet Med. 2017 Jul;19(7):733-742

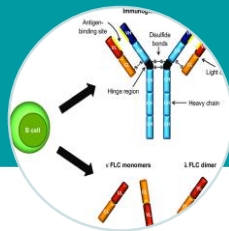
Rapezzi et al. Eur Heart J. 2013;34(7):520-8.

Maurer, M.S. et al. J Am Coll Cardiol. 2016;68(2):161-72.

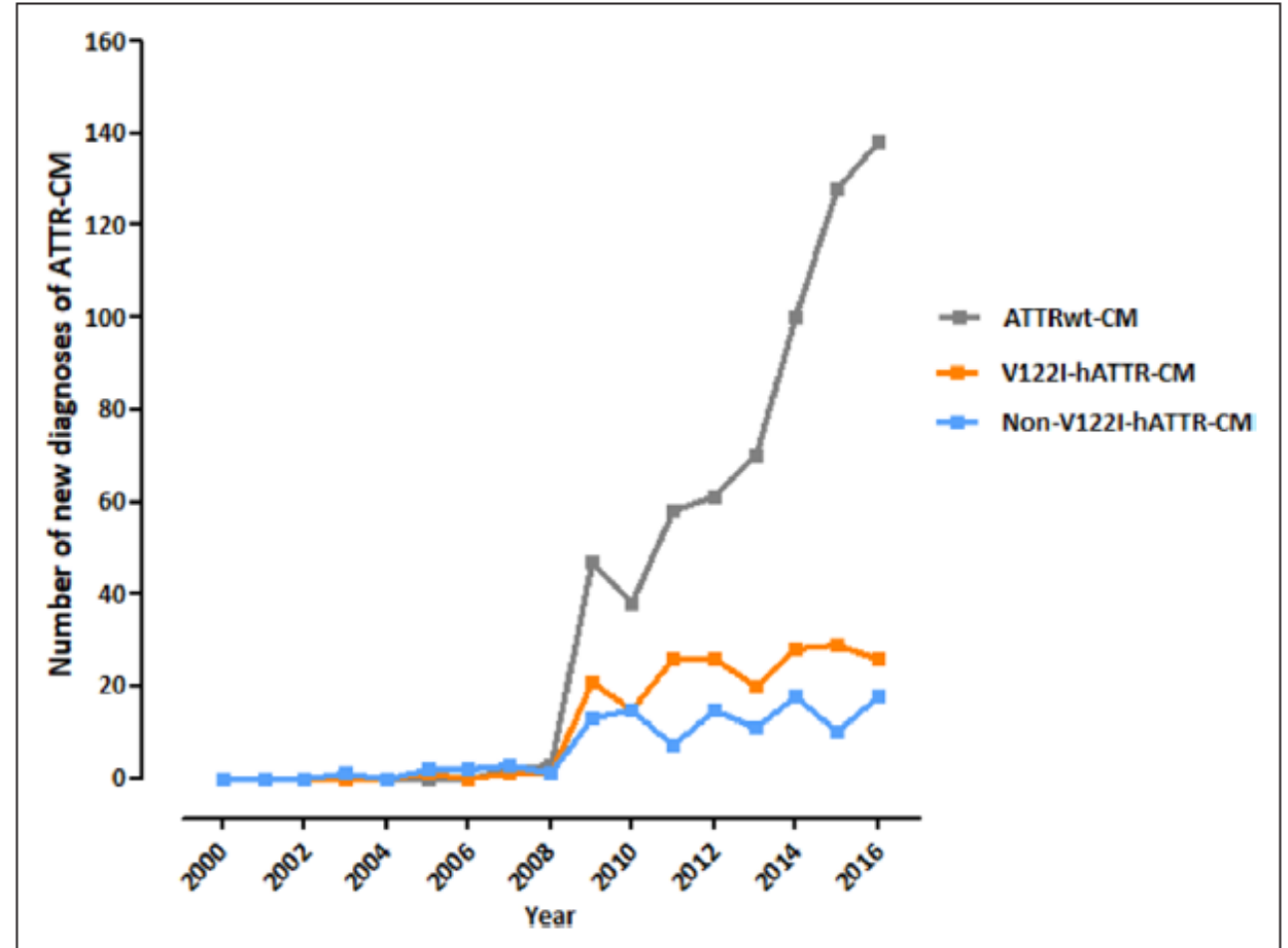
Epidemiology

- 3-12 per million person years
- MGUS- 0.25% per annum
- Myeloma- 10-38%

AL



National Amyloidosis Center, UK



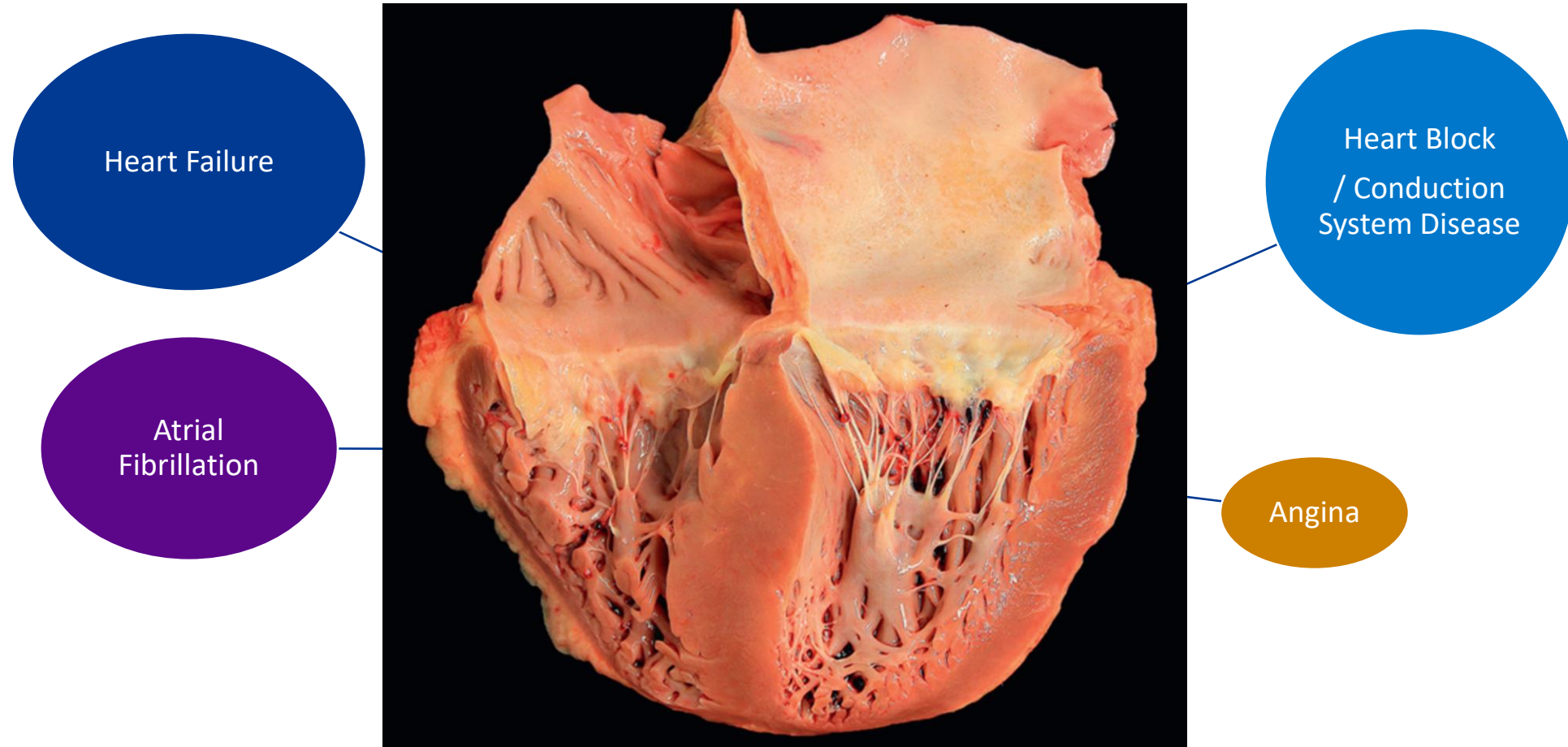
González-López et al. Eur Heart J. 2015;36(38):2585-94.

Castano et al. Eur Heart J. 2017;38(38):2879-2887.

Lane et al. Circulation. 2019;140(1):16-26.



Extracellular deposition of amyloid in the heart



Clinical clues: ATTR

ATTRwt

- Older males
- Carpal Tunnel Syndrome
- Spinal Stenosis
- Biceps Tendon Rupture

ATTRv

- Neuropathy
 - Autonomic and/or peripheral
 - Family history



Clinical Clues: AL

Male=Female

From 5th decade

Cardiac predominant

- Heart Failure
- Exercise intolerance
- Fatigue

Neuropathy

- Autonomic
- Peripheral

Renal

- Nephrotic Syndrome

GI

- Diarrhea
- Weight loss
- Early satiety

Skin

- Petechiae, ecchymoses, periorbital purpura

Soft tissue

- Macroglossia

Erectile Dysfunction

Jaw Claudication



Clinical Clues and Complementary Tests in the Investigation of Cardiac Amyloidosis

Medicines

- β -blocker intolerance
- Vasodilator intolerance

Physical Exam

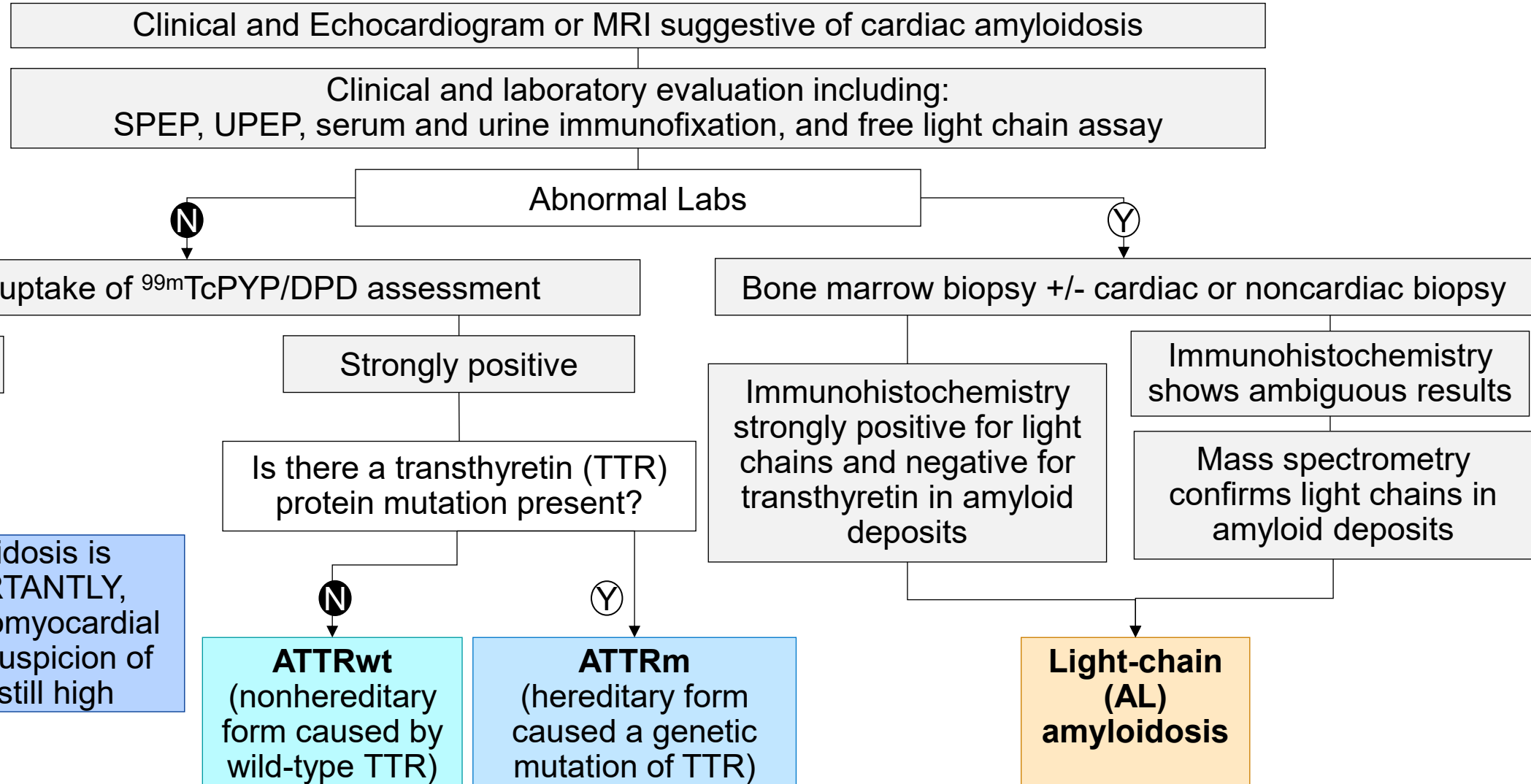
- Orthostatic hypotension
- Hypotension
- HF findings: Right Sided
- ATTR/AL specific features

ECG

- Dissociation between low voltage ECG with ECHO increased wall thickness
- Atrial fibrillation/Flutter
- Atrioventricular block
- Pseudoinfarction pattern



Diagnosing and Typing Cardiac Amyloidosis in a Patient With Unexplained Heart Failure



Classical Features of Cardiac Amyloidosis

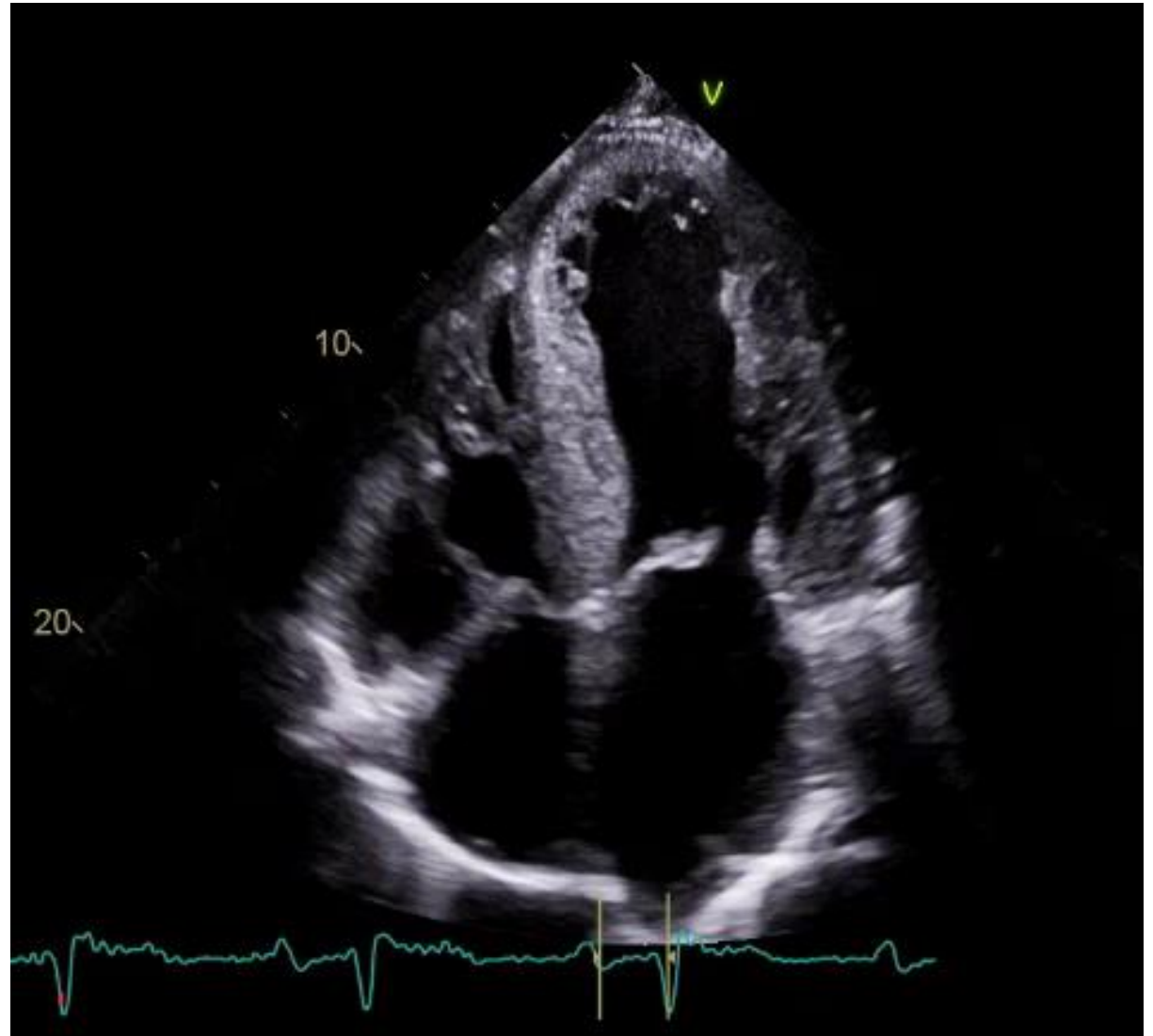
Biventricular Wall Thickening

Atrial dilation

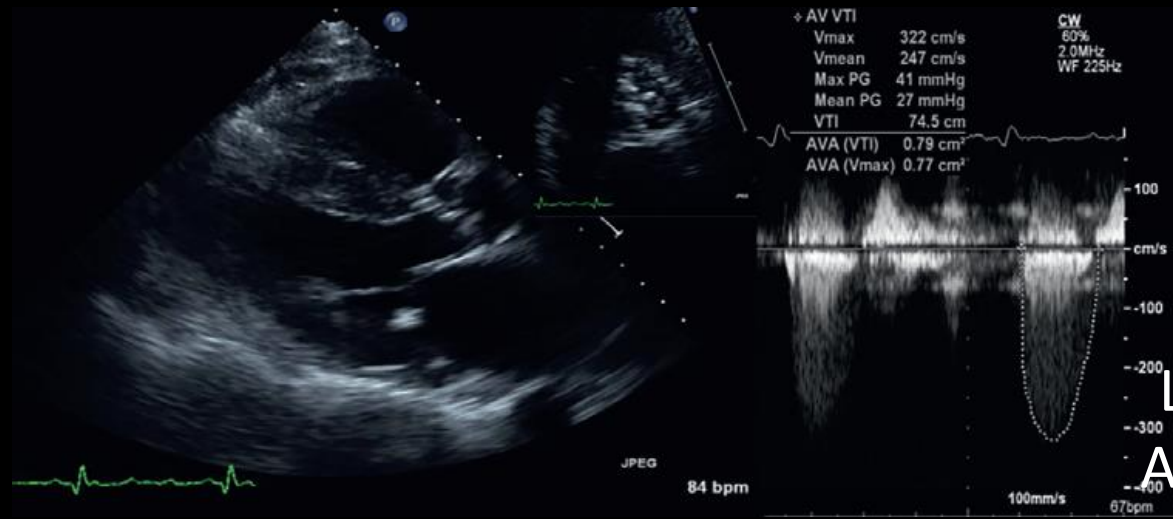
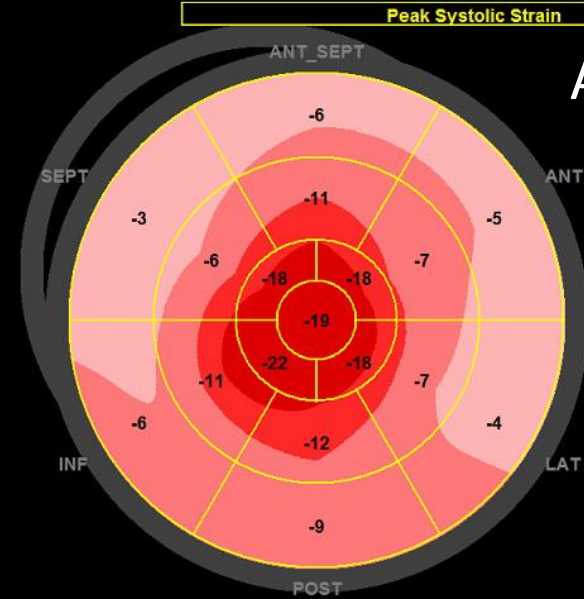
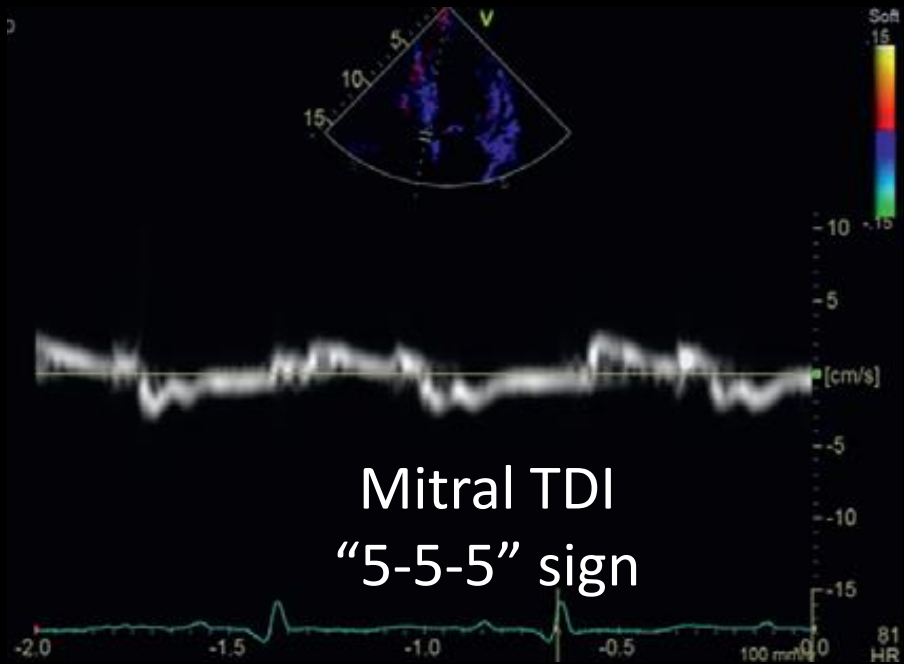
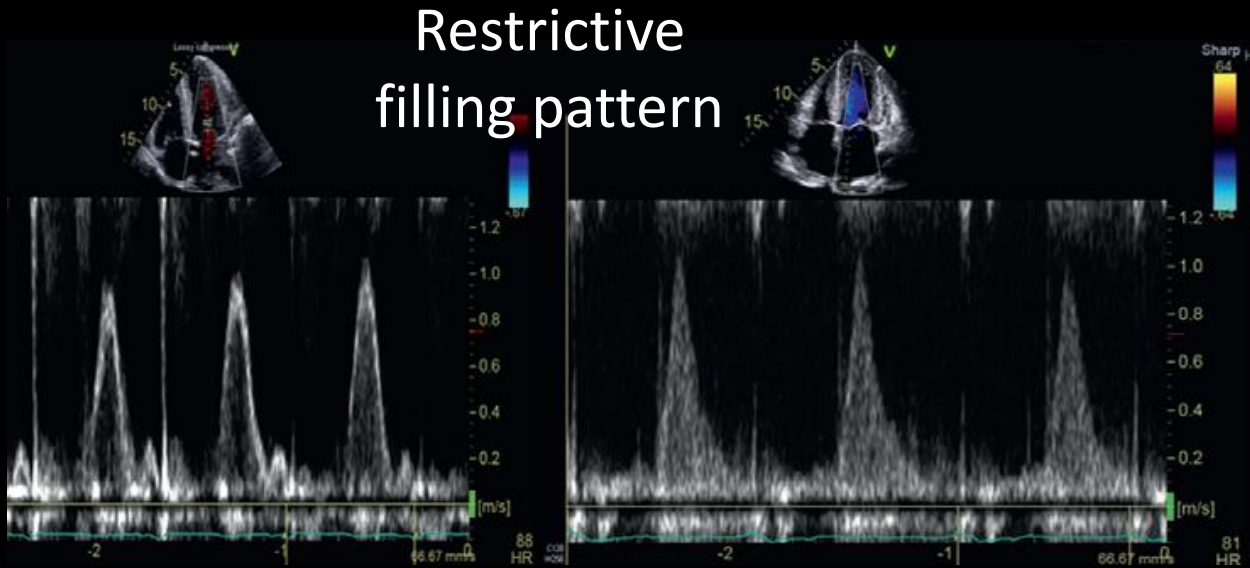
Valve thickening

Pericardial and pleural effusions

Increased echogenicity/ echo-bright appearance



Echocardiography: Diastolic function and strain



Apical Sparing

Low Flow
Low Gradient
Aortic Stenosis

Classical findings not the Rule

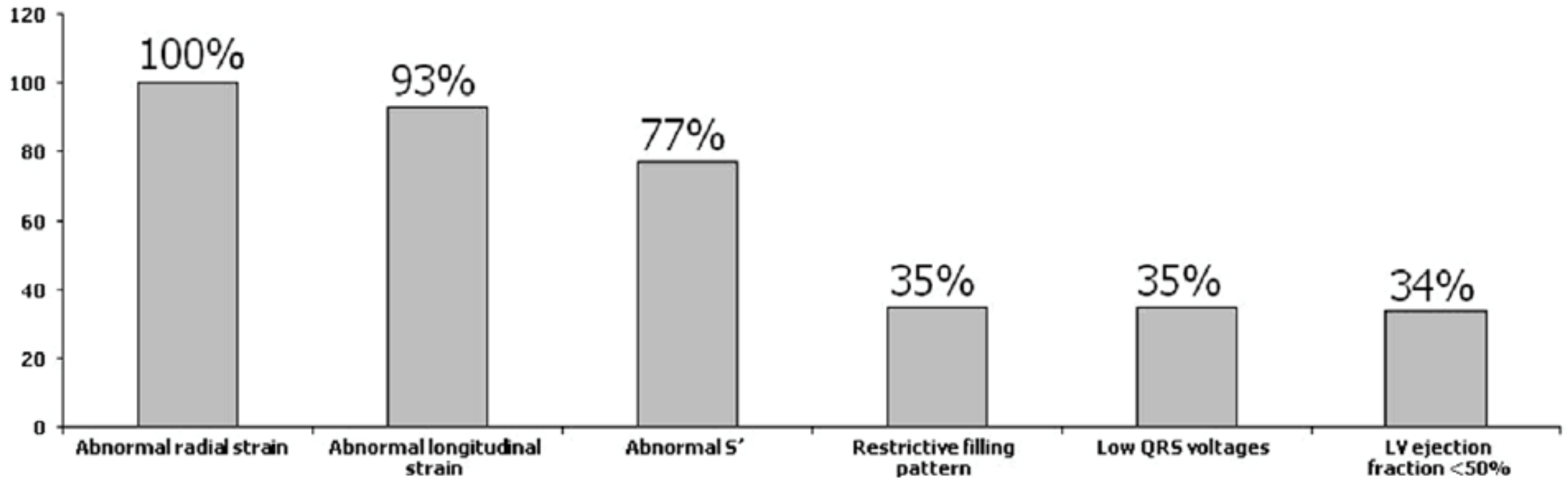


Figure 1. Prevalence of frequency of abnormal indices of systolic and diastolic function in patients with cardiac amyloidosis. Speckle tracking–derived strain parameters were more sensitive than the conventional echocardiographic parameters of systolic and diastolic function in characterizing left ventricular dysfunction. LV indicates left ventricular; and S', lateral mitral systolic velocity.

AI for Diagnosis

ECG

Echo

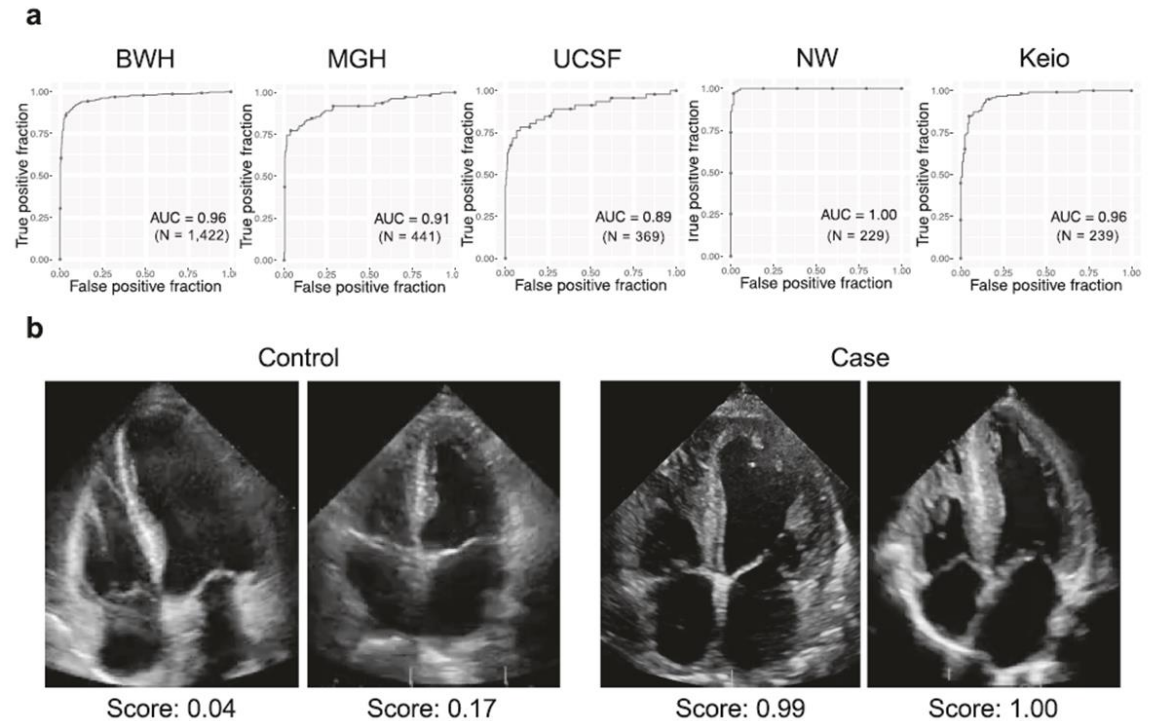
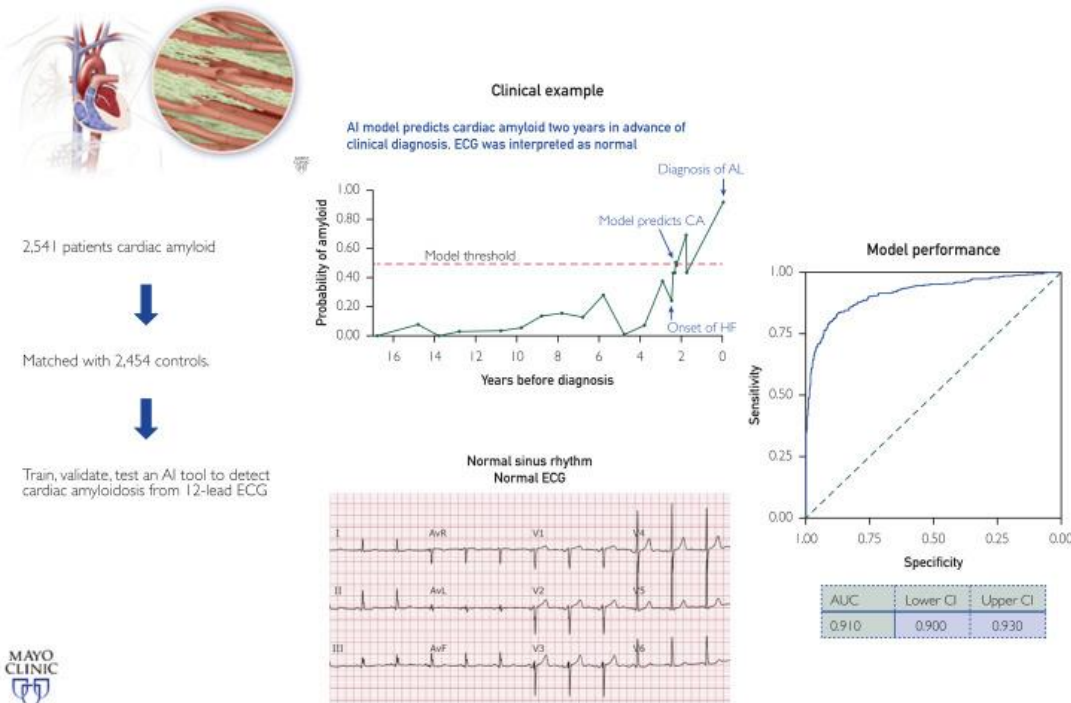


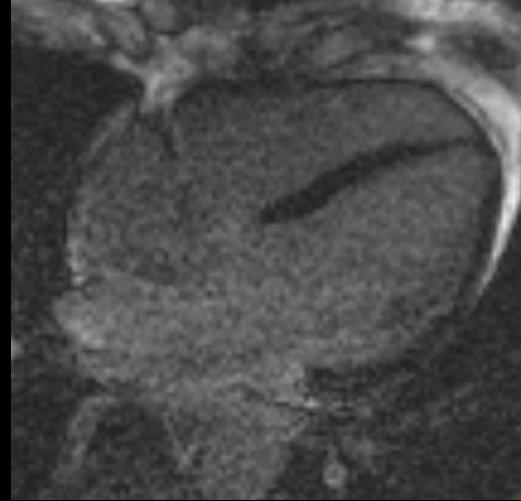
Fig. 2 Performance of the cardiac amyloidosis echocardiography model. **a** ROC plots for detecting cardiac amyloidosis for each institution. The performance on the test dataset is shown for BWH. **b** representative echocardiography images for cases and controls. The score denotes the model output for the video. N is the numbers of studies. Source data are provided as a Source Data file. BWH: Brigham and Women's Hospital, MGH: Massachusetts General Hospital, UCSF: University of California San Francisco, NW: Northwestern University, Keio: Keio University. AUC: area under the curve.

Imaging: Cardiac MRI

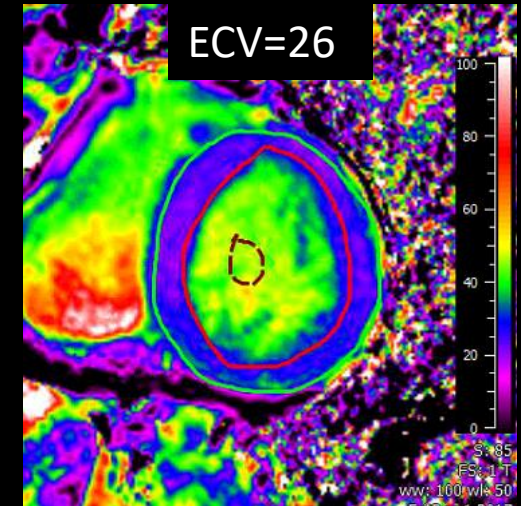
Normal



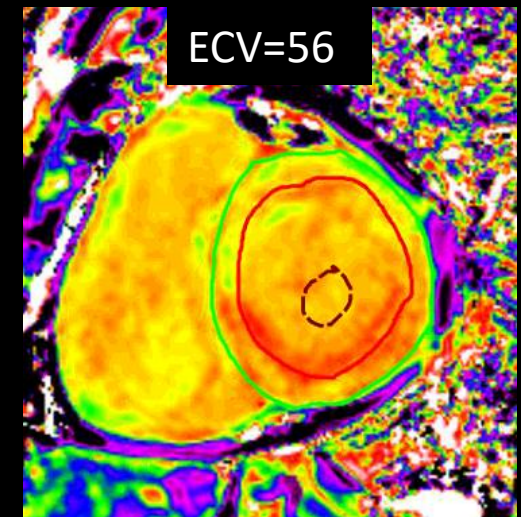
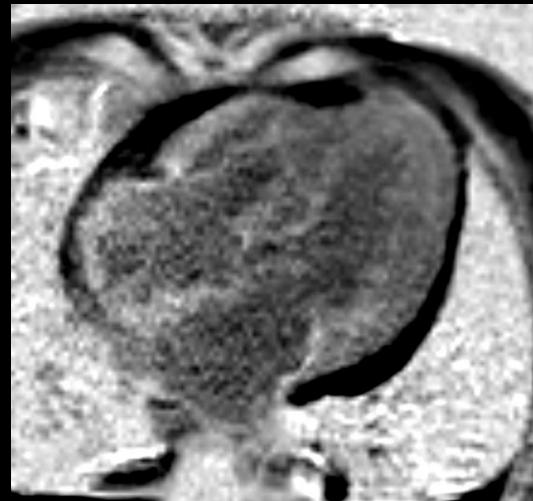
Late Gadolinium Enhancement (LGE)



Extracellular Volume (ECV)

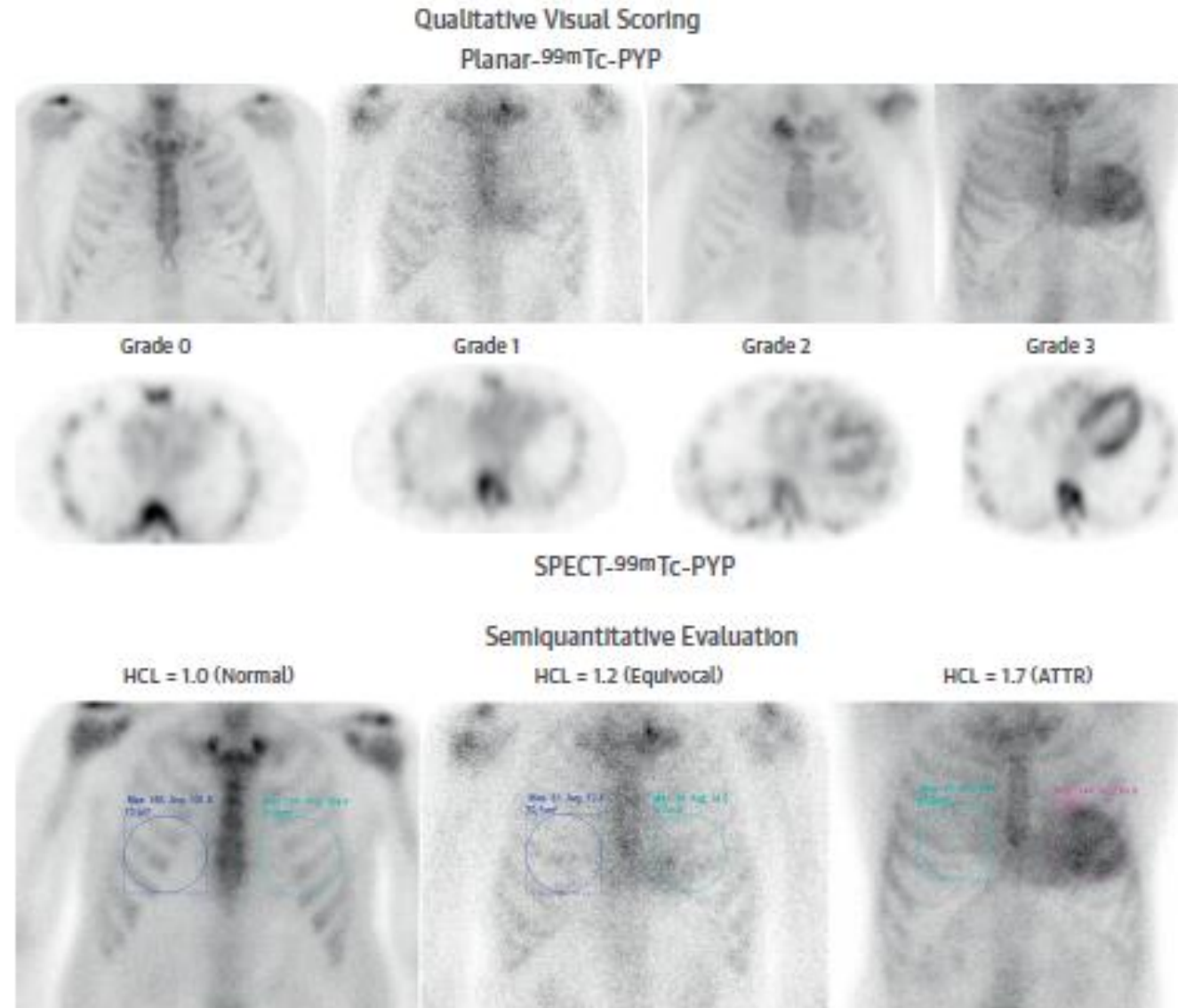


Cardiac Amyloidosis

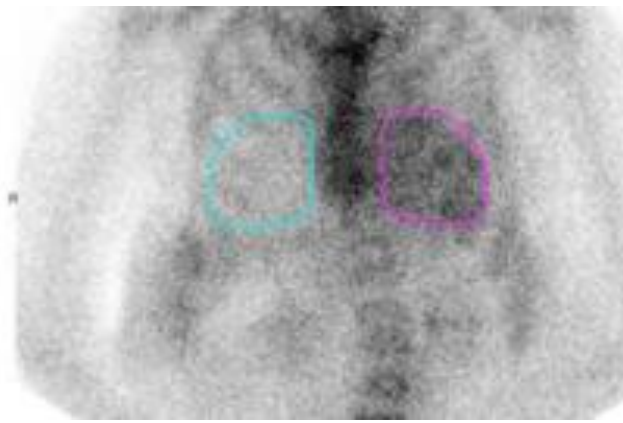


Bone-avid radiotracer Cardiac Scintigraphy for the Non-invasive Diagnosis

- Tc-99mPYP, DPD, or HMDP
- Any uptake (grades 1, 2, and 3) >99% sensitive and 86% specific for detecting ATTR CA
- Grades 2 or 3 myocardial radiotracer uptake and the absence of a monoclonal protein in serum or urine had a specificity and positive predictive value for ATTR CA of 100%, albeit with a significant drop in sensitivity (70%).



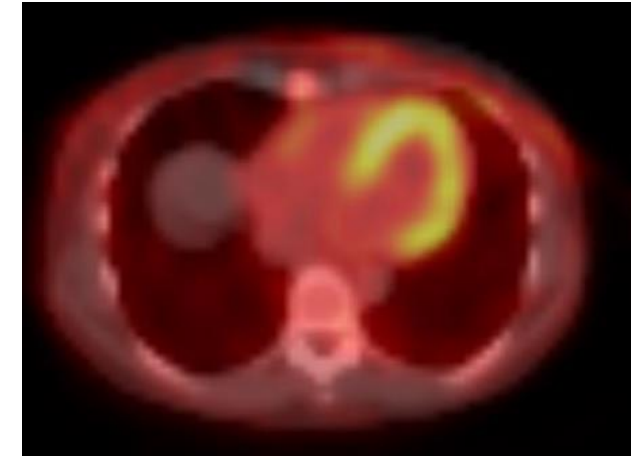
False positives



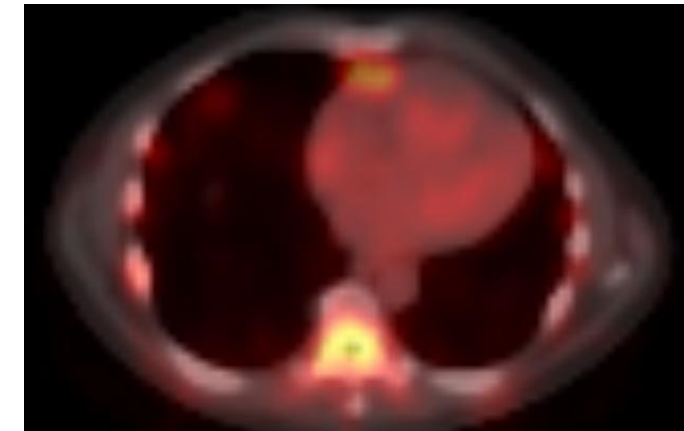
- Light Chain Amyloidosis
- Hot blood pool
- Myocardial infarction
- Rib fractures, valvular/annular calcifications
- Hydroxychloroquine toxicity
- Breast implants

False negatives

- hATTR – type A v's type B fibrils
 - Phe64Leu, Ser77Tyr, V30M-early onset
- wtATTR
 - Early disease



Grade 3



Grade 0

Imaging Summary

- Classic imaging features on echo and CMR do not distinguish light chain amyloidosis from transthyretin amyloidosis.
- Myocardial bone-avid radiotracer uptake is highly specific for transthyretin cardiac amyloidosis when plasma cell dyscrasia has been excluded; replacing the need for biopsy in many patients.
- SPEP & UPEP with Immunofixation and serum free lights required to exclude AL



Tissue Biopsy

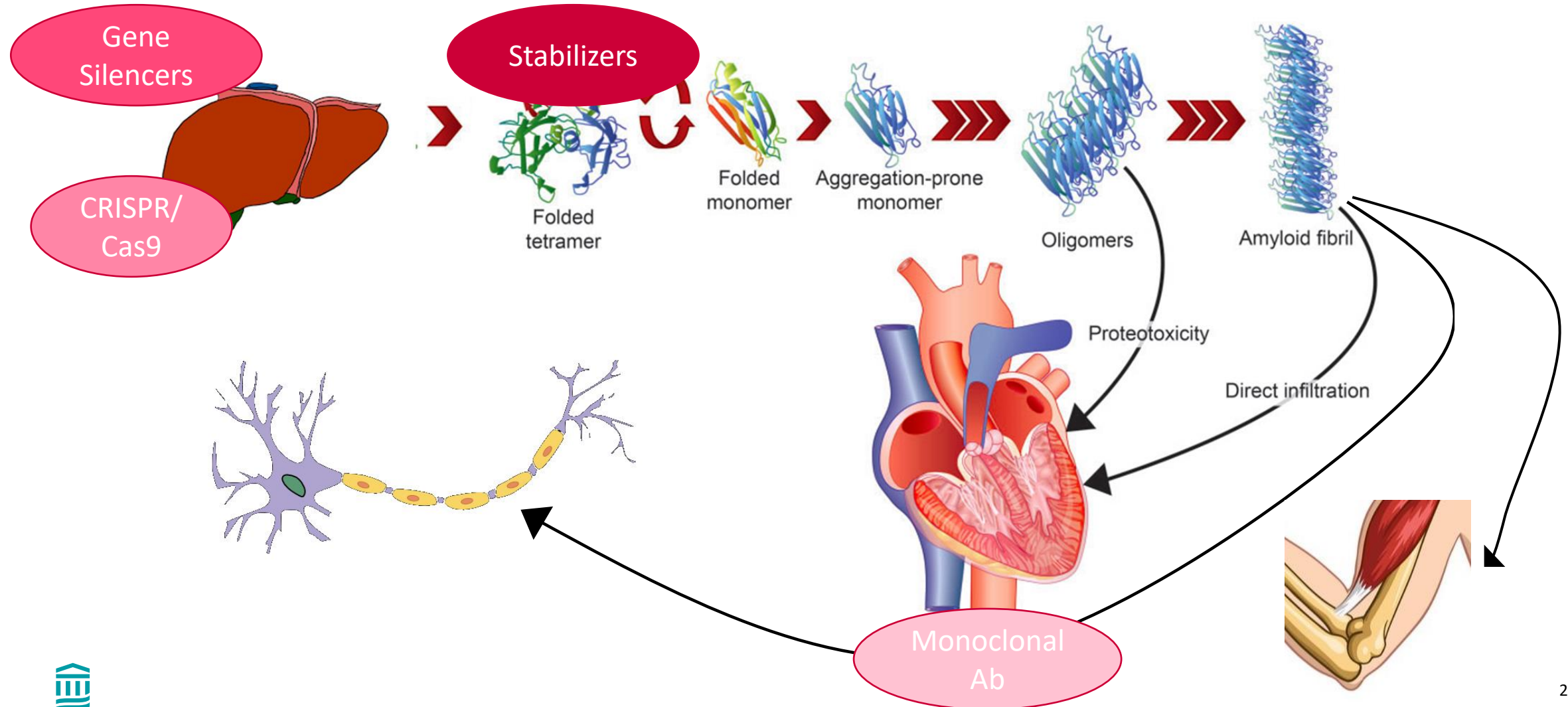
- Tissue biopsy is still the gold standard for diagnosis
- For diagnosis of AL biopsy proof of amyloid deposition is needed
- If the SPEP/UPEP/IFX/SFLC are abnormal: Most centers will do a bone marrow biopsy & fat pad fine needle aspirate (FNA) or biopsy or skin punch biopsy.
- Fat pad FNA is sensitive for AL (~84%), but a lot less for ATTR (45% hATTR, 15% wtATTR)
- If negative, biopsy involved organ = endomyocardial biopsy
- Congo red staining, Sulfated Alcian Blue detect amyloid deposition
- Immunofluorescence types the amyloid precursor protein
- Mass Spectrometry is the gold standard for typing (sensitivity of 88% & specificity of 96%)



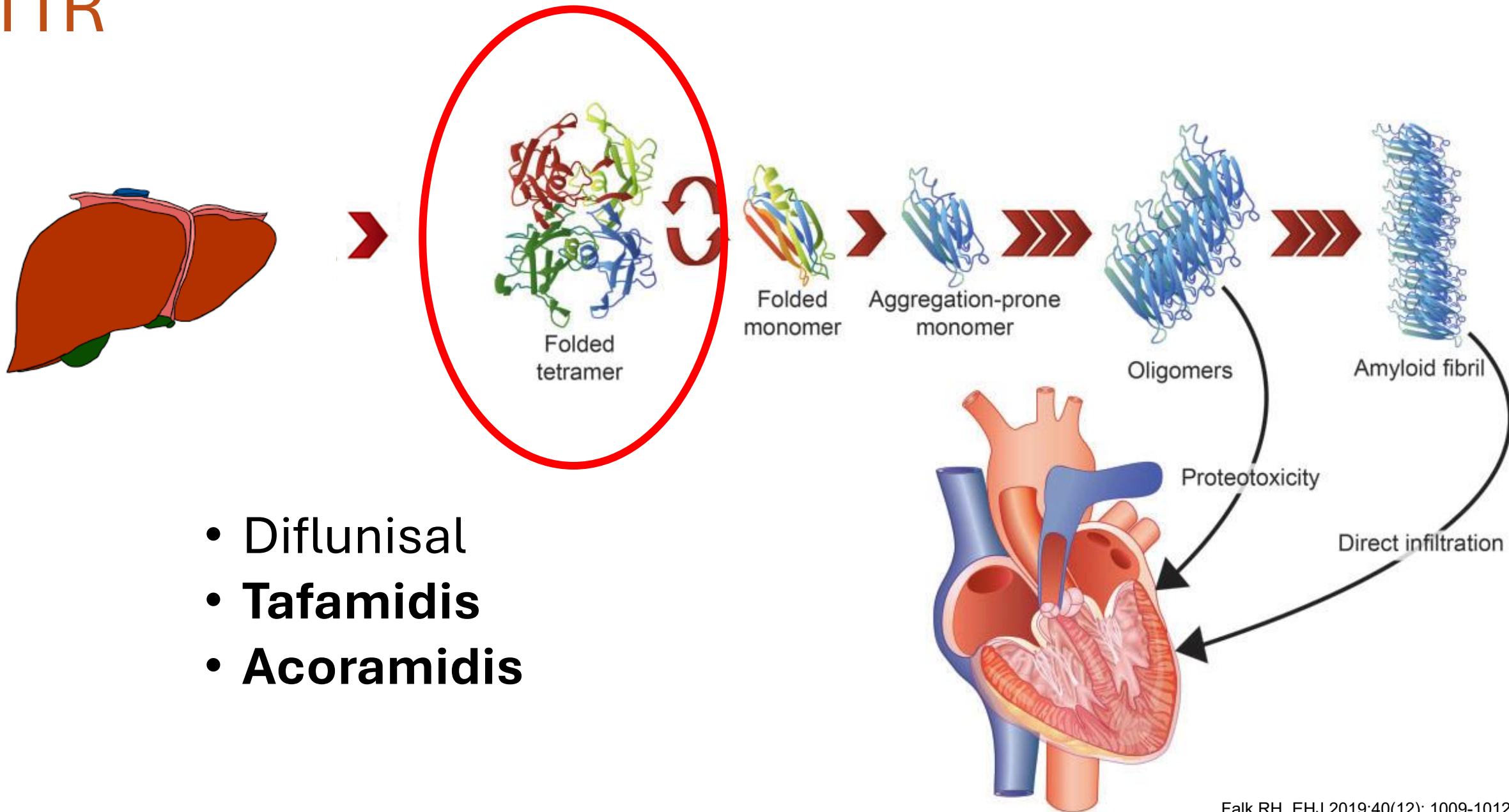
Treatments

Effective therapies

ATTR



ATTR

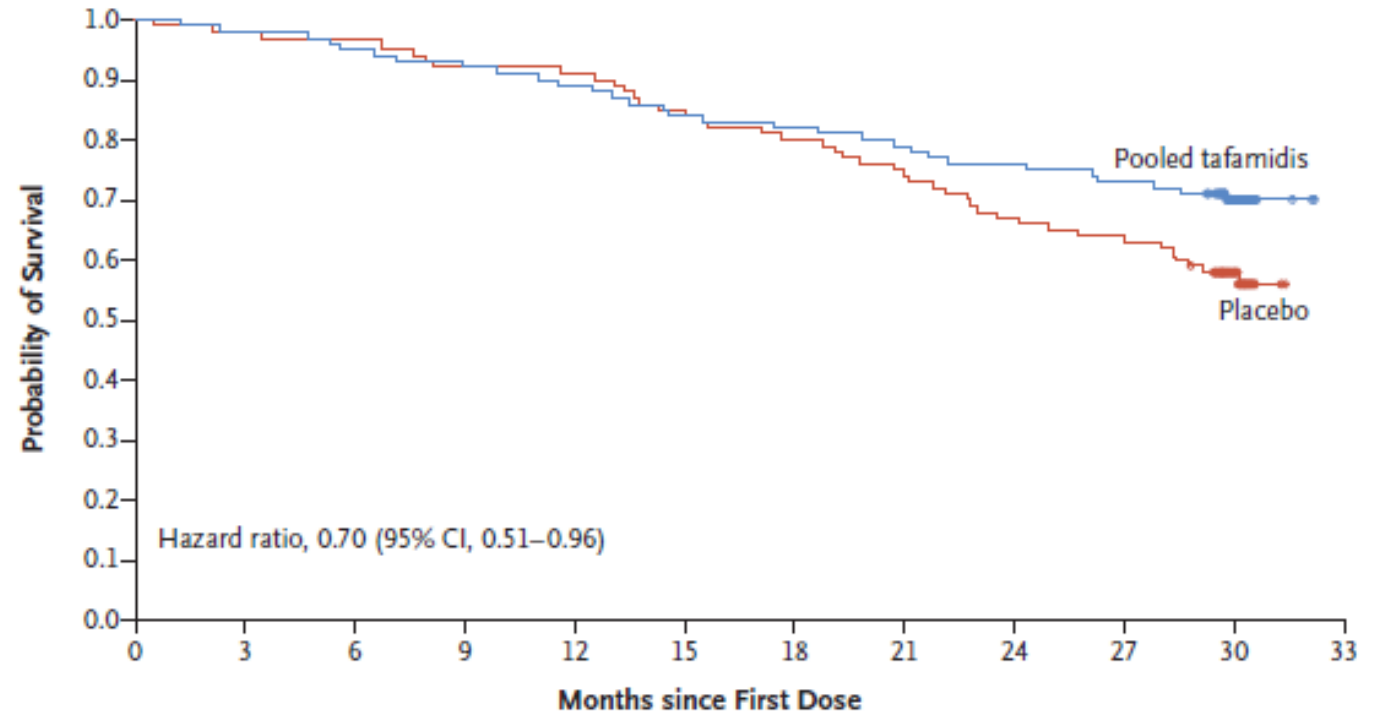


Tafamidis

ATTR-ACT

- 441 Randomized 2:1:2
- Tested 2 doses
 - 80 mg and 20 mg
- 30 months
- Lower all-cause mortality
 - 29.5% vs. 42.9%; HR 0.7
- Reduced hospitalization
 - Relative risk ratio of 0.68
- 0.48 per year vs. 0.70 per year (95% CI, 0.33 to 0.81).

B Analysis of All-Cause Mortality



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)

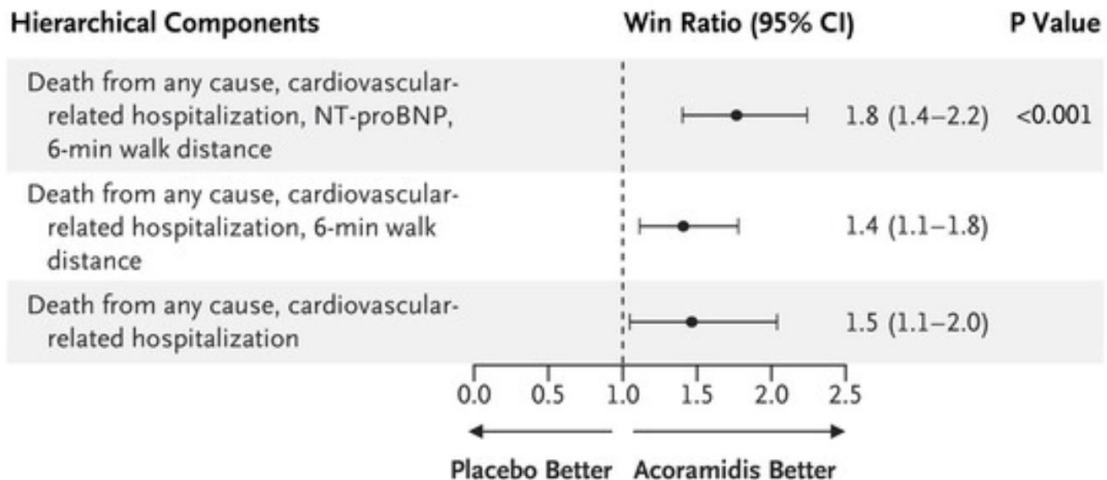


Acoramidis

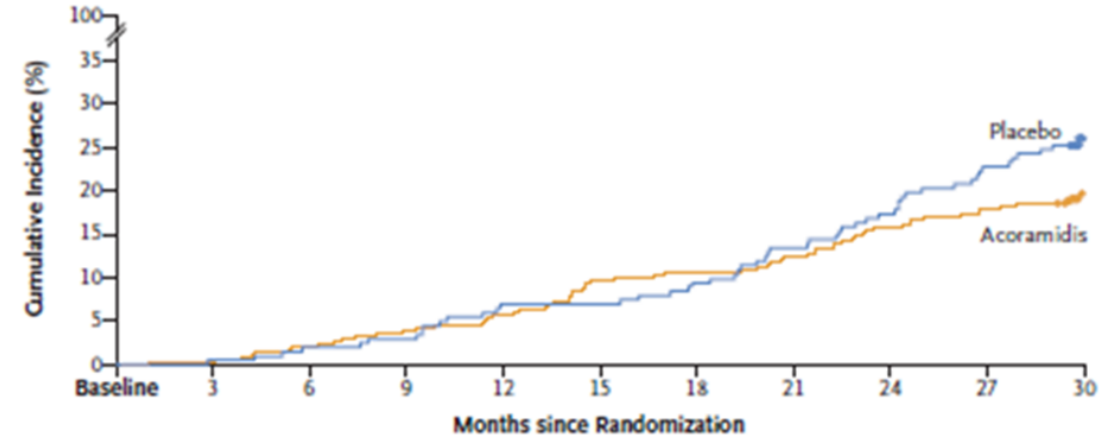
ATTRibute-CM

- 632 Randomized 2:1
- 800 mg BID
- 30 months

Primary Efficacy Analysis and Prespecified Secondary Analyses



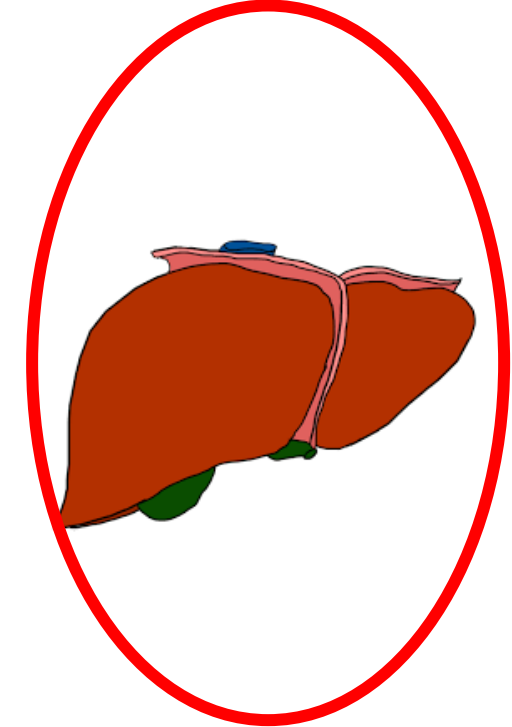
Death from Any Cause



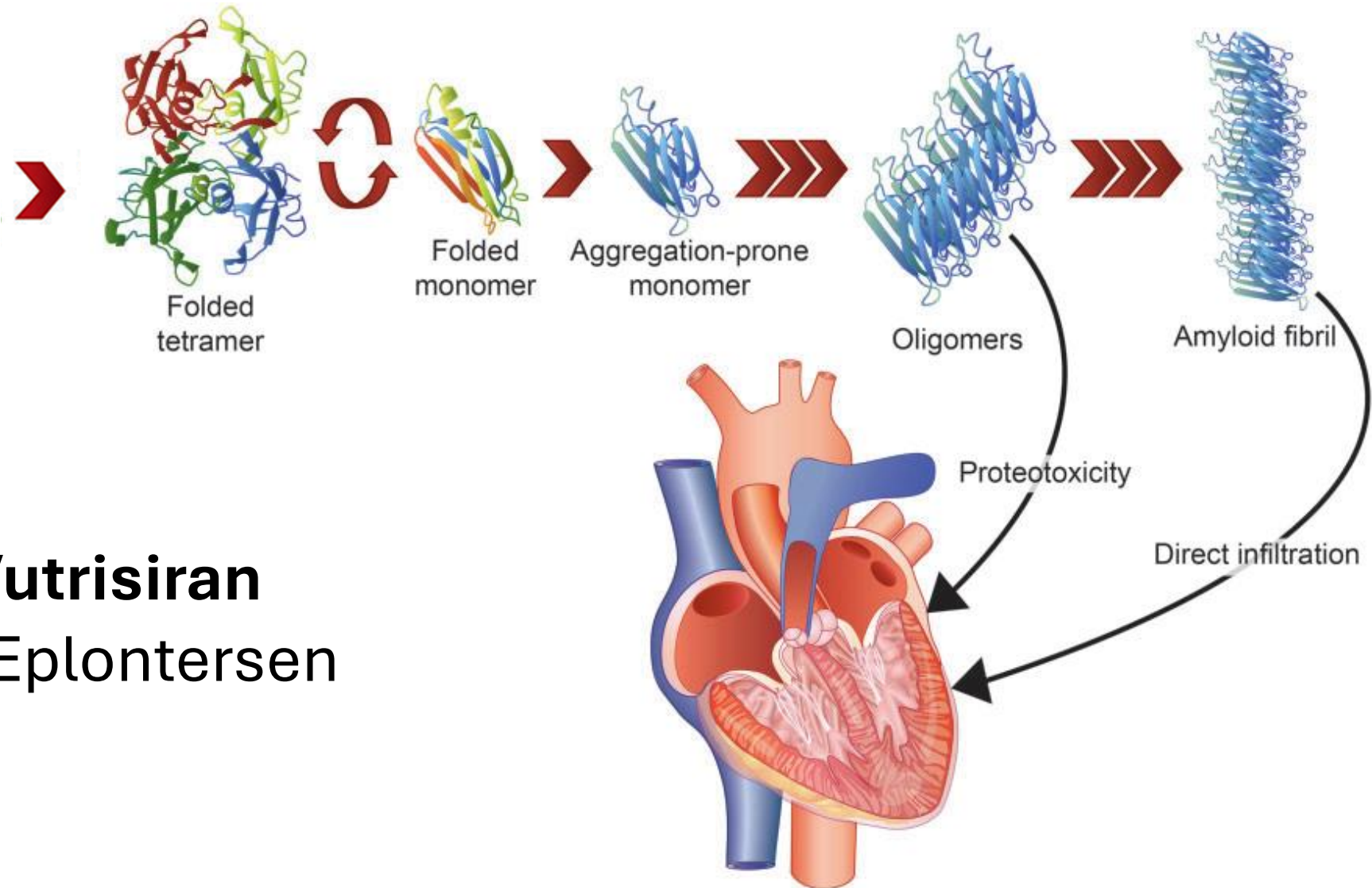
No. at Risk (no. of events)

Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)

ATTR



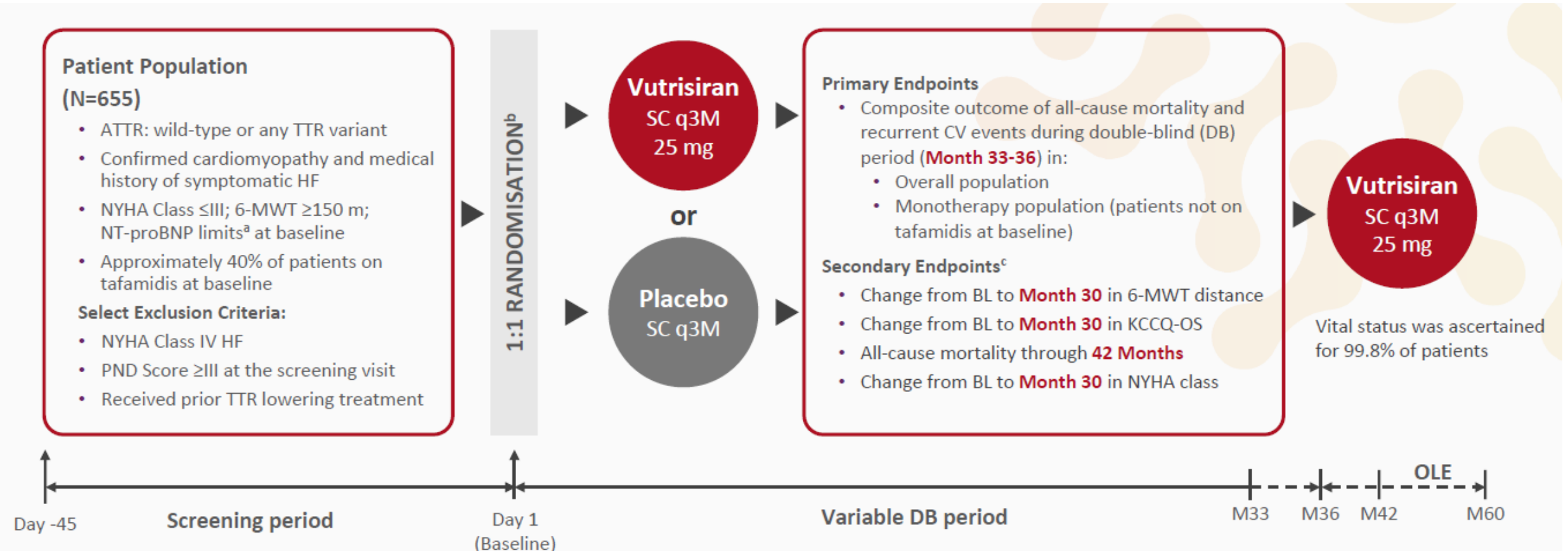
- Patisiran > **Vutrisiran**
- Inotersen > Eplontersen



Vutrisiran in ATTR-CM

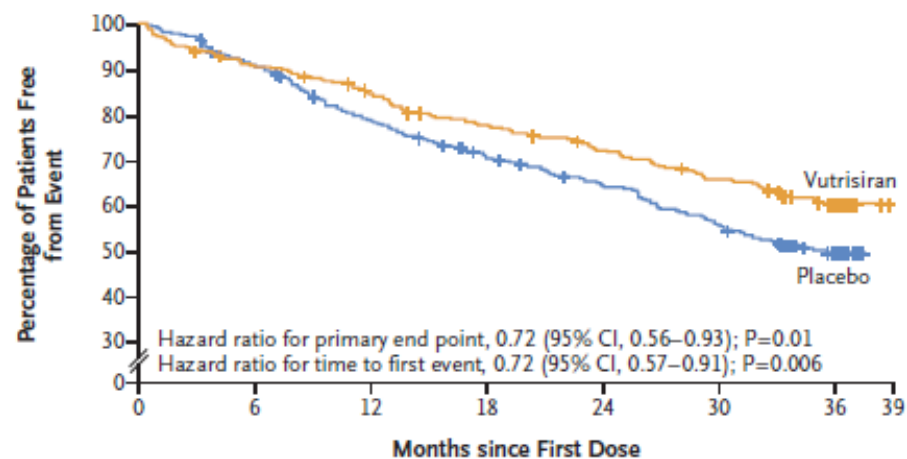
HELIOS-B Study Design

- HELIOS-B is a phase 3 randomized trial was to evaluate the efficacy and safety of vutrisiran, a SC-administered RNAi therapeutic, compared with placebo among patients with ATTR-CM



Click to
• See

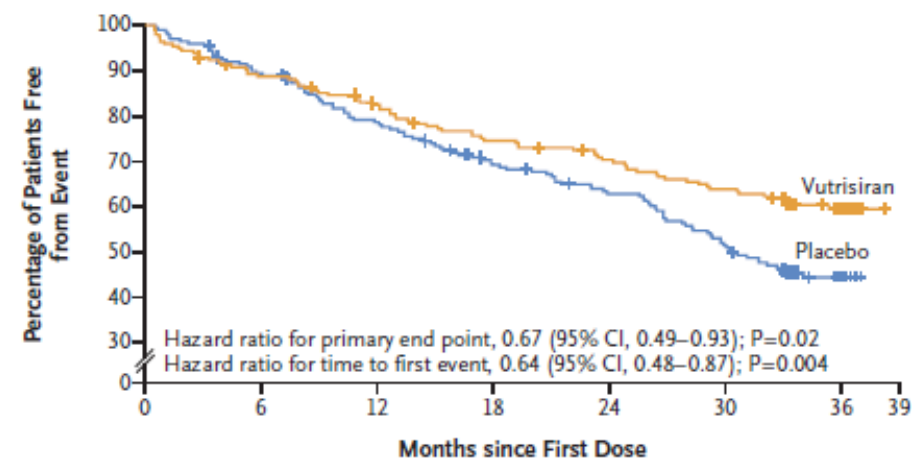
A Time to First Event in the Overall Population



No. at Risk (cumulative no. of events)

Vutrisiran	326 (0)	294 (30)	271 (50)	247 (72)	227 (90)	206 (110)	62 (125)	0 (125)
Placebo	328 (0)	295 (31)	253 (70)	221 (96)	199 (115)	172 (142)	52 (159)	0 (159)

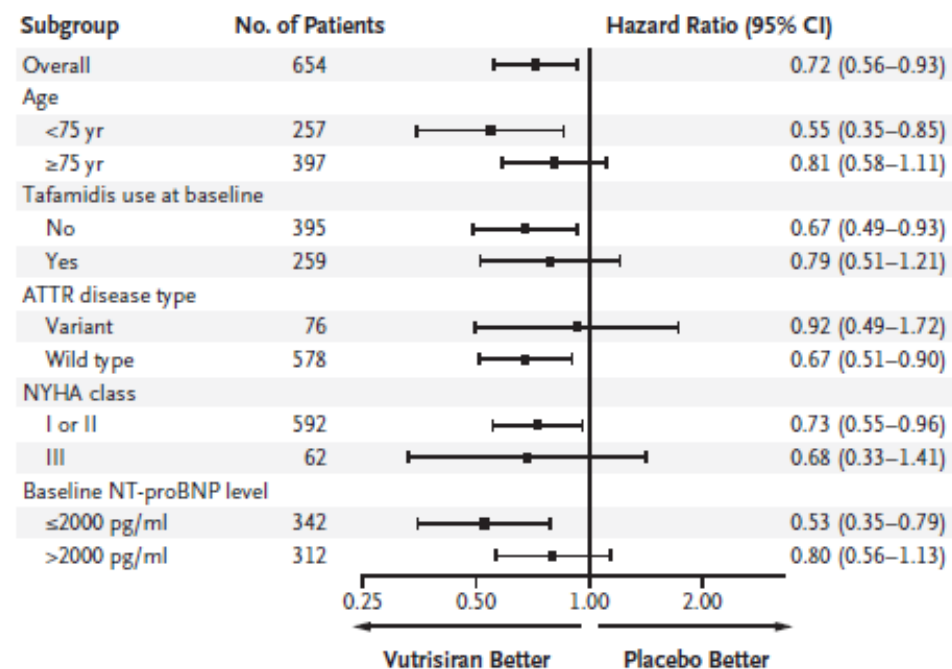
B Time to First Event in the Monotherapy Population



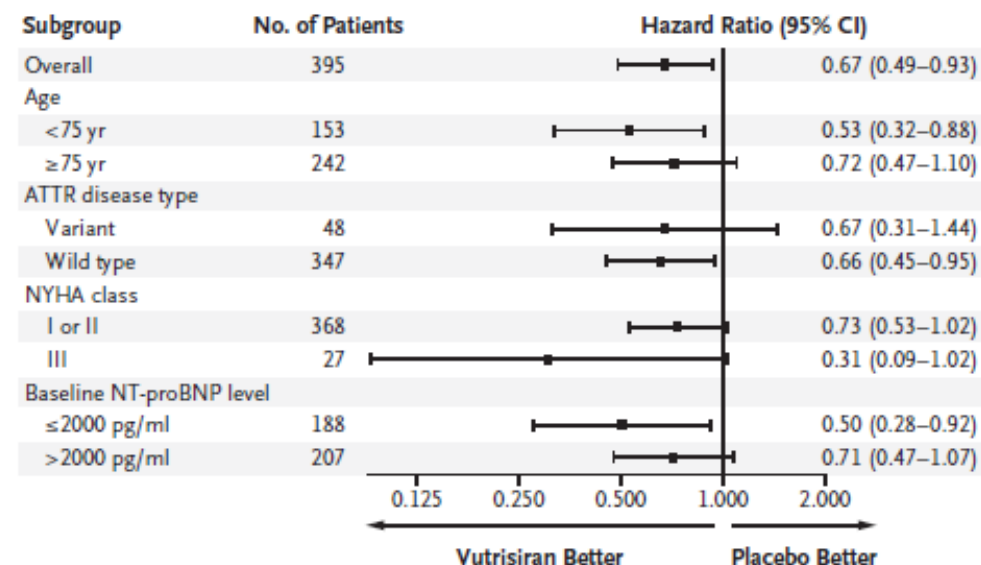
No. at Risk (cumulative no. of events)

Vutrisiran	196 (0)	172 (22)	157 (34)	141 (49)	131 (57)	119 (69)	32 (76)	0 (76)
Placebo	199 (0)	175 (22)	152 (43)	130 (60)	116 (72)	95 (93)	26 (105)	0 (105)

C Subgroup Analyses of the Primary End Point (overall population)



D Subgroup Analyses of the Primary End Point (monotherapy population)

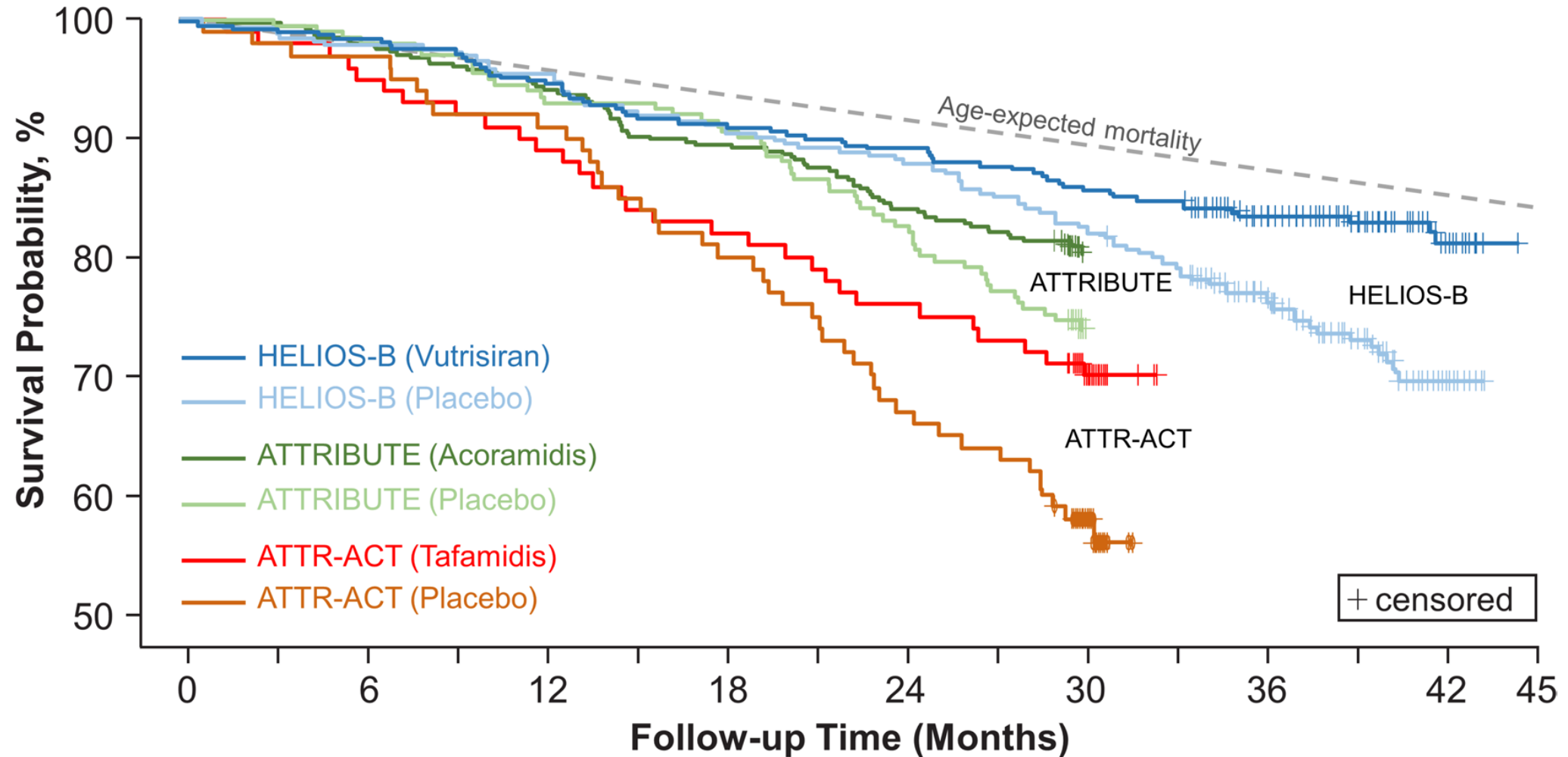


3 Pivotal Clinical Trials in the Treatment of ATTR-CM

	ATTR-ACT ^{3,4}	ATTRIBUTE-CM ^{5,6}	HELIOS-B ^{1,2}
Therapy	Tafamidis	Acoramidis	Vutrisiran
Enrollment time	December 2013 to August 2015	April 2019 to October 2020	December 2019 to August 2021
Total patients	441	632	655
Treatment	264 (60%)	421 (67%)	326 (50%)
Placebo	177 (40%)	211 (33%)	328 (50%)
Age, y	75 (46-89)	77 (52-92)	77 (45-85)
Wild type	76%	90%	89%
Variant	24%	10%	11%
NYHA functional class			
I	8%	12%	15%
II	60%	70%	77%
III	32%	18%	8%
NT-proBNP, pg/mL ^a	2,996 [1,752-4,862]	2,326 [1,332-4,019]	2,021 [1,138-3,312]
Concomitant tafamidis ^b			
Baseline	N/A	0%	40%
Drop-in	N/A	18%	13%
Primary trial all-cause mortality			
Mortality treatment	30% at 30 mo	19% at 30 mo	16% at 36 mo
Mortality placebo	43% at 30 mo	26% at 30 mo	21% at 36 mo
Extended follow-up including open label extension all-cause mortality			
Mortality treatment	45% at 58 mo	23% at 42 mo	18% at 42 mo
Mortality placebo	63% at 58 mo	35% at 42 mo	29% at 42 mo

Marked increase in Survival in ATTR-CM

Shift in Curves due to earlier detection



Light Chain (AL) Amyloidosis

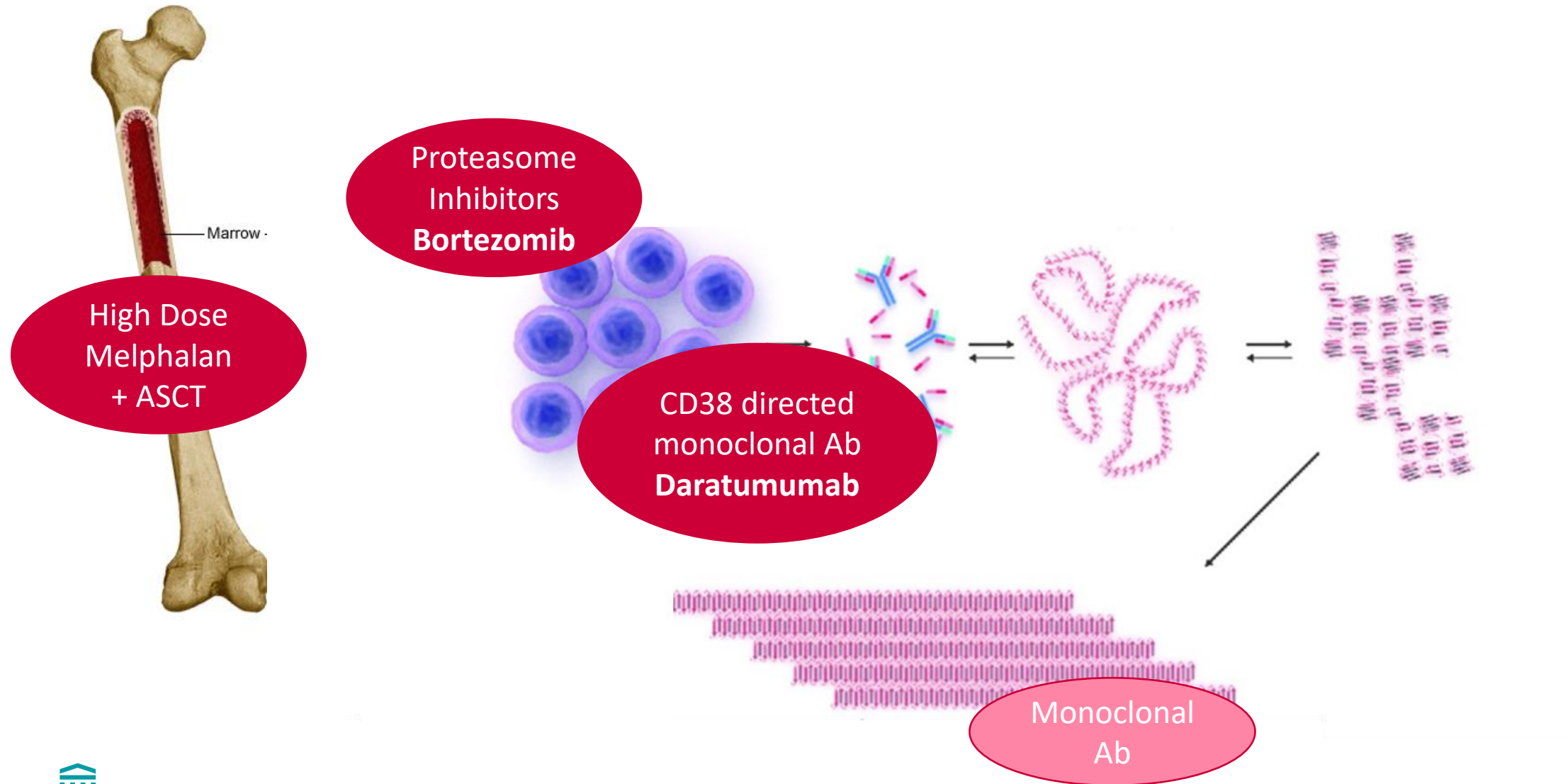
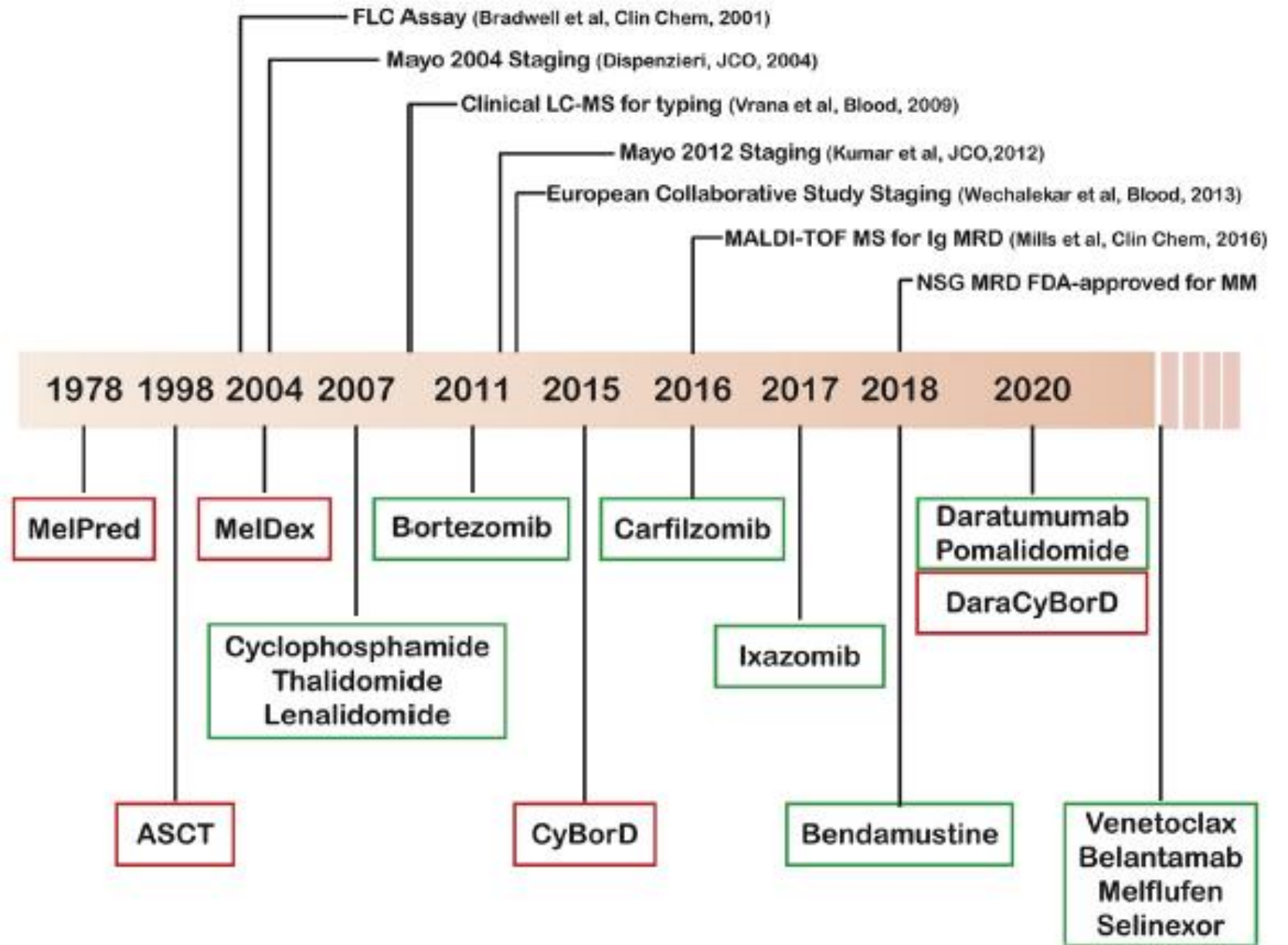


FIGURE 1 Evolution of Treatment in AL Amyloidosis



Red is more commonly used

Green is less commonly used

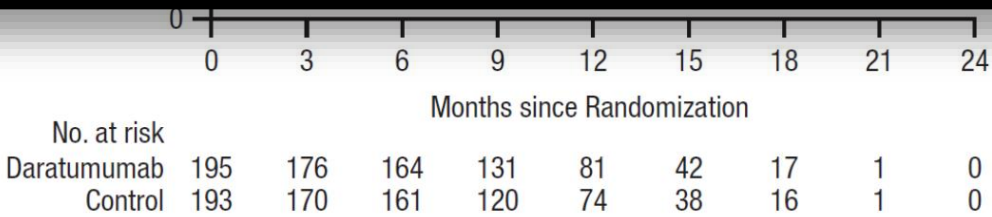
Mel= Melphalan
Cy = cyclophosphamide
Bor = Bortezomib (Velcade)
D = Dex = Dexamethasone

Andromeda Trial: Change to survival comparison

Daratumumab + CyBorD

388 randomized

Subgroup	Control <i>no. of patients with a response/total no. (%)</i>	Daratumumab <i>no. of patients with a response/total no. (%)</i>	Odds Ratio (95% CI)
Cardiac stage at baseline			
I	12/43 (28)	21/47 (45)	2.09 (0.87–5.03)
II	16/80 (20)	41/76 (54)	4.69 (2.30–9.53)
IIIA or IIIB	7/70 (10)	42/72 (58)	12.60 (5.07–31.32)
Cardiac involvement at baseline			
Yes	22/137 (16)	80/140 (57)	6.97 (3.96–12.27)
No	13/56 (23)	24/55 (44)	2.56 (1.13–5.80)



- NYHA IIIB or IV at screening.

Take Home Messages

- Increasing awareness of disease, with improved diagnostic tools, leading to increase in detection in ATTR, but also AL
- ATTR: heart, tendons and ligaments, with PNS and ANS involvement in some forms of hATTR
- AL: systemic disease, cardiac involvement has worst prognosis.
- Tissue biopsy proof still needed for AL amyloidosis and in the presence of a monoclonal gammopathy
- When a monoclonal gammopathy is ruled out; ATTR can be diagnosed by grade 2 or 3 uptake with bone-avid radiotracer (PYP/HMDP/DPD) cardiac scintigraphy & typical echocardiographic or MRI features are seen.
- Advances in therapies in last several years for ATTR and AL
 - Tafamidis, Acoramidis and Vutrisiran
 - Daratumumab with Bortezomib (Velcade), cyclophosphamide and dexamethasone is first line therapy in AL



Questions

The following tests are required to make a diagnosis of ATTR cardiac amyloidosis

1. FDG PET and serum protein electrophoresis.
2. Echo and Cardiac MRI and Serum protein electrophoresis (SPEP).
3. Echo or Cardiac MRI, and PYP and serum and urine protein electrophoresis with immunofixation, and serum free light chains
4. Cardiac MRI and FDG PET and serum and urine protein electrophoresis with immunofixation, and serum free light chains
5. PYP and and serum and urine protein electrophoresis with immunofixation, and serum free light chains.

Rationale: Grade 2 or 3 uptake on a PYP scan, with typical features seen on echo or MRI, in the absence of a plasma cell dyscrasia is diagnostic for ATTR amyloidosis. SPEP alone is not sufficient. It is important that typical features of cardiac amyloidosis are seen on echo or MRI to avoid false positives. FDG-PET is used to aid the detection of cardiac sarcoidosis, but is a non-specific tracer.

Reference: Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin Amyloidosis. Circulation. 2016;133:2404–2412.



References

- I. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379: 1007–1016.
- II. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin Amyloidosis. *Circulation*. 2016;133:2404–2412.
- III. Merlini G, Dispenzieri A, Sanchorawala V, et al. Systemic immunoglobulin light chain amyloidosis. *Nat Rev Dis Primers*. 2018;4:38.
- IV. Kittleson M, Ruberg F, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis. *J Am Coll Cardiol*. null2023, 0 (0) [.https://doi.org/10.1016/j.jacc.2022.11.022](https://doi.org/10.1016/j.jacc.2022.11.022)
- V. Dorbala S, Cuddy S, Falk R. How to Image Cardiac Amyloidosis. *J Am Coll Cardiol Img*. 2020 (6) 1368–1383.
- VI. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light chain amyloidosis. *N Engl J Med*. 2021;385:46–58.

