UNIVERSITÀ DI TORINO

Department of Medical Sciences
Division of Internal Medicine

Update: amiloidosi cardiaca da transtiretina nel paziente iperteso: diagnosi e terapia

Torino 14 ottobre 2023

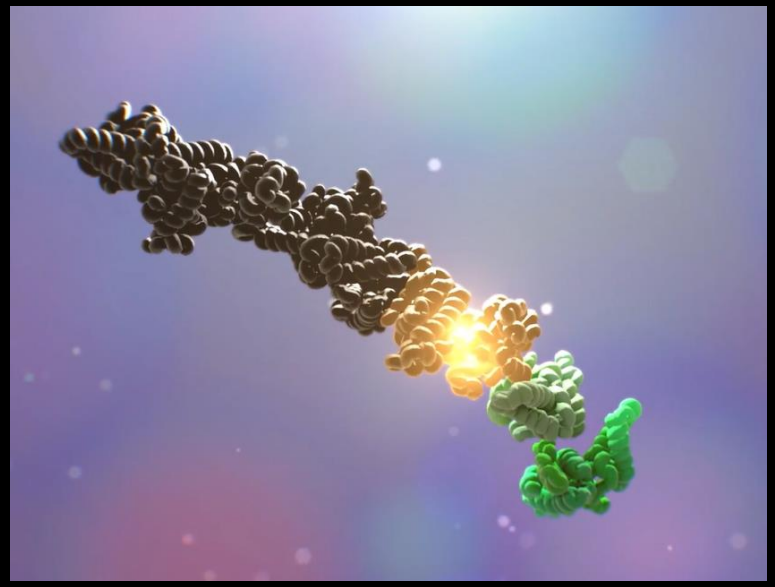
Agenda

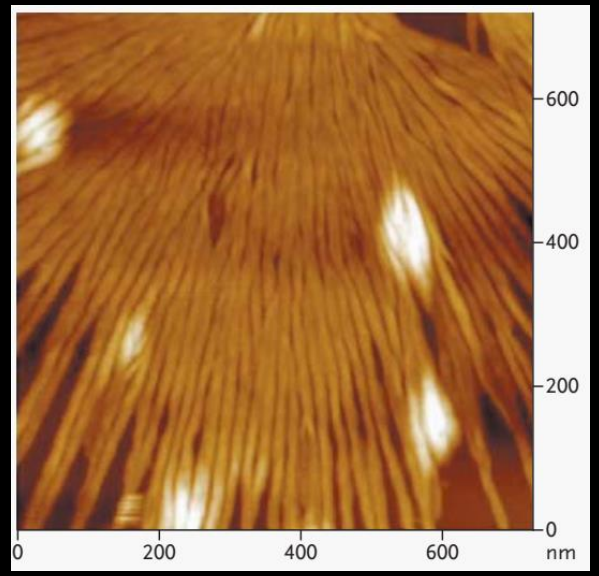
Agenda

Cos'è?

Merlini NEJM 2003

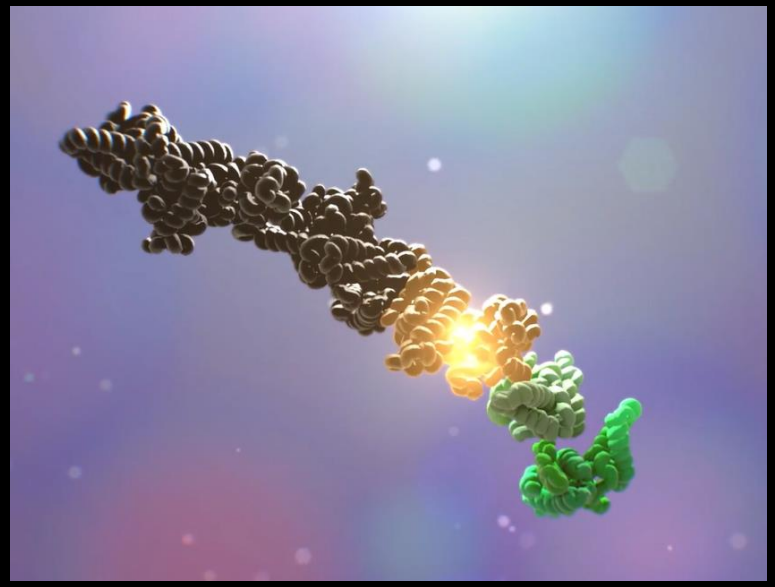
Cos'è?

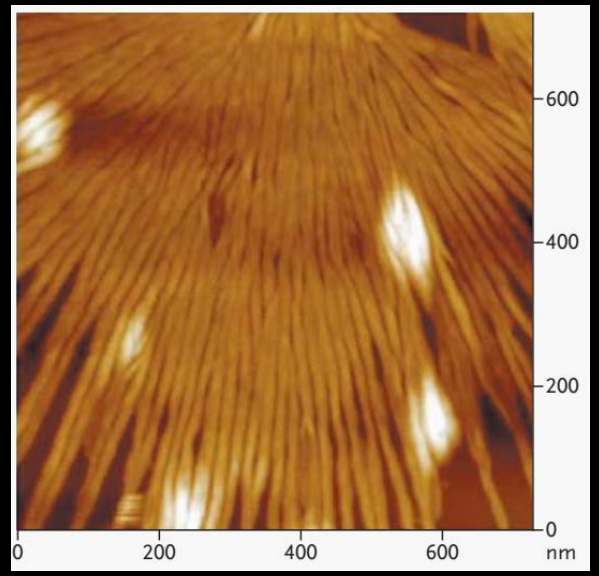




Merlini NEJM 2003

Cos'è?

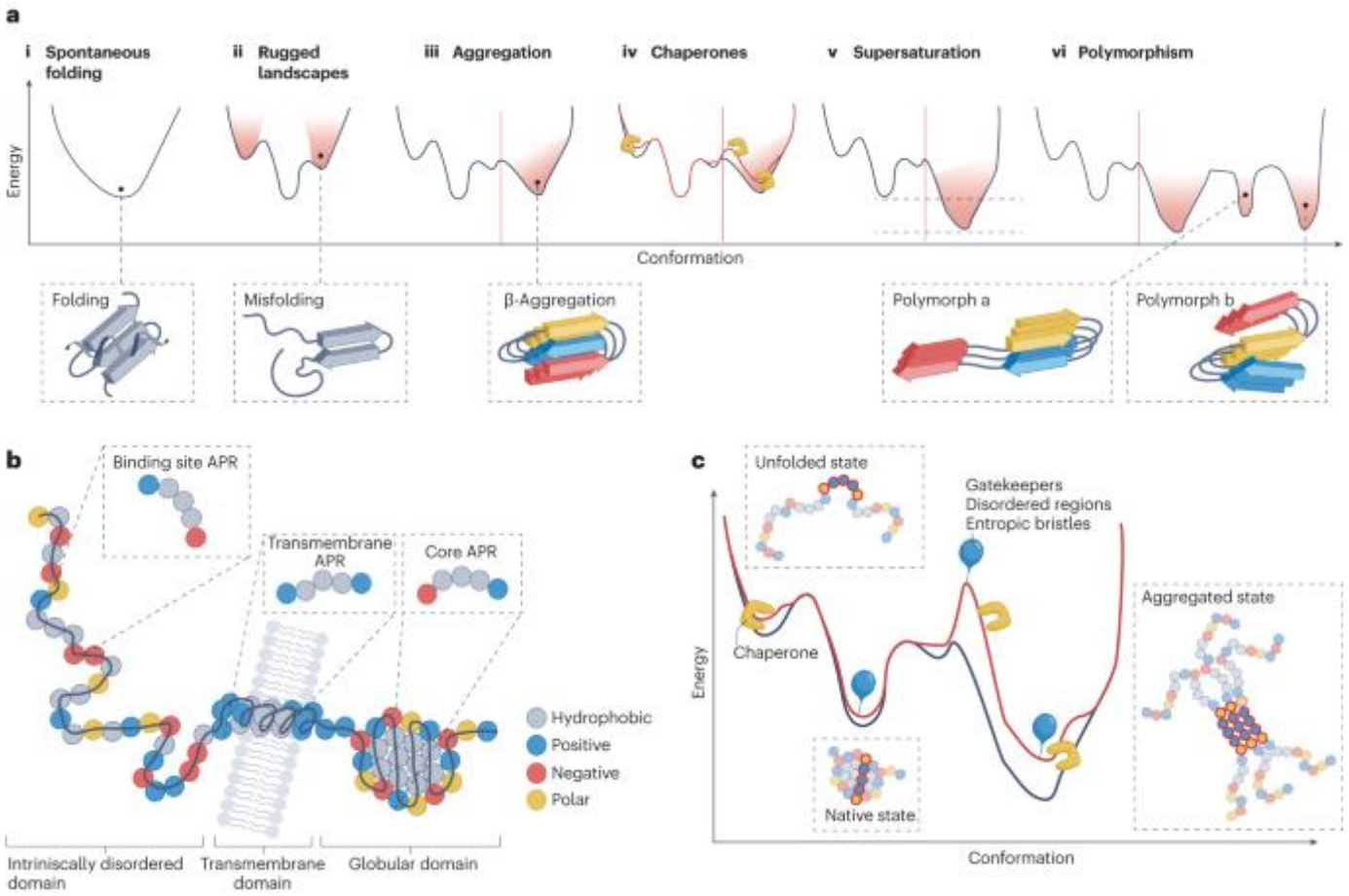




Merlini NEJM 2003

Cos'è?

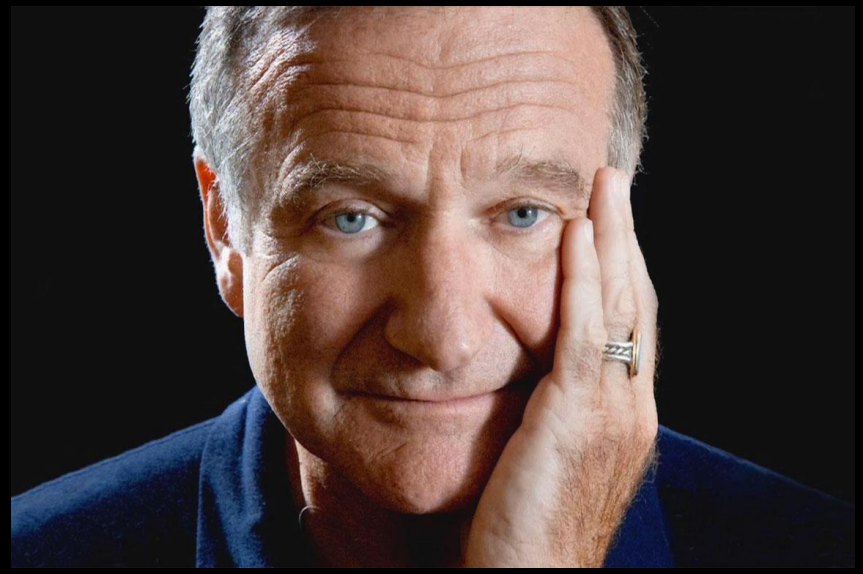
Meccanismo di ripiegamento



~~Ripiegamento spontaneo~~

Ripiegamento **guidato**

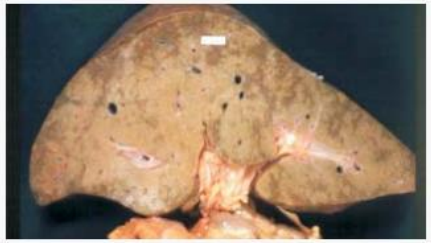
Assemblaggio **non casuale**



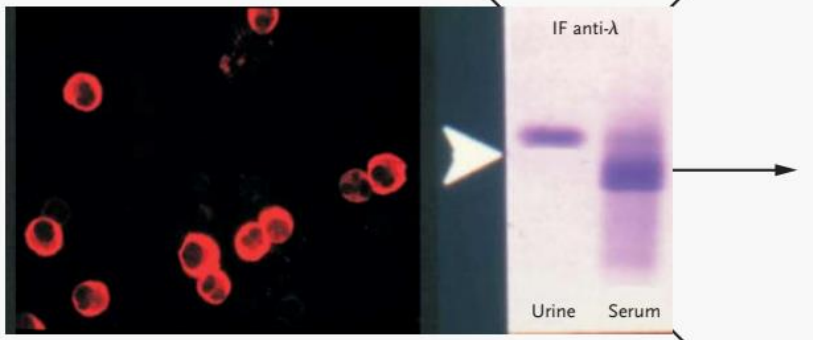
Merlini NEJM 2003

Kidney (46%)

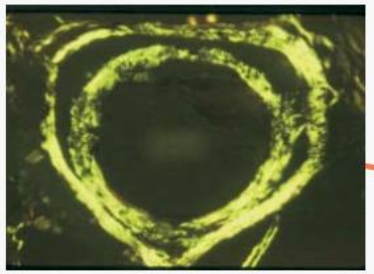
Heart (30%)



Liver (9%)



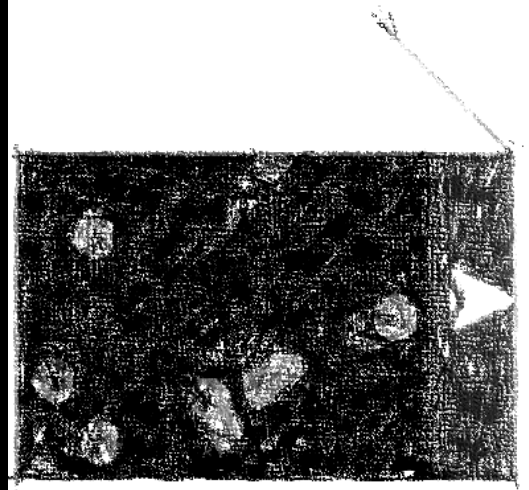
Gastrointestinal tract (7%)

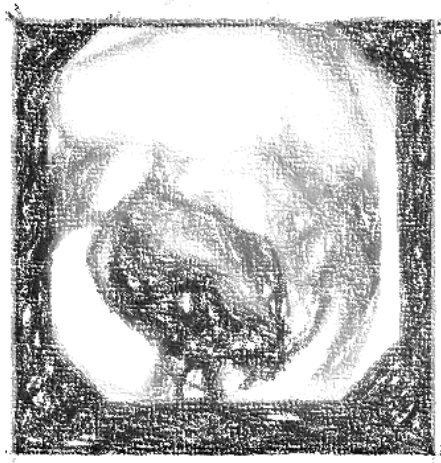


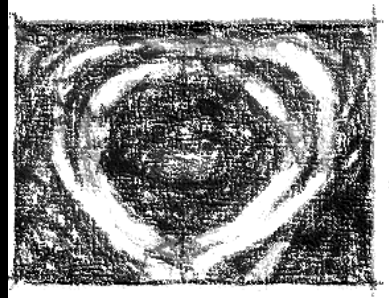
Soft tissues (3%)

Peripheral nervous system (5%)

Heart (30%)







Tipi di amiloidosi

30 Tipi di amiloidosi

9 Coinvolgimento cardiaco

Tipi di amiloidosi

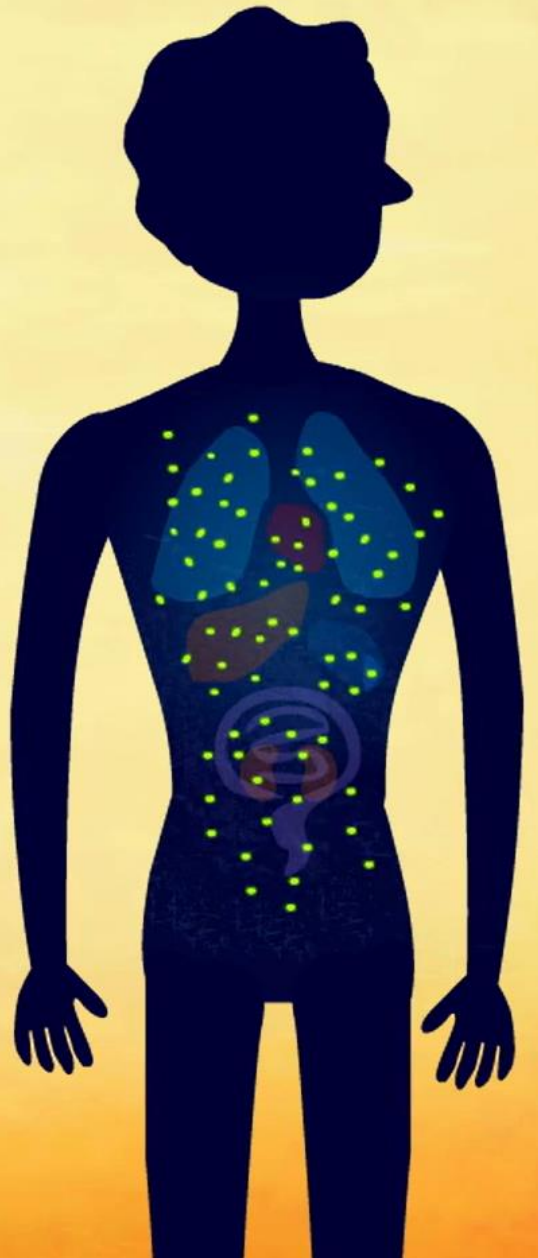
Table I **Amyloidosis subtypes that affect the heart**

Amyloidosis type	Protein	Hereditary	Frequency of heart involvement	Median survival from diagnosis (months)	Usual extracardiac signs
AL	Immunoglobulin light chain	No	70%	24 6 (if HF at diagnosis and not treated)	Nephropathy, proteinuria, autonomic dysfunction, polyneuropathy, macroglossia, spontaneous bruising, liver involvement
ATTRwt	Transthyretin	No	100%	57	CTS, LSS, ruptured biceps tendon
ATTRv	Transthyretin	Yes	30–100% Depending on the mutation	31 (Val142Ile) 69 (non-Val142Ile)	Polyneuropathy, orthostatic hypotension, vitreous opacities, gastrointestinal problems
AA	Serum amyloid A	No	5%	133	Renal impairment (95%), proteinuria, hepatomegaly, gastrointestinal problems
AFib	Fibrinogen α	Yes	Rare	180	Renal impairment, proteinuria
AApoAI	Apolipoprotein A-I	Yes	Rare Depending on the mutation	No data. Probably >120	Primarily renal impairment, proteinuria, hepatosplenomegaly, adrenal insufficiency, dysphonia due to laryngeal involvement
AApoAII	Apolipoprotein A-II	Yes	Rare Depending on the mutation	No data	Primarily renal impairment, proteinuria
AApoAIV	Apolipoprotein A-IV	No	Unknown	79	Primarily renal impairment
Aβ2M	β2-microglobulin	No	80%	No data	Long-term dialysis, CTS, joint problems
AGel	Gelsolin	Yes	5% Primarily conduction disease	Near normal life expectancy	Corneal lattice dystrophy, cutis laxa, drooping eyelids, paresthaesia, proteinuria (rare)

AA, serum amyloid A amyloidosis; AApoAI, apolipoprotein AI amyloidosis; AApoAII, apolipoprotein AII amyloidosis; AApoAIV, apolipoprotein A-IV amyloidosis; Aβ2M, β2-microglobulin amyloidosis; AFib, fibrinogen amyloidosis; AGel, gelsolin amyloidosis; AL, light-chain amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CTS, carpal tunnel syndrome; HF, heart failure; LSS, lumbar spinal stenosis.

ATTR Amyloidosis

TYPE	SOURCE	SYNDROME
AL	Plasma cells in bone marrow	Kidneys, heart, liver, GI tract, nervous system
AA	Circulating inflammatory proteins	Kidneys, liver
ATTR	**Mutant and wild-type protein produced in liver**	**Nervous system, heart, kidneys**
Localized	Plasma cells in local tissues	Bladder, skin, airways



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AA	Circulating inflammatory proteins	Kidneys, liver
ATTR	Mutated or wild-type protein produced in liver	Nervous system, heart, kidneys
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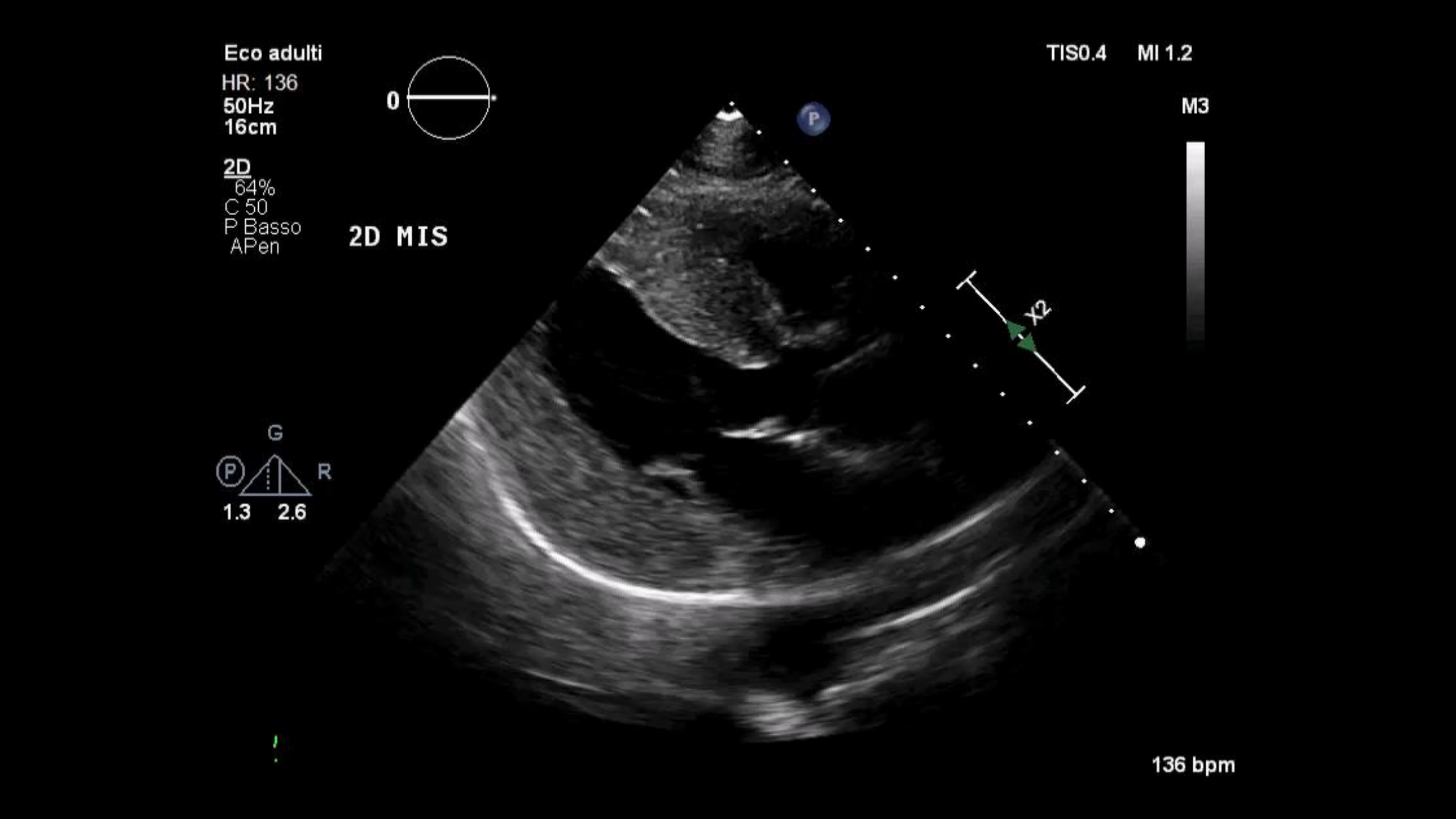
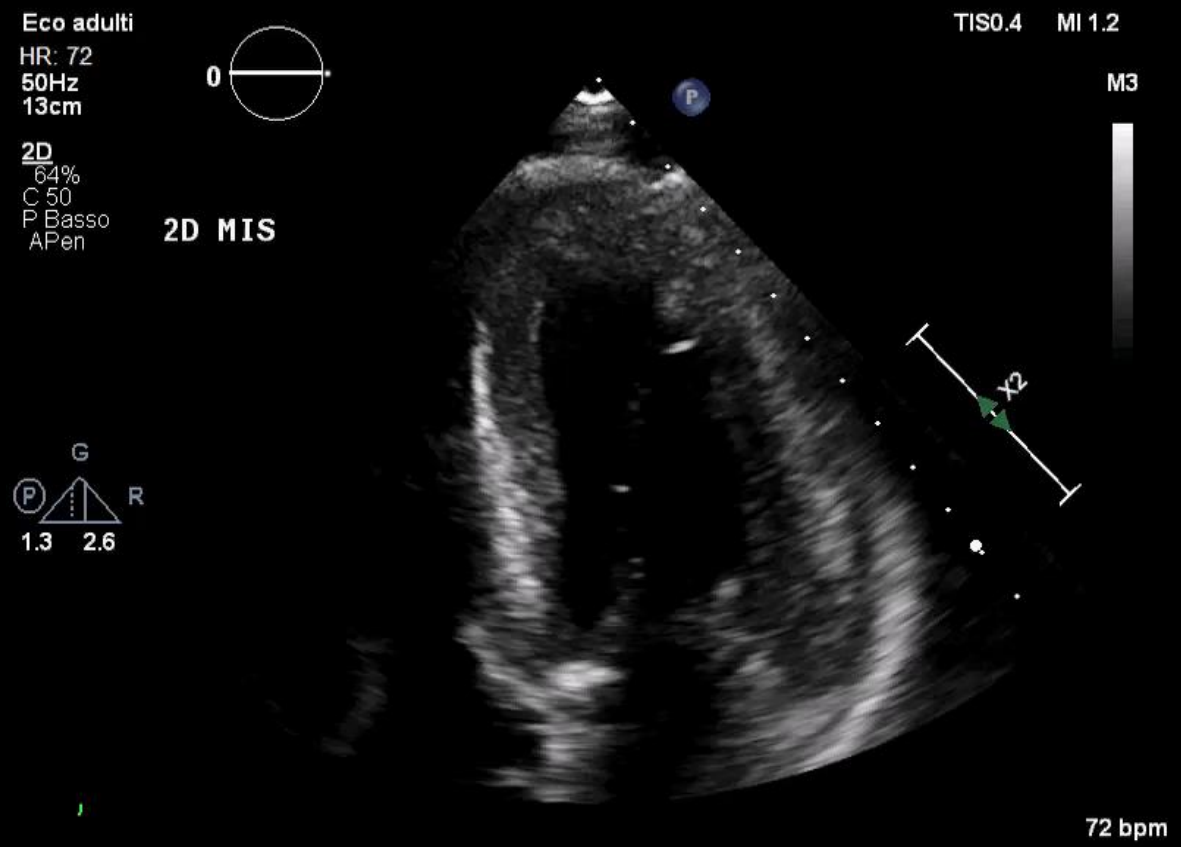
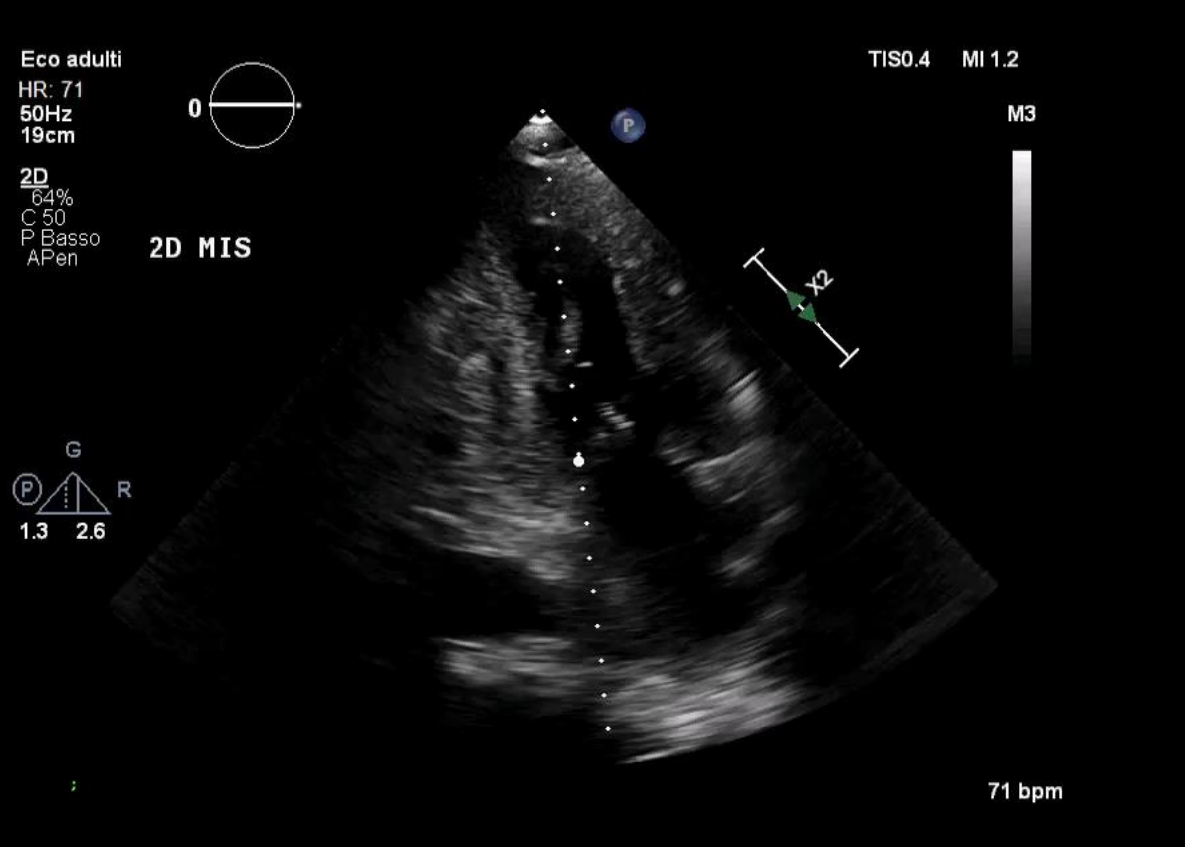
TTR amyloid can often be seen in 10-15% of patients (over the age of 60) showing clinical heart failure with preserved ejection fraction


Eco adulti
HR: 136
50Hz
16cm
2D
64%
C 50
P Basso
APen
2D MIS
0
TIS0.4
MI 1.2
M3
X2
G
P
R
1.3
2.6
136 bpm


Eco adulti
HR: 72
50Hz
13cm
2D
64%
C 50
P Basso
APen
2D MIS
TIS0.4 MI 1.2
M3
X2
G
P
R
1.3 2.6
72 bpm


Eco adulti
HR: 71
50Hz
19cm
2D
64%
C 50
P Basso
APen
2D MIS
TIS0.4 MI 1.2
M3
X2
G
P
R
1.3 2.6
71 bpm

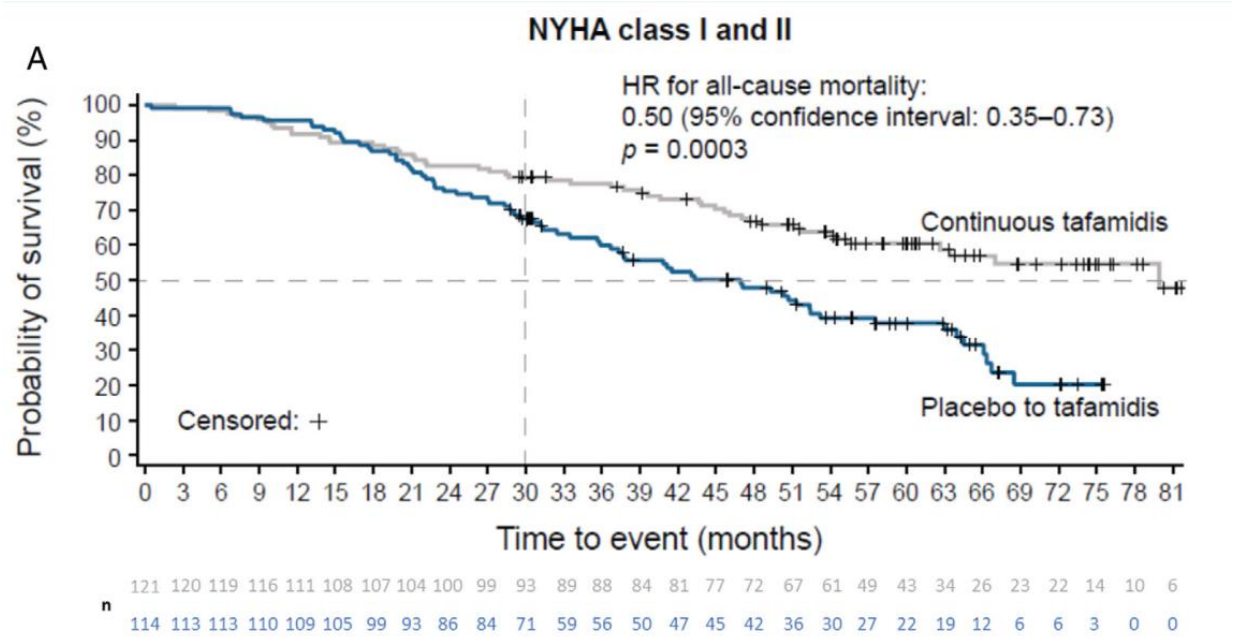
Agenda

Cos'è?

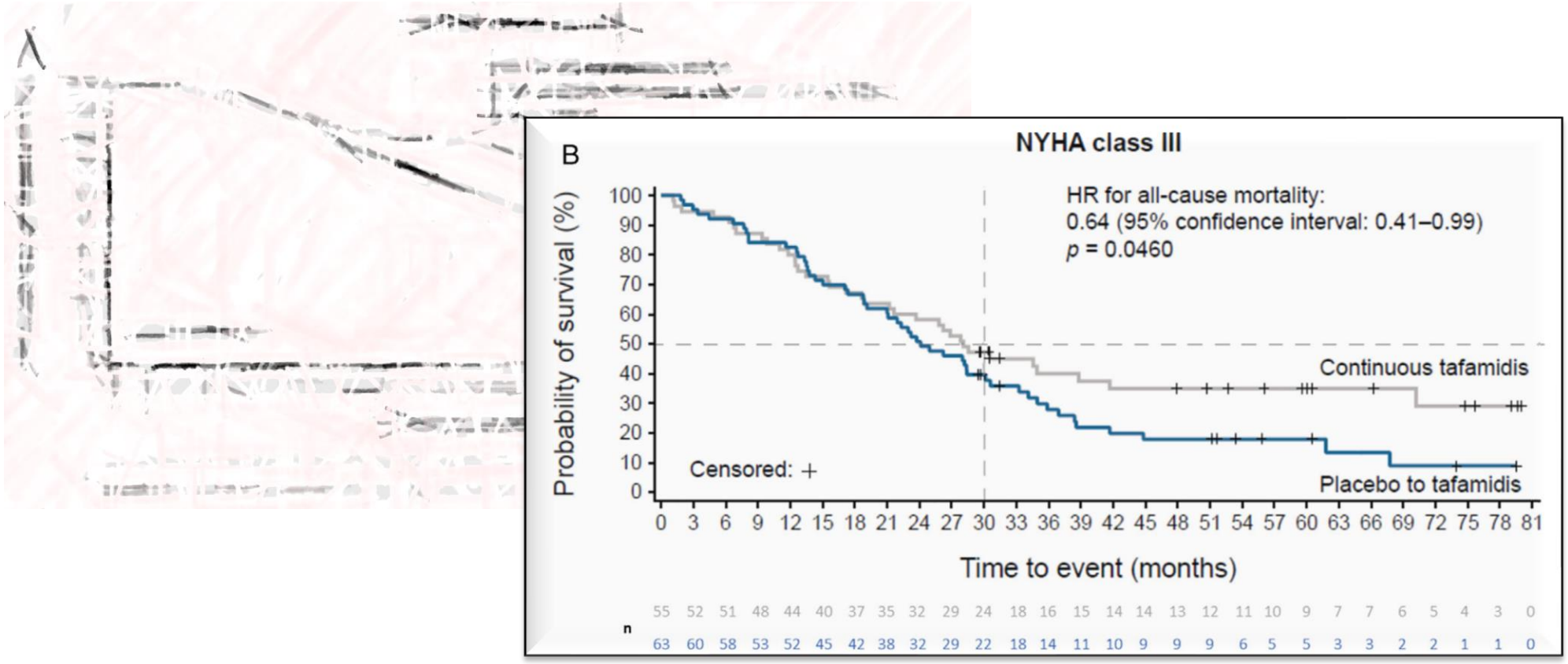
Perchè?

Come?

Prognosi 50% mortalità a 3,5 anni (2-6)



Prognosi 50% mortalità a 3,5 anni (2-6)



Elloitt P et al EHJ of HF 2023

Treatment of Cardiac Complications and Comorbidities in Cardiac Amyloidosis

Aortic Stenosis

- Severe AS confers worse prognosis.
- Concomitant ATTRwt risk factor for periprocedural AV block.
- TAVR improves outcome in amyloid-AS.

Thromboembolism

- High risk, common.
- Anticoagulate if AF, consider in selected cases in SR.
- Anticoagulate independent of CHADS-VASC score.

Conduction disorders

- PPM according to standard indications.
- Consider CRT if high paced burden expected.

Heart failure

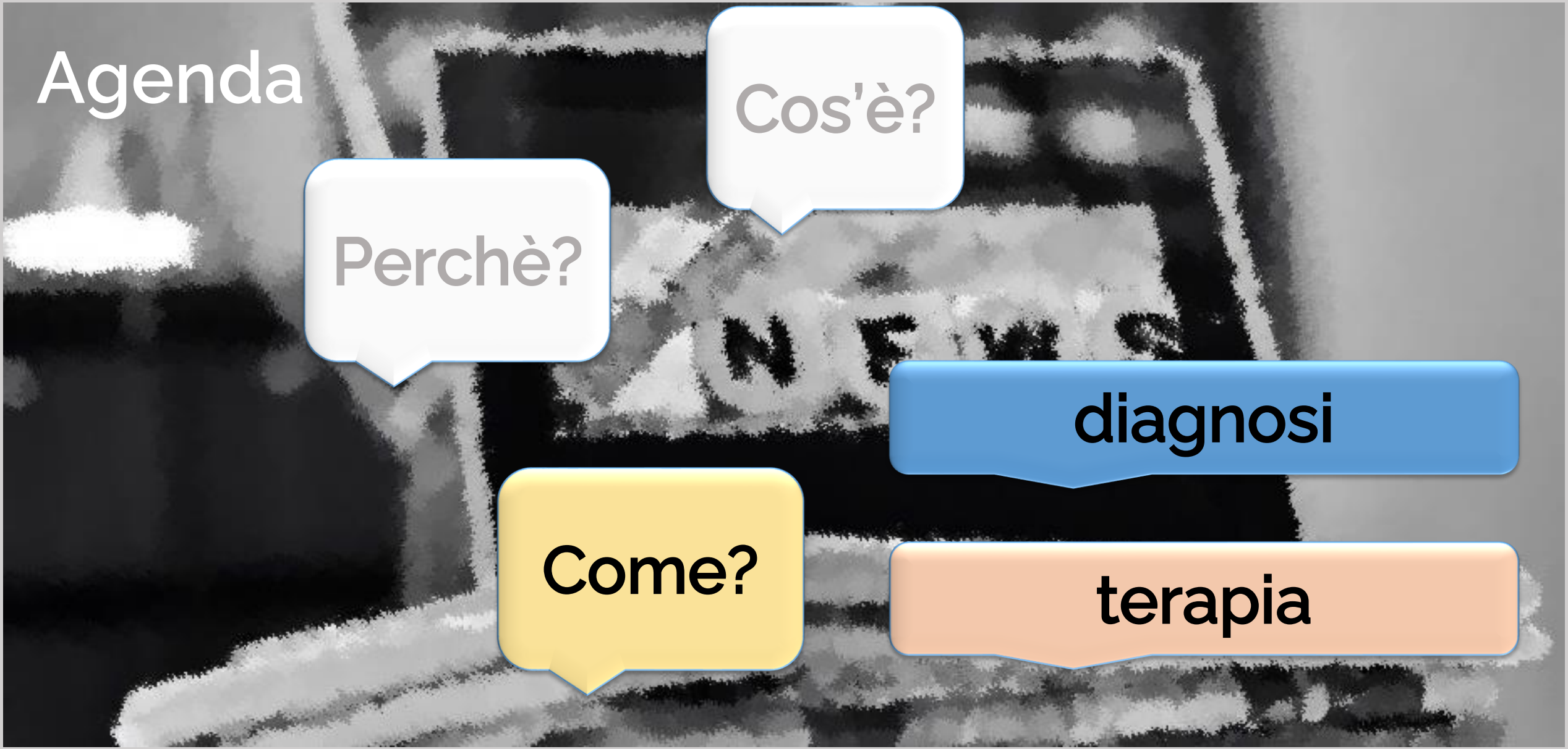
- Control fluid.
- Diuretics.
- Deprescribe B-Blockers.
- Avoid ACEI/ARB.
- LVAD not suitable for most patients.
- Heart transplant for selected cases.

Atrial Fibrillation

- Amiodarone, preferred AA.
- Use digoxin cautiously.
- Electrical CV has significant risk of complications and AF recurrence is frequent.
- Exclude thrombi before electrical CV.
- AF ablation data scarce and controversial.

Ventricular arrhythmias

- ICD for secondary prevention.
- ICD in primary prevention usually not recommended.
- Transvenous ICD preferred over subcutaneous ICD.


Agenda
Cos'è?
Perchè?
diagnosi
Come?
terapia

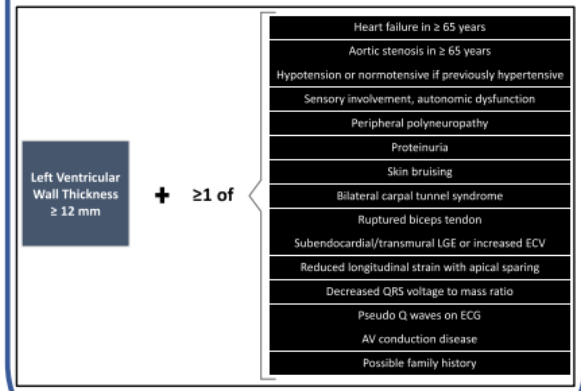
Cardiac amyloidosis

ESC Myocardial WG position paper

SUSPECT

Screen if

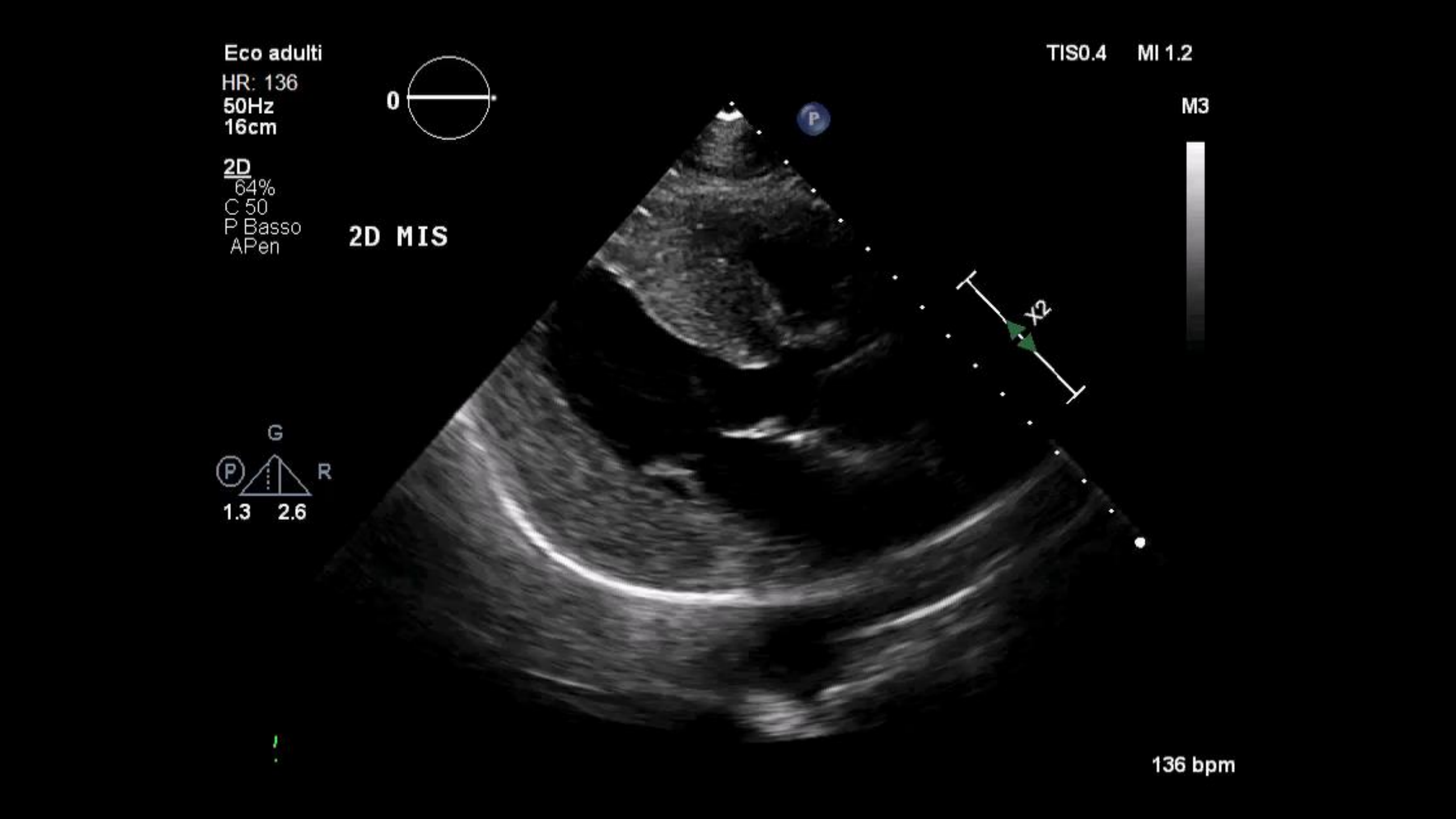
Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or
Clinical Scenario



Left Ventricular Wall Thickness ≥ 12 mm

\+ **≥1 of**

- Heart failure in ≥ 65 years
- Aortic stenosis in ≥ 65 years
- Hypotension or normotensive if previously hypertensive
- Sensory involvement, autonomic dysfunction
- Peripheral polyneuropathy
- Proteinuria
- Skin bruising
- Bilateral carpal tunnel syndrome
- Ruptured biceps tendon
- Subendocardial/transmural LGE or increased ECV
- Reduced longitudinal strain with apical sparing
- Decreased QRS voltage to mass ratio
- Pseudo Q waves on ECG
- AV conduction disease
- Possible family history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X2
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P
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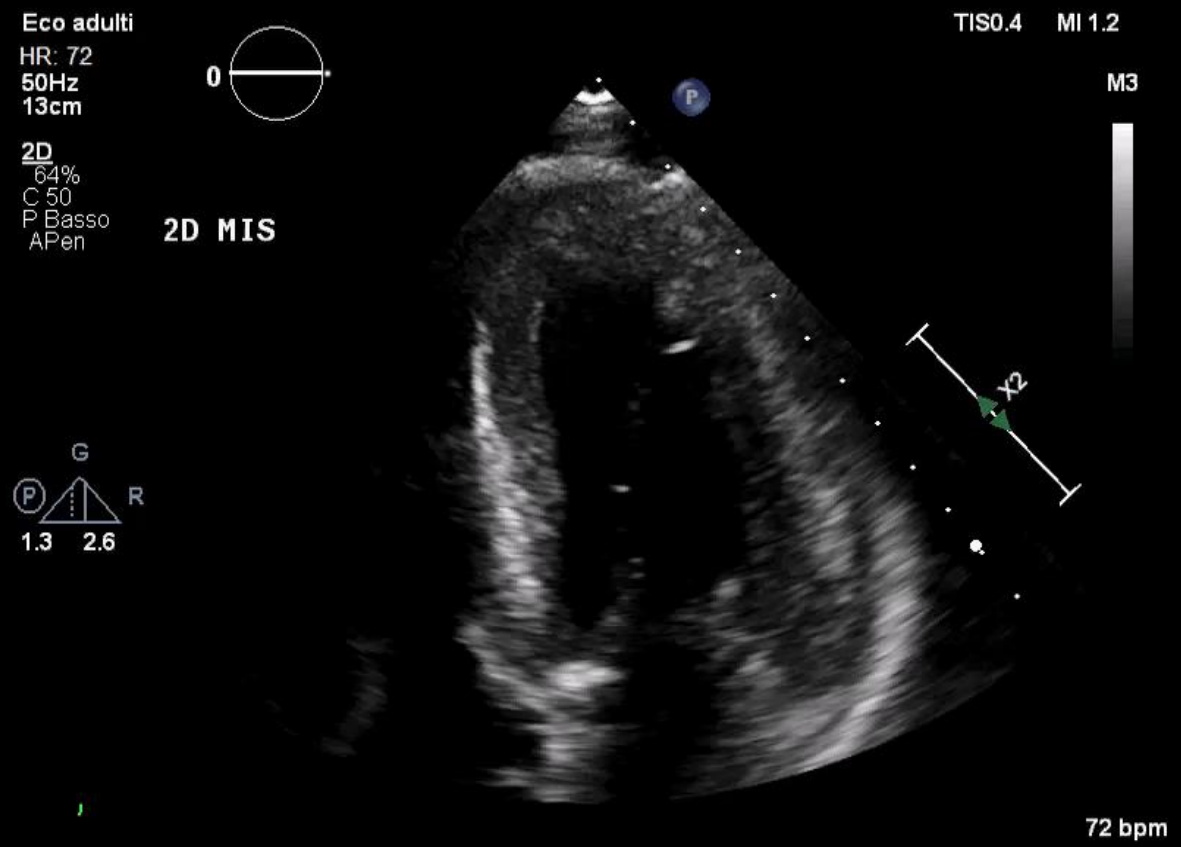
1.3
2.6
136 bpm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13cm
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M3
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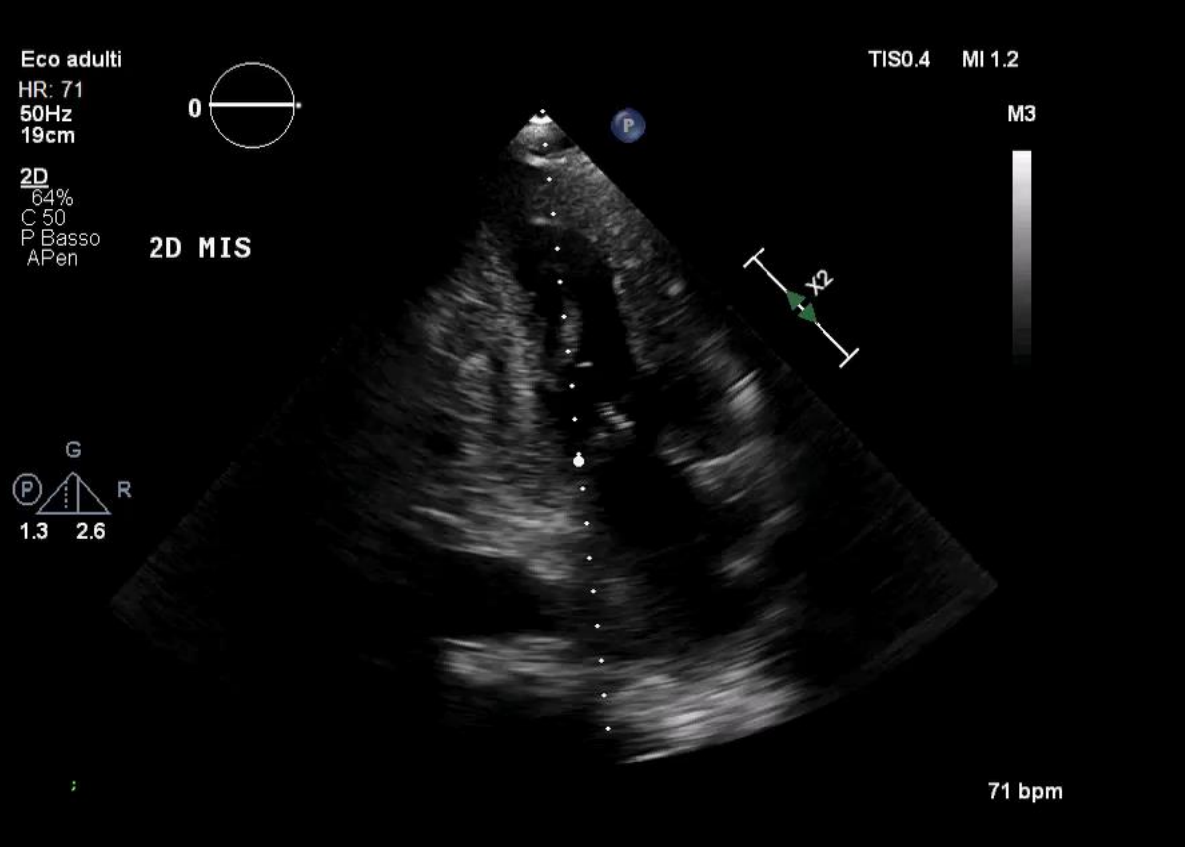
R
1.3 2.6
72 bpm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M3
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R
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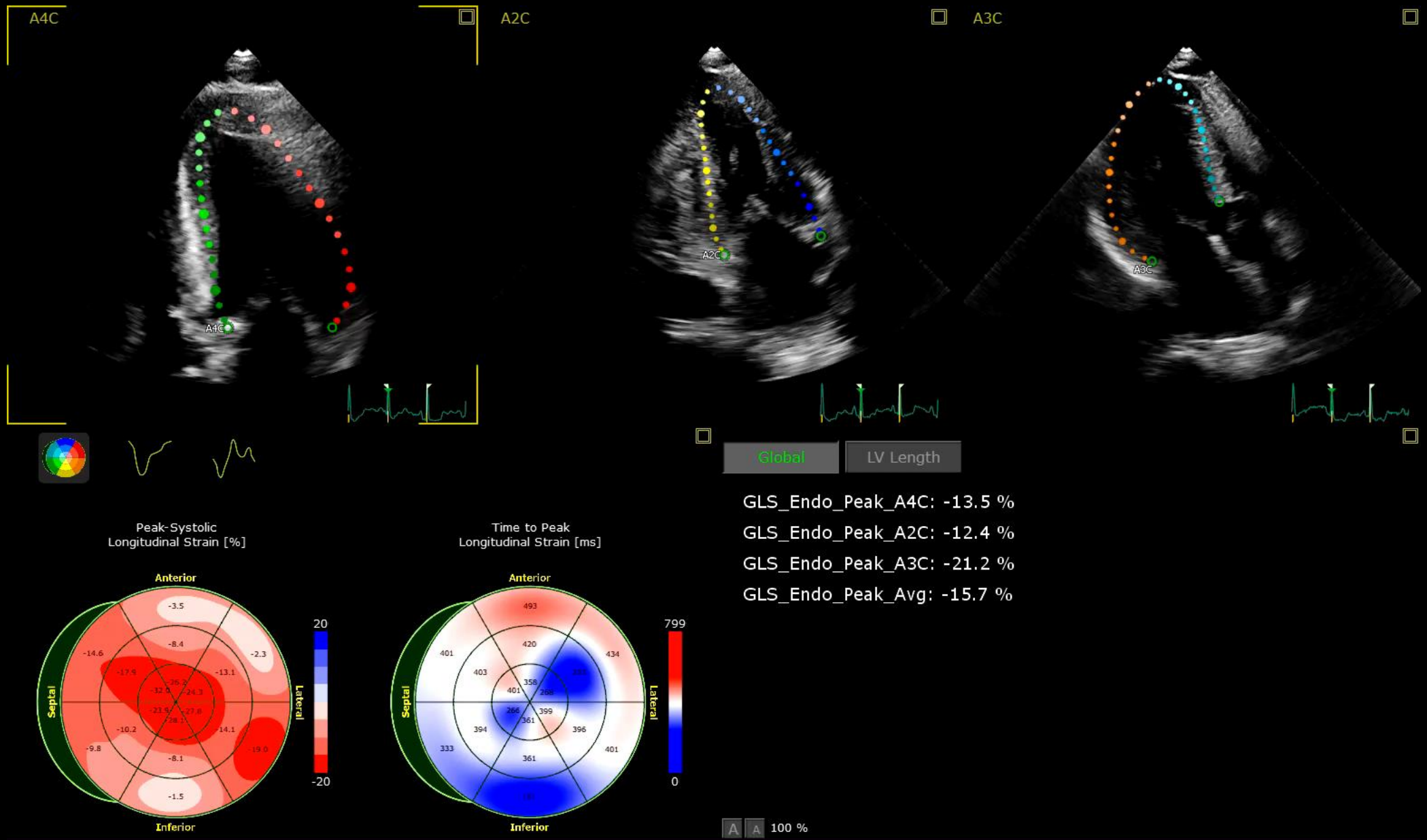
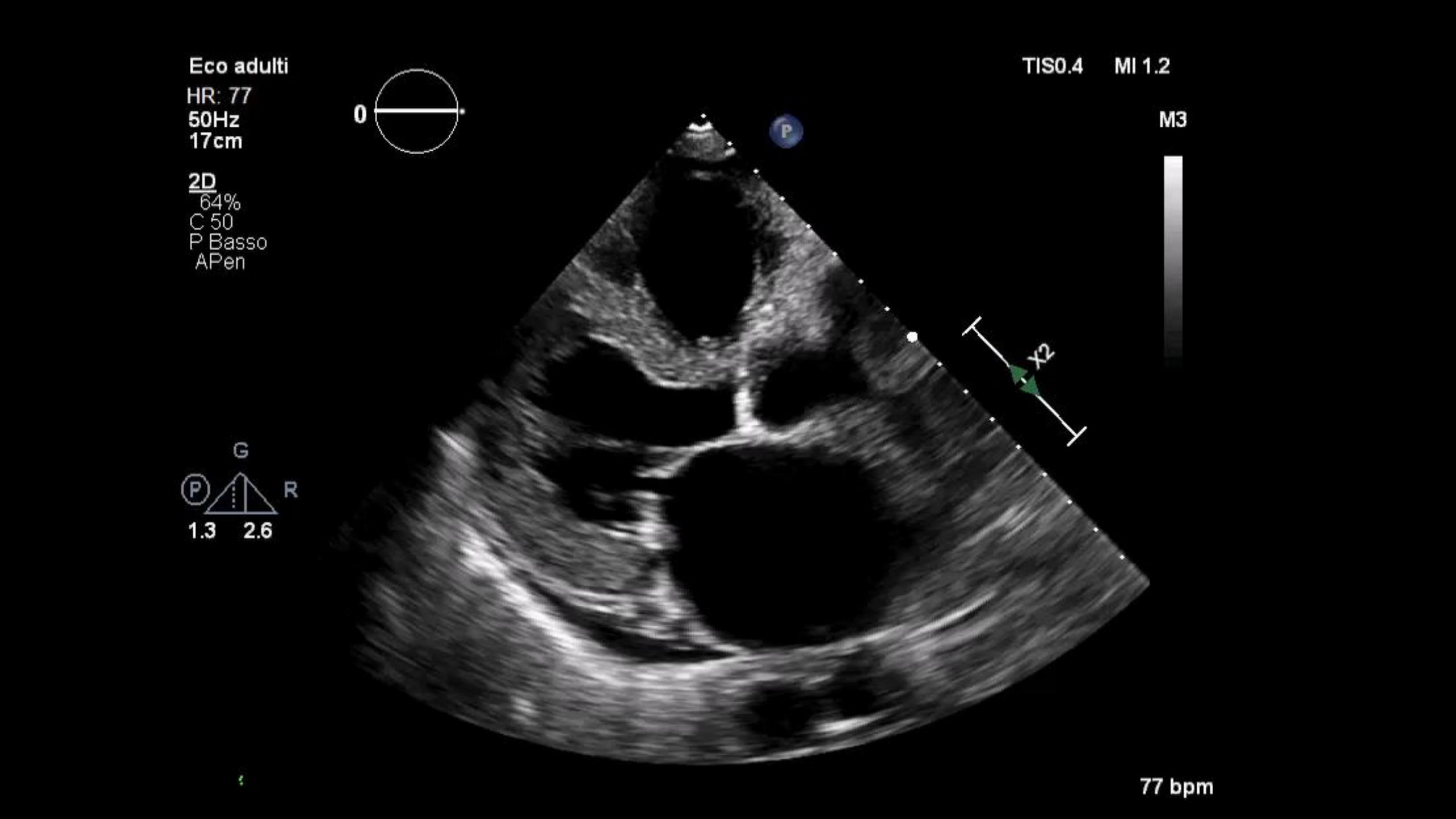
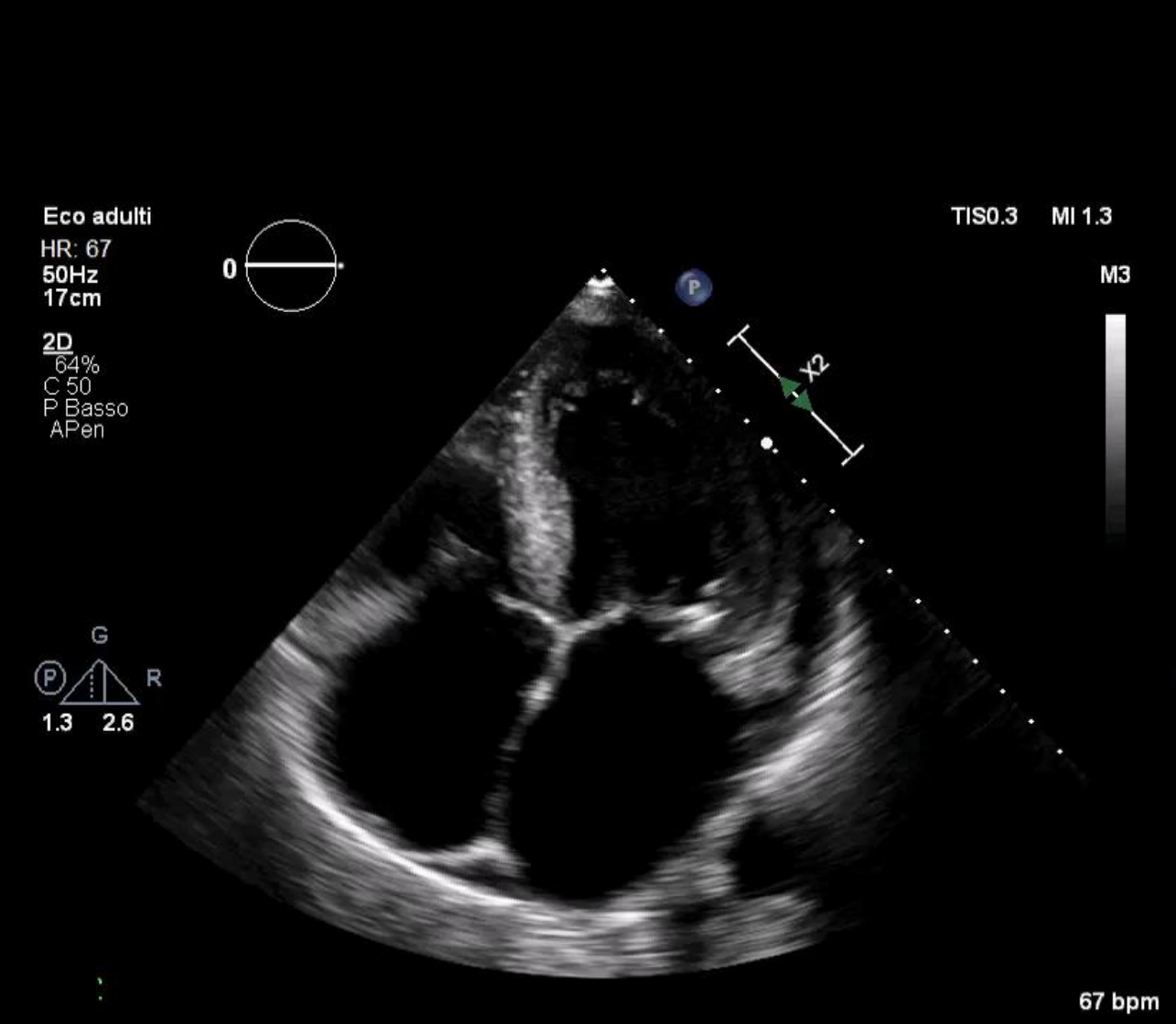
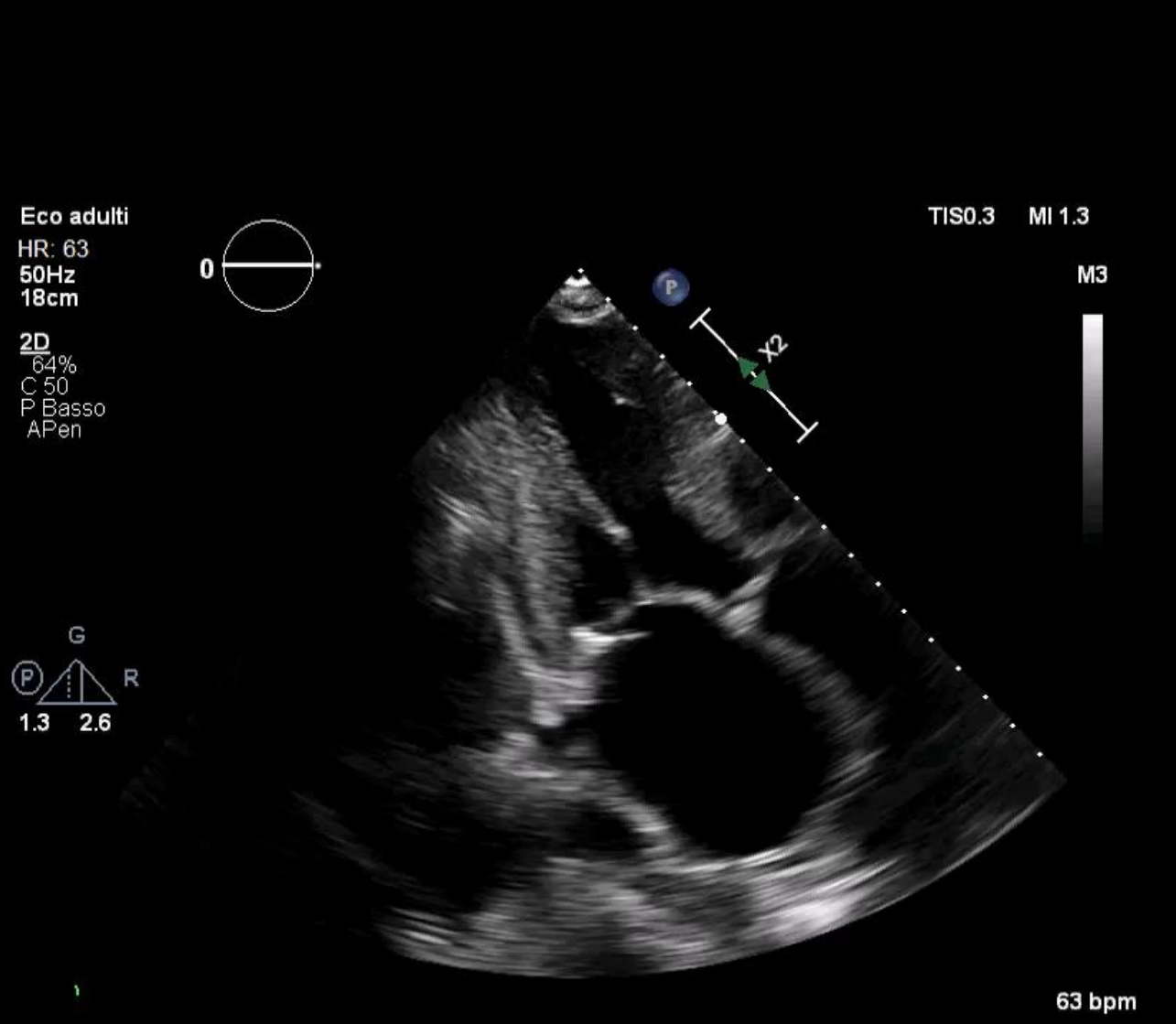
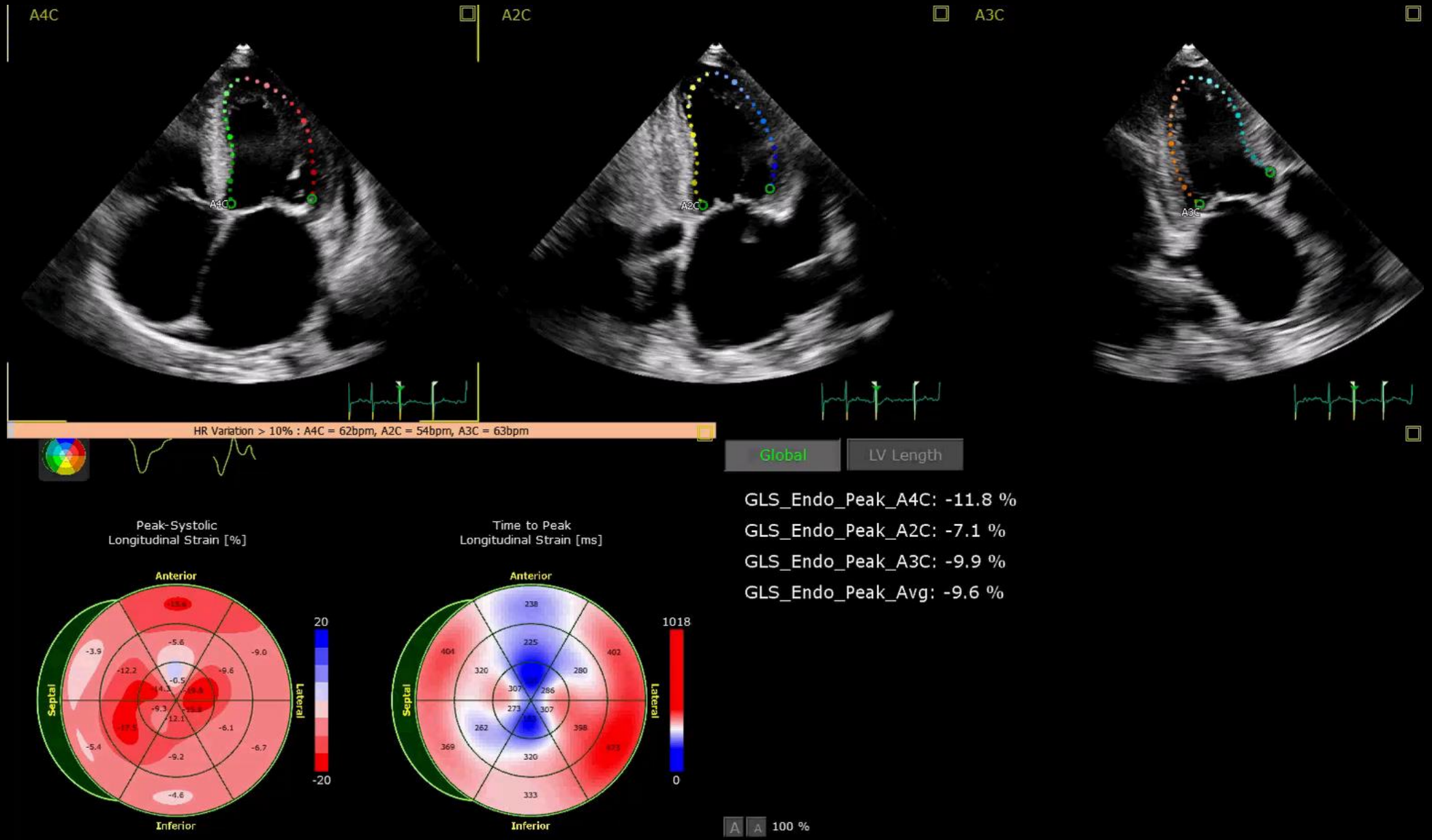
71 bpm


A4C
A2C
A3C
Global
LV Length
GLS_Endo_Peak_A4C: -13.5 %
GLS_Endo_Peak_A2C: -12.4 %
GLS_Endo_Peak_A3C: -21.2 %
GLS_Endo_Peak_Avg: -15.7 %
Peak-Systolic
Longitudinal Strain [%]
Time to Peak
Longitudinal Strain [ms]
Anterior
Septal
Lateral
Inferior
20
-20
799
0
100 %


Eco adulti
HR: 77
50Hz
17cm
2D
64%
C 50
P Basso
APen
0
TIS0.4
MI 1.2
M3
P
X2
G
P
R
1.3
2.6
77 bpm


Eco adulti
HR: 67
50Hz
17cm
2D
64%
C 50
P Basso
APen
TIS0.3 MI 1.3
M3
X2
G
P
R
1.3 2.6
67 bpm


Eco adulti
HR: 63
50Hz
18cm
2D
64%
C 50
P Basso
APen
TIS0.3 MI 1.3
M3
X2
G
P
R
1.3 2.6
63 bpm


A4C
A2C
A3C
HR Variation > 10% : A4C = 62bpm, A2C = 54bpm, A3C = 63bpm
Global
LV Length
GLS_Endo_Peak_A4C: -11.8 %
GLS_Endo_Peak_A2C: -7.1 %
GLS_Endo_Peak_A3C: -9.9 %
GLS_Endo_Peak_Avg: -9.6 %
Peak-Systolic
Longitudinal Strain [%]
Anterior
Septal
Lateral
Inferior
20
-20
-5.6
-9.0
-3.9
-12.2
-9.6
-0.5
-9.3
-12.1
-6.1
-5.4
-6.7
-9.2
-4.6
Time to Peak
Longitudinal Strain [ms]
1018
0
238
225
404
402
320
280
307
286
273
307
262
398
369
320
333
100 %

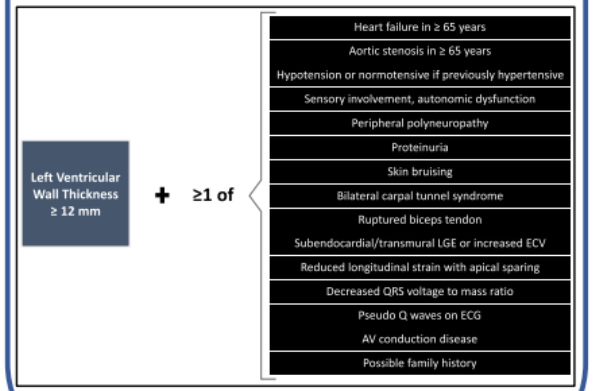
Cardiac amyloidosis

ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario



DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT & **Haematologic tests** (serum free-light chain quantification & serum and urine immunofixation)

Diagnosis made or proceed to **CMR and/or biopsy** according to results

Scintigrafia con tracciante osseo

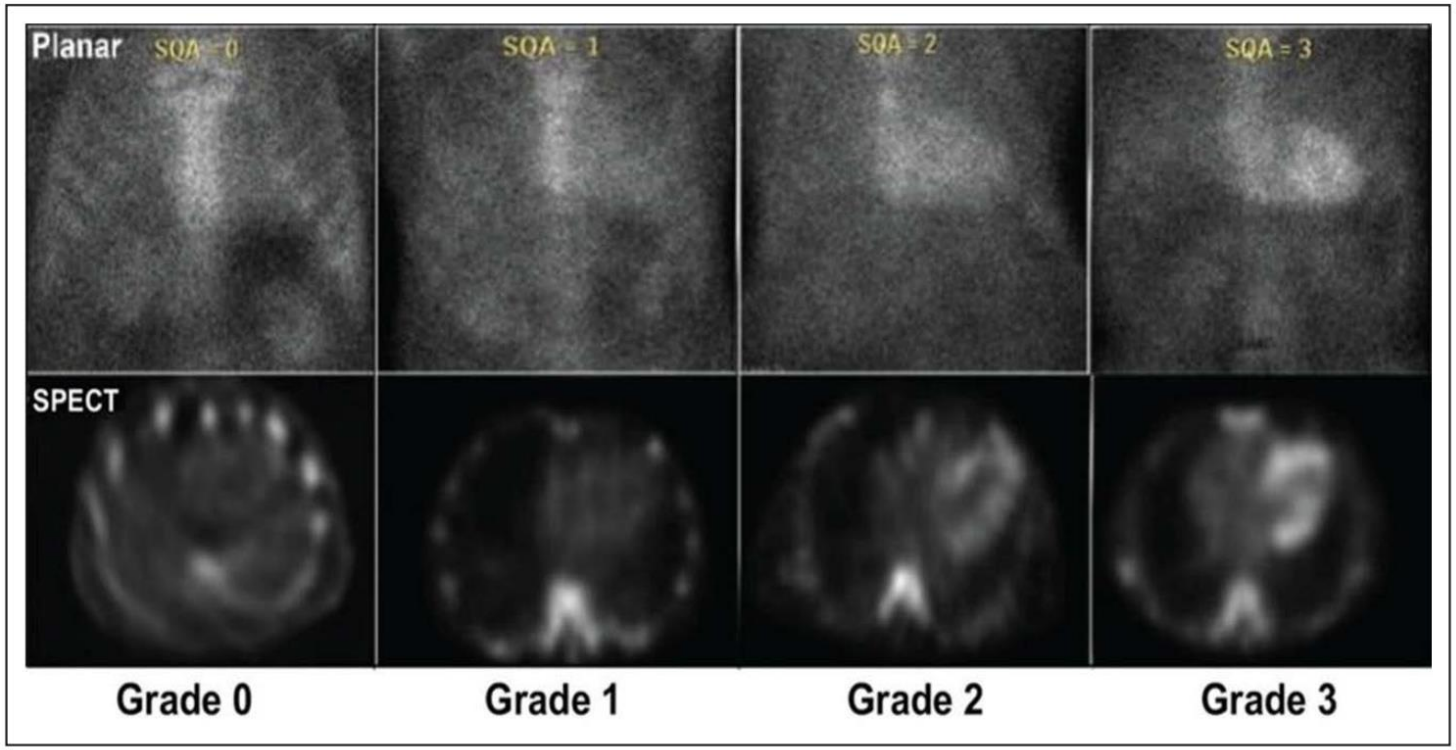


Figure 2. ^{99m}**Technetium-pyrophosphate imaging for transthyretin cardiac amyloidosis.**
Single-photon emission computed tomography (SPECT) imaging to identify myocardial retention of technetium-based isotopes is useful in discriminating blood pool on planar scans that result in a false-positive test from myocardial uptake of the isotope indicative of transthyretin amyloidosis with cardiomyopathy. SQA indicates semiquantitative analysis. Reprinted from Maurer et al.[26] Copyright © 2019, American Heart Association, Inc. Source figure adapted from Bokhari et al[27] with permission of the American Society of Nuclear Cardiology. Copyright © 2016, American Society of Nuclear Cardiology.

Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT &

Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT & **Haematologic tests** (serum free-light chain quantification & serum and urine immunofixation)

Scintigraphy grade 0
Haematologic tests -

AL/ATTR cardiac amyloidosis unlikely

If suspicion persists consider CMR followed by biopsy

Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT &

Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)

Scintigraphy grade 0
Haematologic tests -

AL/ATTR cardiac amyloidosis unlikely

If suspicion persists consider CMR followed by biopsy

Scintigraphy grade 0
Haematologic tests +

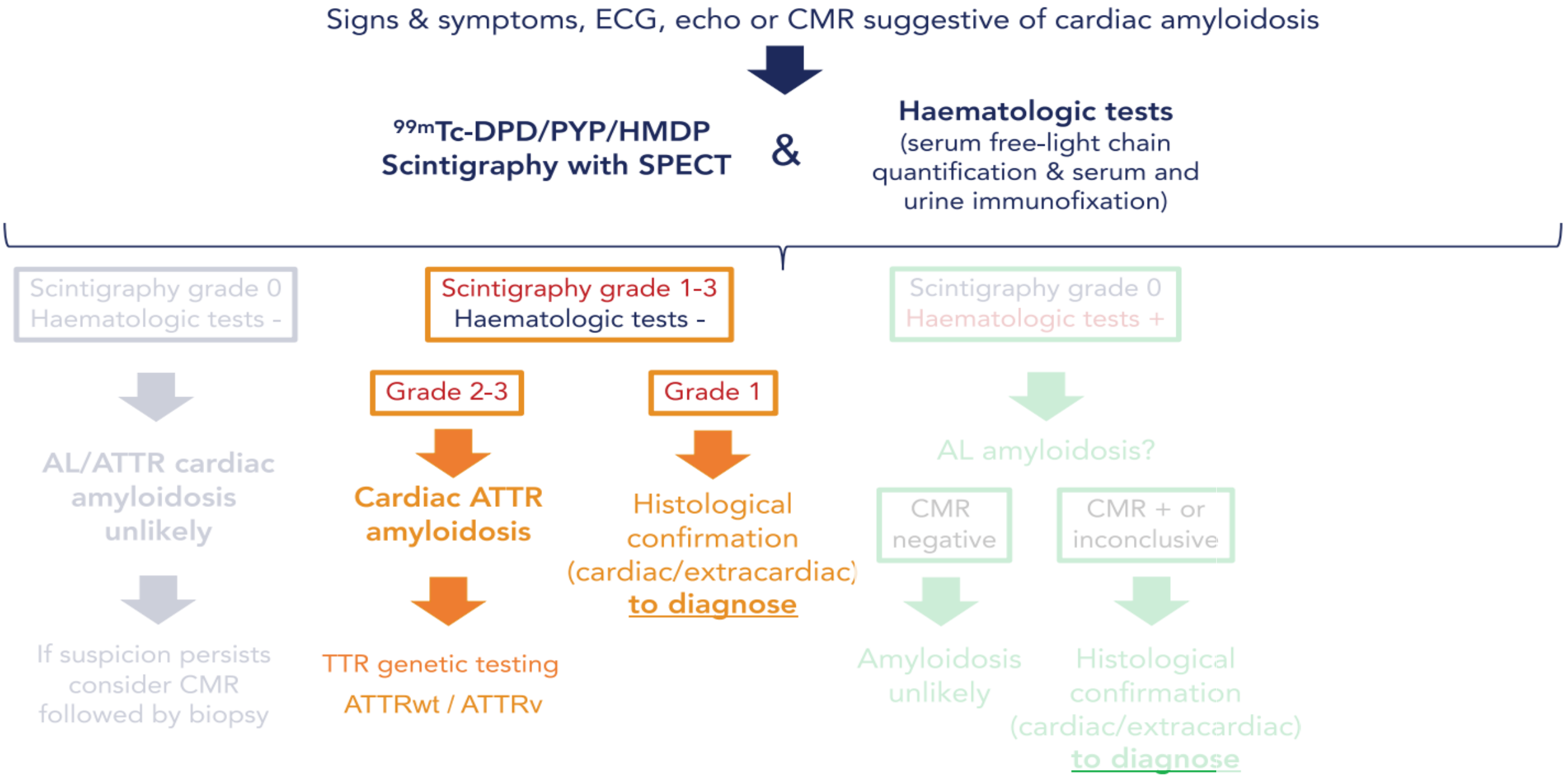
AL amyloidosis?

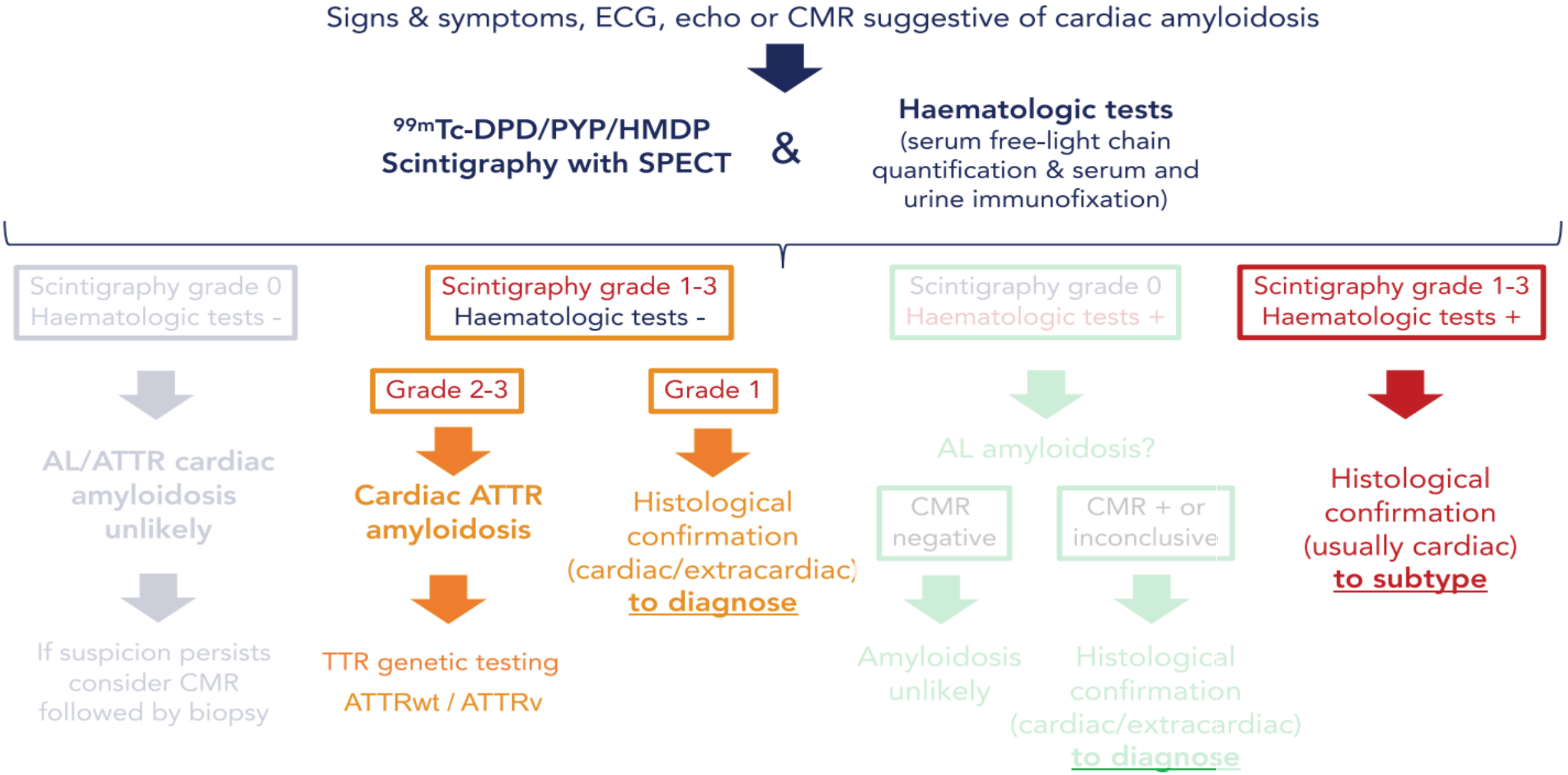
CMR negative

Amyloidosis unlikely

CMR + or inconclusive

Histological confirmation (cardiac/extracardiac) **to diagnose**


Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis
99mTc-DPD/PYP/HMDP Scintigraphy with SPECT
&
Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)
Scintigraphy grade 0 Haematologic tests -
Scintigraphy grade 1-3 Haematologic tests -
Scintigraphy grade 0 Haematologic tests +
AL/ATTR cardiac amyloidosis unlikely
If suspicion persists consider CMR followed by biopsy
Grade 2-3
Cardiac ATTR amyloidosis
TTR genetic testing
ATTRwt / ATTRv
Grade 1
Histological confirmation (cardiac/extracardiac) to diagnose
AL amyloidosis?
CMR negative
Amyloidosis unlikely
CMR + or inconclusive
Histological confirmation (cardiac/extracardiac) to diagnose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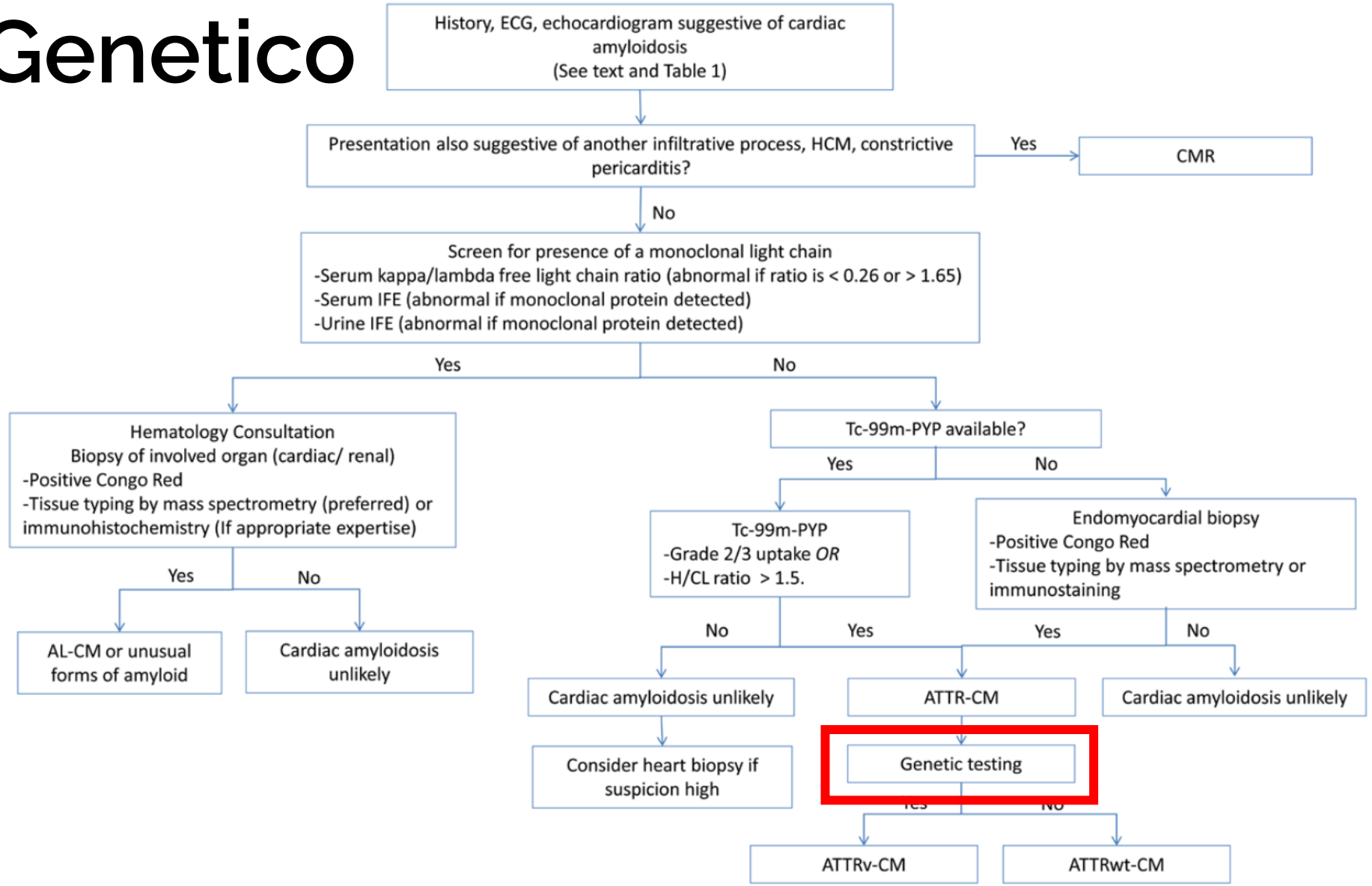
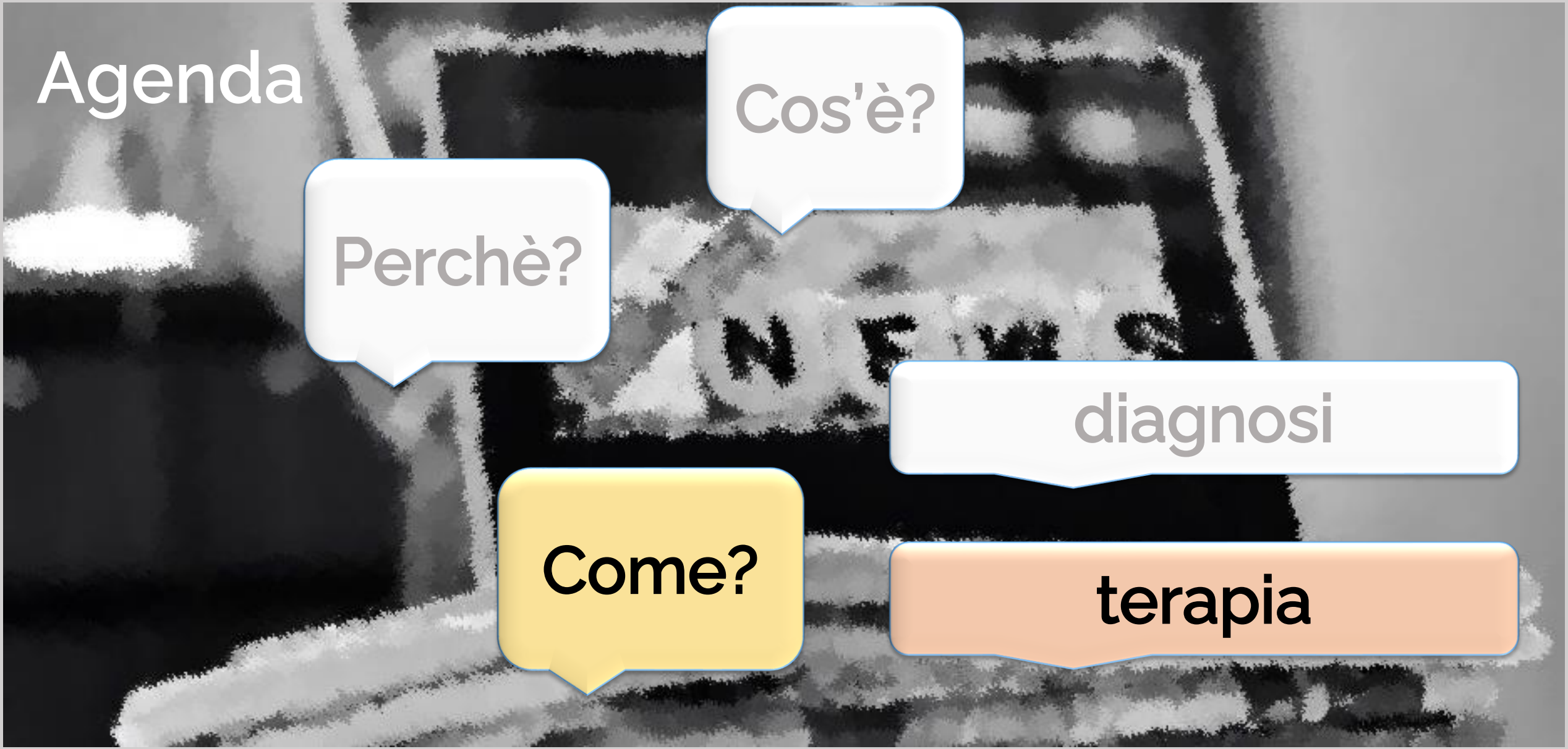
&
Haematologic tests (serum free-light chain quantification & serum and urine immunofixation)
Scintigraphy grade 0 Haematologic tests -
Scintigraphy grade 1-3 Haematologic tests -
Scintigraphy grade 0 Haematologic tests +
Scintigraphy grade 1-3 Haematologic tests +
AL/ATTR cardiac amyloidosis unlikely
If suspicion persists consider CMR followed by biopsy
Grade 2-3
Cardiac ATTR amyloidosis
TTR genetic testing
ATTRwt / ATTRv
Grade 1
Histological confirmation (cardiac/extracardiac) to diagnose
AL amyloidosis?
CMR negative
Amyloidosis unlikely
CMR + or inconclusive
Histological confirmation (cardiac/extracardiac) to diagnose
Histological confirmation (usually cardiac) to subtype

Test Genetico




Agenda
Cos'è?
Perchè?
diagnosi
Come?
terapia

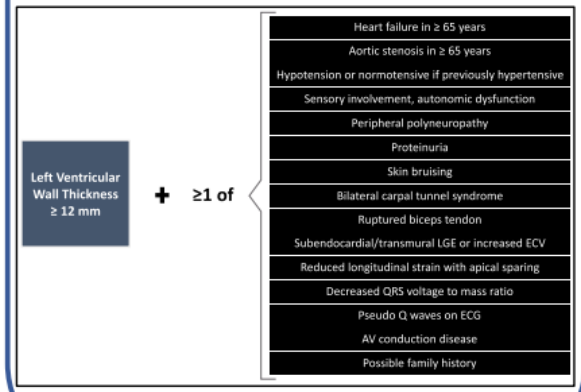
Cardiac amyloidosis

ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario



DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT & **Haematologic tests** (serum free-light chain quantification & serum and urine immunofixation)

Diagnosis made or proceed to **CMR and/or biopsy** according to results

TREATMENT

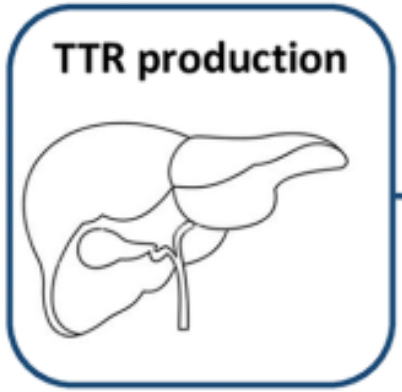
Cardiac complications and comorbidities

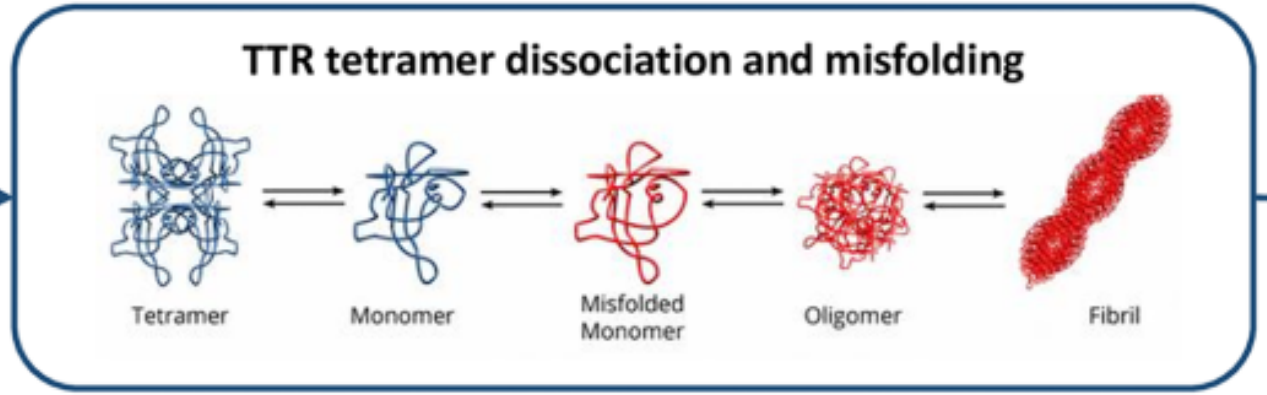
- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

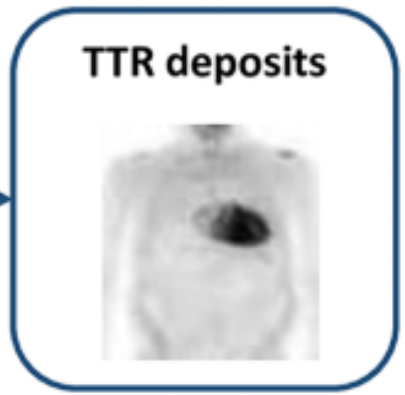
Disease modifying treatment

- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

Approccio terapeutico







Inhibition of TTR synthesis

- **Liver transplantation**
- **RNA silencing**

siRNA:
- Patisiran
- Revusiran
- Vutrisiran

ASO
- Inotersen
- Eplontersen

- **Gene editing**

CRISPR–Cas9:
- NTLA-2001

TTR stabilization

Non-selective agents
- Diflusinal

Selective agents
- Tafamidis
- Acoramidis

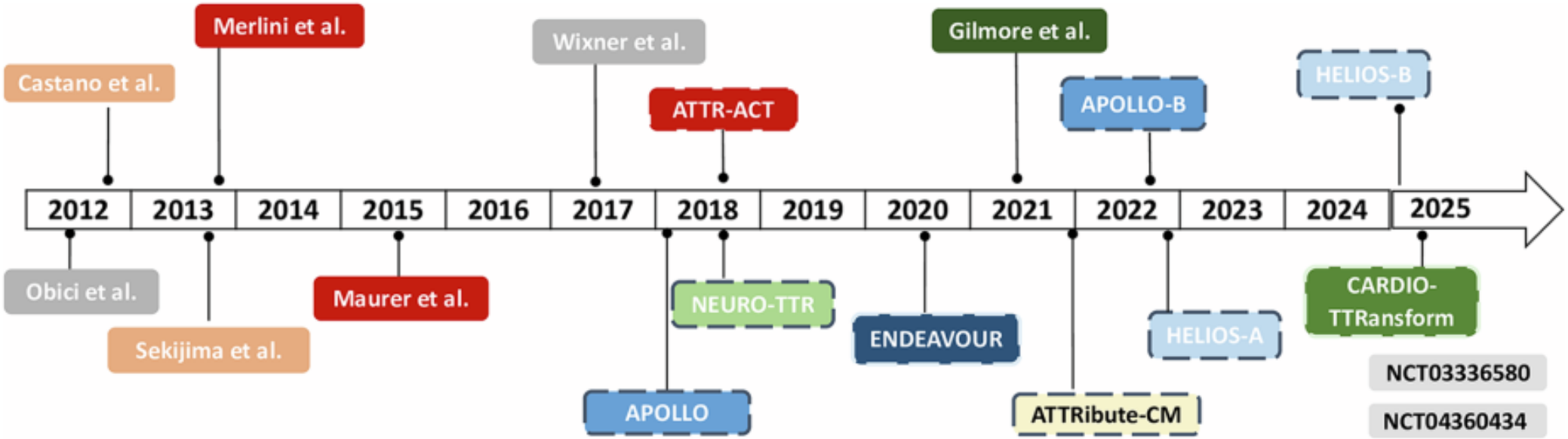
TTR degradation

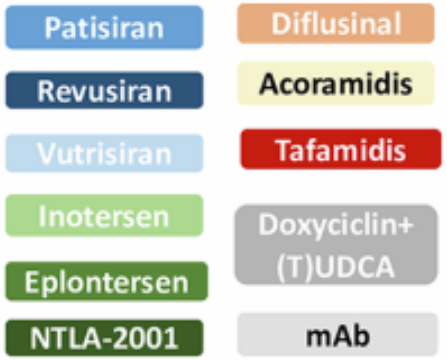
- Doxyciclin and (T)UDCA

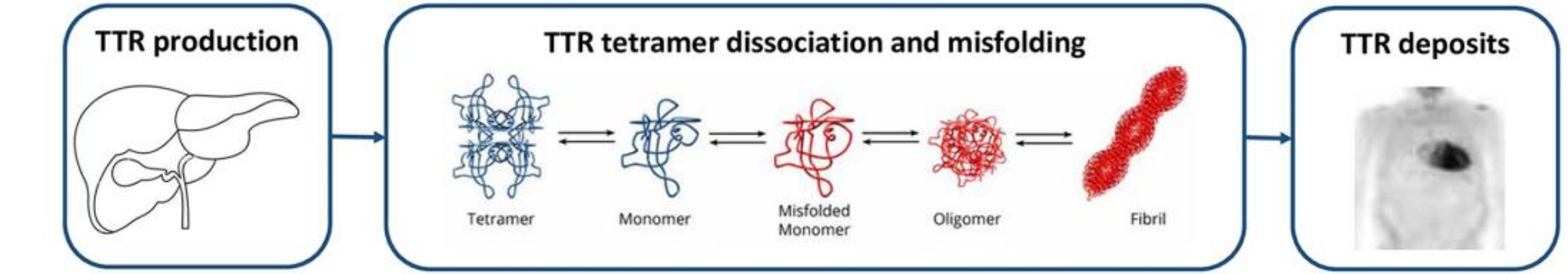
Monclonal Ab
- PRX004
- NI006

Tomasoni D et al Frontiers 2023

Approccio terapeutico







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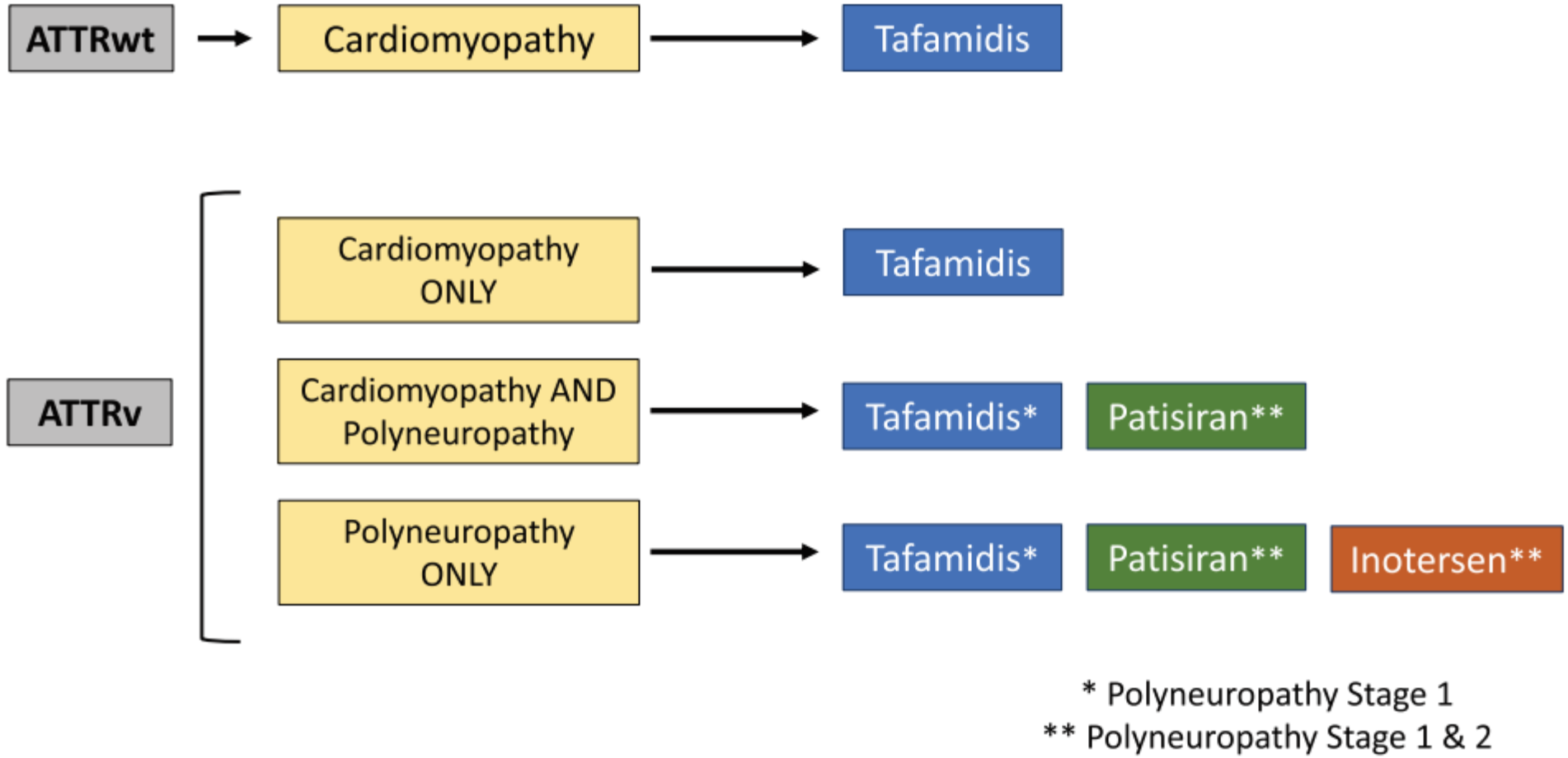
ATTRwt
Cardiomyopathy
Tafamidis
ATTRv
Cardiomyopathy ONLY
Tafamidis
Cardiomyopathy AND Polyneuropathy
Tafamidis*
Patisiran**
Polyneuropathy ONLY
Tafamidis*
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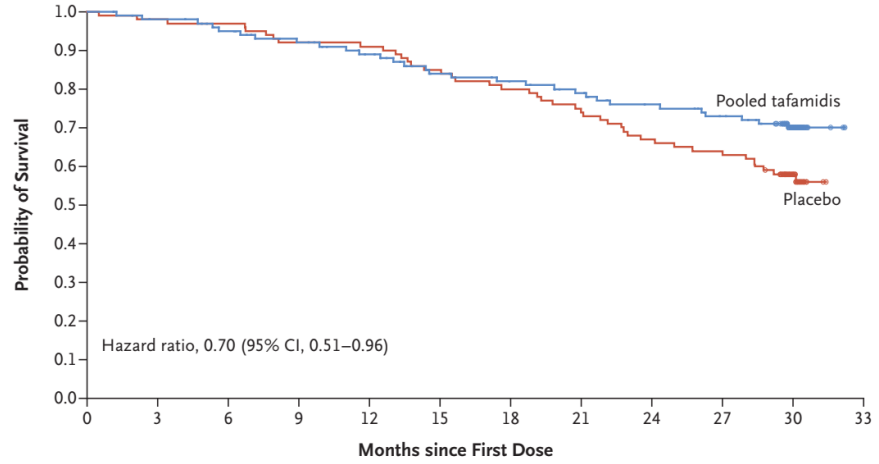
Inotersen**
* Polyneuropathy Stage 1
** Polyneuropathy Stage 1 & 2

Tafamidis

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)

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	
Placebo	177	107 (60.5)	0.70	0.68 (0.56–0.81)

Tafamidis

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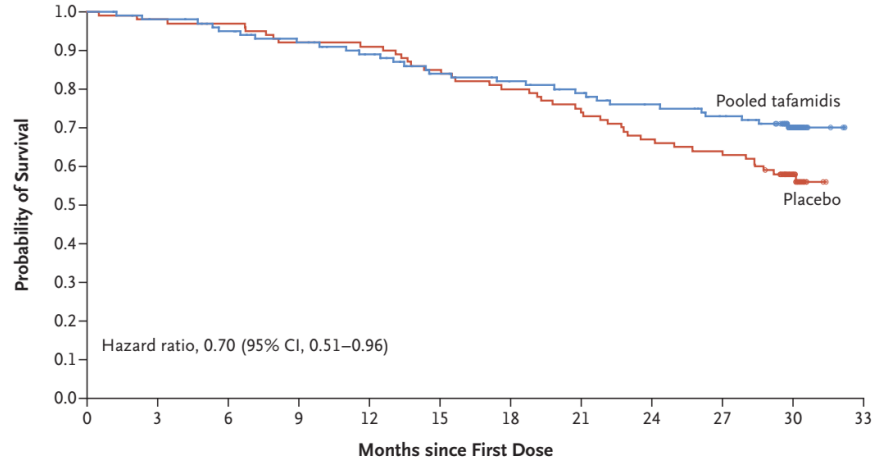

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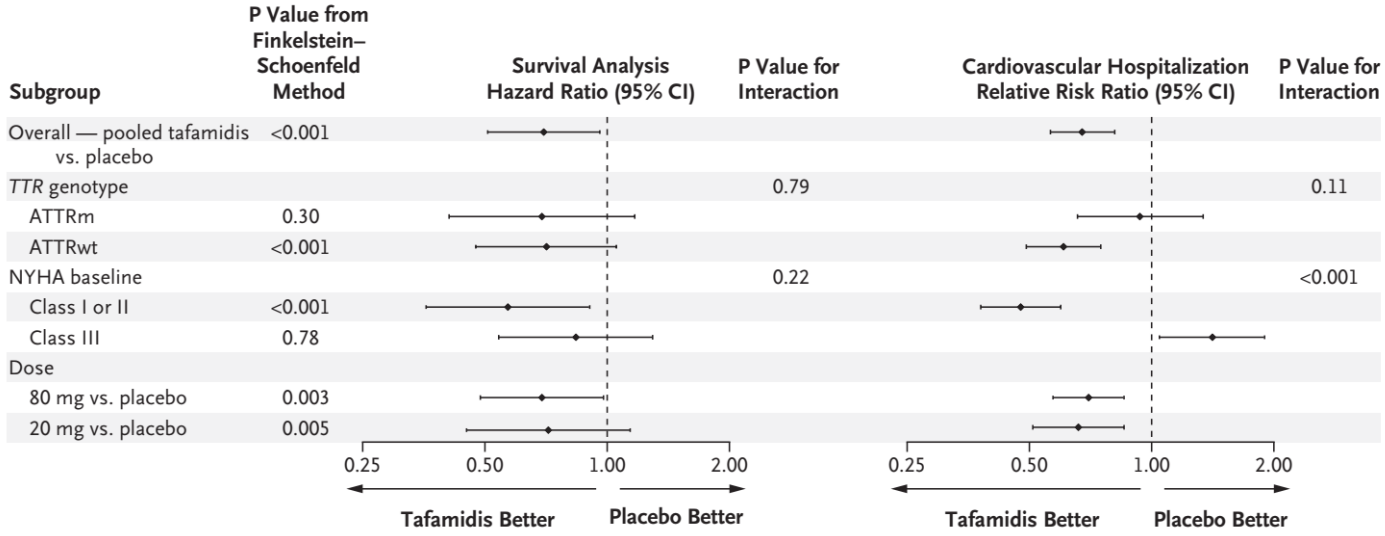

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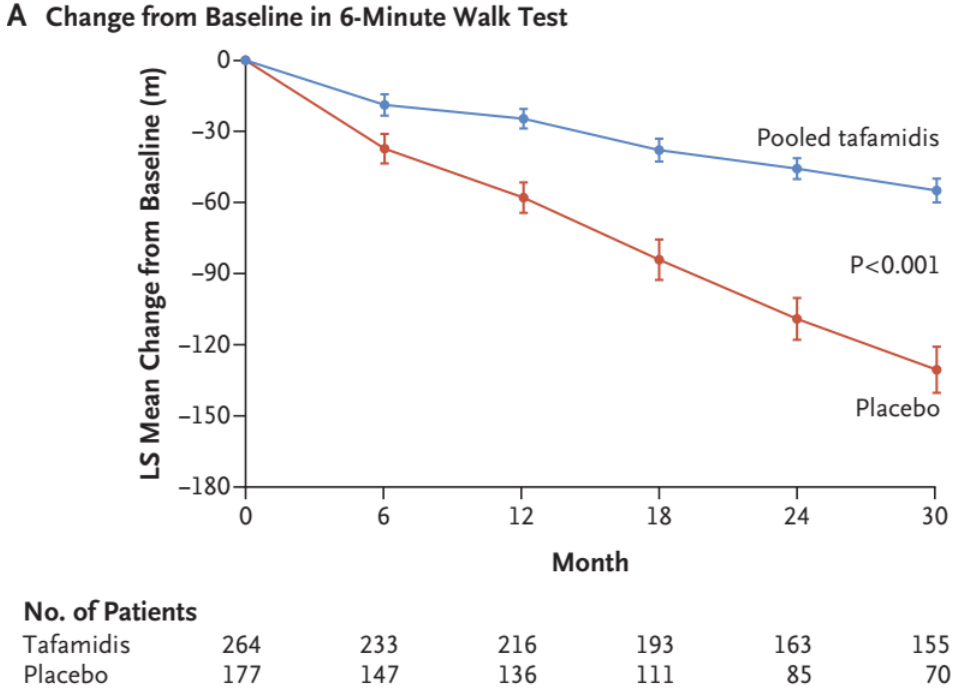
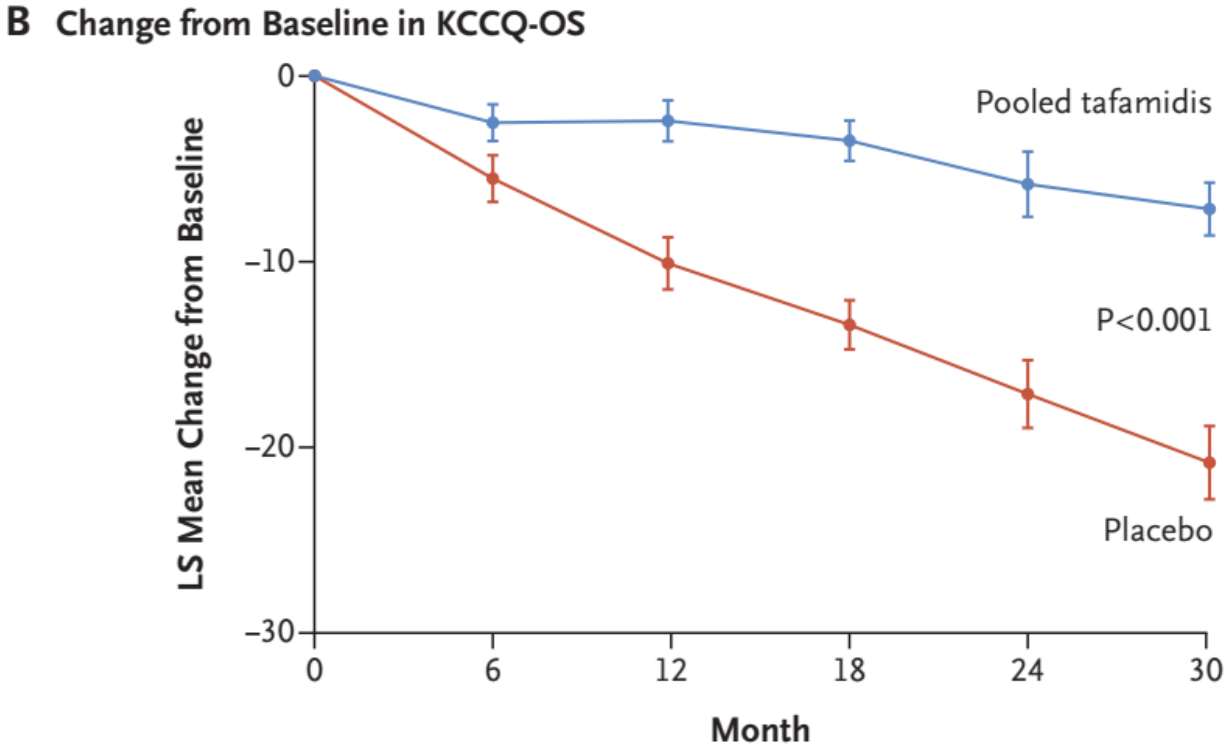

A Change from Baseline in 6-Minute Walk Test
LS Mean Change from Baseline (m)
0
−30
−60
−90
−120
−150
−180
Pooled tafamidis
P<0.001
Placebo
0
6
12
18
24
30
Month
No. of Patients
Tafamidis 264 233 216 193 163 155
Placebo 177 147 136 111 85 70


B Change from Baseline in KCCQ-OS
LS Mean Change from Baseline
0
−10
−20
−30
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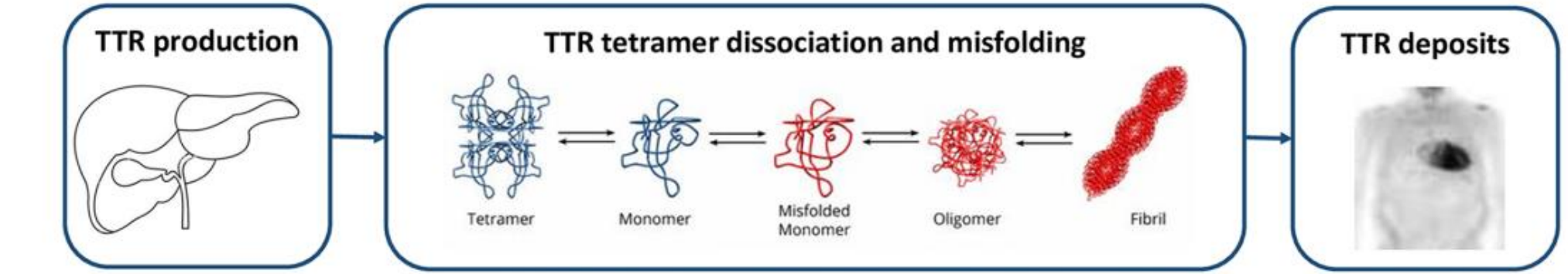
P<0.001
Placebo
0
6
12
18
24
30
Month



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Revusiran	ENDEAVOUR (2020) (30)	Phase III, multicentre, randomized, double-Blind, placebo-controlled; 2:1 randomization to SC revusiran (500 mg) or placebo daily for 5 days, then weekly for 18 months	206 patients with ATTRv- CM (revusiran $n = 140$; placebo $n = 66$)	NA (trial stopped early due to increased mortality compared with placebo
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ASO				
Inotersen	NEURO-TTR (2018) (29)	Phase III trial, randomized, double-blind, placebo controlled; 2:1 randomization to weekly subcutaneous injections of inotersen (300 mg) or placebo.	172 patients with stage 1–2 ATTRv-PN (inotersen $n = 112$; placebo $n = 60$) 108 (63%) patients had ATTRv-CM	Inotersen improved the course of neurologic disease and QoL. No differences in global longitudinal strain and other echocardiographic variables at 15 months Several adverse events, including severe events such as glomerulonephritis and thrombocytopenia, causing durg discontinuation.
Eplontersen	CARDIO-TTRansform	Phase III, multicentre, randomized, double-blind, placebo- controlled trial; randomization to SC injections of either eplontersen or placebo once every 4 weeks	Patients with ATTR-CM (estimated 1400 participants)	Estimated study completion date 2025
Monoclonal antibodies (mAb)				
PRX004	NCT03336580	Phase I study	Subjects with ATTR amyloidosis	Ongoing
NI006	NCT04360434	Phase I study	Patients with hereditary or wild-type ATTR-CM	Ongoing

Take Home messages

Cos'è?

Perchè?

Come?

Patologia dovuta all'accumulo di proteine a livello extracellulare 'malripiegate'
Patologia Rara in assoluto, ma frequente causa di scompenso cardiaco 11-15%

Take Home messages

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Prognosi infausta: mortalità 50% a 3.5 anni dalla diagnosi
Complicanze frequenti

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Terapia: Tafamidis (NYHA<III)

	Drug	Phase of study	Indication by amyloid type	Mechanism of action	Dose	Adverse effects	Concomitant therapy and monitoring	Annual cost	Primary end points
KNOCK-DOWN	Inotersen *(Tegsedi)*	Phase 2 NCT03702829	ATTRv and ATTRwt-CA NYHA I-III	2′-O-methoxyethyl-modified ASO, binds to nuclear target mRNA in the liver and via RNase H2 initiates mRNA degradation	300 mg SC per week	Glomerulonephritis Thrombocytopenia Vitamin A deficiency	Vitamin A supplementation CBC, BMP and UA every 2 wk	≈$450 000	Systolic strain imaging on echo compared with baseline at month 6
	Patisiran (*Onpattro*)	Phase 3 APOLLO-B NCT03997383	ATTRv and ATTRwt-CA NYHA I–III	siRNA which targets the 3′ untranslated region of the TTR mRNA, forming the RISC and subsequent mRNA degradation	0.3 mg/kg IV infusion q 3 wk (max dose 30 mg)	Infusion reactions Vitamin A deficiency	Steroid IV, APAP, H1 and H2 blocker IV and Vitamin A Supplement	≈$450 000	Change from baseline at month 12 in 6-MWT
	Vutrisiran	Phase 3 HELIOS-B NCT04153149	ATTRv and ATTRwt-CA NYHA I–III	siRNA conjugated to GalNAc, binds to TTR mRNA in the nucleus and initiates mRNA degradation via RNase H2	25 mg SC every 3 mo	Unknown	Vitamin A supplement	Unknown	Composite outcome of all-cause mortality and recurrent CV hospitalizations at 30–36 mo
	AKCEA-TTR-LRx/ION 682884	Phase 3 Cardio-TTRansform NCT04136171	ATTRv and ATTRwt-CA NYHA I–III	ASO conjugated to GalNAc, ASO portion shares the same base sequence as inotersen, thus same mechanism of action	45 mg SC every 4 wk	Unknown	Vitamin A supplement Platelets every week BMP, LFTs and UPCR every 2 wk	Unknown	Composite of CV mortality and frequency of CV clinical events at 120 wk
	CRISPR *(NTLA-2001)*	Phase 1 Open label and Single Dose Expansion Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics	ATTRv-FAP	Cas9/CRISPR genome editing	IV dose-escalation study	Unknown	None	Unknown	Adverse events Change from baseline in serum TTR Change from baseline in prealbumin Pharmacokinetics Pharmacodynamics Change from baseline in antidrug antibody and anti-Cas9 antibody levels
STABILIZERS	Tafamidis meglumine[60] *(Vyndaqel)* Tafamidis free salt *(Vyndamax)*	Approved	ATTRv and ATTRwt-CA NYHA I-III	Benzoxazole derivative without NSAID activity which binds to T_4 site on TTR	80 mg PO daily 61 mg PO daily	No safety signals of potential clinical concern	None	$225 000	All-cause mortality lower with tafamidis (29.5% vs 42.9%) Frequency of CV related hospitalizations lower with tafamidis (RRR, 0.68)
	AG-10 *(Acoramidis)*	Phase 3 ATTRIBUTE-CM NCT03860935	ATTRv and ATTRwt-CA NYHA I–III	Mimics super stabilizing activity of T119M, forms hydrogen bonds between neighboring serine residues at position 117 of each monomer	800 mg PO twice daily	Unknown	None	Unknown	Change in 6MWT at 12 mo All-cause mortality and CV-related hospitalizations at 30 mo
	Diflunisal[57]	Phase 2	ATTRv and ATTRwt-CA (off-label use)	NSAID, binds to T_4 binding site on serum TTR	250 mg BID PO	Bleeding Hypertension Fluid retention Renal dysfunction	Proton pump inhibitor Monitor CBC and BMP q 3–6 mo	$420	Safety and efficacy
	Tolcapone[66]	Phase 1 In vitro and ex vivo	ATTRv and ATTRwt-CA (V122I and V30M)	Cathecol-O-methyltransferase (COMT) inhibitor with a high affinity for T_4 binding site on serum TTR	Unknown	Acute liver failure	LFTs at baseline and q 2–4 wk for the first 6 mo	Unknown	No phase 3 trial to date
DEGRADATION/ EXTRACTION	doxycycline± TUDCA	Phase 2	AL-CA*[111] and ATTR-CA[112]	Doxycycline–inhibition of MMP TUDCA–antiamyloid fibril activity Synergistic activity to reduce amyloid fiber burden	Oral	Dermatologic gastrointestinal	None	Unknown	AL-CA: 20% 1-yr mortality and 60% ASCT utilization with CyBorD (no comparison arm)[111] ATTR-CA: No significant changes in NYHA class, cardiac biomarkers or echocardiographic parameters over 22 months[112]
ANTI-SEEDING	Tab FH2	Preclinical	ATTRv	Peptide inhibitor which binds to the amyloid driving F- and H-stands of fragmented fibrils, thereby impeding self-recognition and seeding.	Preclinical	Unknown	Unknown	Unknown	Preclinical

Suppression of TTR

- Liver Transplantation
- TTR Gene silencers (Patisiran/Inotersen)

TTR Stabilization

- Tafamidis
- Diflunisal
- Green Tea
- AG10

TTR disruption/resorption

- Doxycycline/TUDCA
- Monoclonal antibodies