

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

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

Disclosures

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Key Learning Objectives

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



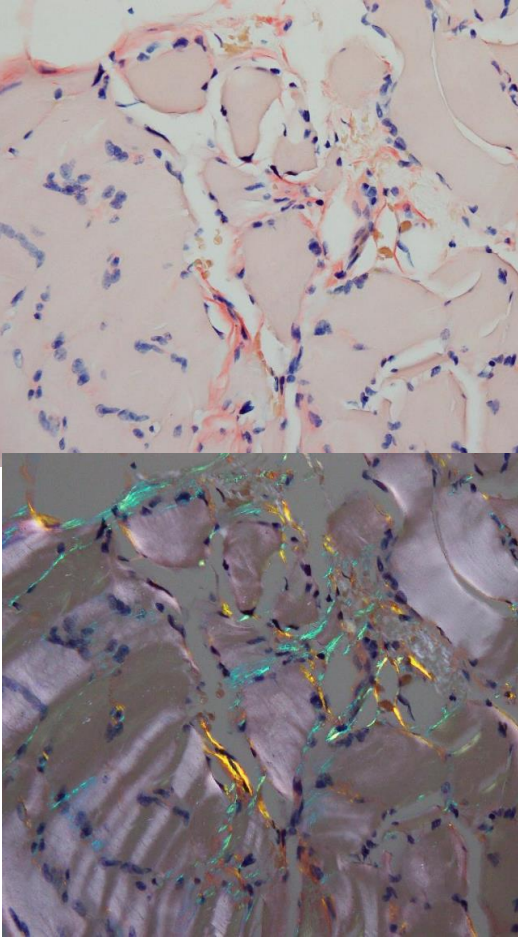
Question

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 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



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)
 - Light Chain (AL)
 - Reactive systemic amyloidosis – serum amyloid A protein (AA)

Cardiac Amyloidosis



Transthyretin
ATTR

Wild-type

Variant
(Mutant/hereditary)

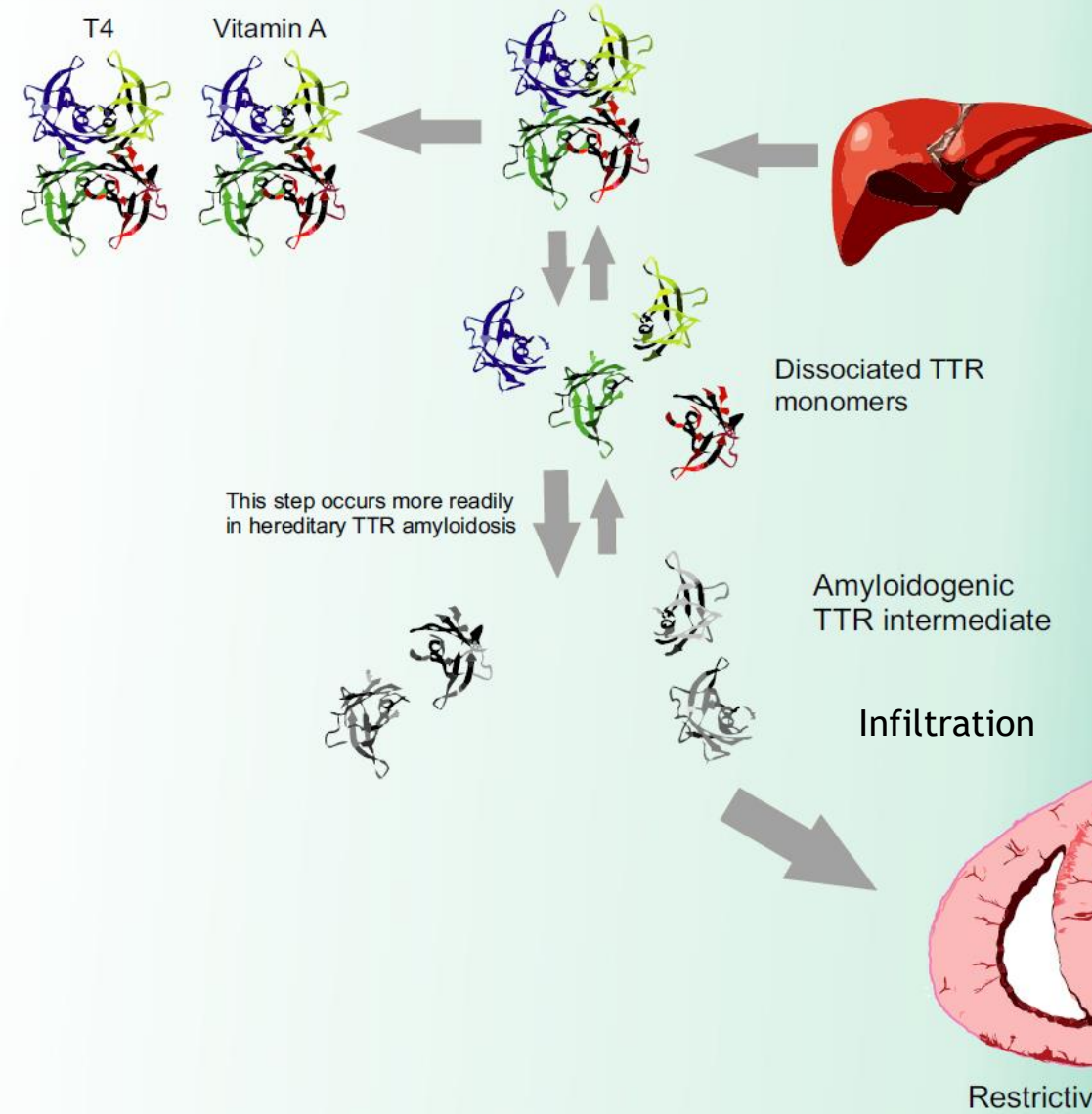
Light Chain
AL

AA,
Apolipoprotein AI-4,
B2Microglobulin

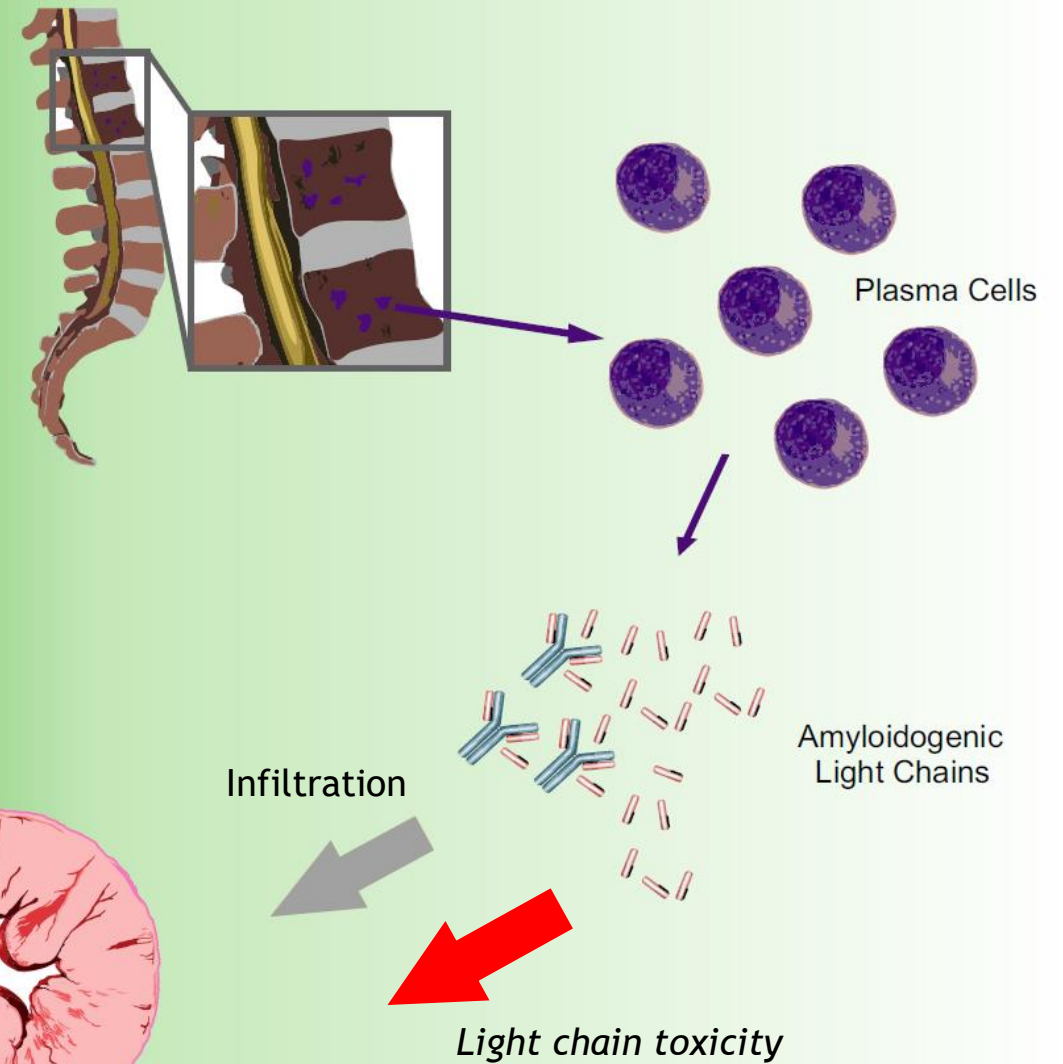
Transthyretin Cardiac Amyloidosis

Normal function to transport

TTR composed of 4 identical subunits



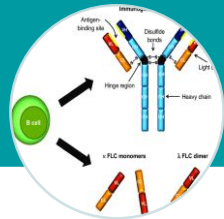
Cardiac AL Amyloidosis



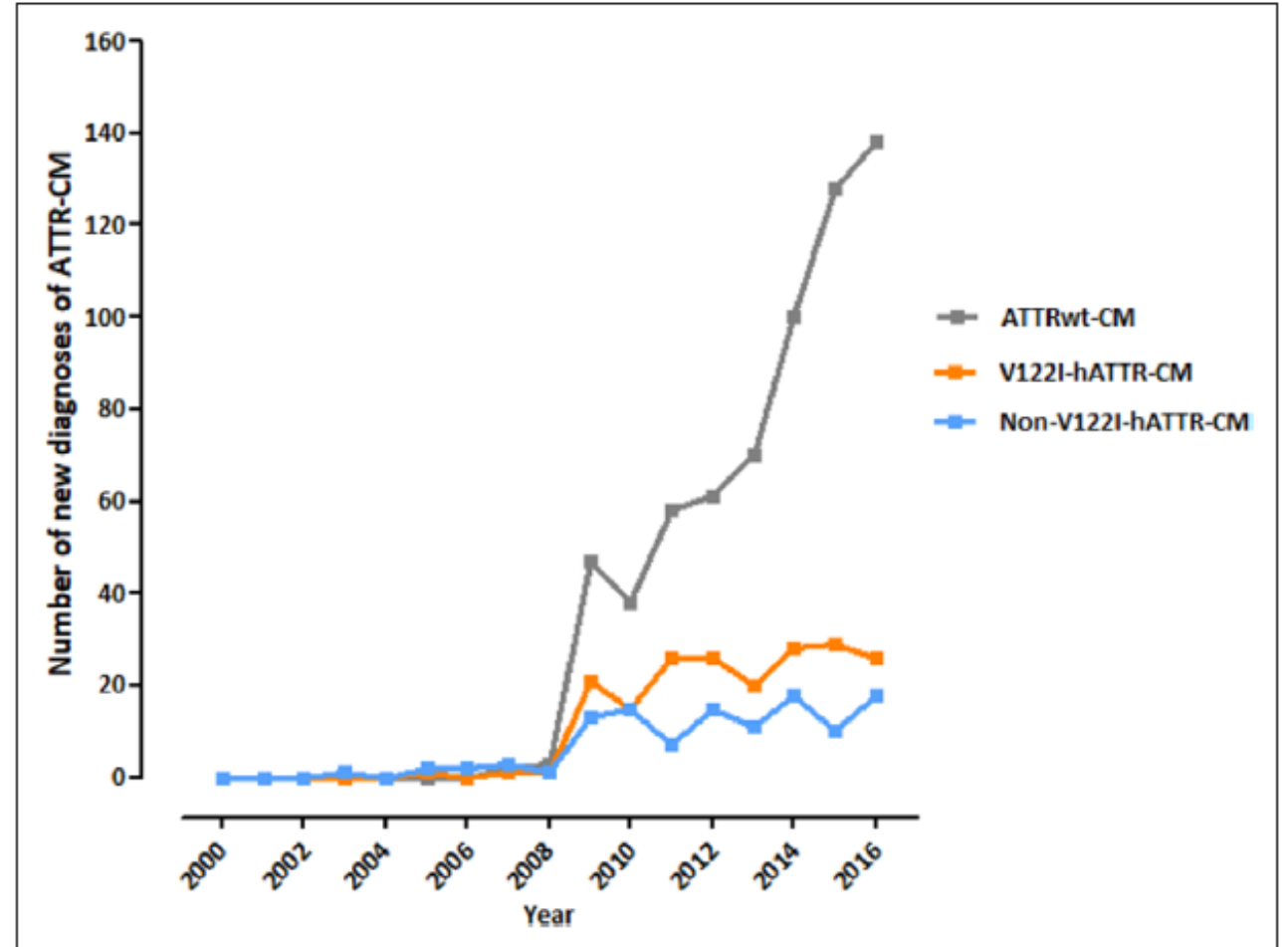
Epidemiology

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

AL



National Amyloidosis Center, UK



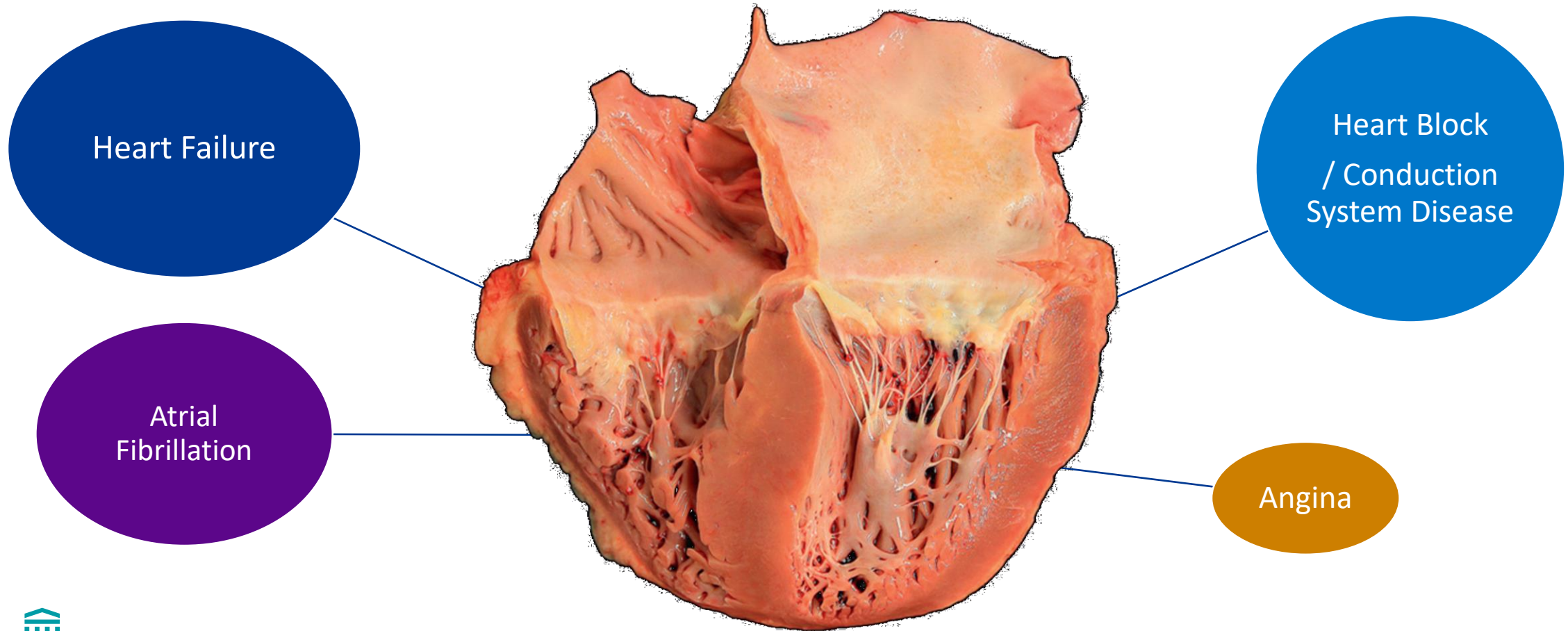
González-López et al. Eur Heart J. 2015;36(38):2585-94.

Castano et al. Eur Heart J. 2017;38(38):2879-2887. 9

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



Extracellular deposition of amyloid in the heart



Clinical clues: ATTR

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

ATTRv

- Neuropathy
 - Autonomic and/or peripheral



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

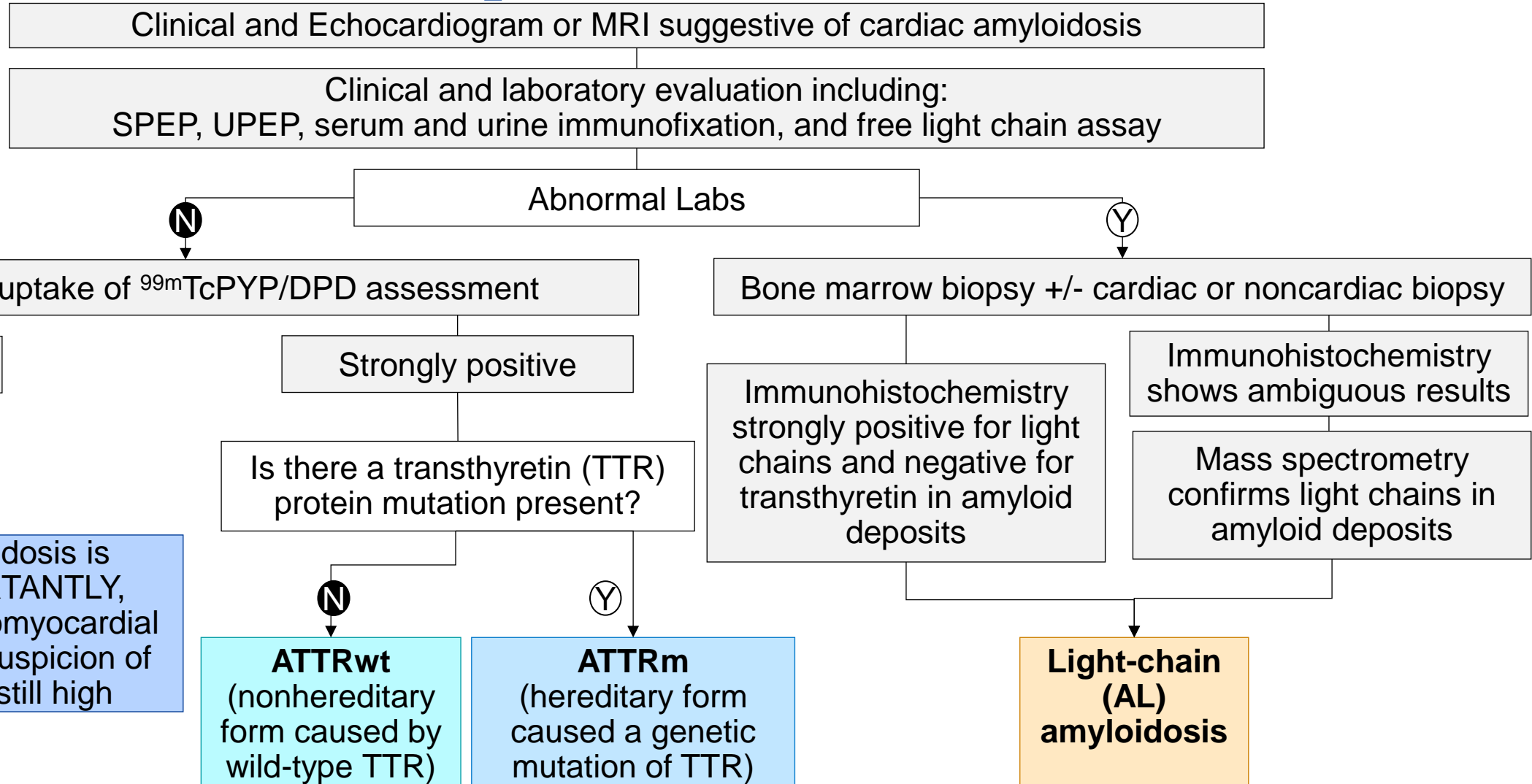
- Orthostatic hypotension
- HF findings
- Biceps Tendon Rupture
- Purpura, Macroglossia, Salivary gland swelling

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

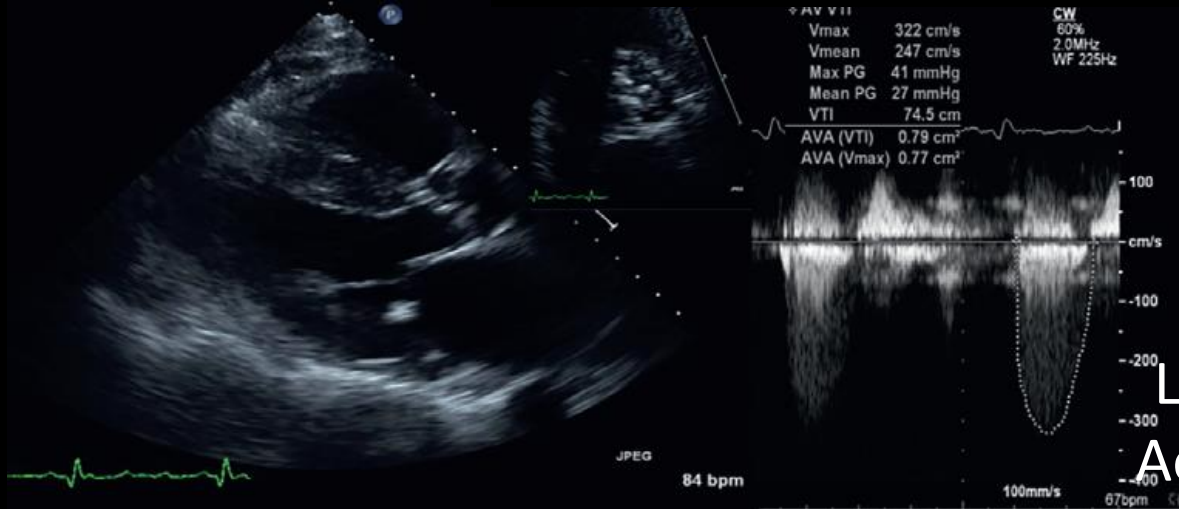
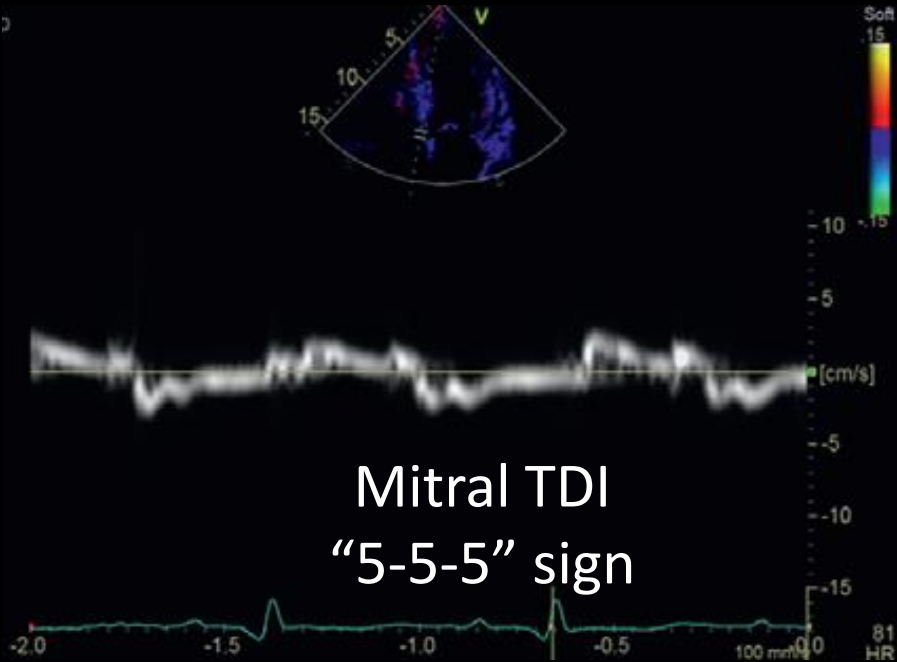
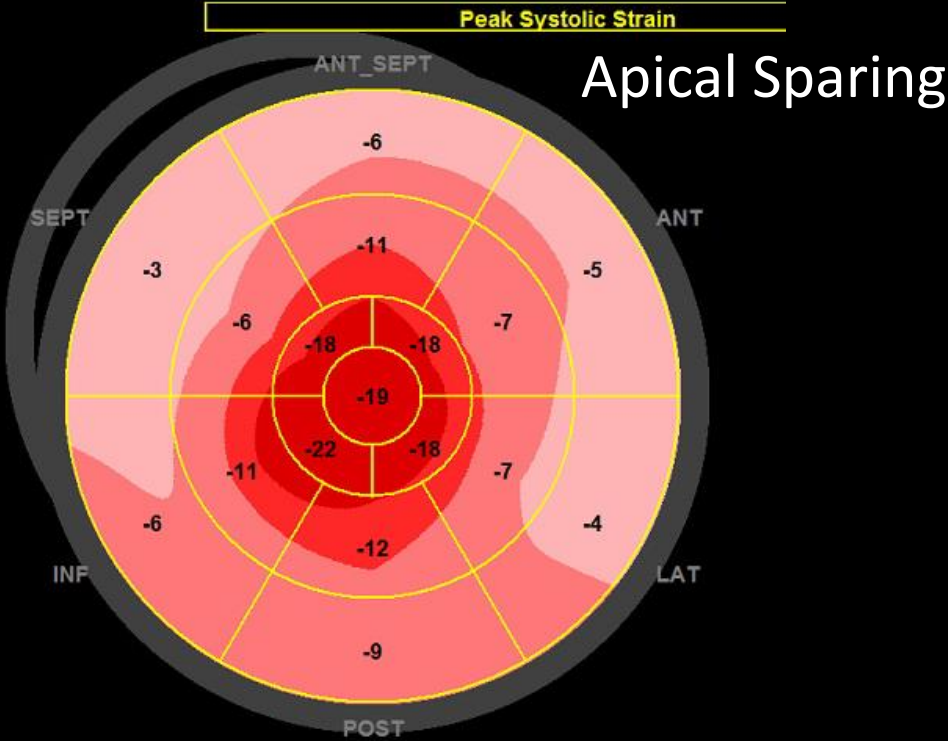
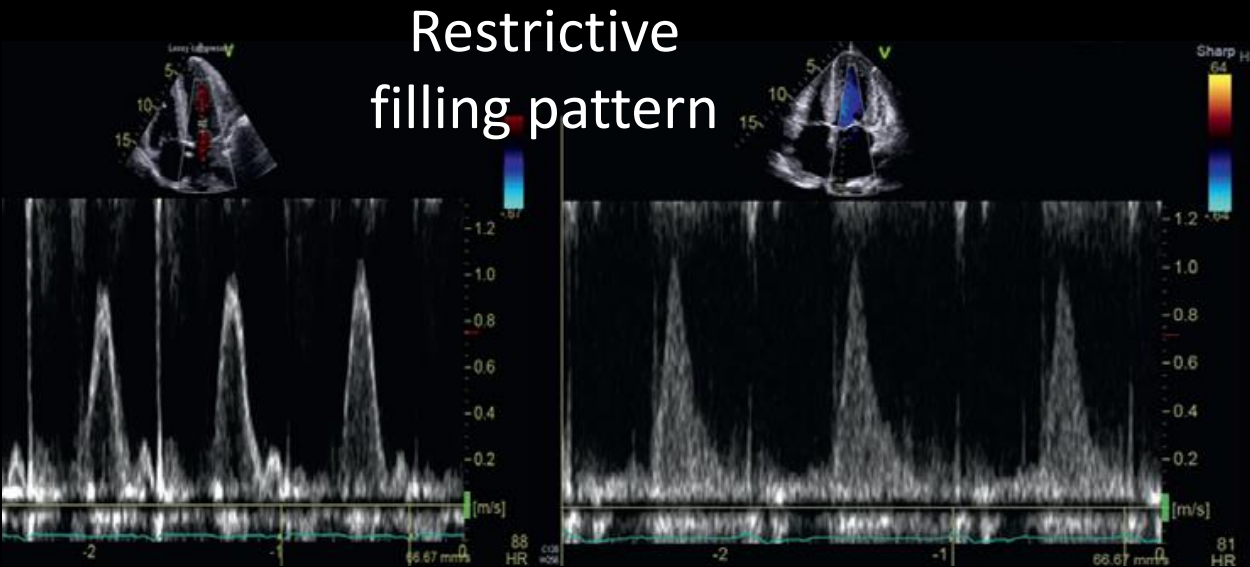
Valve thickening

Pericardial and pleural effusions

Increased echogenicity/ echo-
bright appearance



Echocardiography: Diastolic function and strain



Low Flow

Low Gradient

Aortic Stenosis

Classical findings not the Rule

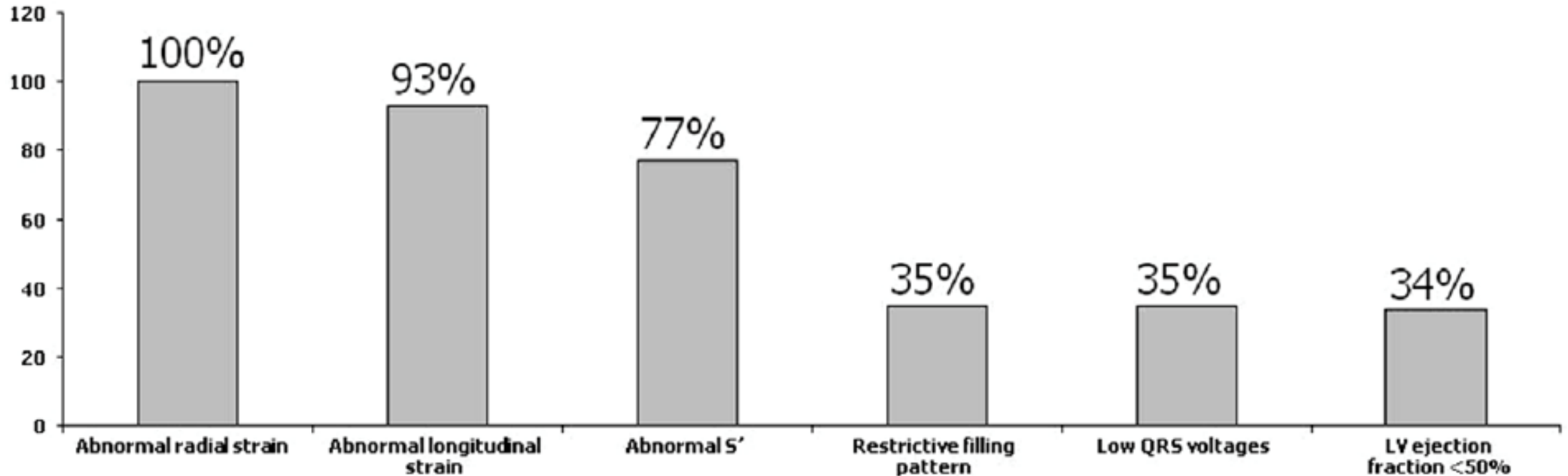
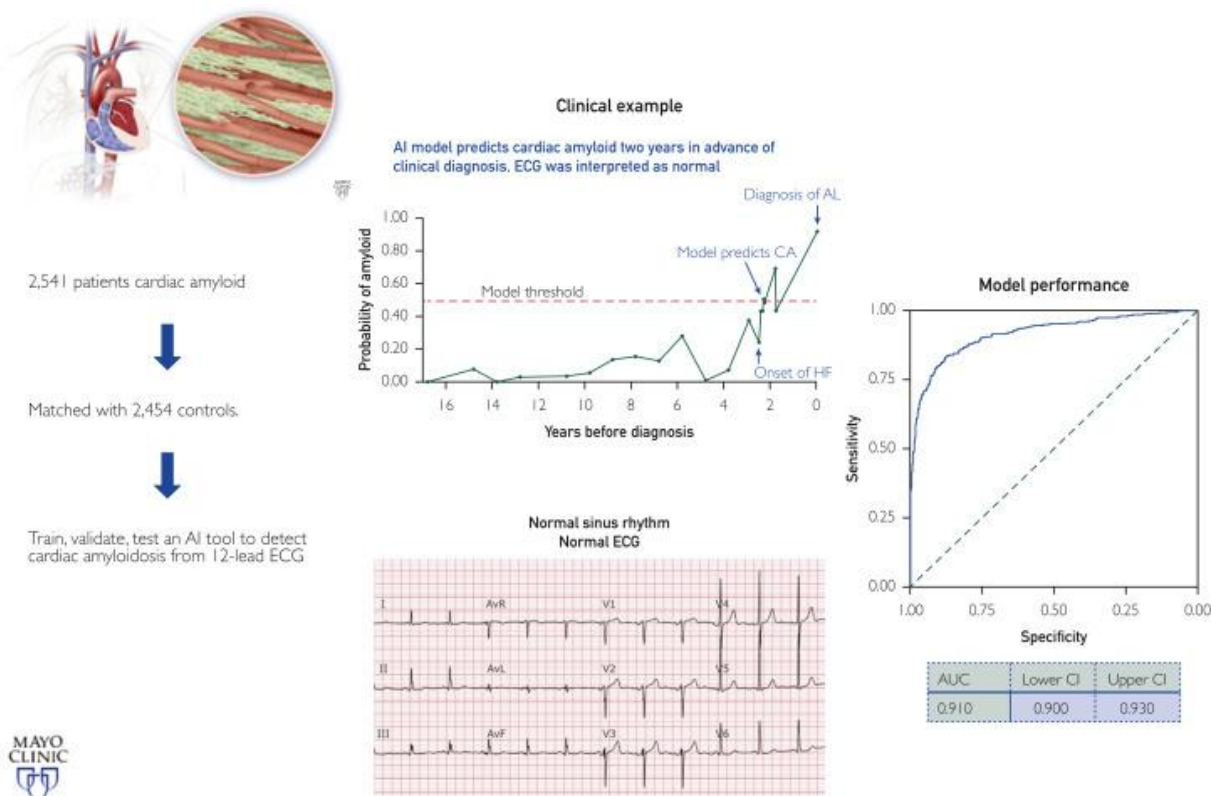


Figure 1. Prevalence of frequency of abnormal indices of systolic and diastolic function in patients with cardiac amyloidosis. Speckle tracking–derived strain parameters were more sensitive than the conventional echocardiographic parameters of systolic and diastolic function in characterizing left ventricular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

AI for Diagnosis

ECG



Echo

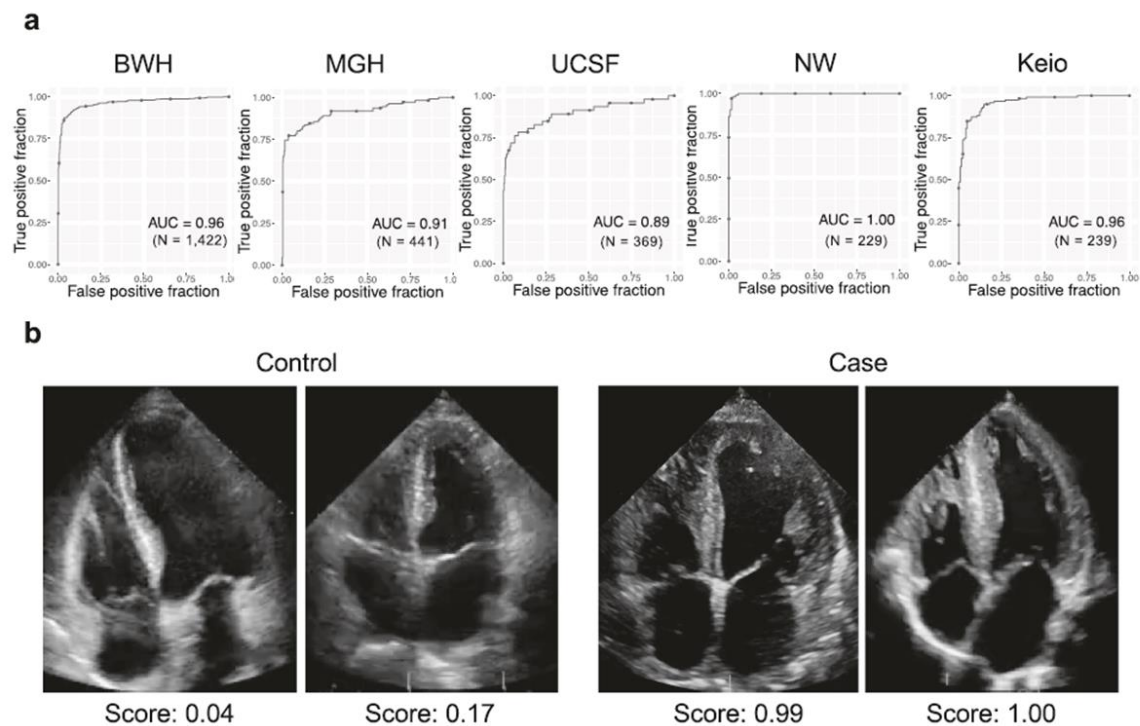


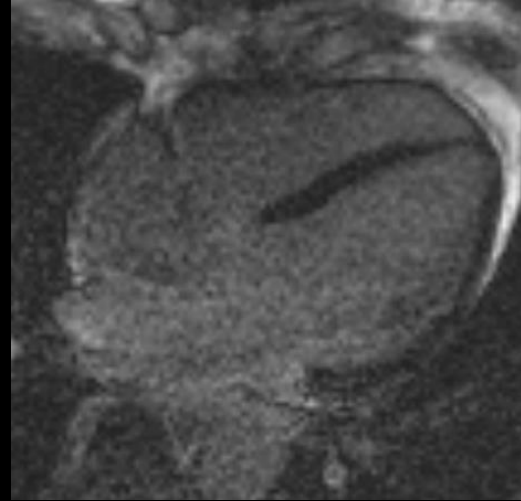
Fig. 2 Performance of the cardiac amyloidosis echocardiography model. **a** ROC plots for detecting cardiac amyloidosis for each institution. The performance on the test dataset is shown for BWH. **b** representative echocardiography images for cases and controls. The score denotes the model output for 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

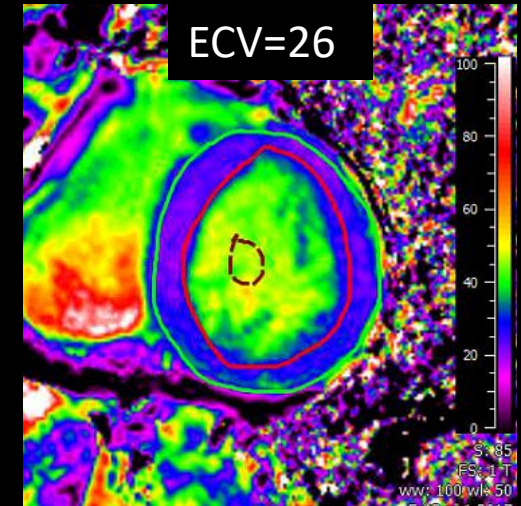
Normal



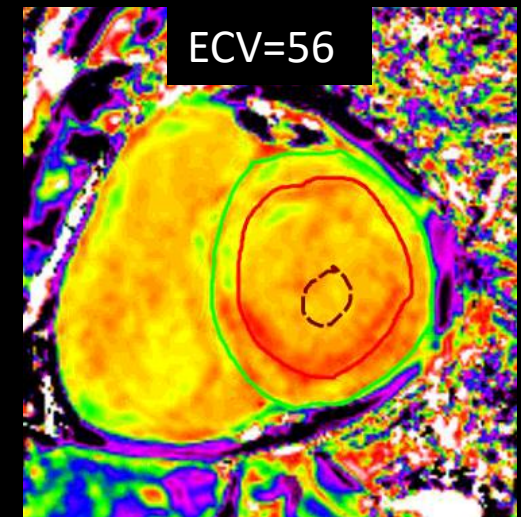
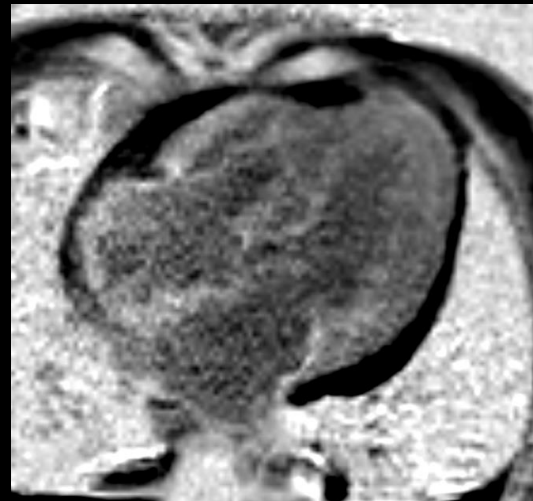
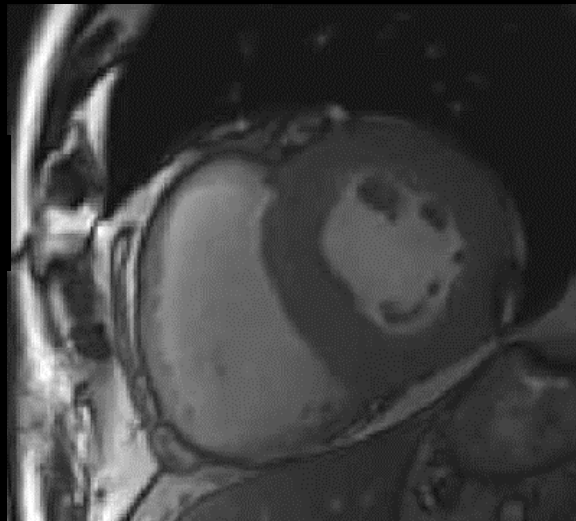
Late Gadolinium Enhancement (LGE)



Extracellular Volume (ECV)



Cardiac Amyloidosis





Patients with suspected transthyretin amyloid cardiomyopathy (ATTR-CM)
based on clinical features + abnormal echocardiogram, or cardiac MRI

Evaluate for monoclonal gammopathy using serum-free light chain (FLC) assay
+ serum and urine immunofixation electrophoresis

Any abnormal

Isolated FLC abnormality

*Refined κ/λ FLC ratio limits

eGFR	κ/λ ratio
>90ml/min	0.26-1.65
60-90ml/min	0.26-2.65
30-60ml/min	0.26-2.50
<30ml/min	0.26-3.10

No

Yes

Apply estimated glomerular
filtration rate (eGFR) adjusted
refined κ/λ FLC ratio

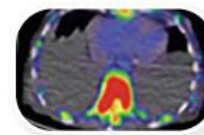
Abnormal

Normal

All normal

Bone-avid tracer cardiac
SPECT/CT

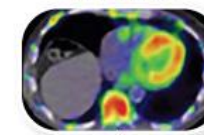
Grade 0/1



High clinical suspicion or
typical echocardiogram
or typical cardiac MRI

Cardiac MRI

Grade 2/3



ATTR-CM
confirmed

TTR gene
testing

Wild type
ATTR-CM

Hereditary
ATTR-CM

Endomyocardial/involved
organ biopsy and typing

Yes

No

Cardiac
amyloidosis and
type confirmed

Cardiac
amyloidosis
excluded

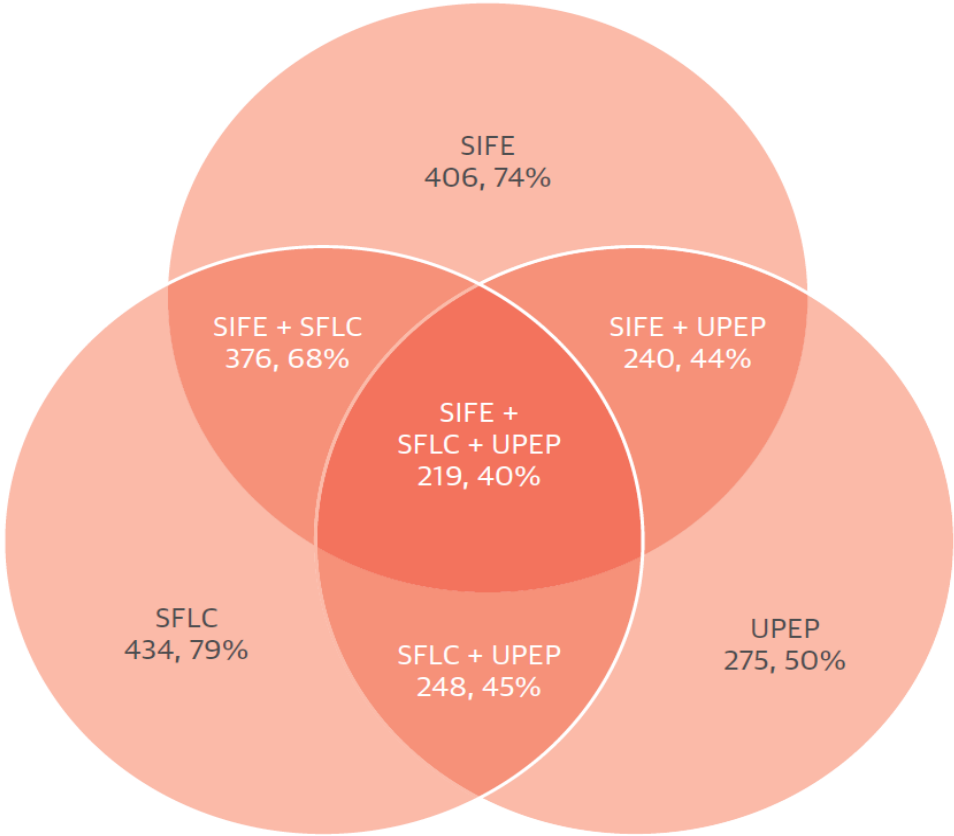
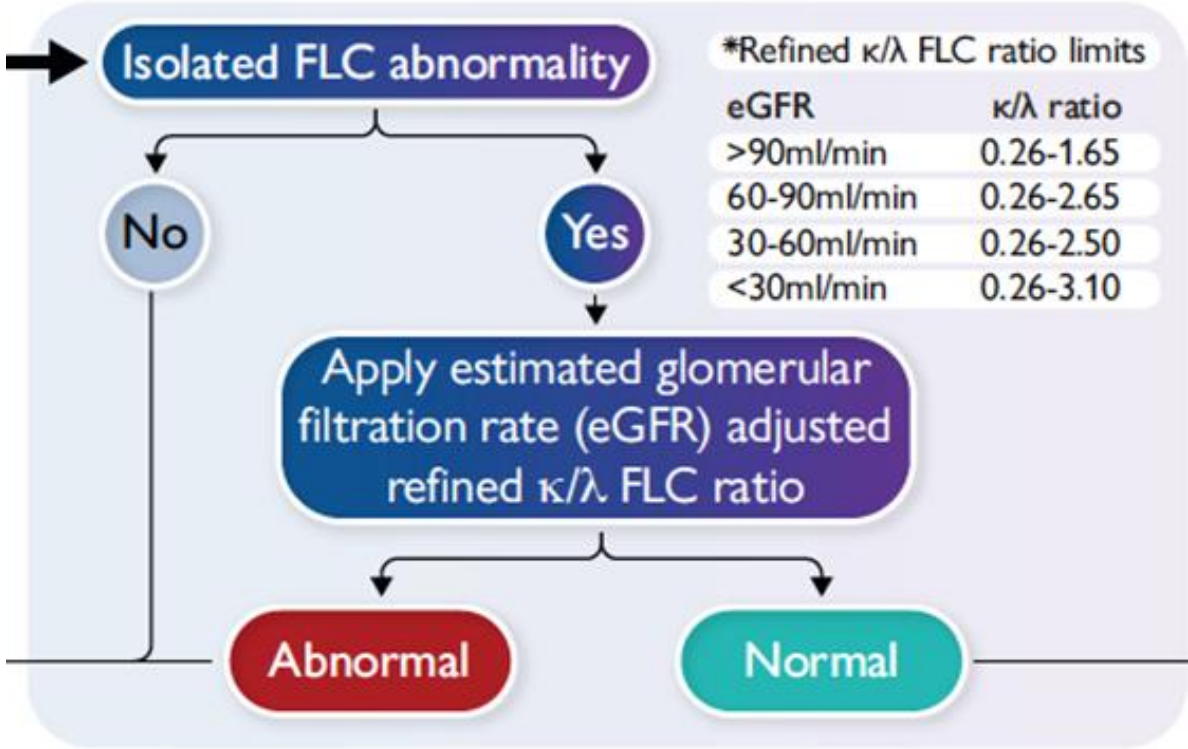


Refer to haematologist

Cardiac MRI



Hematology Referral

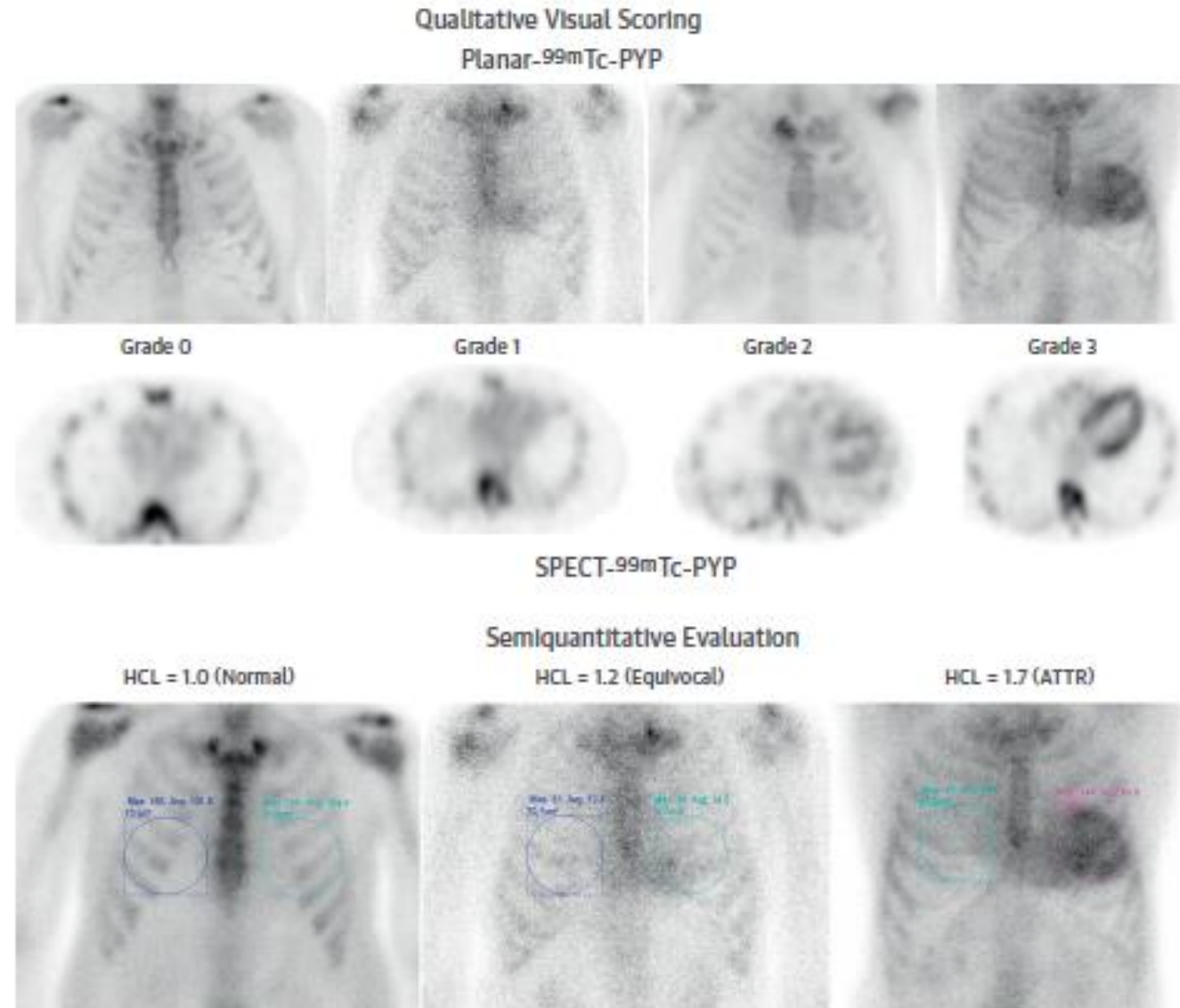


SIFE= Serum immunofixation
UPEP = Urine Protein electrophoresis
SFLC = Serum Free Light Chains



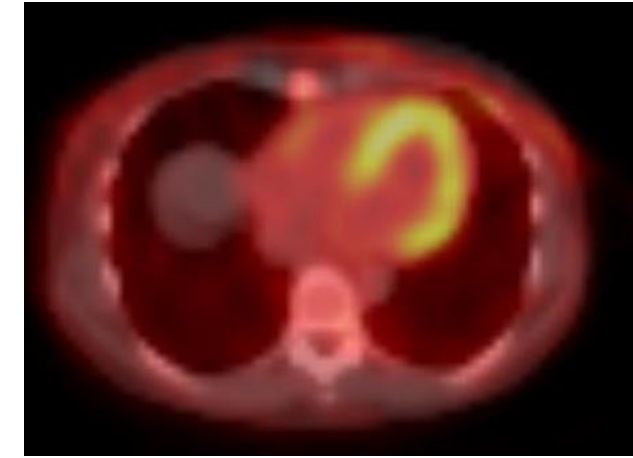
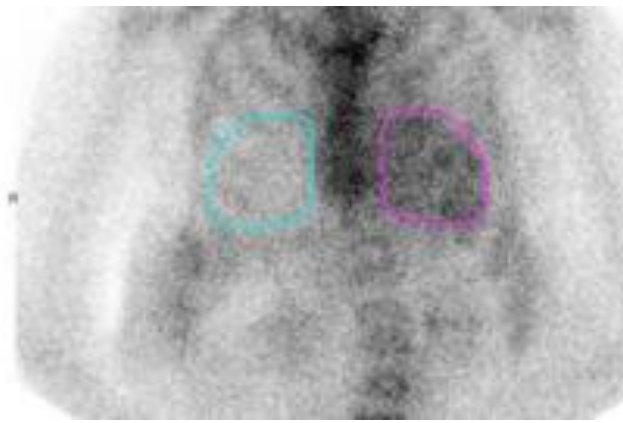
Bone-avid radiotracer Cardiac Scintigraphy for the Non-invasive Diagnosis of ATTR

- 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

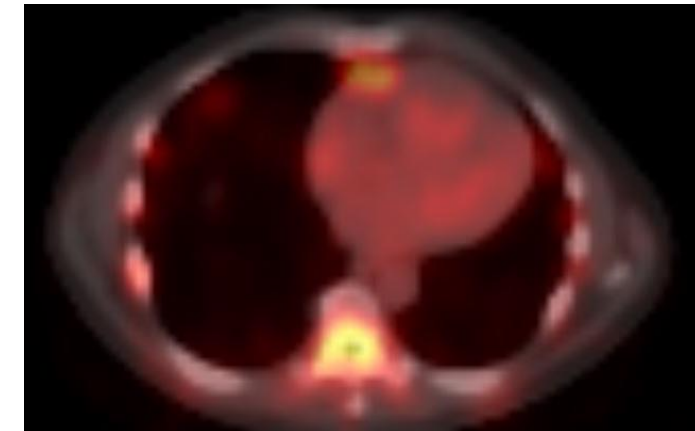
- Light Chain Amyloidosis
- Hot blood pool
- Myocardial infarction
- Rib fractures, valvular/annular calcifications
- Hydroxychloroquine toxicity
- Breast implants



Grade 3

False negatives

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



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



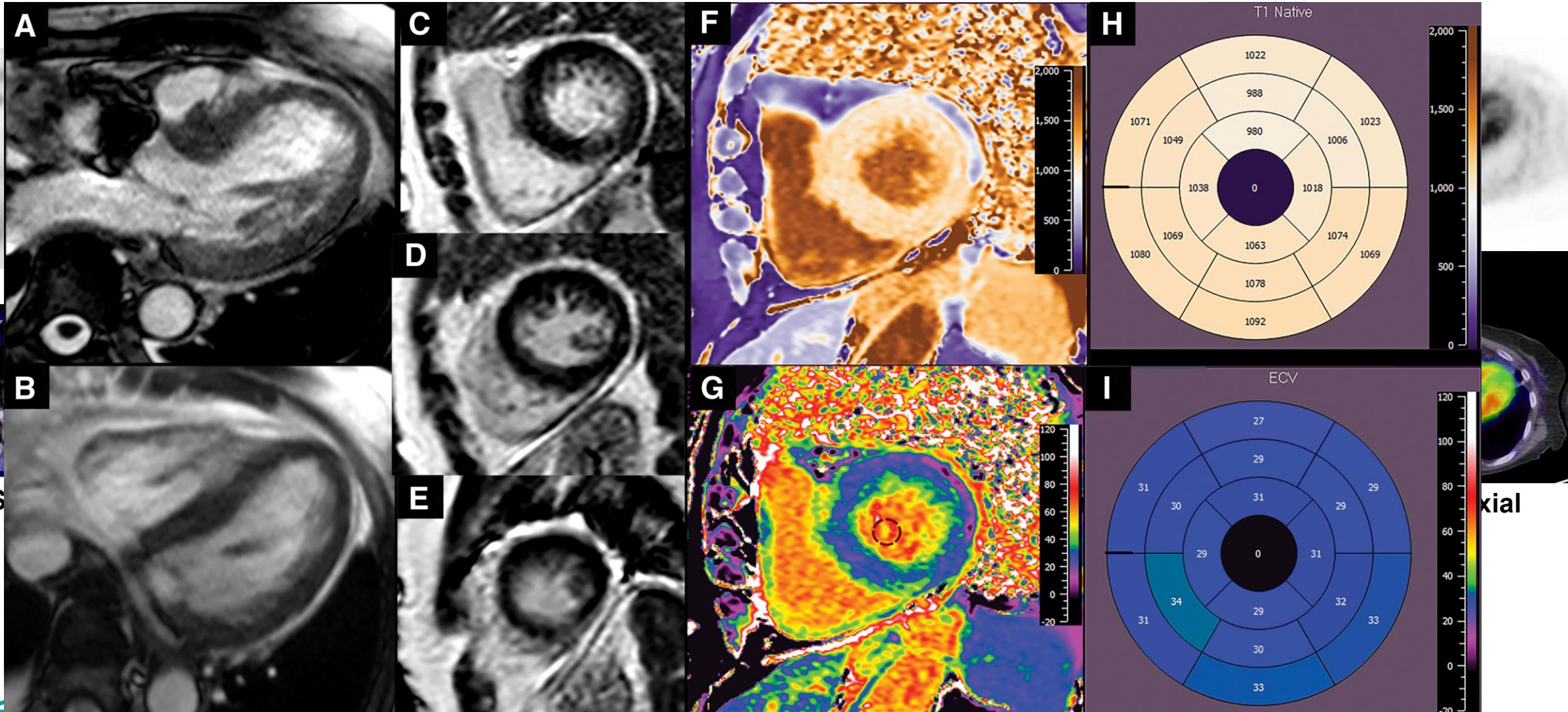
Tissue Biopsy

- 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%)



Case: Septal Myectomy detected Amyloid Deposition

76-year-old woman with severe Aortic Stenosis: SAVR and myectomy

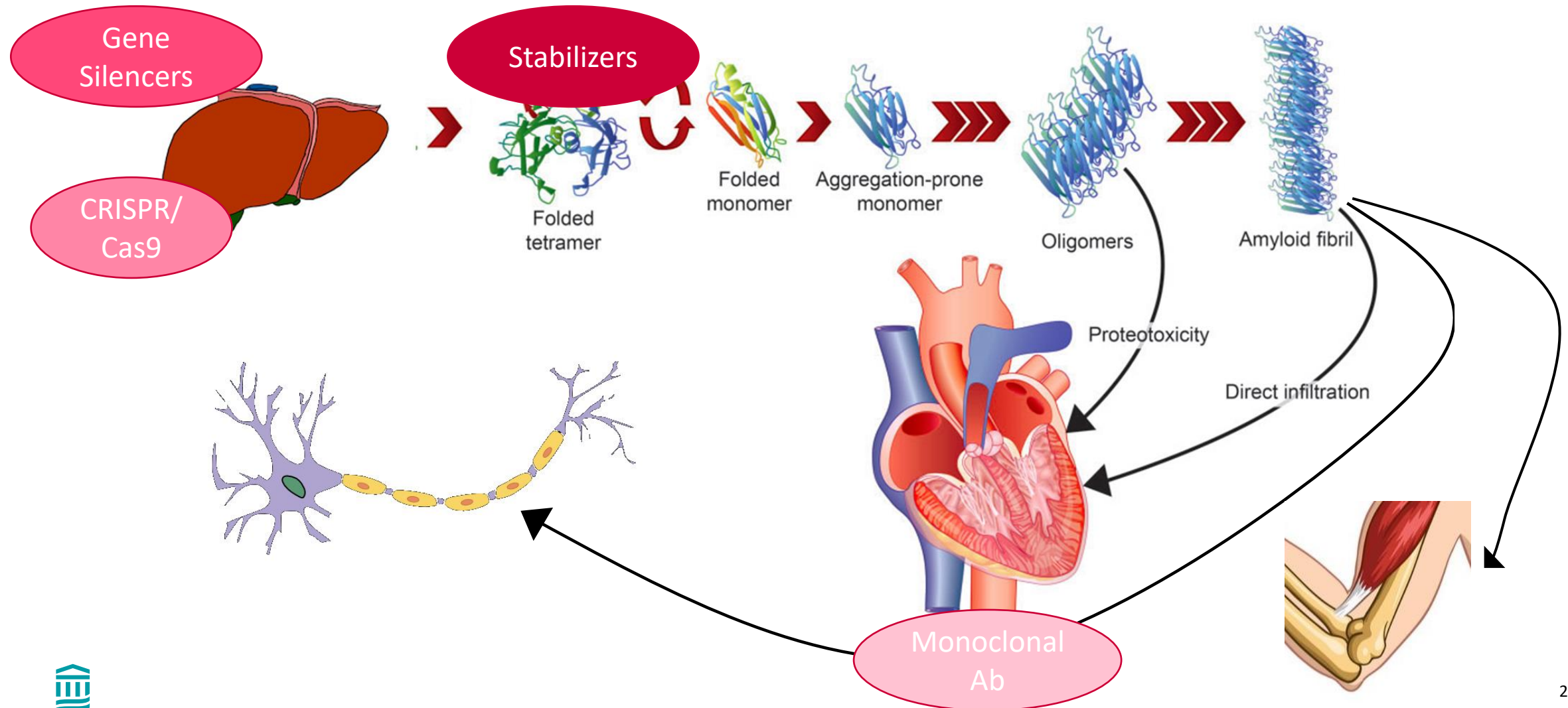


Treatments

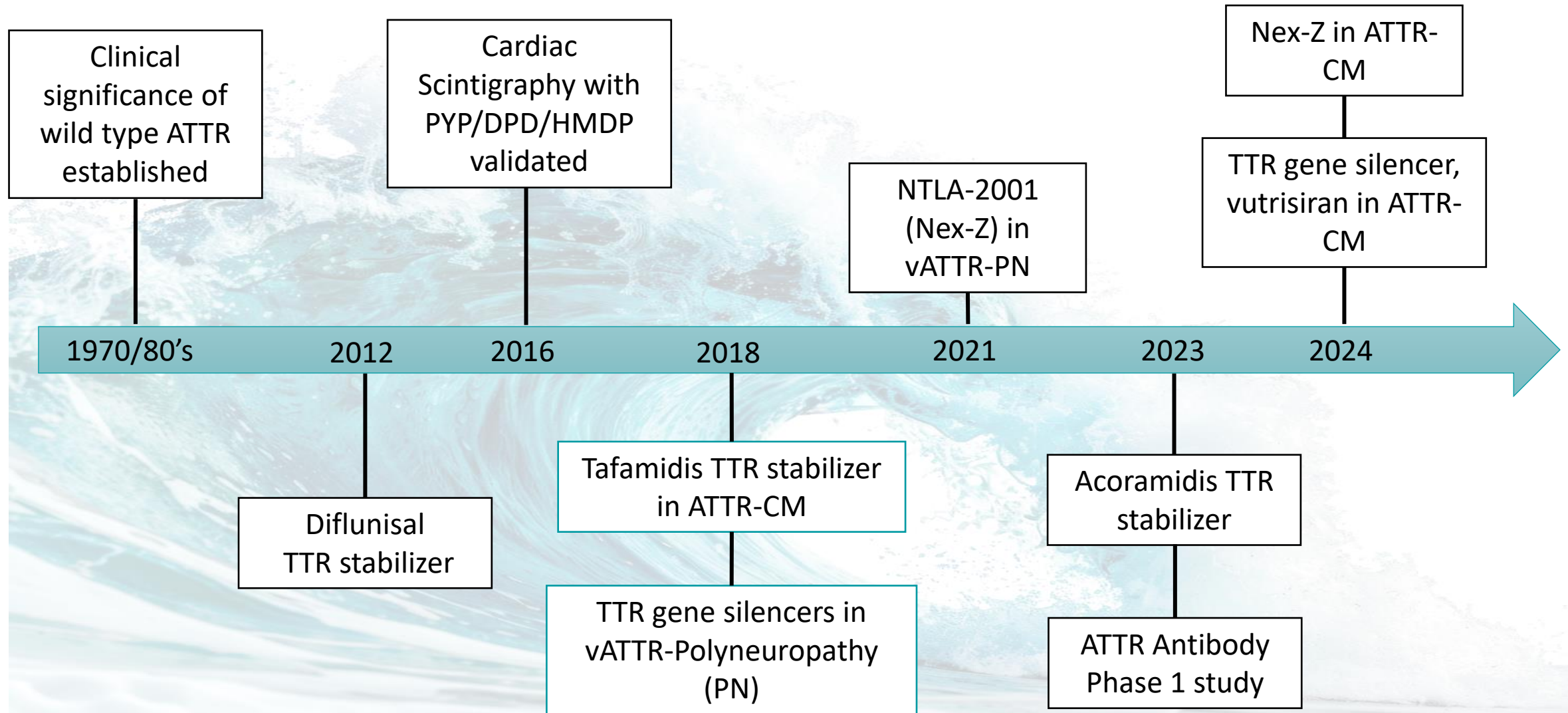


Effective therapies

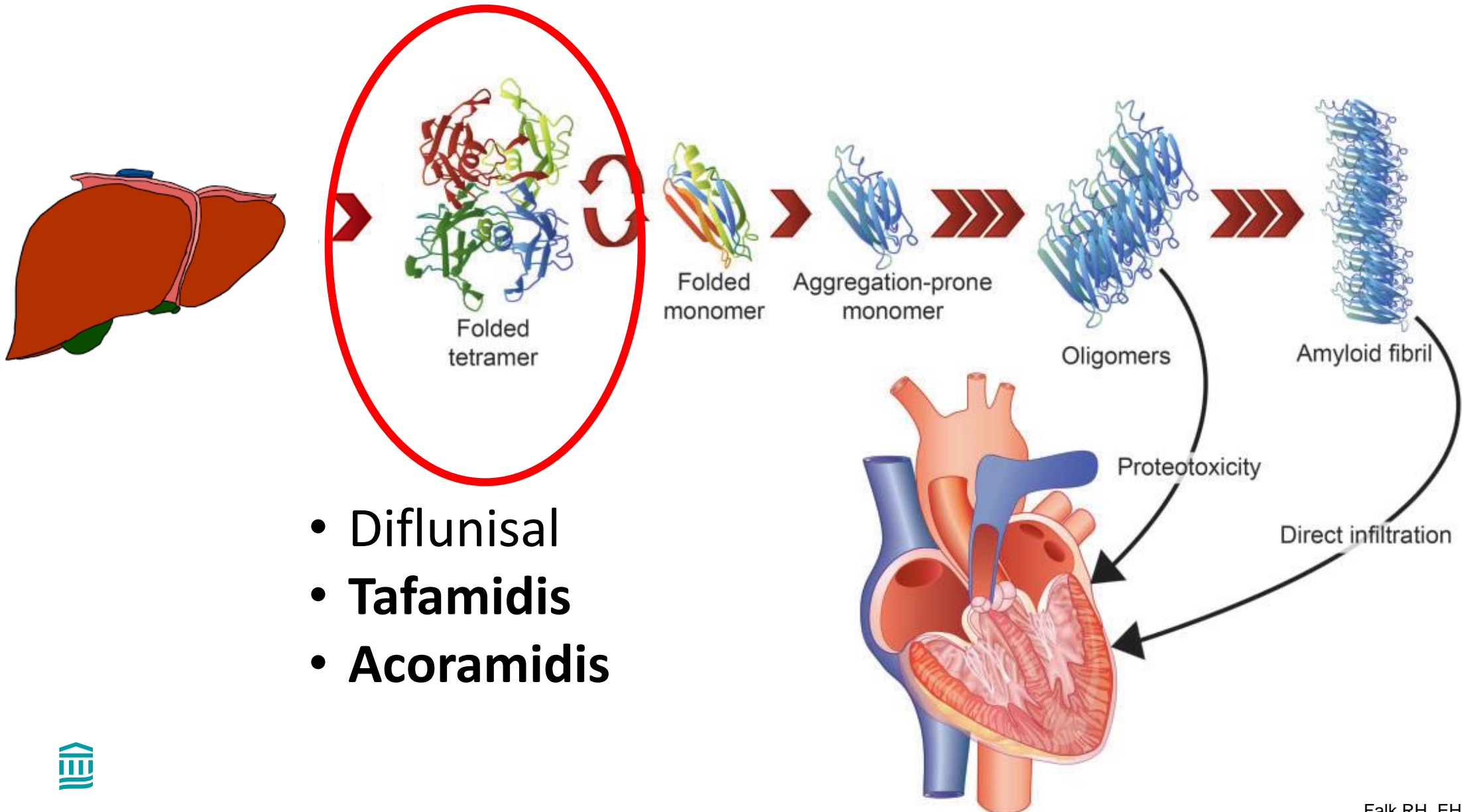
ATTR



ATTR: How Far we have come



ATTR

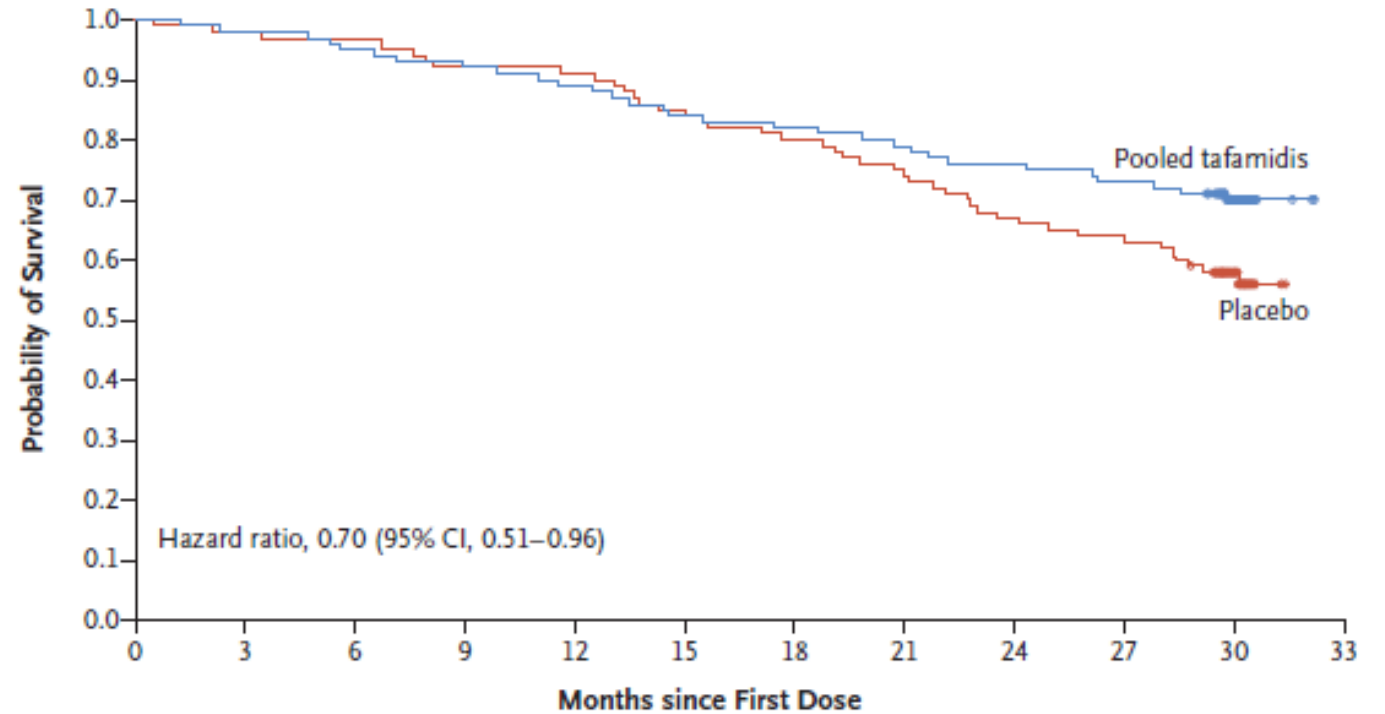


Tafamidis

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 hospitalizations
 - Relative risk ratio of 0.68
 - 0.48 per year vs. 0.70 per year (95% CI, 0.56 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)

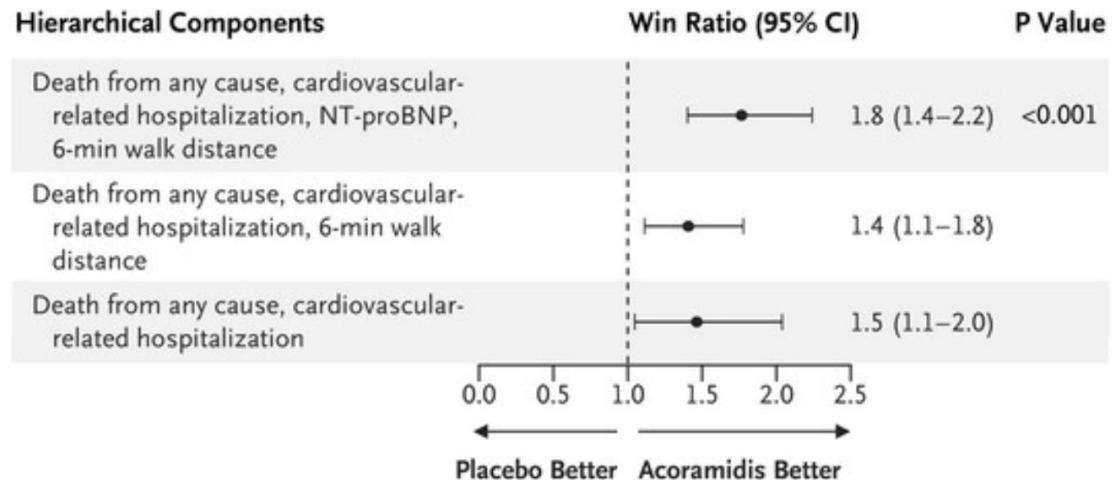


Acoramidis

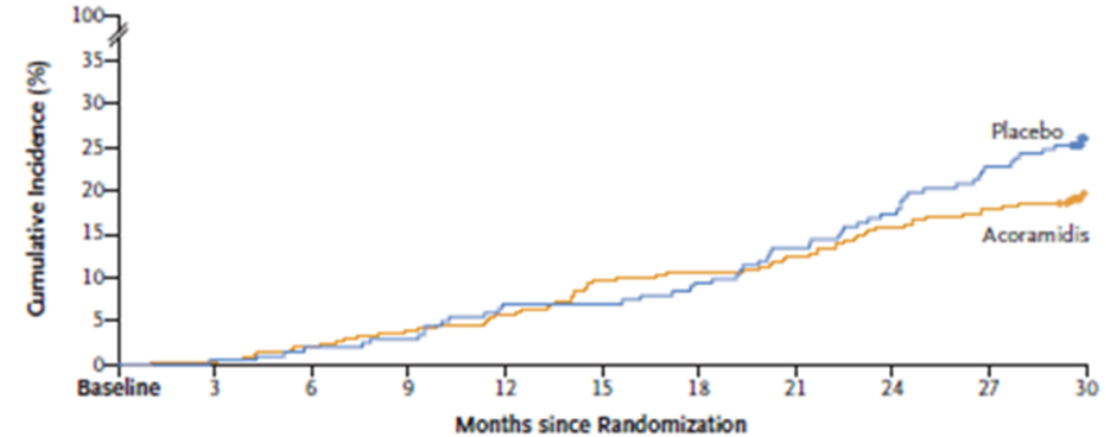
ATTRibute-CM

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

Primary Efficacy Analysis and Prespecified Secondary Analyses



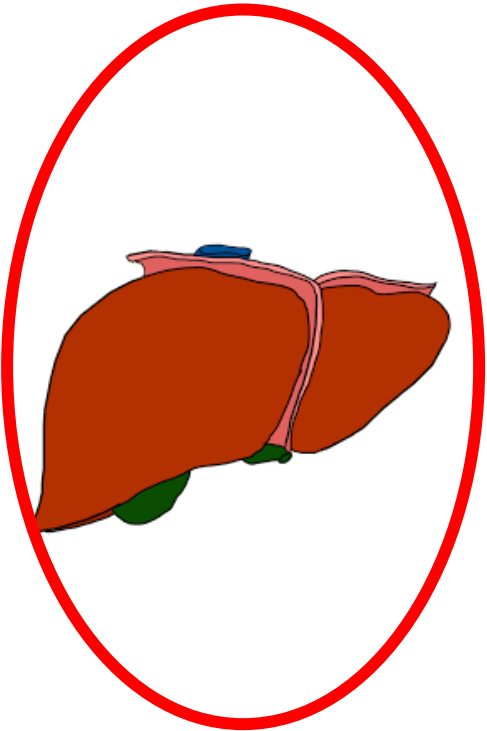
Death from Any Cause



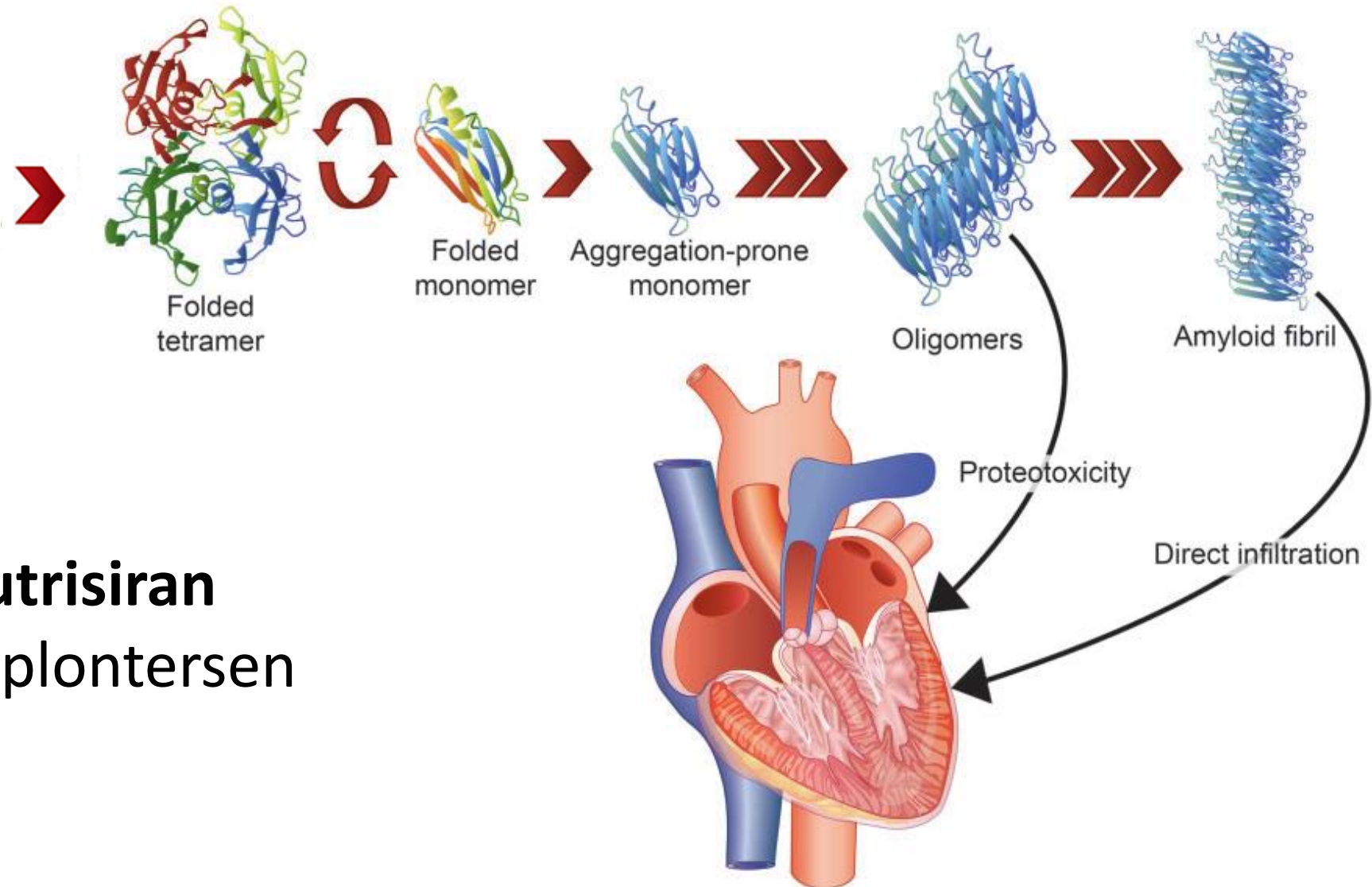
No. at Risk (no. of events)

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



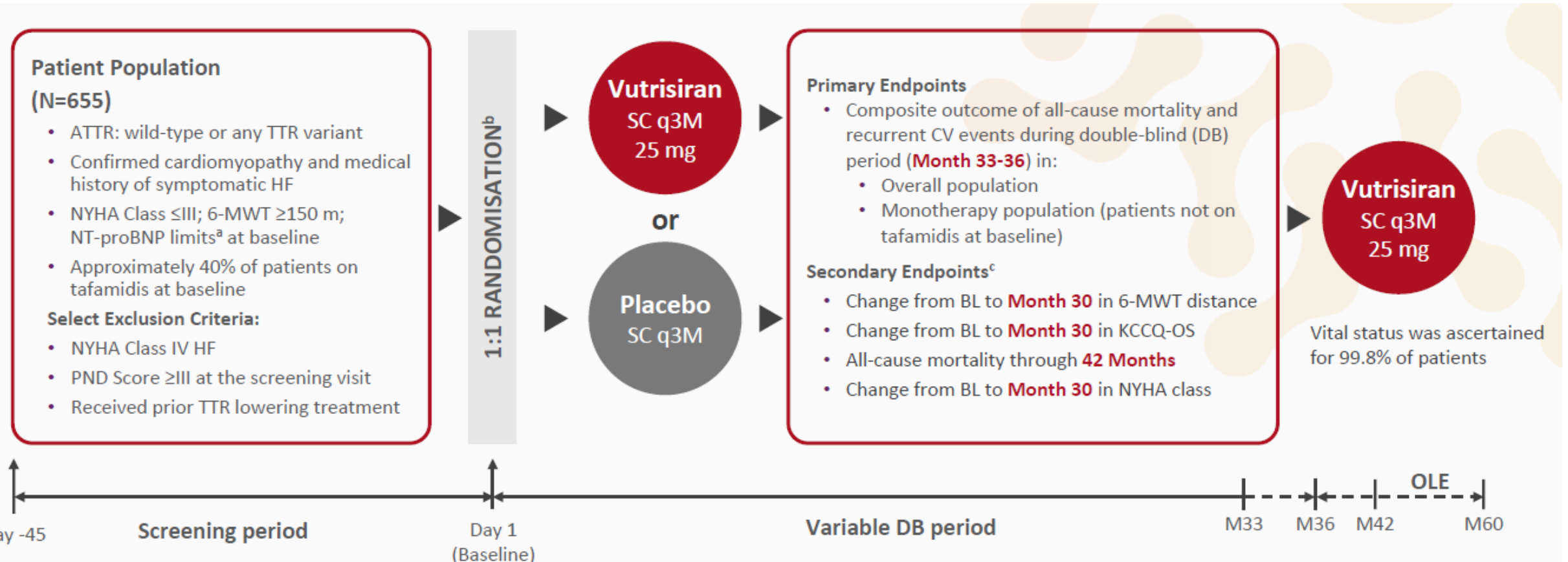
- Patisiran > **Vutrisiran**
- Inotersen > Eplontersen

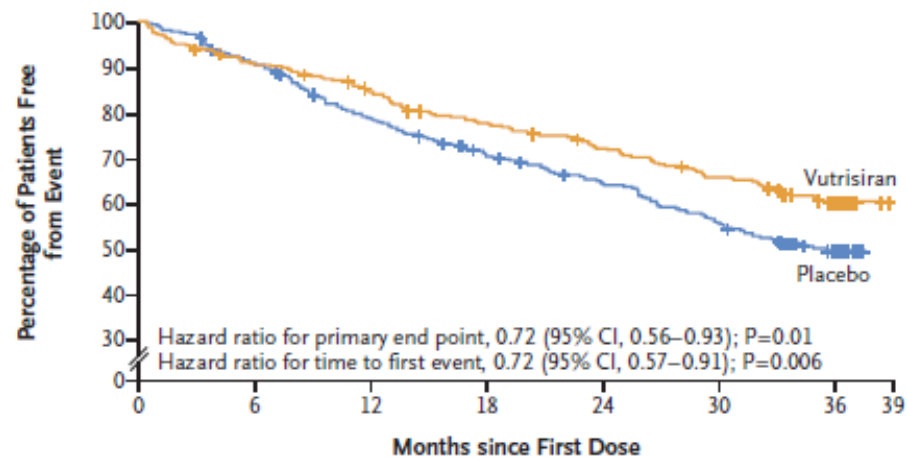


Vutrisiran in ATTR-CM

HELIOS-B Study Design

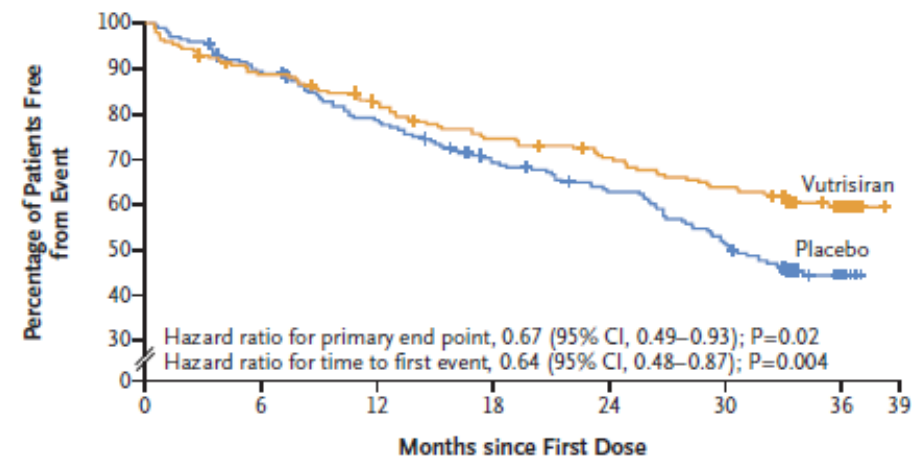
HELIOS-B is a phase 3 randomized trial was to evaluate the efficacy and safety of vutrisiran, a SC-administered RNAi therapeutic, compared with placebo among patients with ATTR-CM



A Time to First Event in the Overall Population

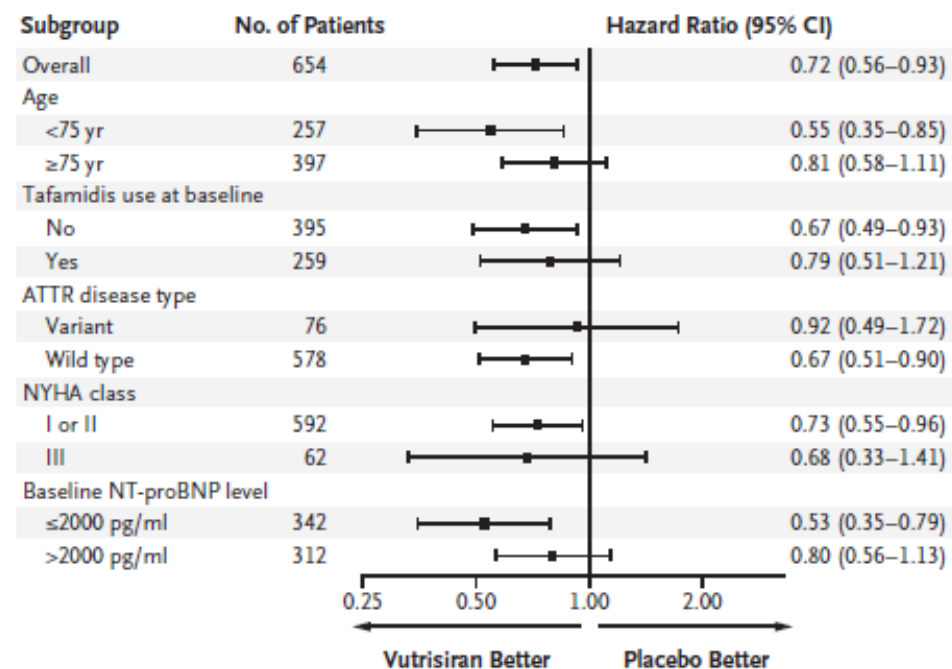
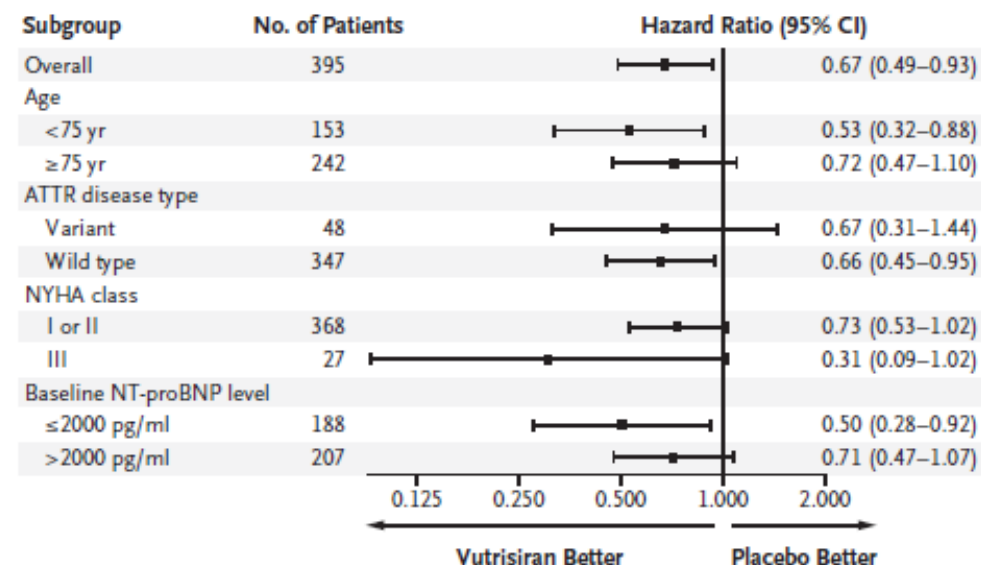
No. at Risk (cumulative no. of events)

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)

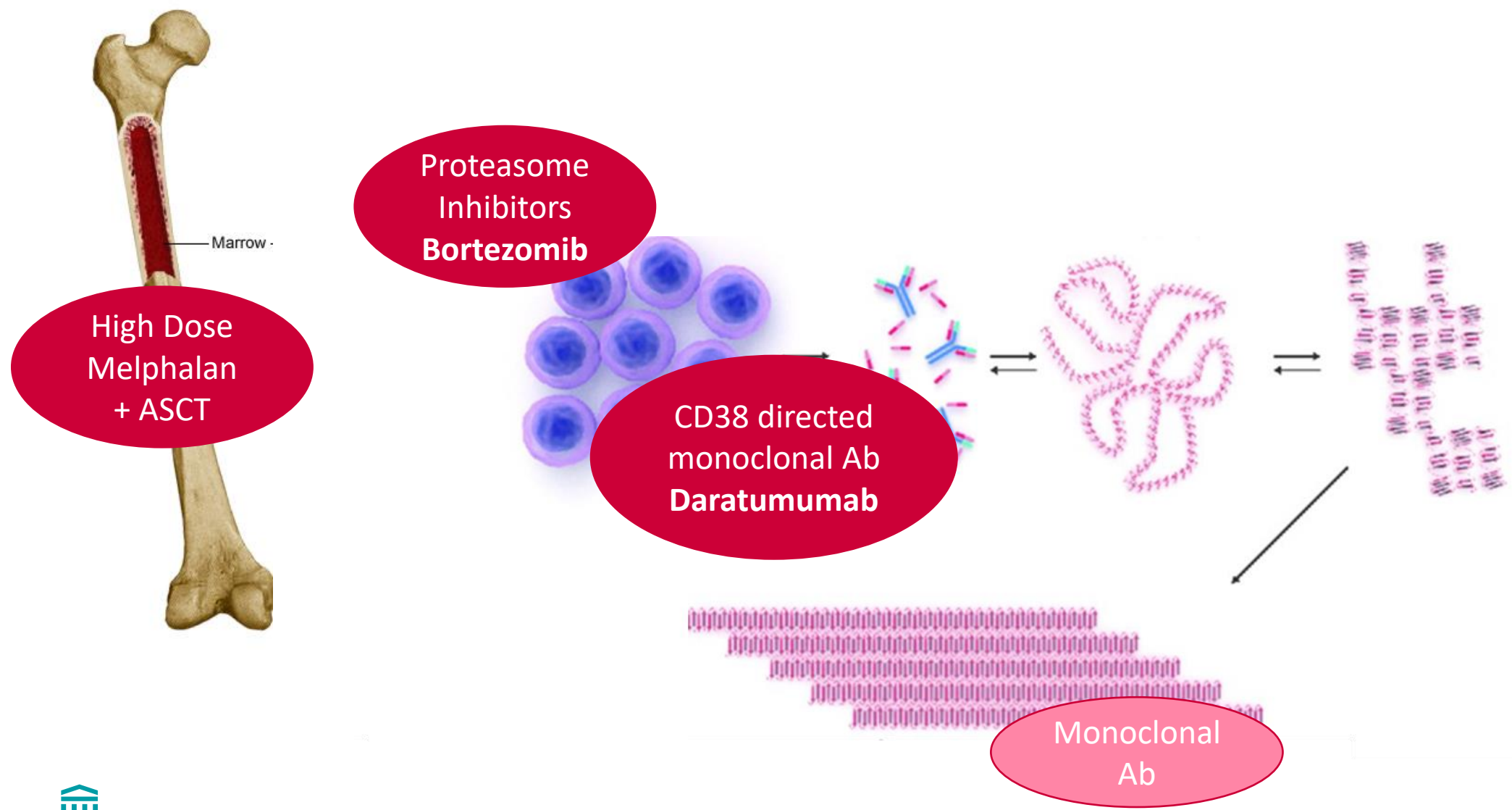
B Time to First Event in the Monotherapy Population

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)**

Light Chain (AL) Amyloidosis



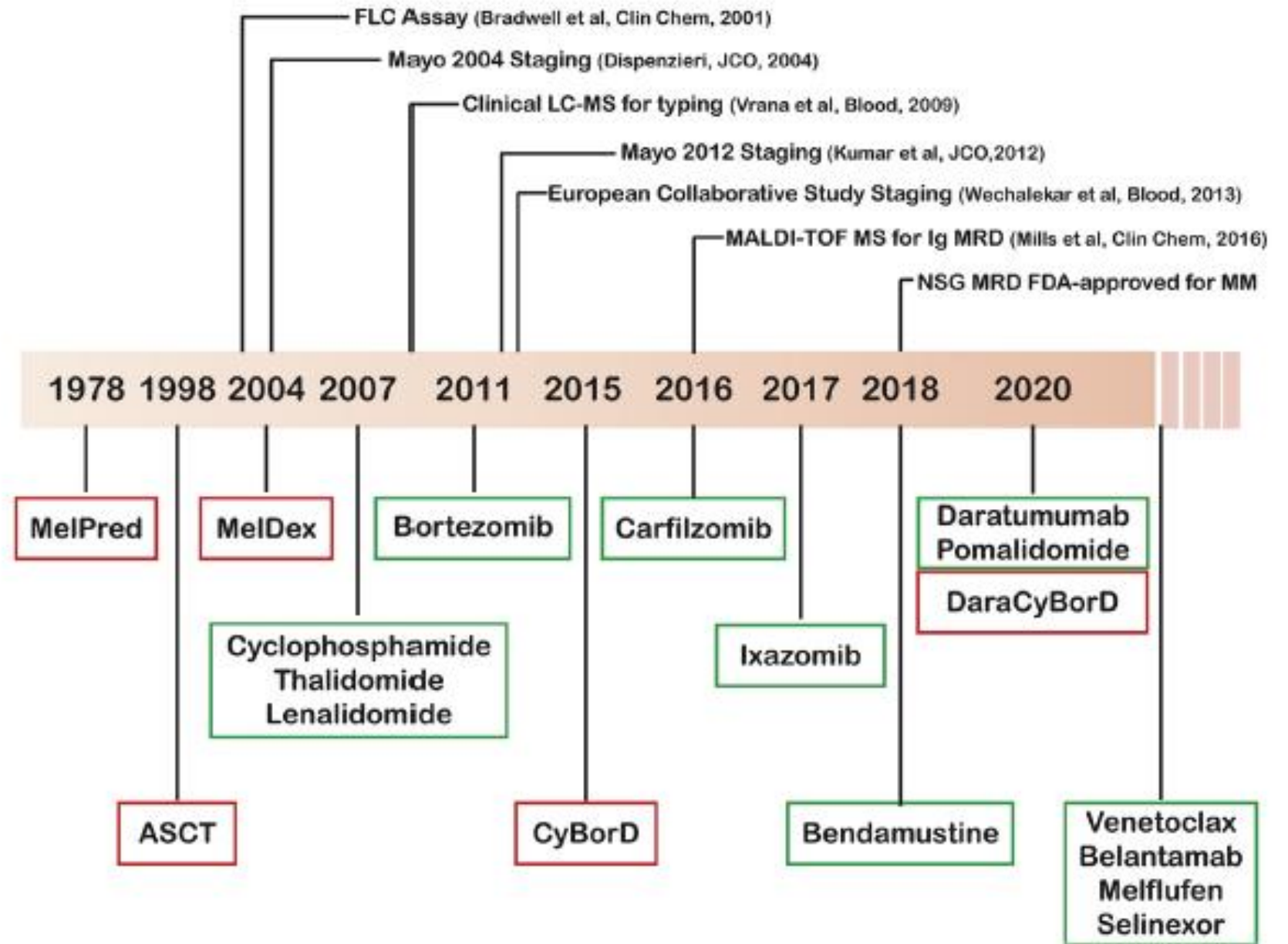
Treatments

Red is more commonly used

Green is less commonly used

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

FIGURE 1 Evolution of Treatment in AL Amyloidosis



Andromeda Trial: Daratumumab

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.



No. at risk									
Daratumumab	195	176	164	131	81	42	17	1	0
Control	193	170	161	120	74	38	16	1	0



ASCT Eligibility Criteria

TABLE 7 Criteria for Autologous Stem Cell Transplant Eligibility in AL Amyloidosis in Our Centers

	Transplant Eligible (All Criteria Must Be Met)	Transplant Ineligible* (Any Criteria)
Age, y	≤70	>70
ECOG PS	0-2	>2
Staging (revised Mayo 2004)	I-II	III
LVEF, %	>45	≤45
NYHA functional class	I-II	III-IV
eGFR	≥30 mL/min/1.73 m ²	<30 mL/min/1.73 m ²
SBP	≥90 mm Hg without orthostatic hypotension	<90 mm Hg or untreated orthostatic hypotension
DLCO, %	>50	<50

The table outlines criteria implemented to determine transplant eligibility in AL amyloidosis in our centers. *Consideration can be given to risk-stratified, dose-reduced melphalan conditioning and ASCT for selected patients, including patients with end-stage renal disease if all other eligibility criteria are satisfied.

DLCO = diffusing capacity for carbon monoxide; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure.

Monitoring Response to Therapy

Hematological Response

Parameter	Complete Response (CR)	Very Good Partial Response (VGPR)	Partial Response (PR)
FLC	Normal ratio	dFLC<40mg/L	dFLC >50%
SPEP & IFE	No M spike. Negative IFE	NA	NA
UPEP & IFE	No M spike. Negative IFE	NA	NA

Criteria for deep hematological response:
iFLC ≤20 mg/L regardless of FLCr

 dFLC<10 regardless of FLCr.

Organ Specific Response

Cardiac

NT-proBNP decrease of >30% AND >300 pg/mL from baseline *

2 NYHA functional class improvement from baseline **

Renal

Decrease in proteinuria by >30% or to <0.5 g/24 h ***

* From baseline NT-proBNP over 650 ng/L.

** Must be NYHA functional class 3 or 4 at diagnosis

*** In the absence of eGFR decline by 25% or more

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.

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References

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