ΚΑΡΔΙΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ ΒΟΡΕΙΟΥ ΕΛΛΑΔΟΣ

Ά Καρδιολογική Κλινική ΑΧΕΠΑ

ΑΜΥΛΟΕΙΔΩΣΗ

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Θεσσαλονίκη, 17 Μαίου 2019

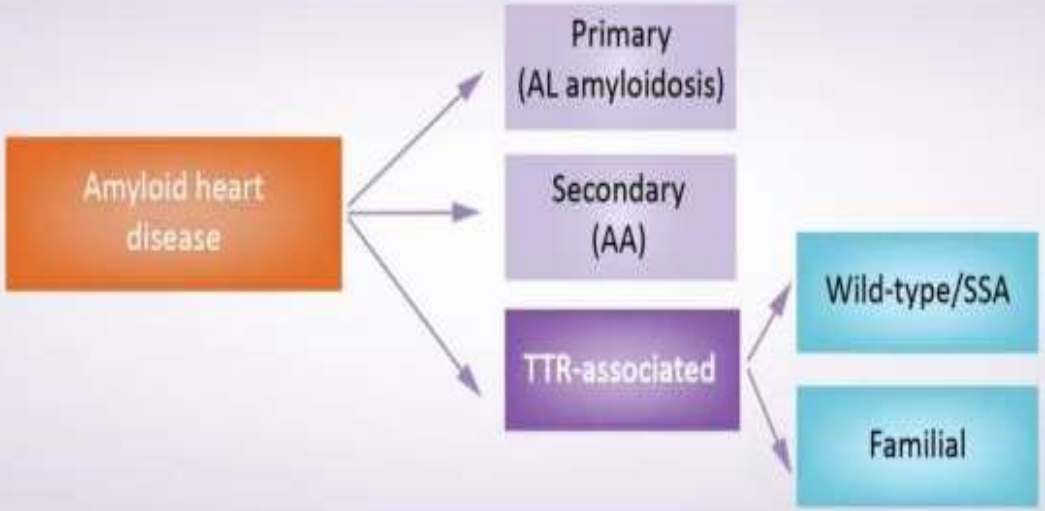
Outline

- Ορισμός / Παθοφυσιολογία
- Διάγνωση
- Πρόγνωση / Επιβίωση
- Αντιμετώπιση

Types of amyloidosis that affect the heart

Αμυλοείδωση είναι κάθε παθοφυσιολογική κατάσταση στην οποία η **λανθασμένη αναδίπλωση πρωτεϊνών** οδηγεί στην **παραγωγή ινιδίων** που εναποτίθενται στην εξωκυττάρια περιοχή ποικίλων ιστών

amyloid protein is derived from immunoglobulin light chains



transthyretin (TTR) protein produced by the liver.

- Primary amyloidosis, or amyloid light chain (AL) amyloidosis
- Secondary (AA) amyloidosis rarely manifests with cardiac symptoms and, if present, they are rarely clinically significant
- TTR-associated cardiomyopathy, two subcategories:
  - Wild-type (WT), or senile systemic amyloidosis (SSA)
  - Familial, or hereditary transthyretin-related amyloidosis

1. Dubrey SW, et al. *Heart* 2011;97:75–84;
2. Falk RH. *Circulation* 2005;112:2047–60

	Acquired or hereditary	Patients seen at UK-NAC (%; n=5100)	Underlying disorder	Precursor protein	Organ involvement				
					Heart	Kidneys	Liver	PN (AN)	Other
AL AL	Acquired	4067 (68%)	Plasma cell dyscrasia	Monoclonal immunoglobulin light chain	+++	+++	++	+(+)	Soft tissue gastrointestinal
AA AA	Acquired	633 (12%)	Inflammatory disorders (RA, JIA, IVDU, FPS)	SAA	−/+ (late)	+++	+(late)	−	Gastrointestinal (late)
ATTR ATTR	Acquired	168 (3·2%)	..	Wild-type TTR	+++	−	−	−	Carpal tunnel syndrome
	Hereditary	339 (6·6%)	Mutations in TTR gene	Abnormal TTR	++	−	−	+++ (+++)	−
+IAA -Isolated atrial Amyloidosis/ANP									
AFib	Hereditary	87 (1·7%)	Mutations in fibrinogen α-chain gene	Abnormal fibrinogen	−	+++	−/+	−	−
ALect2	Acquired	16 (0·3%)	Uncertain	Lect2	−	+++	++	−	−
A ApoA1 AApoA1	Hereditary	40 (0·8%)	Mutations in apolipoprotein A1 gene	Abnormal ApoA1	+	++	++	+/−(−)	Testis
ALys	Hereditary	17 (0·3%)	Mutations in lysozyme gene	Abnormal lysozyme	−	+	++	−	Gastrointestinal or skin
AGel	Hereditary	4 (0·1%)	Mutations in gelsolin gene	Abnormal gelsolin	−	-/+	−	++(−) cranial	−
Aβ2M	Acquired or hereditary	93 (1·8%)	Long-term dialysis	Aβ2M	−	−	−	−(+*)	Carpal tunnel syndrome, arthropathy

Lancet 2016

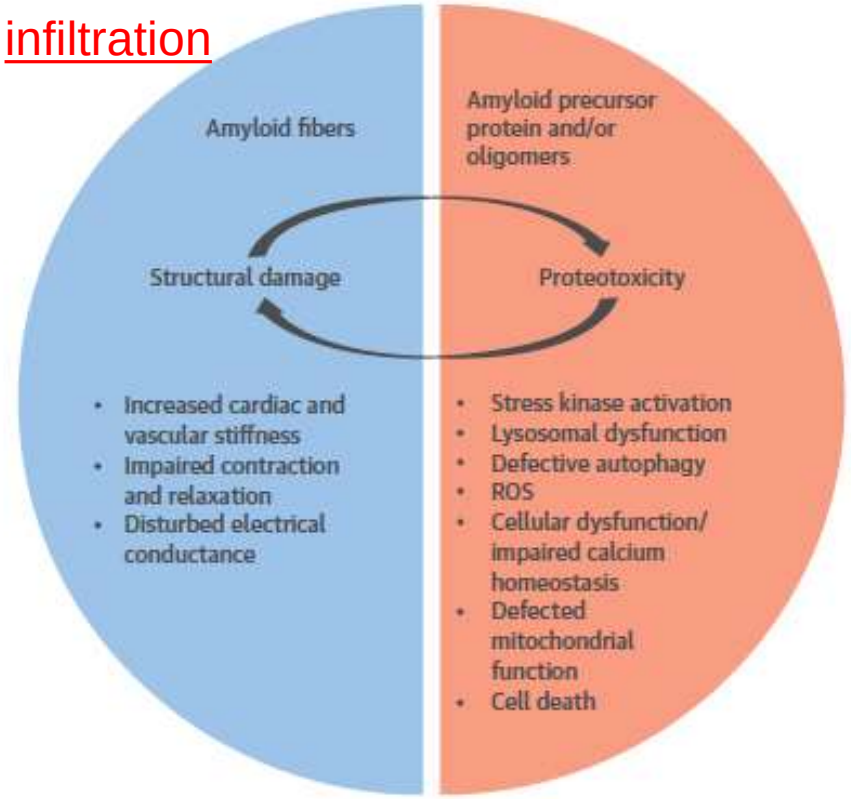
Types of amyloidosis that affect the heart

TABLE 1 Overview of the Common Forms of Amyloidosis That May Affect the Heart

Amyloid Nomenclature	Precursor Protein	Age Range, yrs	Sex	Clinical Clues	Laboratory Abnormalities
AL	Light chains	50+	Either	Multiorgan involvement. Periorbital bruising or macroglossia are almost pathognomonic of AL in setting of typical MRI or echocardiogram. Severe hypotension with ACE inhibitors.	Elevated serum free lambda or kappa, with abnormal ratio. Monoclonal spike in serum and/or urine. Suppressed immunoglobulins. Proteinuria.
ATTRwt	Wild-type (normal) transthyretin	65+	Marked male predominance, >15:1	History of carpal tunnel syndrome 5-10 yrs earlier, with no other organ involvement.	No specific abnormalities. (Normal free light chain values, no proteinuria)
ATTRm	Mutant transthyretin	40+ (mutation dependent). In V122I, the common African-American variant, usual age of clinical onset is 60-65 yrs.	Either, slight male predominance.	African-American/Caribbean origin (for V122I TTR variant).	No specific abnormalities on routine testing. Genetic testing reveals mutation in TTR molecule
AA (Secondary)	Serum amyloid A (an acute phase protein)	May occur in 20s–30s upward with severe inflammatory disease.	Either	Underlying chronic inflammatory disease. Hepatomegaly, splenomegaly. Usually no cardiac involvement, but in rare cases may be severe	High ESR/CRP. Proteinuria.

Pathophysiology

FIGURE 3 Postulated Mechanisms Leading to Progressive Heart Failure in AL Amyloidosis



Infiltration of the myocardium causes physical cellular damage and restrictive pathophysiology, whereas circulating cardiotoxic light chains produce cellular damage through various pathways (see text for details). In other forms of cardiac amyloid, such as TTR, the sole (or overwhelmingly predominant) mechanism of cardiac dysfunction is the infiltrative component. ROS = reactive oxygen species; other abbreviations as in Figure 1.

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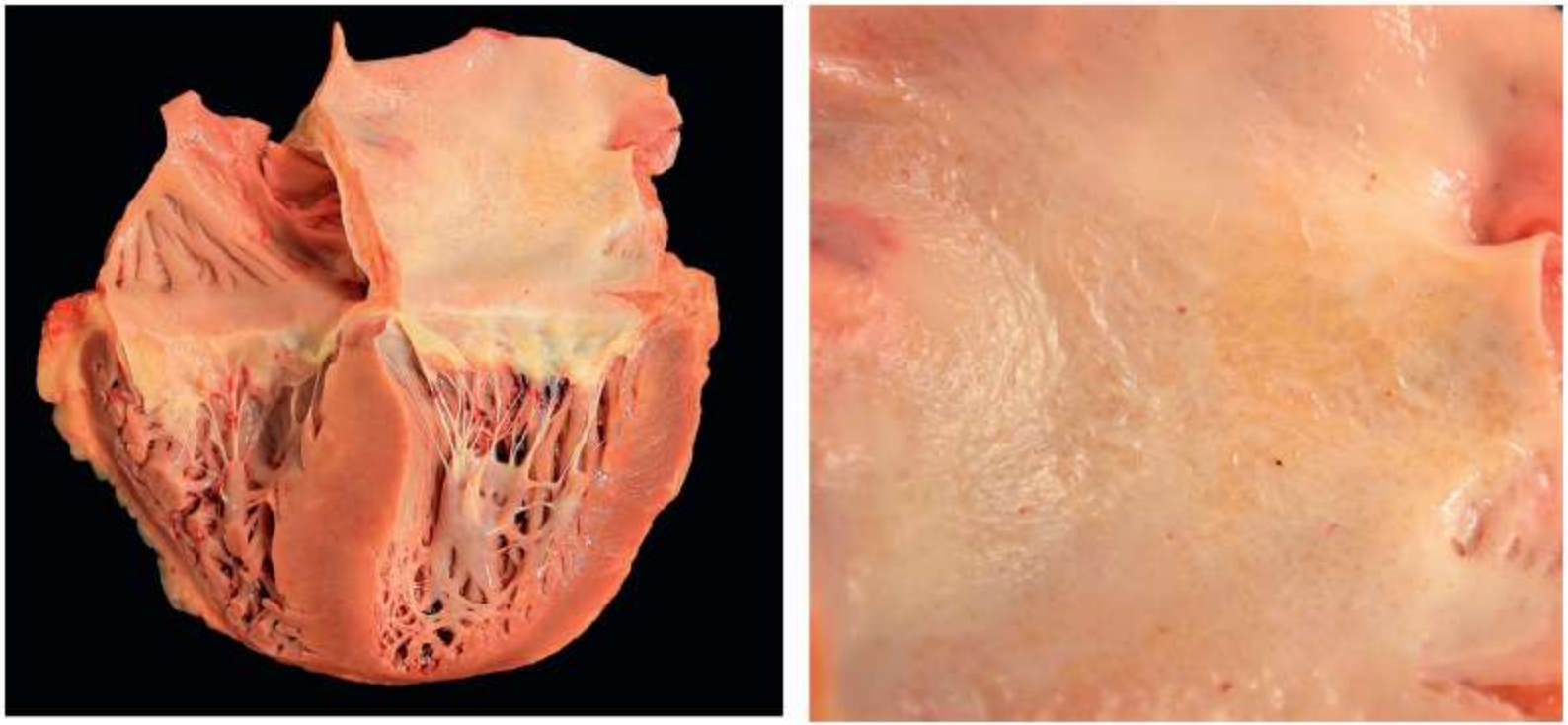
Autopsy

FIGURE 2 Autopsy Specimen of the Heart From a Patient Who Died of Cardiac Amyloidosis



(Left) Biatrial dilation with thickened atrial septum and extensive thickening of the left ventricle (and, to a lesser degree, the right ventricle), due to amyloid infiltration. **(Right)** Close-up view of the atrium, showing the waxy, irregular surface due to amyloid deposition. Atrial infiltration leads to atrial dysfunction, and the irregular endocardial deposits can form a nidus for thrombus formation, accounting for the high prevalence of atrial thrombi in amyloid cardiomyopathy. Courtesy of Robert Padera, MD, Brigham and Women's Hospital, Boston, Massachusetts.

Diagnostic Algorithm

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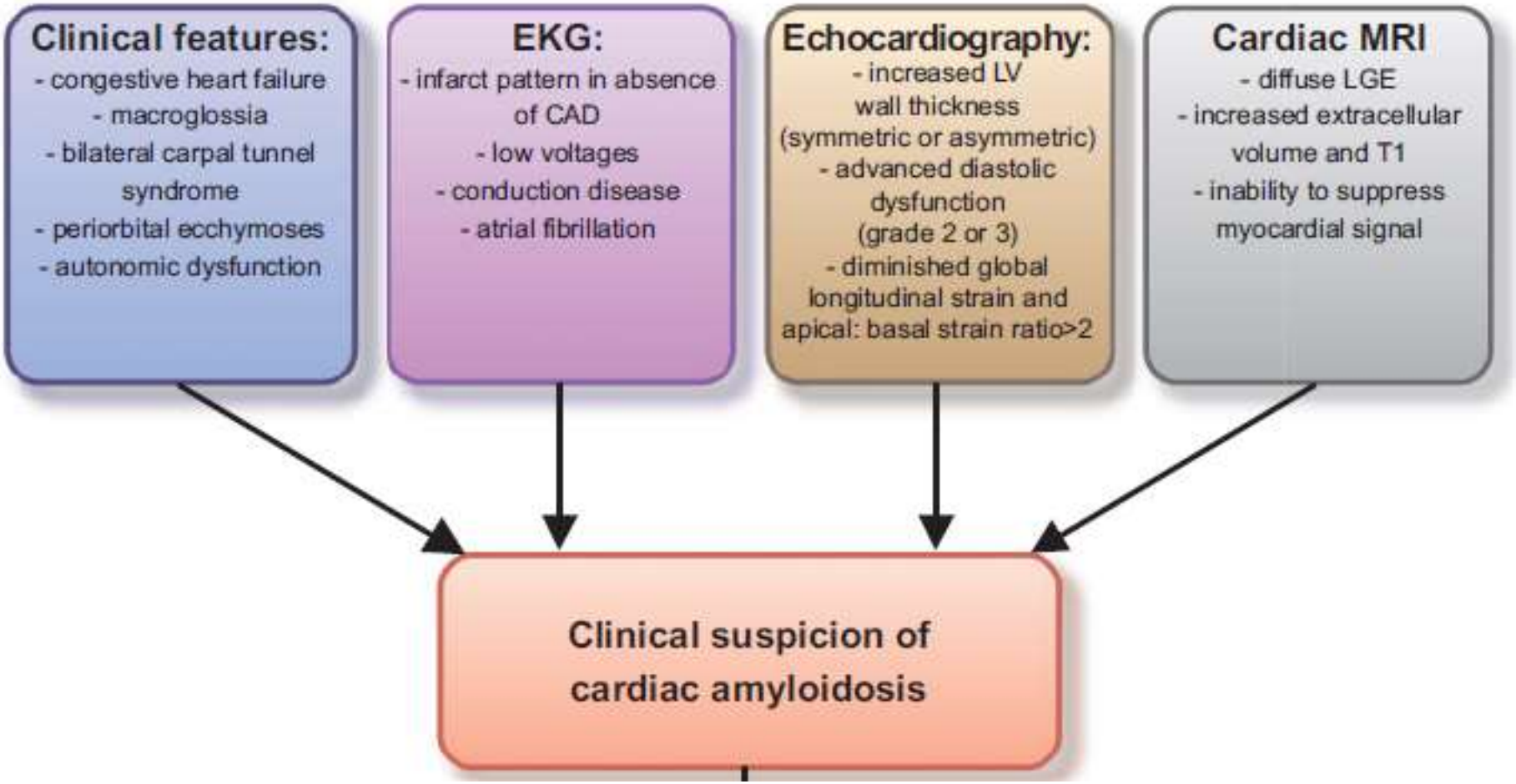

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AL Amyloidosis

FIGURE 4 Two Noncardiac Clinical Clues to the Presence of AL Amyloidosis

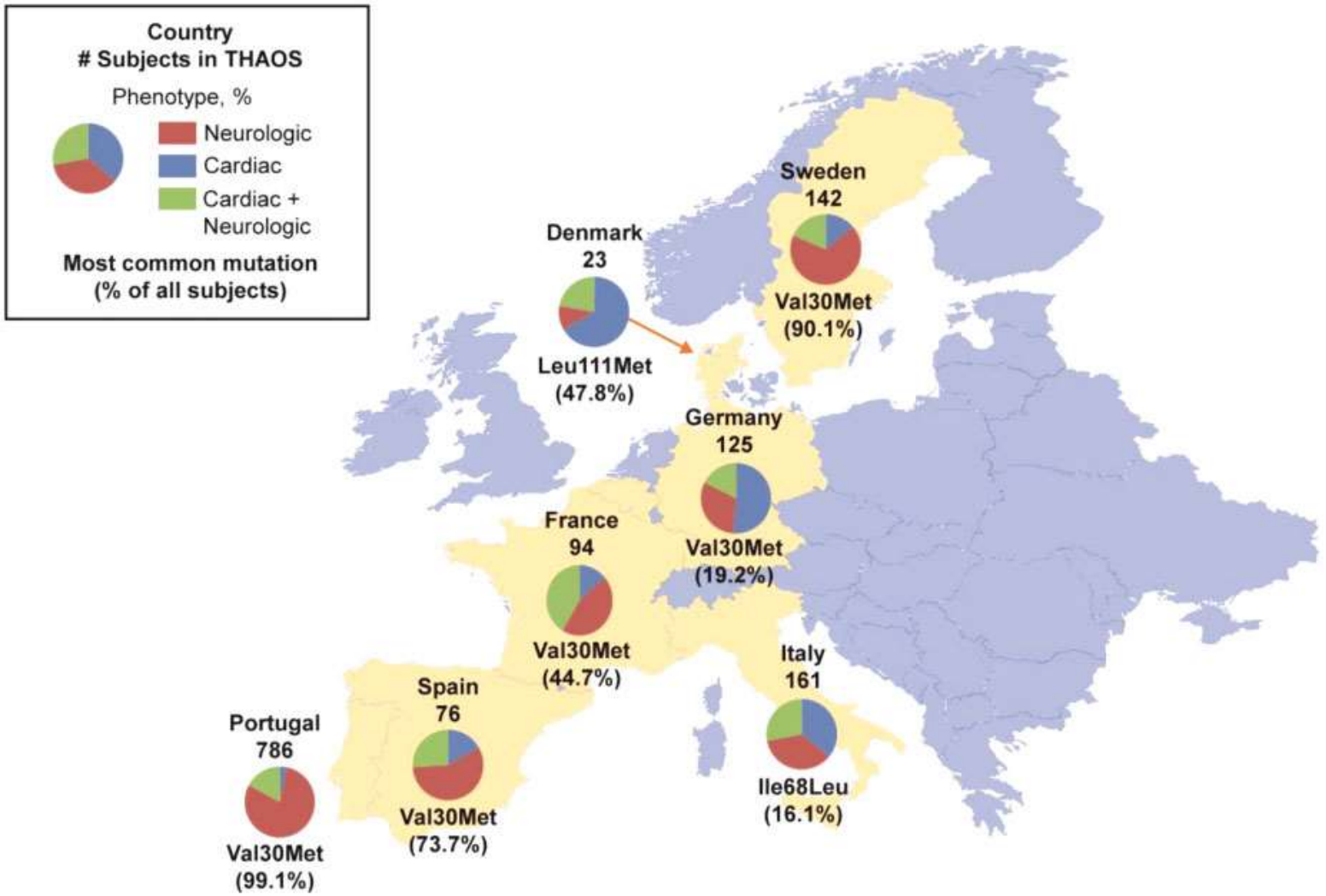
(Left) Small periorbital spontaneous bruise in a man with cardiomyopathy due to AL amyloidosis. He had had recurrent spontaneous bruising of the eyes for >1 year and dyspnea for 6 months before the diagnosis was recognized. The combination of spontaneous periorbital bruising and heart failure is virtually pathognomonic of AL amyloidosis cardiomyopathy. **(Right)** Macroglossia in a 65-year-old woman with AL amyloidosis of the heart and soft tissues. Note the prominent tooth indentations on the tongue. She had seen 2 ear, nose, and throat specialists because of her large tongue. Despite the fact that the differential diagnosis is small, neither was aware of the association with amyloidosis, and both failed to recognize the cause. This is unfortunate, because early diagnosis would have allowed her to tolerate treatment better. Abbreviation as in Figure 1.

AL amyloidosis

Extramedullary and extra cardiac features of systemic AL amyloidosis (3). Specific criteria for diagnosis of proteinuria and hepatomegaly are used mostly for research purposes and are subject to refinement and updates.

Organ system	Clinical Manifestations	Diagnostic Criteria
Kidney	Albuminuria; may progress to nephrotic syndrome	1. Proteinuria > 0.5g/24 hours 2. Biopsy
Liver	Hepatomegaly/Splenomegaly	1. Liver edge > 4 cm below the costal margin 2. Serum alkaline phosphatase > 1.5 times upper limit of normal 3. Biopsy
Gastrointestinal tract	Diarrhea Constipation Early satiety Weight loss	1. Biopsy
Nervous system	Ascending, symmetric sensorimotor polyneuropathy Autonomic dysfunction: orthostatic hypotension and gastroparesis	1. Neurological exam 2. Positional BP monitoring 3. Sural nerve biopsy
Pulmonary	Diffuse alveolar infiltrates due to alveolar-septal involvement in systemic AL amyloidosis Nodules and tracheobronchial involvement in localized AL amyloidosis Pleural effusions	1. Biopsy 2. Suggestive chest CT findings in the appropriate clinical setting
Soft tissue	Macroglossia Subcutaneous nodules Rash Bilateral Carpal Tunnel Syndrome Muscle pseudohypertrophy Vascular amyloid: jaw claudication Amyloid lymphadenopathy	1. Physical exam in the appropriate clinical setting 2. Biopsy (rarely required)
Heme: coagulation	Periorbital ecchymosis Bleeding diathesis	1. Abnormal coagulation parameters 2. Factor X levels (most often involved)

ATTR Amyloidosis



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ATTR Amyloidosis

ATTR Mutation	Clinical Manifestations	Geographic Location/Ethnicity
Val30Met (Met30)	Peripheral neuropathy ≫ cardiac involvement	Portugal Sweden Japan
Thr60Ala (Ala60)	Peripheral neuropathy = cardiac involvement	England Northern Island
Val122Ile (Ile122)	Cardiac involvement ≫ peripheral neuropathy	African African American Afro Caribbean

ATTR hereditary

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NEUROPATHY

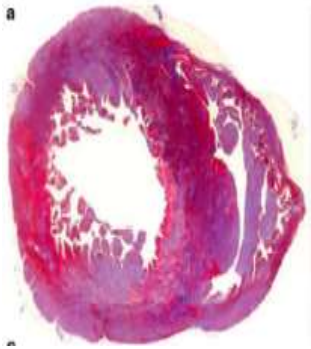
Sensory, motor, progressive distal-proximal

- Sensory disturbances & pain in LL
- Muscular atrophy, weakness & walking problems

DYSAUTONOMY

- Orthostatic hypotension
- Unintentional weight loss
- Erectile dysfunction
- Constipation - diarrhoea

CARDIAC



50–80%

OCULAR

Nat. Rev. Cardiol. 2010.
NEJM 1975

ATTRwt red flags

History:

→ **Paresthesias**

→ **Carpal Tunnel Syndrome**

→ **Lumbar spinal stenosis**

Family history:

→ **Not present**

Physical examination:

→ **Aortic stenosis murmur**

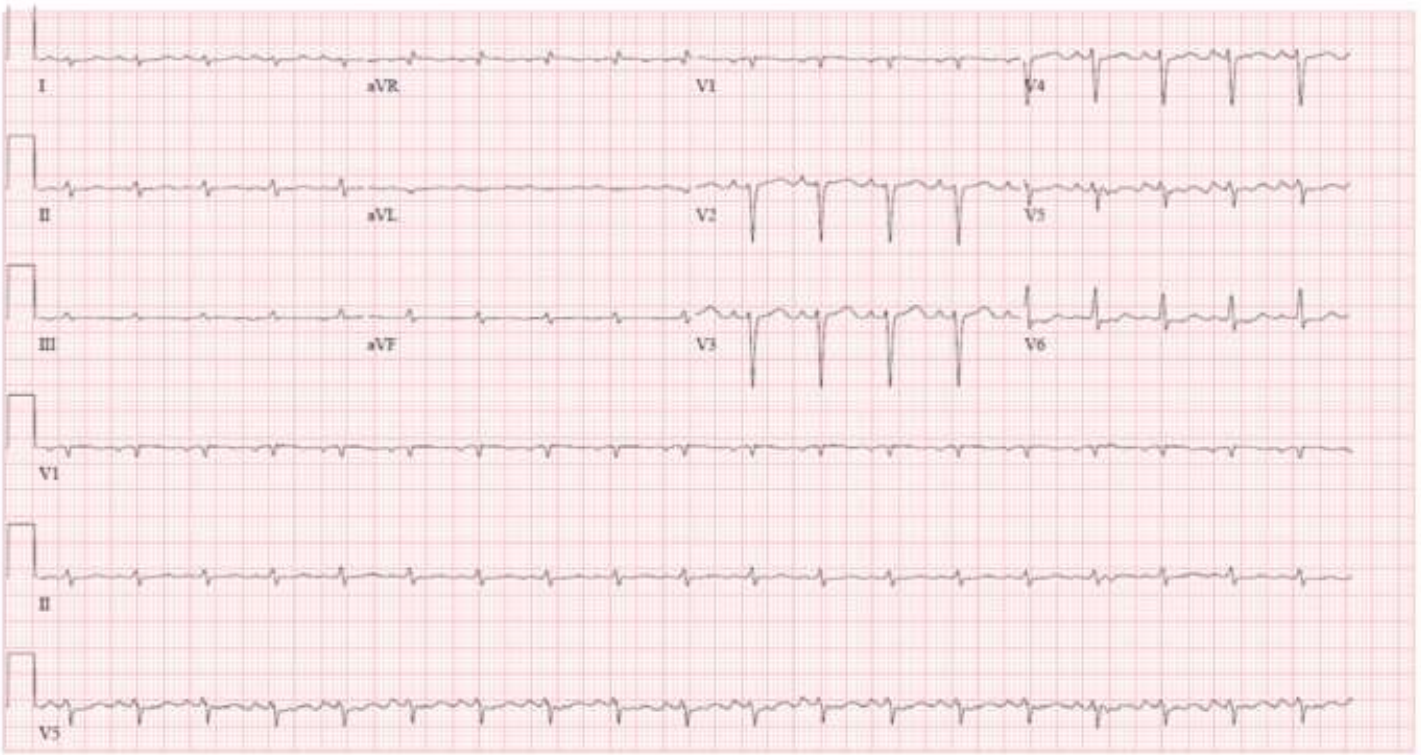
→ **Hearing problems**

→ **“Popeye” sign**

Rev Esp Cardiol 2017.

ECG in AL Amyloidosis

FIGURE 5 Example of Typical Electrocardiograms in AL Amyloidosis



Electrocardiogram showing very low limb lead voltage with indeterminate axis and poor precordial R-wave progression in AL amyloid cardiomyopathy. Coronary angiography was normal, and the echocardiogram showed a thick left ventricle and no pericardial effusion. This voltage/left ventricular mass mismatch strongly suggests cardiac amyloidosis. Abbreviation as in Figure 1.

ECG in ATTR Amyloidosis

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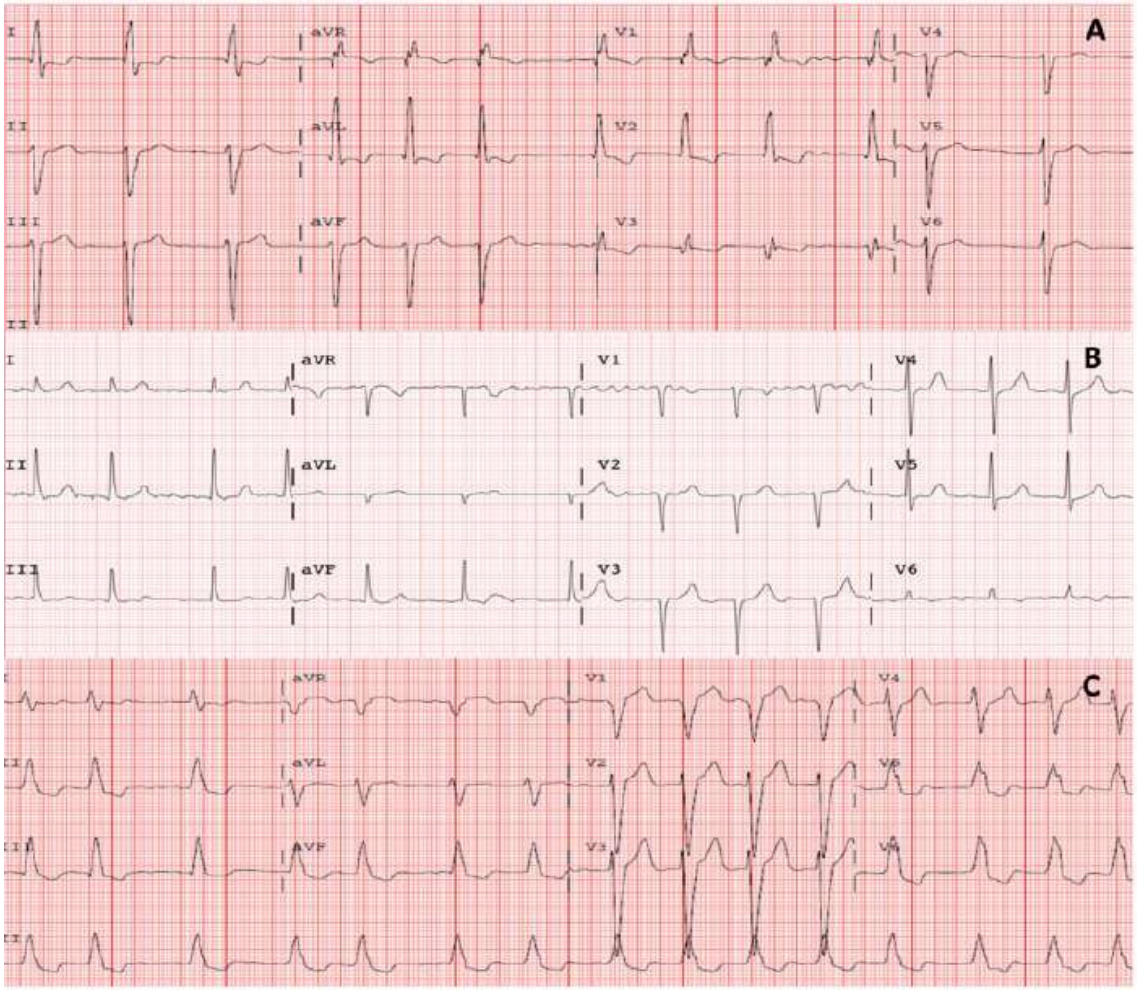
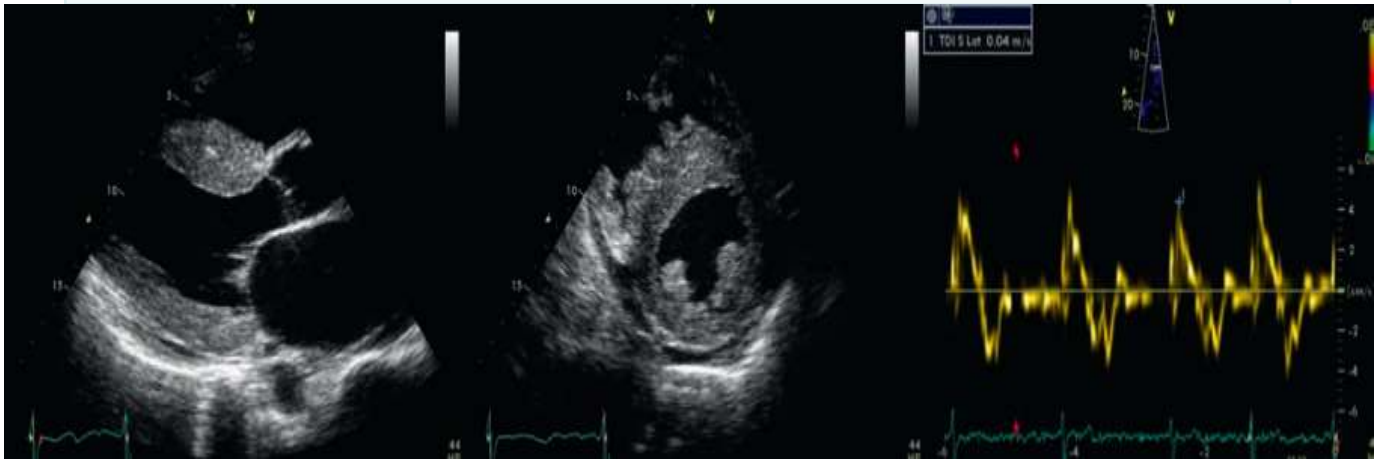


Diversity of ECG patterns in ATTRwt. (*A*) ECG showing right bundle-branch block and fulfilling LVH criteria by Sokolow. (*B*) ECG showing atrial fibrillation and pseudoinfarct pattern in precordial leads. (*C*) ECG showing atrial fibrillation and left bundle-branch block.

Echocardiography

Concentric LVH >12, RVH
Increased thickness of AV valves
Atria enlargement / interatrial septum hypertropy
Granular sparking of myocardium
Pericardial effusion
Preserved or slighly decreased LVEF



Rev Esp Cardiol 2011

ECHO in AL Amyloidosis

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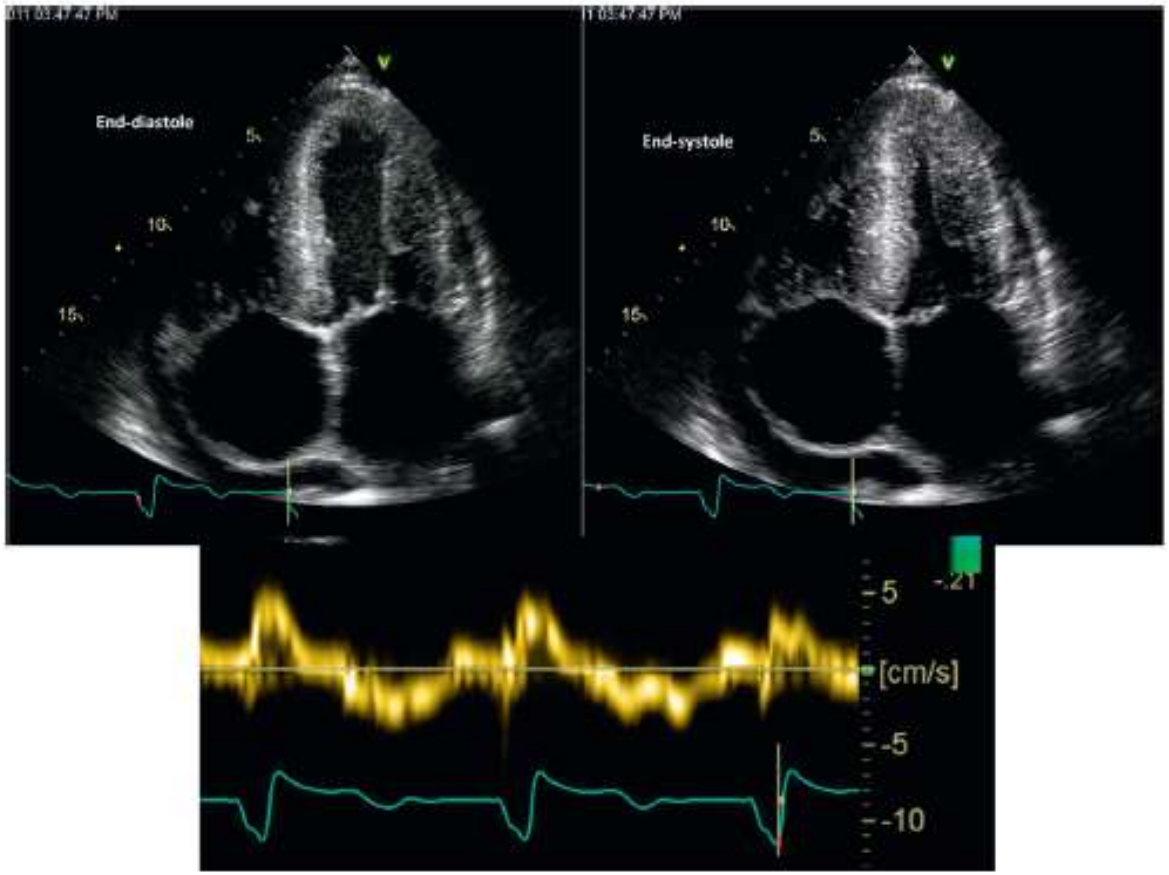

(Top left and right) End-systolic and end-diastolic frames, respectively, demonstrating normal ejection fraction. Note moderately thick left ventricular walls with biatrial enlargement. The atrial size changes minimally throughout the cardiac cycle, representing failure of atrial function, despite sinus rhythm. **(Bottom)** Septal tissue Doppler recording in the same patient, showing reduction in both systolic and diastolic longitudinal velocities, despite normal ejection fraction, typical of amyloid cardiomyopathy.

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ECHO in ATTR Amyloidosis

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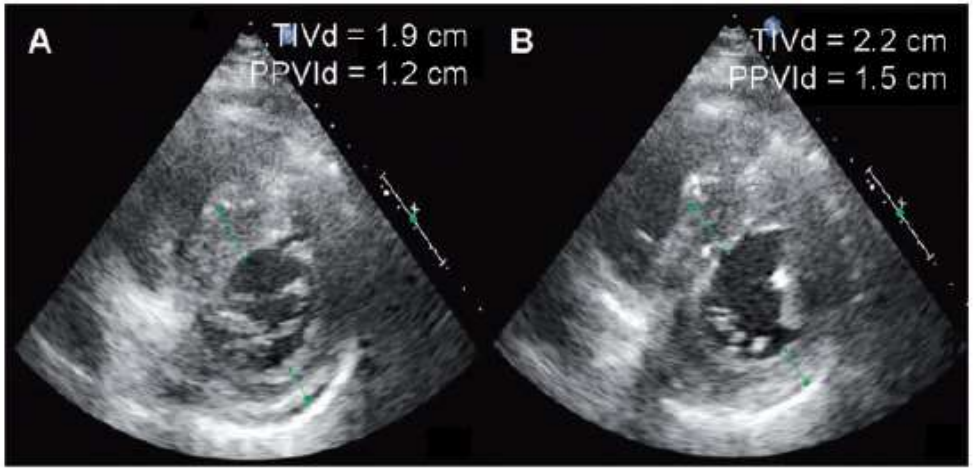

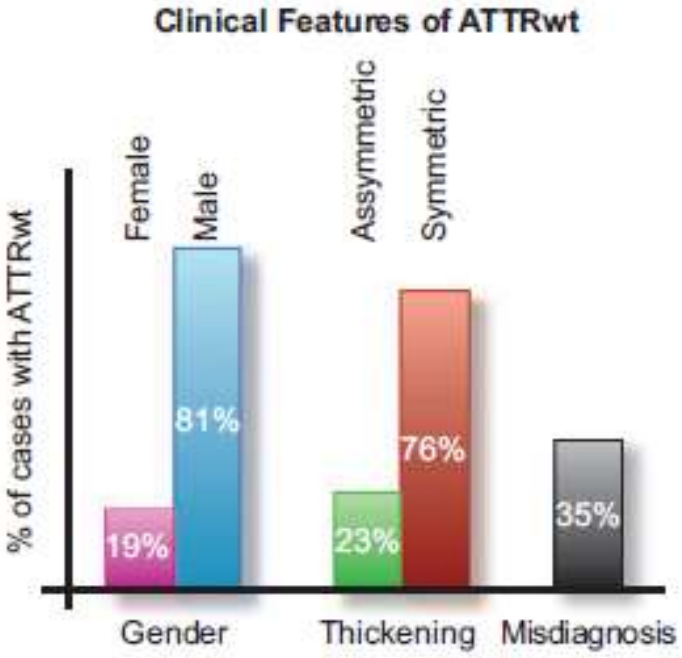

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CMR in

ATTR Amyloidosis

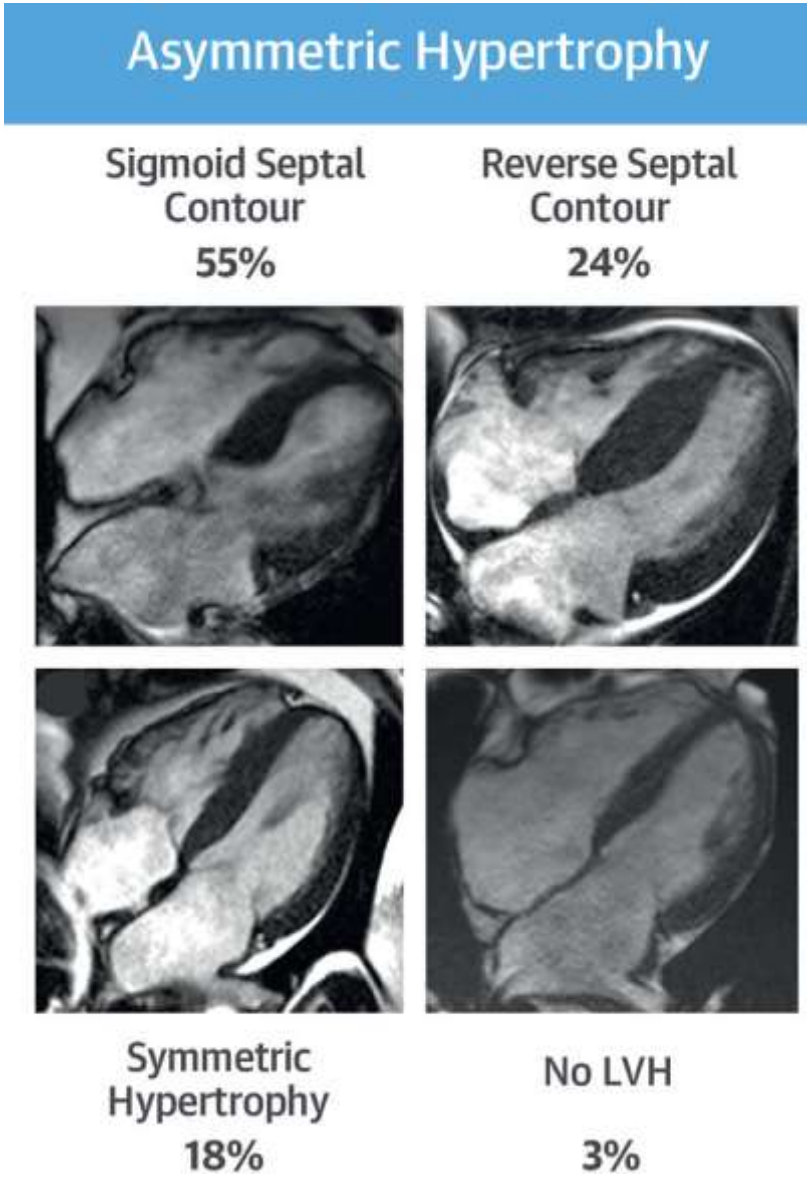

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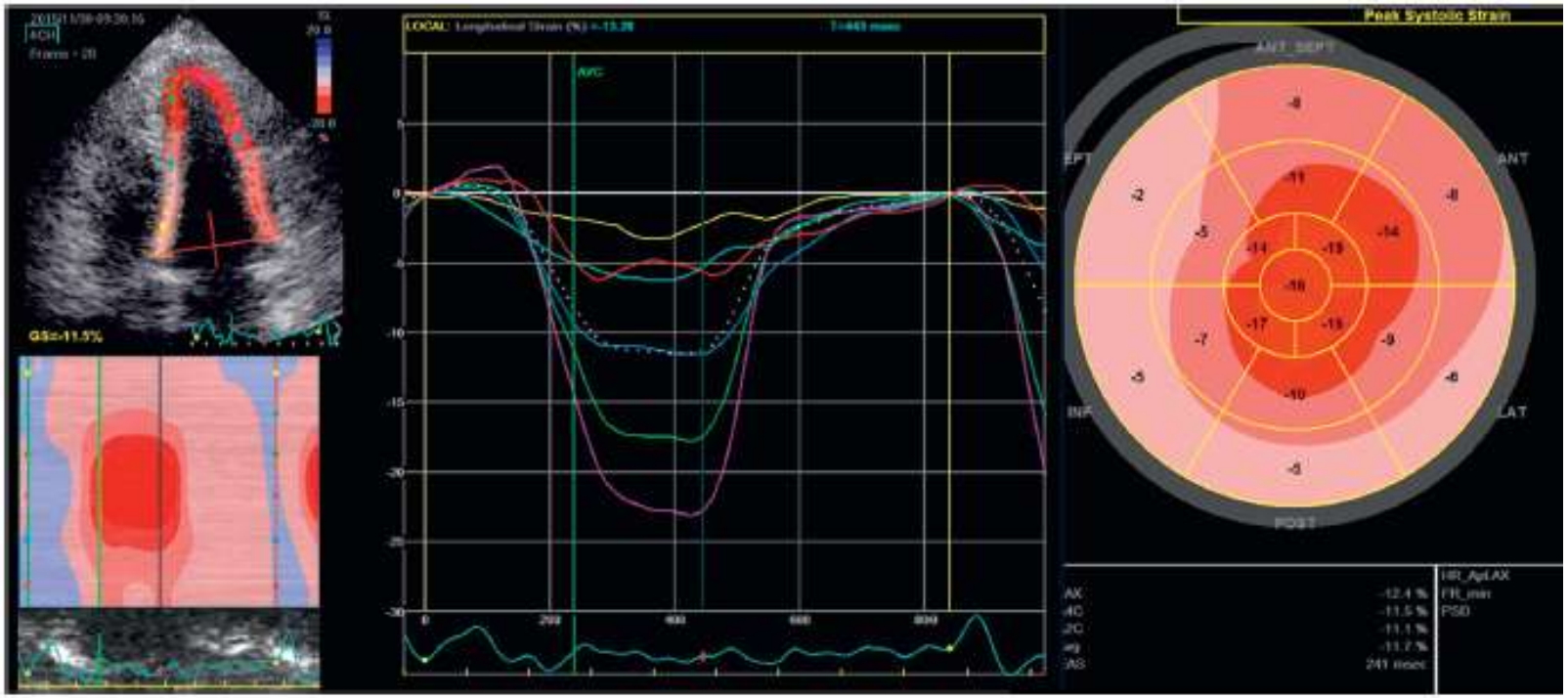
Table 1
Specific Signs and Symptoms for Etiologic Diagnosis in Hypertrophic Cardiomyopathy

Symptoms	• Acroparesthesia, *tinnitus*, deafness (Anderson-Fabry) Muscular weakness (mitochondrial diseases, Danon, *FHL1*)
Signs	• Retinitis pigmentosa (Danon, mitochondrial diseases) • Cornea *verticillata* (Anderson-Fabry) • Orthostatic hypotension (amyloidosis) • Carpal tunnel syndrome (amyloidosis) • Angiokeratoma, hypohidrosis (Anderson-Fabry) • Lentigos (LEOPARD) • Facial phenotype (Anderson-Fabry, Noonan)
Electrocardiogram	• Preexcitation (*PRKAG2*, Danon, mitochondrial diseases) • Short P-R (Anderson-Fabry) Atrioventricular block (desminopathy, *PRKAG2*, Anderson-Fabry, amyloidosis, mitochondrial diseases) • Low voltages, pseudoinfarct pattern (amyloidosis)
Echocardiography	• Biventricular, concentric involvement (infiltrative or metabolic diseases) • Valvular thickening (amyloidosis, Anderson-Fabry)
Family history	• Diabetes, epilepsy, deafness (mitochondrial) • X-linked (Anderson-Fabry, Danon, *FHL1*) • Maternal inheritance (mitochondrial)
Biochemical	• Creatinine kinase elevation (mitochondrial, Danon, *FHL1*) • ALT and AST elevation (Danon) • Lactate (mitochondrial) • Renal insufficiency (amyloidosis, Anderson-Fabry, mitochondrial) • Paraprotein disorders (amyloidosis)
Ergometry	• Severe acidosis of prematurity (mitochondrial)

HCM vs Amyloidosis

Garcia-Pavia P, et al. *Rev Esp Cardiol* 2015;68:4-9.

FIGURE 8 Typical Pattern of Color-Coded Speckle Tracking Strain Imaging in a Patient With AL Amyloidosis and a Normal LV Ejection Fraction



(Left panel) Segmental color coding in the apical 4-chamber view, with apex showing **darker red**, indicating more negative strain compared with **pink**, lesser strain at base. **(Middle panel)** Individual segmental strain for the same view. **(Right panel)** A bull's-eye plot derived from the 3 apical views, showing sparing of apical strain (center of plot) with impaired mid and basal strain. LV = left ventricular; other abbreviation as in Figure 1.

FIGURE 3 LV Regional Variations of LS and LGE (CMR)

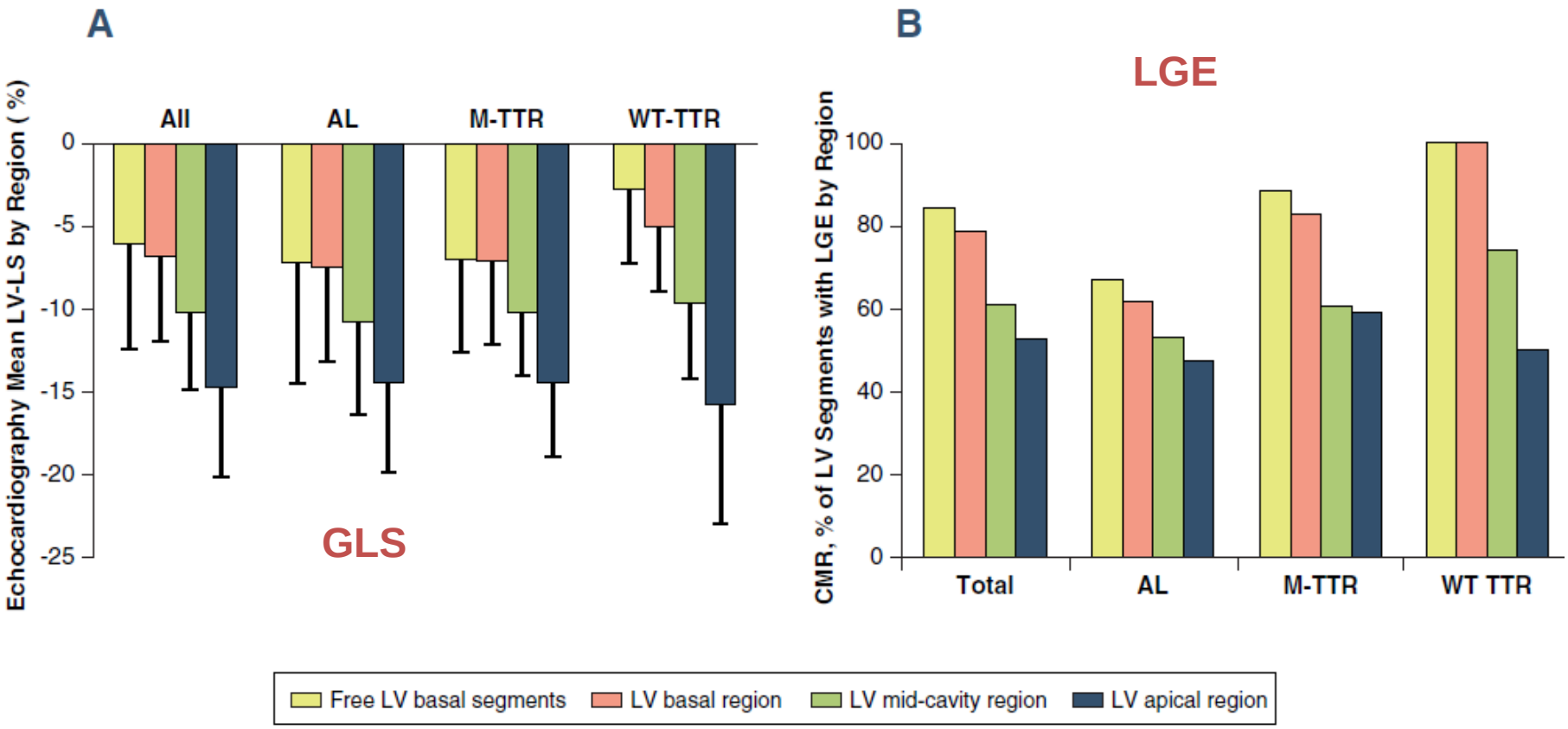
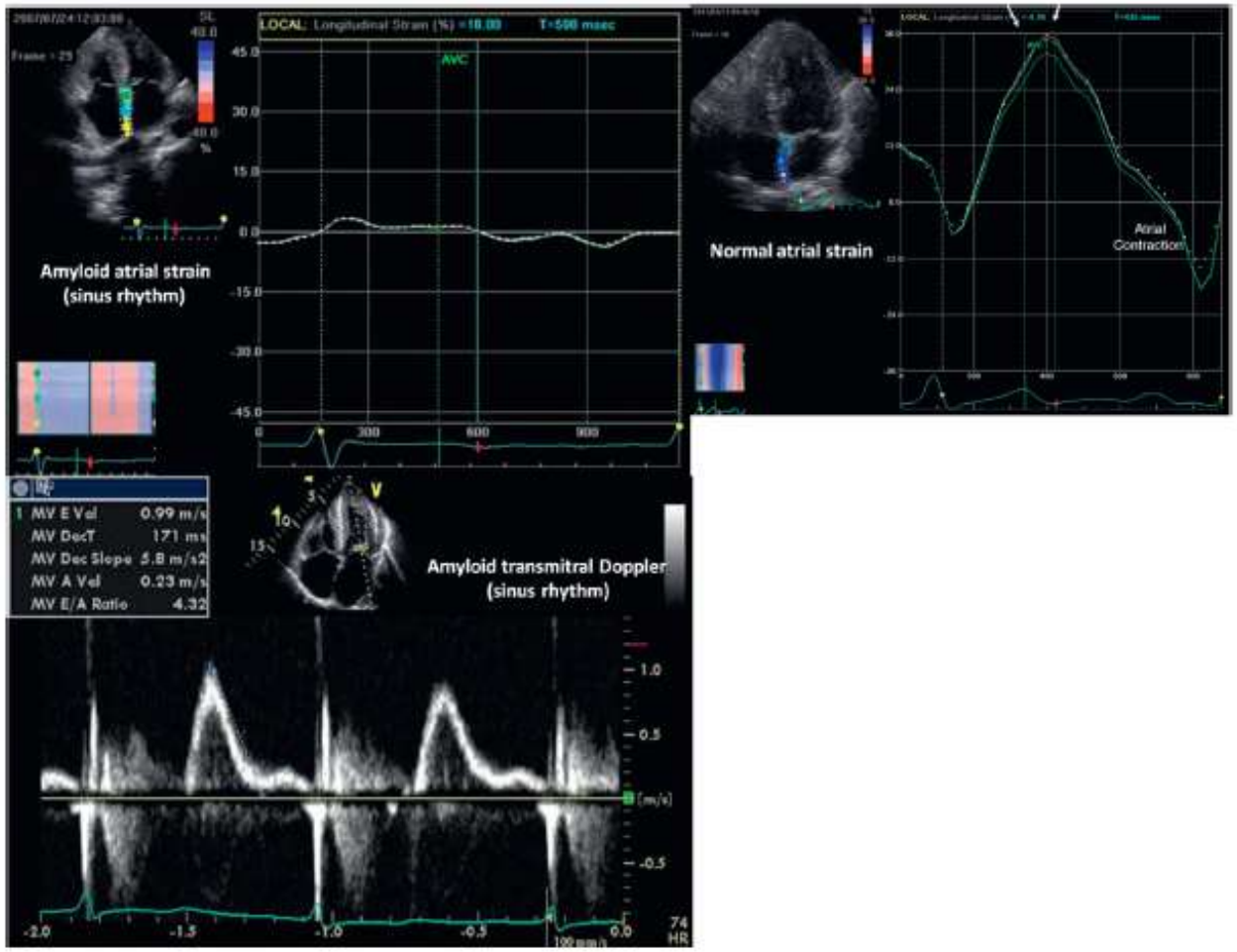


FIGURE 7 Typical Impairment of Atrial Function in Cardiac Amyloidosis Despite Sinus Rhythm, Measured by Strain Imaging



(Top left) Absence of atrial expansion during ventricular systole (loss of reservoir function) and absence of atrial contraction during late ventricular diastole (loss of contractile function). The atrium is acting as a conduit only. **(Top right)** Normal atrial function in a normal patient. **(Bottom left)** A transmitral Doppler pattern corresponding to the atrial strain images. Note the diminutive A-wave, despite normal E-wave deceleration time, indicating atrial contractile dysfunction.

ATTR Amyloidosis - subtypes

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Table 2 Selected electrocardiogram and echocardiogram characteristics by genotype category

Genotype	Total (*N* = 1411)	ATTRwt (*N* = 125)	Four main cardiac mutations (*N* = 58)	Val30Met early-onset (*N* = 761)	Val30Met late-onset (*N* = 277)	Other mutations (*N* = 190)	*P*-value
Phenotype, *n* (%)							
Cardiac	210 (14.9)	99 (79.2)	28 (48.3)	25 (3.3)	25 (9.0)	33 (17.4)	<0.0001
Cardiac + neurologic	298 (21.1)	23 (18.4)	17 (29.3)	126 (16.6)	74 (26.7)	58 (30.5)	<0.0001
Neurologic	903 (64.0)	3 (2.4)	13 (22.4)	610 (80.2)	178 (64.3)	99 (52.1)	<0.0001
ECG abnormal, *n* (%)	514 (53.8)	104 (96.3)	39 (81.3)	188 (36.2)	102 (62.6)	81 (69.2)	<0.0001
Pathologic Q-waves observed, *n* (%)	113 (26.8)	48 (50.0)	17 (47.2)	2 (1.4)	18 (25.4)	28 (35.9)	<0.0001
Low voltage, *n* (%)	98 (12.8)	23 (24.0)	15 (40.5)	32 (7.5)	4 (3.7)	24 (24.5)	<0.0001
Interval PR, median (Q1–Q3)	168.0 (146.0–194.0)	185.0 (130.0–208.0)	186.0 (126.0–226.0)	168.0 (148.0–191.5)	172.0 (149.0–200.0)	160.0 (140.0–183.0)	0.2434
Interval QRS, median (Q1–Q3)	98.0 (89.0–112.0)	122.0 (104.0–153.0)	112.0 (90.0–124.0)	94.0 (88.0–102.0)	104.0 (94.0–118.0)	98.0 (86.0–117.0)	<0.0001
LBBB, *n* (%)	53 (17.6)	24 (31.2)	10 (37.0)	5 (5.2)	8 (17.0)	6 (11.1)	<0.0001
RBBB, *n* (%)	45 (14.7)	17 (21.8)	5 (17.9)	3 (3.1)	7 (14.6)	13 (23.6)	0.0019
Diastolic interventricular septum thickness, median (Q1–Q3)	15 (11–19)	18 (16–21)	17 (13–20)	10 (9–12)	15.5 (12–18)	16 (12–20)	<0.0001
LV diastolic diameter, median (Q1–Q3)	45 (42–50)	46 (42–50)	46 (43–49)	45 (42–49)	47 (44–51)	45 (40–49)	0.0521
LV ejection fraction (%), median (Q1–Q3)	65.1 (54.3–71.1)	55.5 (46.0–66.3)	59.2 (51.1–69.0)	69.5 (63.3–74.0)	70.2 (61.8–74.9)	62.5 (50.2–68.7)	<0.0001
E-wave deceleration time (ms), median (Q1–Q3)	183.0 (141.0–221.0)	180.0 (144.0–205.0)	160.0 (140.0–215.0)	178.0 (129.0–204.0)	228.0 (180.0–261.0)	182.0 (141.0–218.0)	0.0008
Stroke volume (mL), median (Q1–Q3)	68.0 (54.0–83.0)	54.0 (39.0–68.0)	50.0 (45.0–56.0)	70.0 (56.5–82.0)	82.0 (69.0–94.0)	52.5 (42.0–64.5)	<0.0001
RV free wall thickness, median (Q1–Q3)	7.0 (5.0–8.0)	9.0 (7.0–11.0)	7.0 (7.0–9.0)	6.0 (5.0–7.0)	7.0 (5.0–9.0)	6.0 (5.0–8.0)	0.0008
Aortic thickening, *n* (%)	50 (24.3)	16 (26.7)	5 (20.8)	10 (21.3)	6 (27.3)	13 (24.5)	0.9537
Mitral thickening, *n* (%)	58 (27.9)	23 (37.7)	6 (24.0)	5 (10.6)	2 (9.1)	22 (41.5)	0.0009
Tricuspid thickening, *n* (%)	19 (9.5)	12 (20.0)	2 (8.7)	0 (0.0)	1 (4.5)	4 (8.2)	0.0100
Sparkling, *n* (%)	192 (50.7)	63 (74.1)	11 (39.3)	42 (42.9)	33 (44.6)	43 (45.7)	<0.0001

Percentages shown are the proportion of subjects with each measure out of the total number of subjects for which data on that measure was available. Analysis of variance was performed to calculate *P*-values by comparing means between groups for continuous variables. The Pearson χ^2 test was performed to calculate *P*-values for variables with cell counts >5. The Kruskal–Wallis test was performed to calculate *P*-values by comparing medians between groups for continuous variables. The Fisher's exact test was performed to calculate *P*-values for non-ordinal variables with cell counts ≤5.
ATTRwt, wild-type ATTR amyloidosis; LBBB, left bundle branch block; LV, left ventricular; Q1, lower quartile; Q3, upper quartile; RBBB, right bundle branch block.

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Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg?

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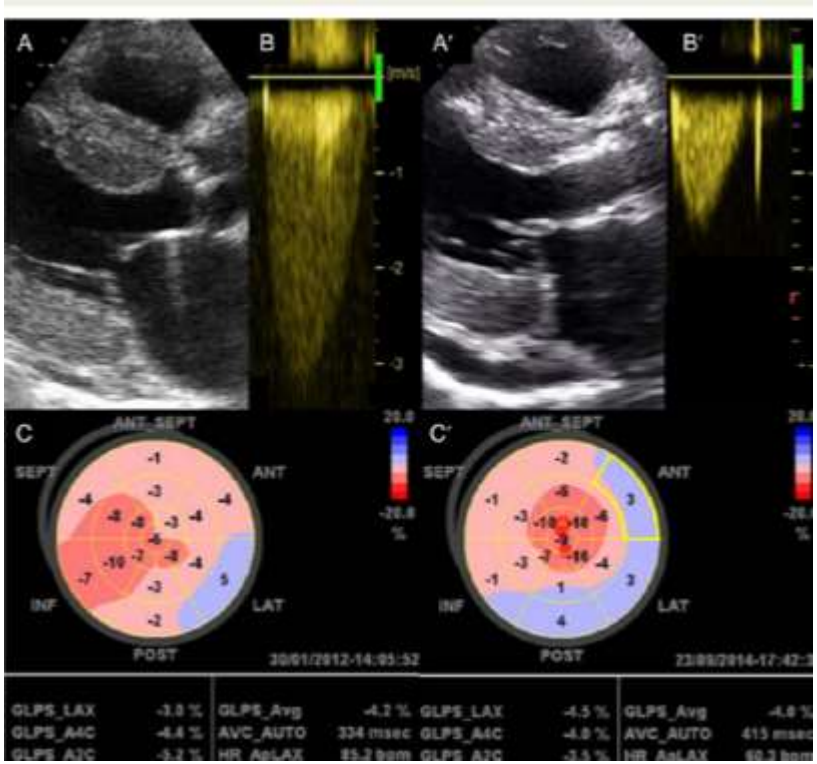


33 months post-TAVI

specific features:

1. age ≥ 70 years, male gender,
2. carpal tunnel syndrome,
3. severe dyspnoea,
4. low-flow AS, and
5. excessive ‘hypertrophic remodelling’.

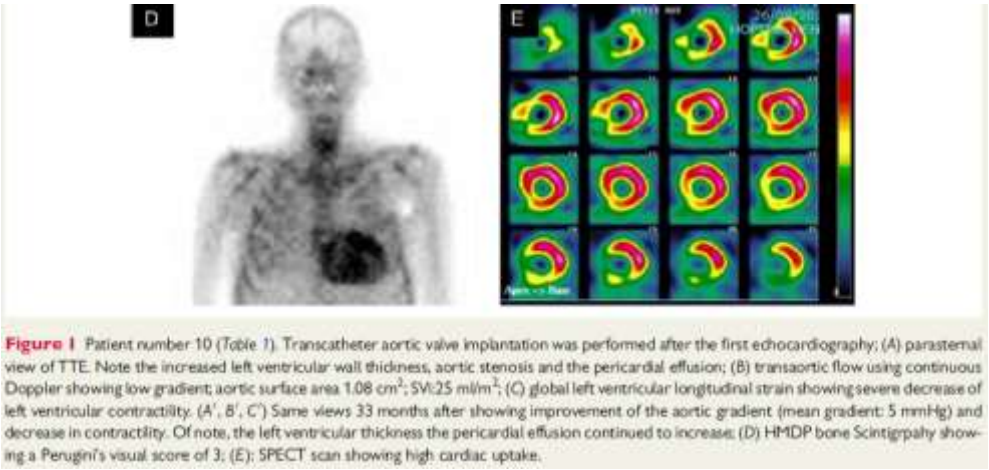
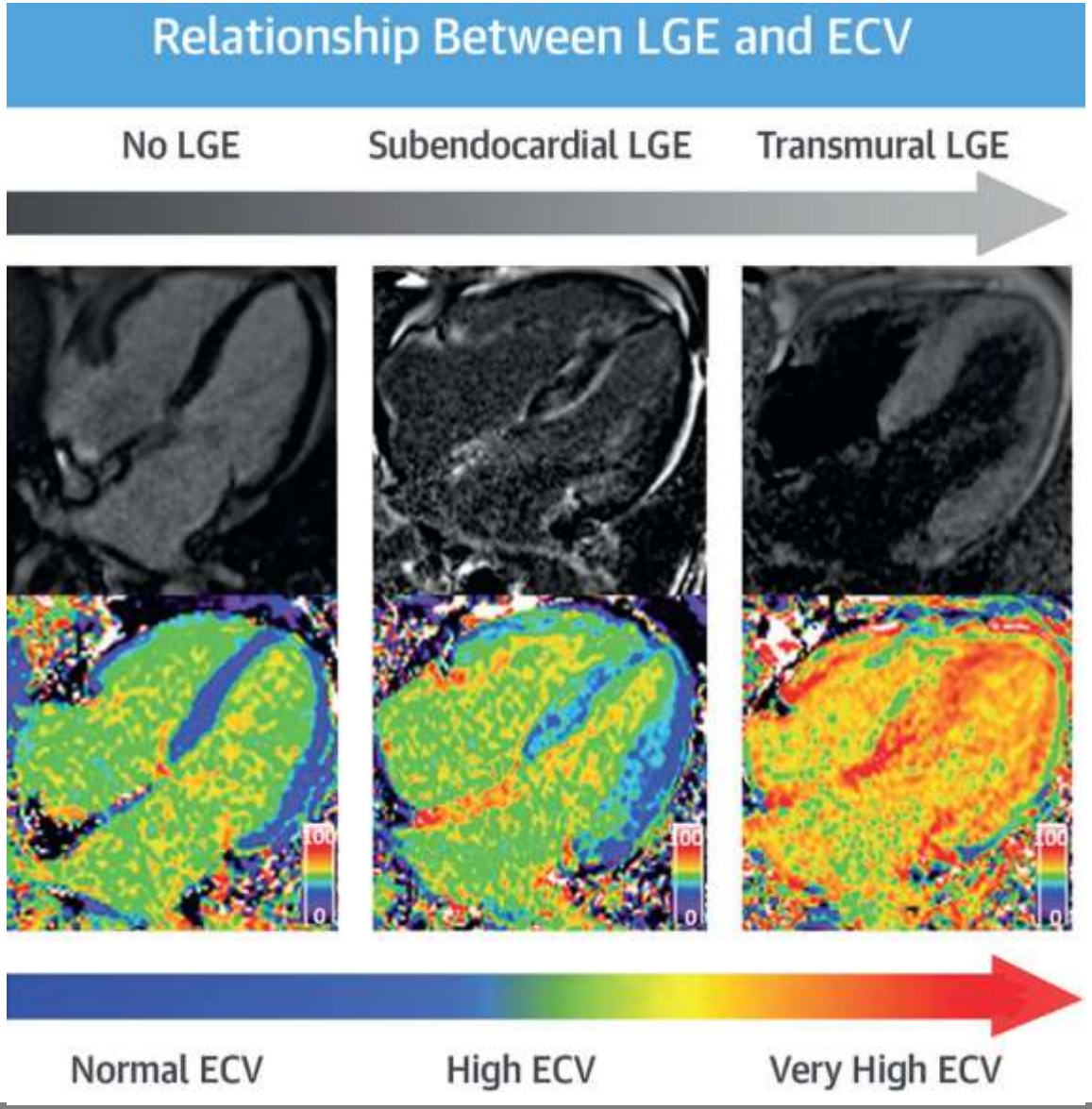


Figure 1 Patient number 10 (*Table 1*). Transcatheter aortic valve implantation was performed after the first echocardiography; (*A*) parasternal view of TTE. Note the increased left ventricular wall thickness, aortic stenosis and the pericardial effusion; (*B*) transaortic flow using continuous Doppler showing low gradient; aortic surface area 1.08 cm^2; SVi:25 ml/m^2; (*C*) global left ventricular longitudinal strain showing severe decrease of left ventricular contractility. (*A'*, *B'*, *C'*) Same views 33 months after showing improvement of the aortic gradient (mean gradient: 5 mmHg) and decrease in contractility. Of note, the left ventricular thickness the pericardial effusion continued to increase; (*D*) HMDP bone Scintigrpahy showing a Perugini's visual score of 3; (*E*): SPECT scan showing high cardiac uptake.

CMR in ATTR Amyloidosis



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CMR in ATTR vs AL Amyloidosis

Table 2. Comparison of AL and ATTR Amyloidosis (CMR)

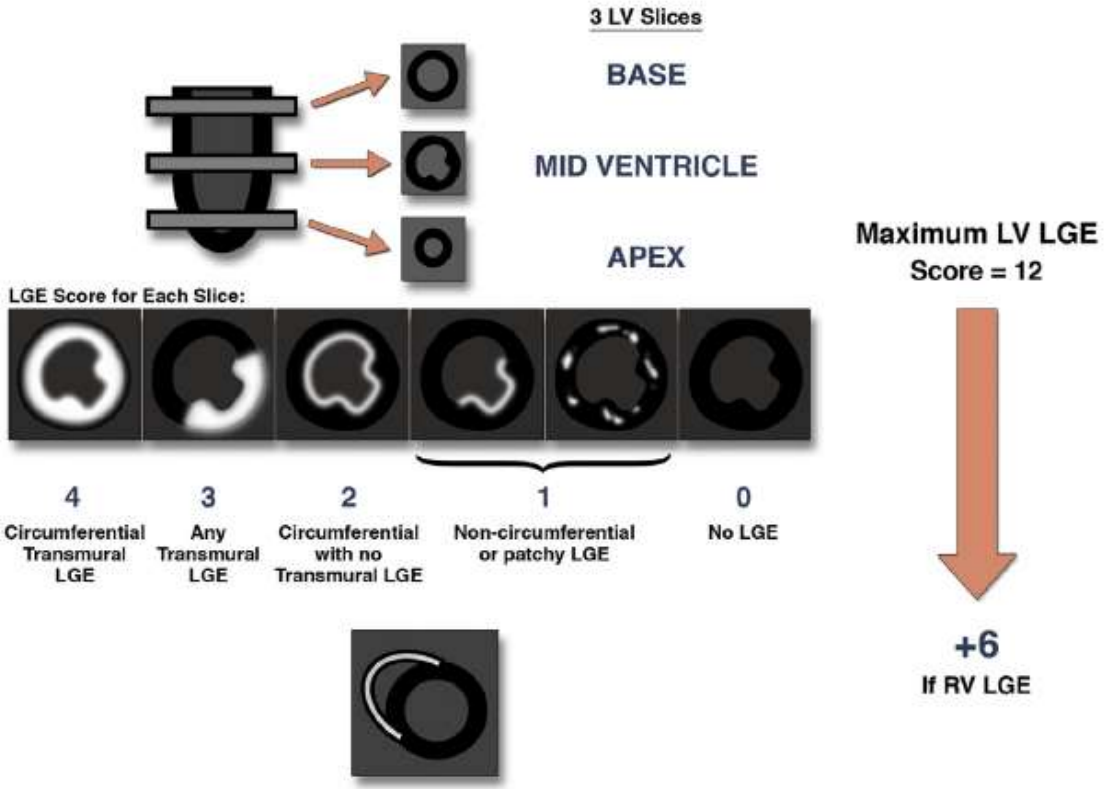
	AL Amyloidosis (n = 46)	ATTR (n = 51)	p Value
LVEDV, ml	114 ± 31	131 ± 39	0.023
Men (normalized range 60–95 ml)	64 ± 16	69 ± 20	0.258
Women (normalized range 53–87 ml/m^2)	60 ± 16	62 ± 11	0.789
LVESV, ml	43 ± 20	59 ± 28	0.001
Men* (normalized range 14–36 ml/m^2)	24 ± 10	32 ± 15	0.011
Women† (normalized range 13–31 ml/m^2)	22 ± 13	25 ± 12	0.632
LV SV, ml	71 ± 19	72 ± 20	0.997
Men* (normalized range 40–64 ml/m^2)	41 ± 11	38 ± 10	0.256
Women† (normalized range 36–60 ml/m^2)	37 ± 9	37 ± 4	0.944
LVEF, %	64 ± 12	56 ± 12	0.002
Men* (range 55%–81%)	63 ± 11	55 ± 12	0.008
Women† (range 57%–81%)	66 ± 13	62 ± 14	0.538
LV mass, g	167 (137–191)	228 (202–267)	<0.001
Men* (normalized range 57–90 g/m^2)	93 (82–106)	122 (106–140)	<0.001
Women† (normalized range 48–78 g/m^2)	83 (67–102)	104 (95–116)	0.050
Interventricular septum thickness, mm	14 ± 3	18 ± 2	<0.001
RV free wall thickness, mm	6 ± 2	8 ± 2	<0.001
Left atrium area, cm^2	23 ± 7	26 ± 7	0.04
Right atrium area, cm^2	20 ± 7	25 ± 8	0.001
Pericardial effusion	17 (37)	17 (33)	0.71
Pleural effusion	26 (57)	21 (41)	0.13

Table 3. Comparison of AL and ATTR Amyloidosis (LGE)

	Cardiac AL Amyloidosis (n = 46)	Cardiac ATTR (n = 51)	p Value
LV LGE	45 (98)	51 (100)	0.47
RV LGE	33 (72)	51 (100)	<0.001
Global subendocardial LGE	18 (39)	6 (12)	0.002
Global transmural LGE	2 (4)	11 (22)	0.01
Any transmural LGE	17 (37)	46 (90)	<0.001
Base-apex gradient	19 (41)	36 (71)	0.004
Atrial LGE	34 (74)	47 (92)	0.02
Suboptimal myocardial nulling	8 (17)	17 (33)	0.07

JACC 2014

CMR in
ATTR vs AL Amyloidosis

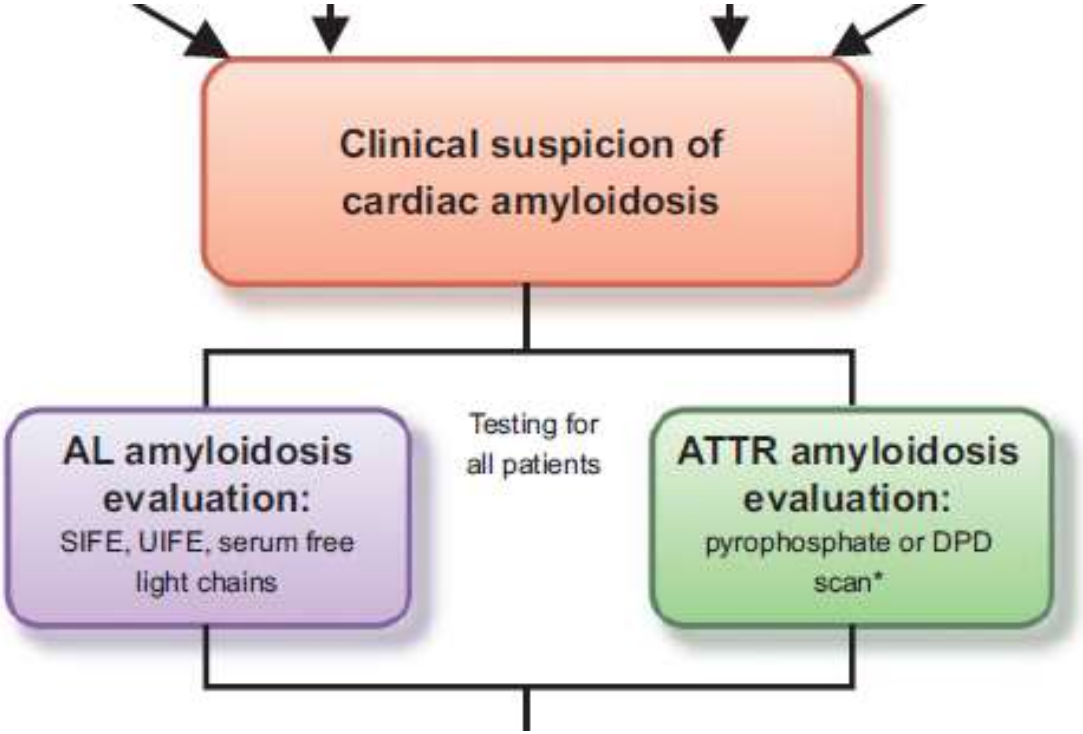


QALE score >13

differentiated ATTR from AL type with 82% sensitivity and 76% specificity.

JACC 2014

Diagnostic Algorithm



SPECT in Amyloidosis

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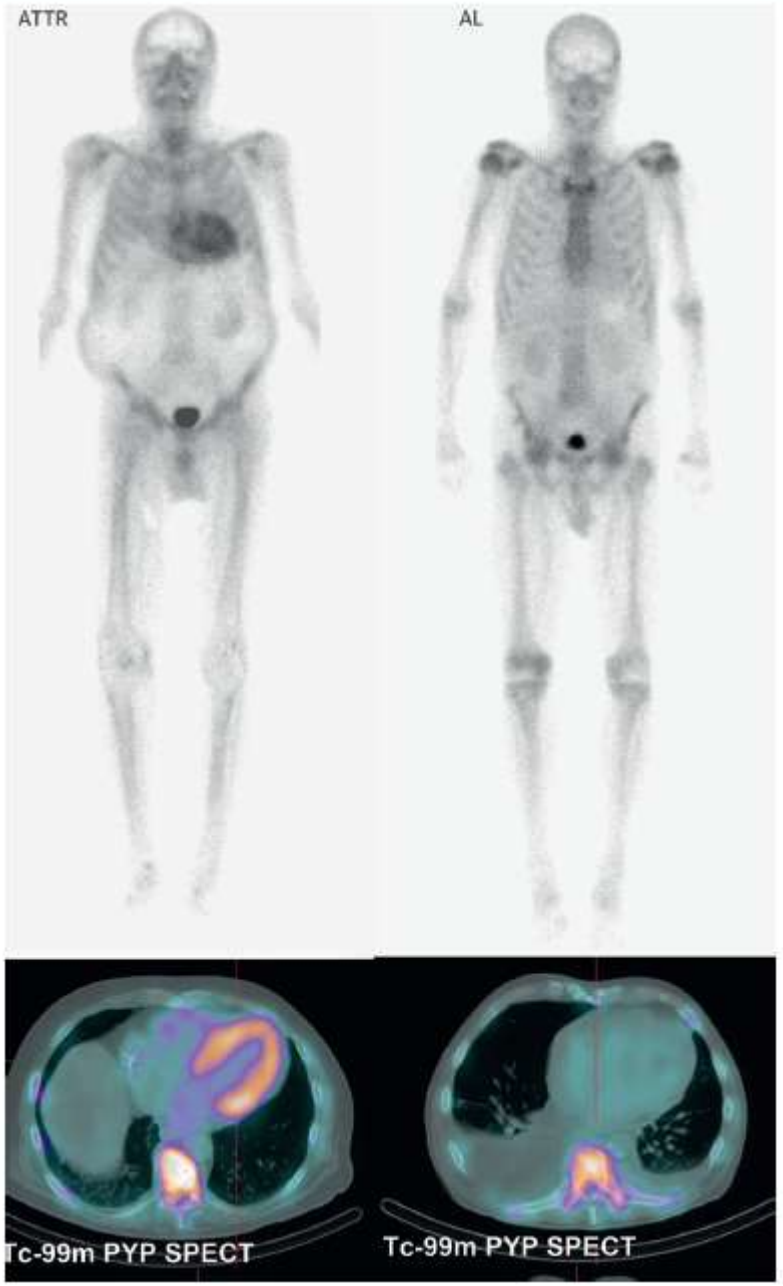
SPECT

99m technetium pyrophosphate (Tc99mPYP)

or

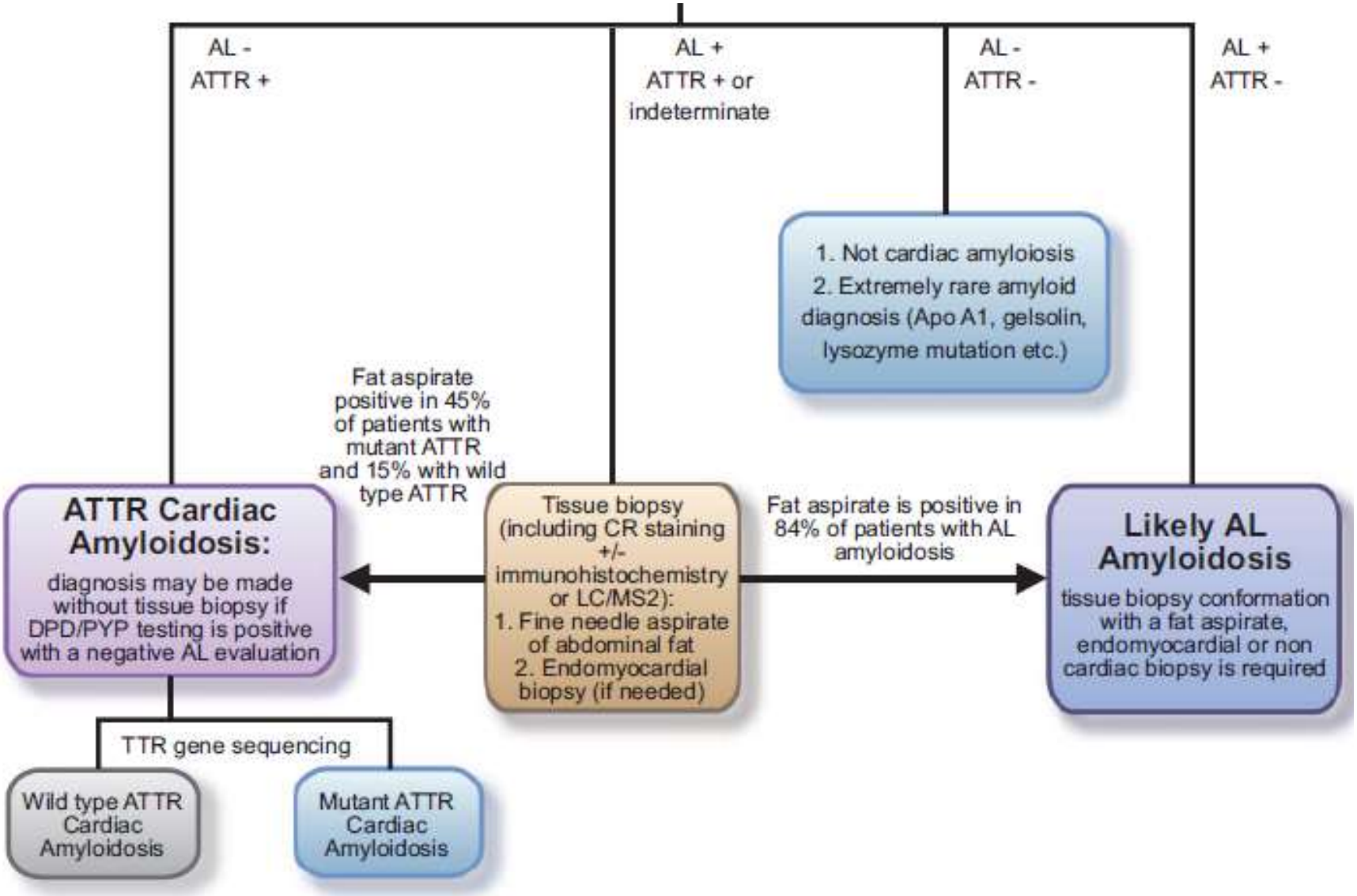
2,3-dicarboxypropane-1, 1-diphosphonate [DPD]

FIGURE 10 Multimodality Imaging for Determining Presence and Type of Cardiac Amyloidosis



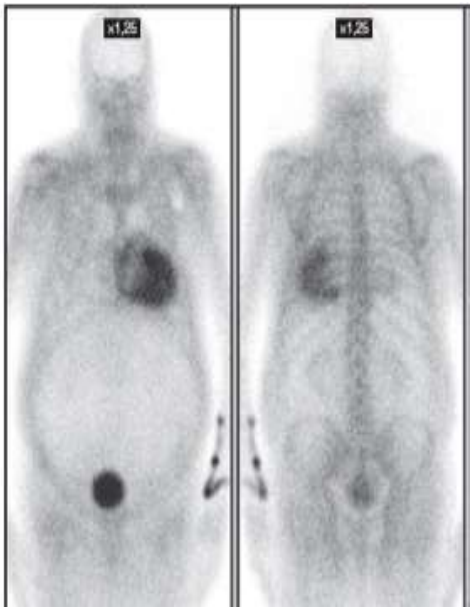
JACC 2016

Diagnostic Algorithm



Non-invasive diagnosis of Cardiac ATTR

Ά Καρδιολογική Κλινική ΑΧΕΠΑ



+

Negative

Serum/Urine

Immunofixation &

Serum FLC assay

Cardiac ATTR

Circulation 2016

Biopsy

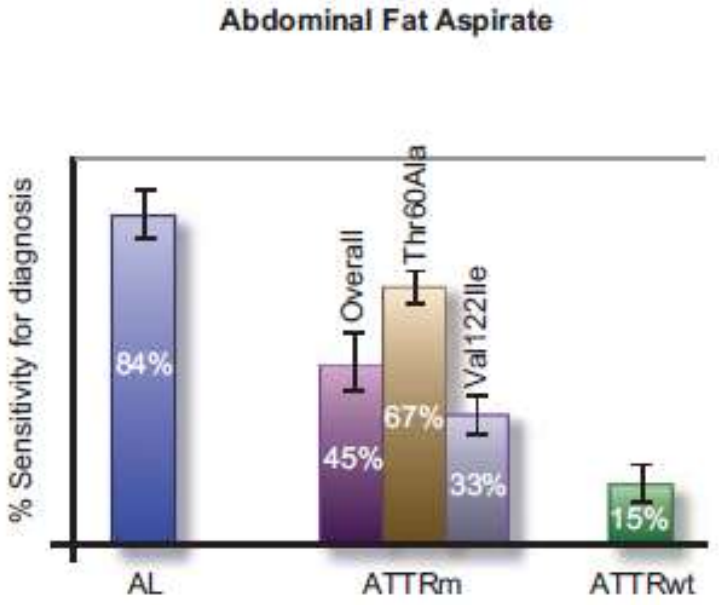
Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis

Table 2 Relationship between diagnostic sensitivity of fat pad fine needle aspiration and total body amyloid burden

N=600

Amyloid type	Total body amyloid load by SAP scintigraphy	Amyloid detected on FNFPA	Diagnostic sensitivity
Systemic AL amyloidosis	Large	28/28	100%
	Moderate	33/34	97%
	Small	120/154	78%
ATTRm	Small[a,b]	51/113	45%
ATTRwt	Small[a]	42/271	15%

Amyloid deposits in the gastrointestinal tract[a] and nerves[b] are not visualized by SAP scintigraphy. Large/moderate load vs. Small load in AL, $P < 0.001$ (Fisher's exact test), Large/moderate load vs. Small load (all patients), $P < 0.001$ (Chi Square test).



Congo red staining of an endomyocardial biopsy is the diagnostic **gold-standard**

PROGNOSIS

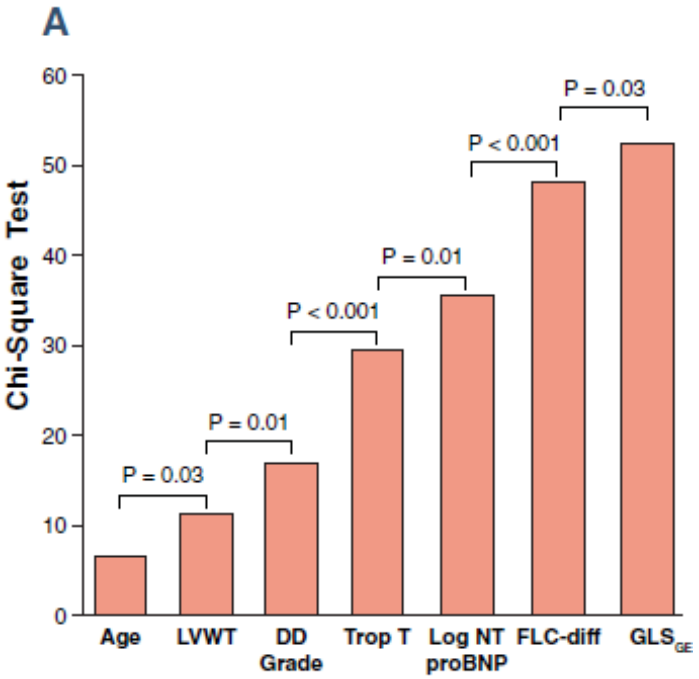
Ά Καρδιολογική Κλινική ΑΧΕΠΑ

AL Amyloidosis

Prognosis of Light Chain Amyloidosis With Preserved LVEF

Added Value of 2D Speckle-Tracking Echocardiography to the Current Prognostic Staging System

	Patients		
	Total (N = 150)	Group 1 (n = 63)	Group 2 (n = 87)
GE software, %			
GLS	−15.23 ± 3.87	−12.85 ± 3.65	−16.95 ± 3.03
		cardiac	*Non-cardiac*



abnormal biomarkers

NT-proBNP > 1,800 pg/l

cTnT > 0.025 mg/l

GLS < -15%

JACC 2017

PROGNOSIS

ATTR Amyloidosis

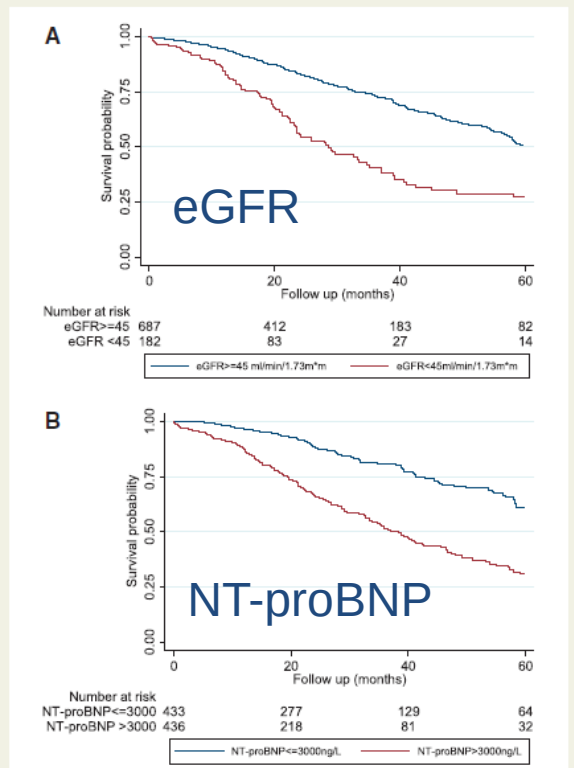
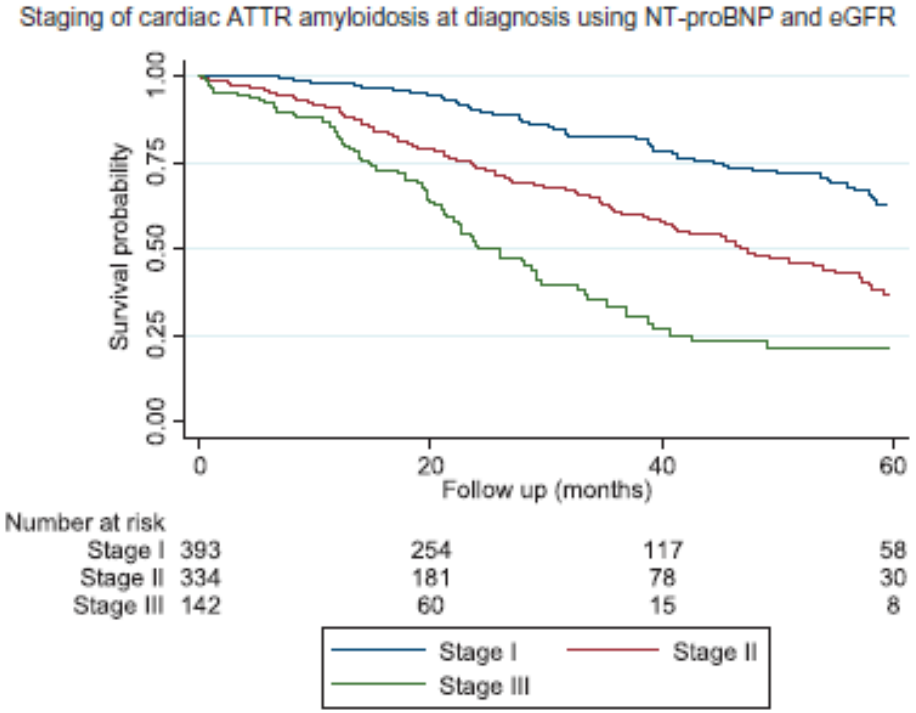


Figure 1 Kaplan–Meier curves showing survival probabilities in patients with cardiac transthyretin amyloidosis. (*A*) Stratified by estimated glomerular filtration rate (eGFR) ≥45 ml/min/1.73 m^2 vs. <45 ml/min/1.73 m^2 (log-rank test, $P < 0.0001$). (*B*) Stratified by N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≤3000 ng/L vs. >3000 ng/L (log-rank test, $P < 0.0001$).

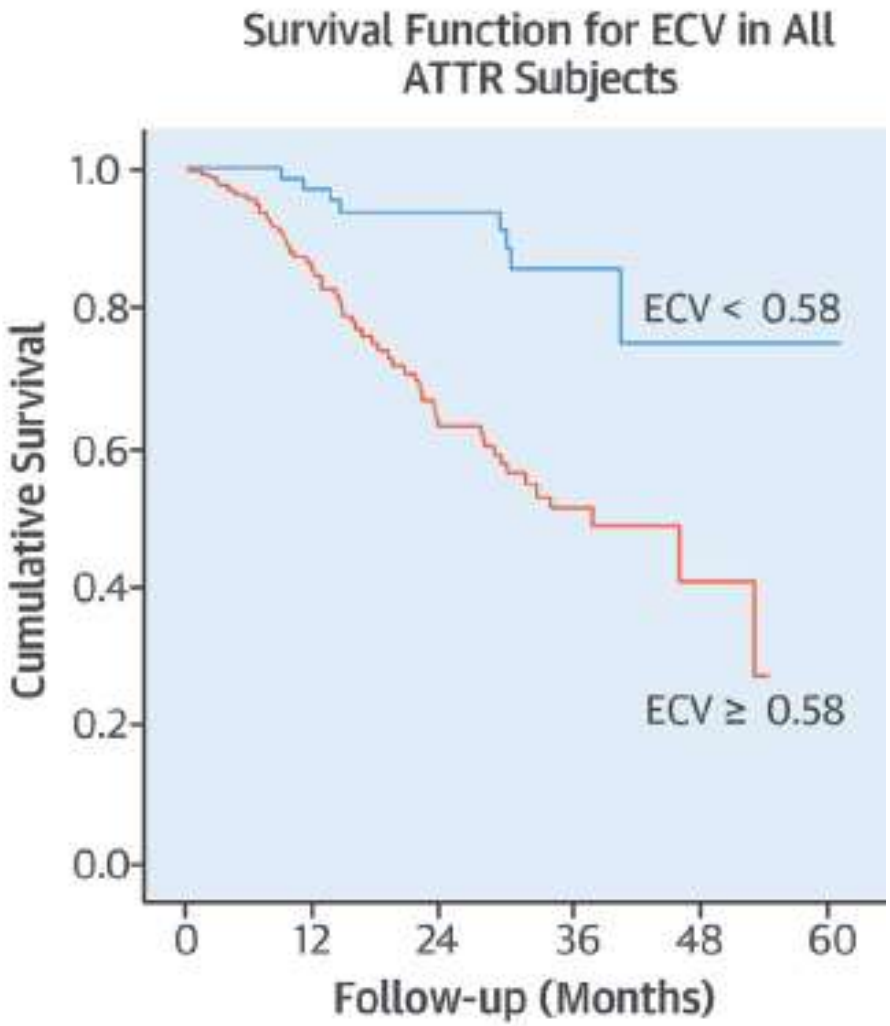


NT-proBNP <_3000 ng/L

eGFR >_45ml/min

EHJ 2018

Prognosis



JACC 2017

SURVIVAL

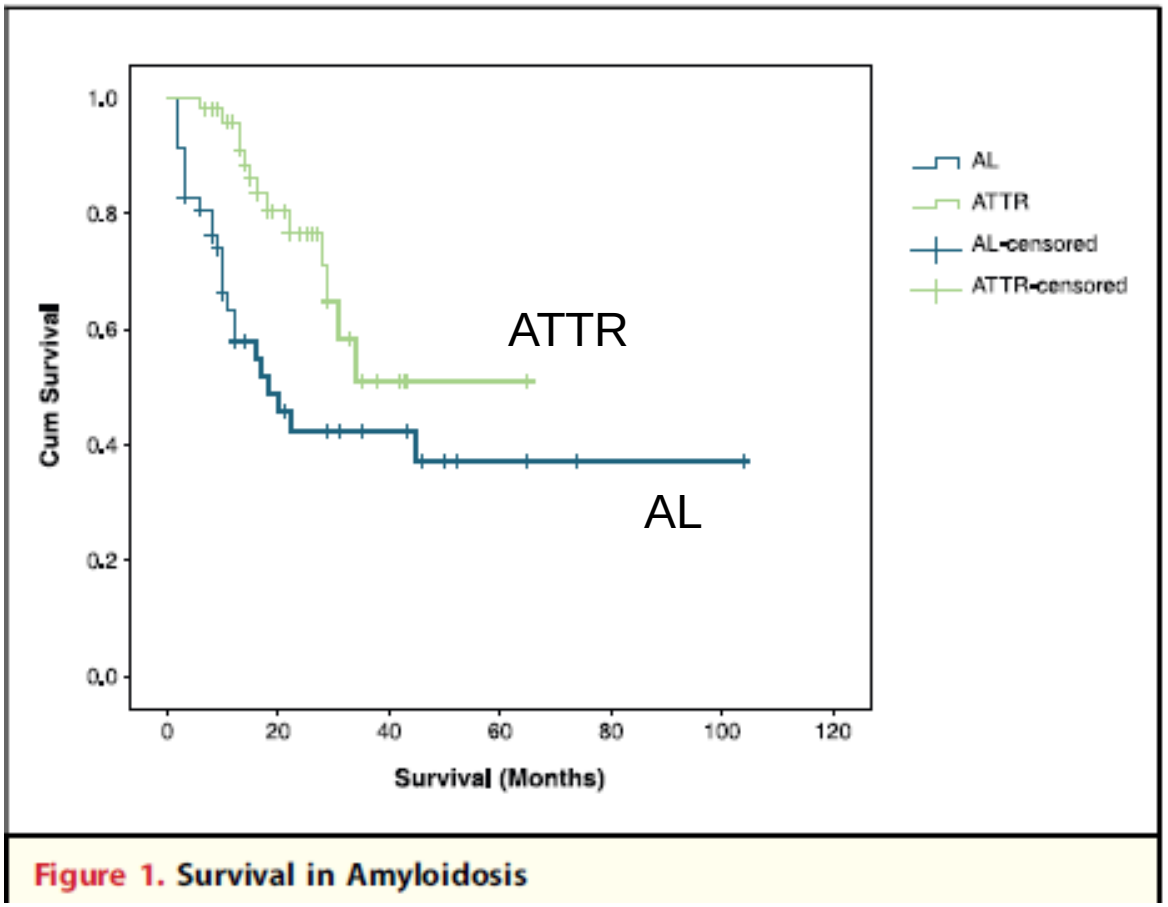
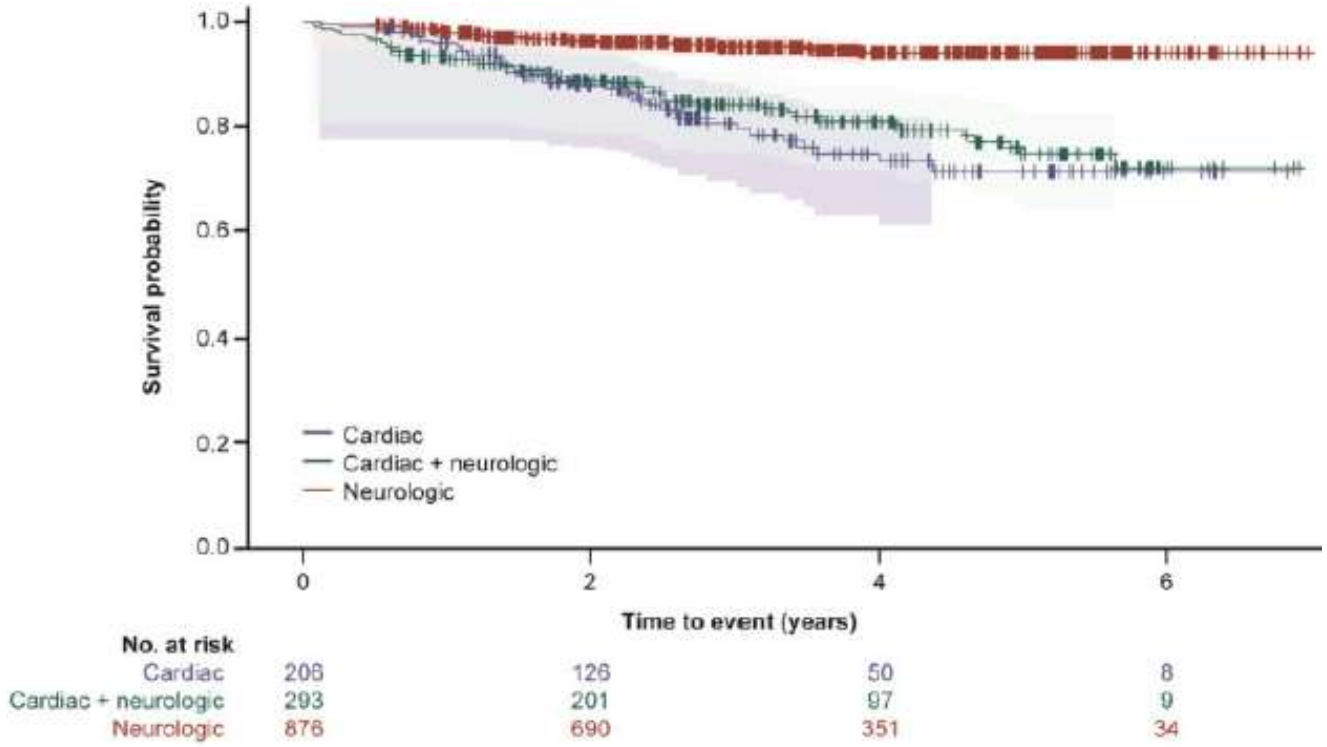


Figure 1. Survival in Amyloidosis

JACC 2014

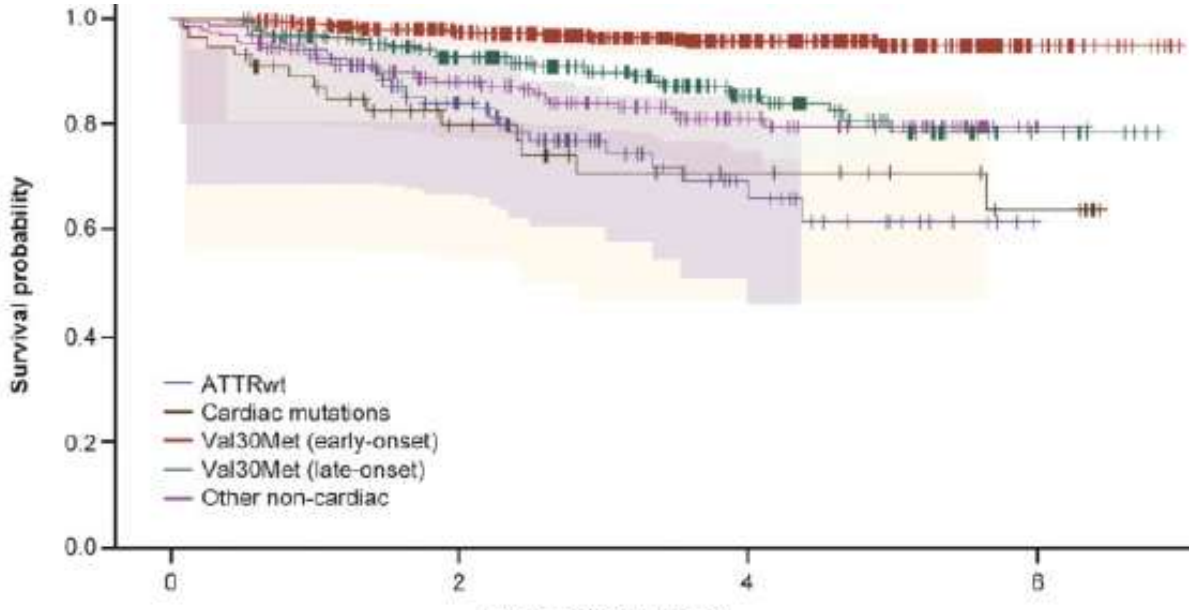
Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS)



EHJ 2019

Ά Καρδιολογική Κλινική ΑΧΕΠΑ

Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS)



No. at risk				
ATTRwt	122	67	21	0
Cardiac mutations	56	30	16	8
Val30Met (early-onset)	741	603	320	32
Val30Met (late-onset)	270	189	76	9
Other non-cardiac	186	128	63	2

EHJ 2019

Treatment AL

Συμπτωματική θεραπεία καρδιακής αμυλοείδωσης

- **Διουρητικά**
- Αποφυγή ανταγ-Ca και διγοξίνης
- Προσοχή σε β-αναστολείς, ΑΜΕΑ (ορθοστατική υπόταση, συχνοεξαρτώμενη παροχή)
- Βηματοδότης σε διαταραχές ΚΚ αγωγής
- Απινιδιστής;

CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 86 • NUMBER 1 JANUARY 2019

Treatment AL

Table VI. Risk-adapted treatment strategy for patients with AL amyloidosis.

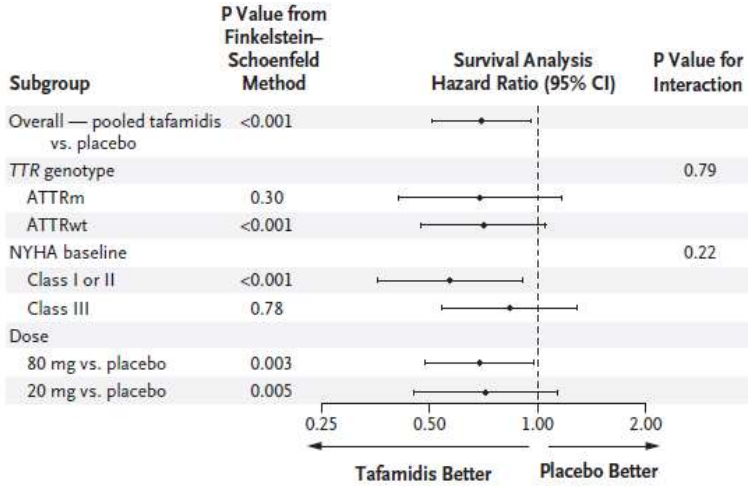
Risk category	Primary options	Secondary options
Stage I, PS 0-1, eGFR >60 ml/min/1·73 m^2, age < 65 years	1 HDM with ASCT (induction with bortezomib-based therapy before HDM may be considered)	1 VCD 2 BMDex 3 MDex 4 Lenalidomide-based
Stage II/III with NTproBNP <5000 ng/l and cTnT < 0·06 ng/l* PS 0-1, eGFR >60 ml/min/1·73 m^2, no neuropathy, age < 65 years	1 HDM with ASCT (if experienced centre) 2 VCD (full or adjusted dose)	1 BMDex 2 MDex
Stage I/II, NTproBNP <5000 ng/l, PS 0-1, no neuropathy, age > 65 years	1 VCD (full or adjusted dose) 2 BMDex 3 MDex	1 Lenalidomide-based
Stage II, NTproBNP >5000 ng/l but <8500 ng/l, PS 1-2, age > 65 years	1 VCD (adjusted dose) 2 BMDex (adjusted dose) 3 MDex (full Dex dose)	1 VD (adjusted dose) 2 MDex (adjusted Dex dose)
Stage I/II, AL-related neuropathy	1 MDex 2 Lenalidomide-based	1 VCD adjusted dose
High risk: stage III (but NTproBNP <8500 ng/l)	1 VCD adjusted dose 2 BMDex (adjusted dose)	1 MDex
Stage III, NTproBNP >8500 ng/l, low SBP	1 Low dose VCD (Consider in-hospital administration of therapy)	1 Low dose VD

PS, performance status; eGFR, estimated glomerular filtration rate; NTproBNP, N-terminal of the prohormone brain natriuretic peptide; cTnT, cardiac troponin; SBP, systolic blood pressure; ASCT, autologous stem cell transplantation; HDM, high dose melphalan; VD, bortezomib with dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; BMDex, bortezomib, melphalan, dexamethasone; MDex: melphalan, dexamethasone; Dex, dexamethasone.

BJH 2015

Treatment ATTR

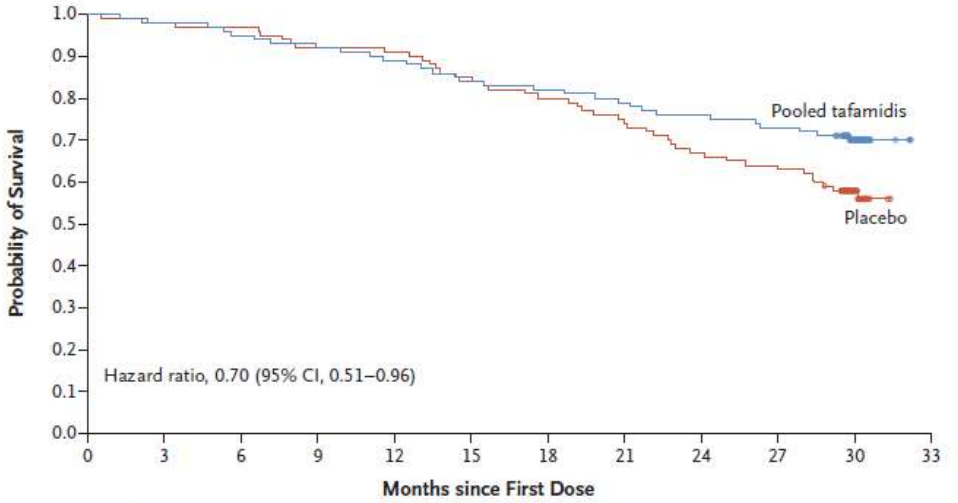
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy



A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 *no. (%)*	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 *per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

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)

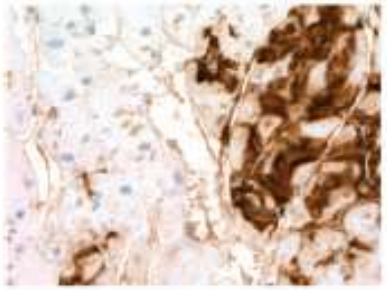
NEJM 2018

Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths

Ά Καρδιολογική Κλινική ΑΧΕΠΑ

ATTRwt`s clinical spectrum

Mode of presentation:
- **HF** (67.6%)
- **AV block** (7.4%)
- **Stroke**
- **HCM or RCM** (13.9%)
- **Degenerative AS**
- **Incidental** (11.1%)



Age, gender and comorbidities

- Males (81.5%)
- **Females (18.5%)**
- Late 70s symptoms onset
- HTN (54.6%)

ECG

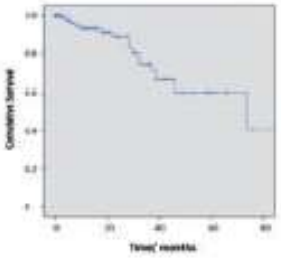
- **AF (55.6%)**
- **Pseudoinfarct** pattern (63.2%)
- Low voltage (22%)
- LVH (10.5%)
- L/RBBB (17-15%)

Echocardio

- Symmetric LVH (75.7%)
- **Asymmetric LVH (23.4%)**
- **LVEF<50% (36.8%)**
- Restrictive diastolic pattern (35%)
- Pericardial effusion (42.1%)

Survival

Overall survival at 12, 24 and 36 months: **93, 89** and **74%**, respectively



EHJ 2017

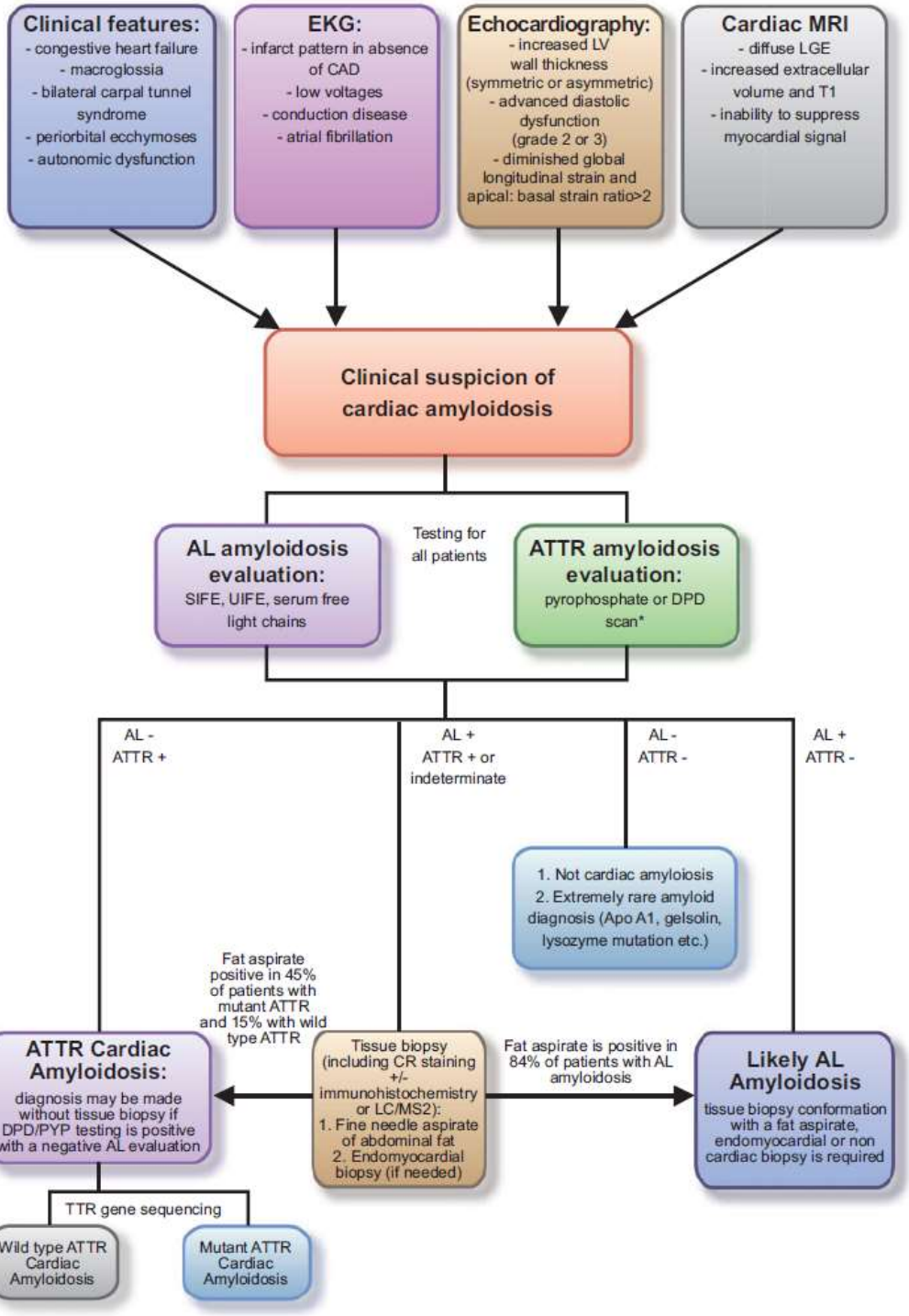
Conclusion

ΥΠΟΨΙΑΣΤΕΙΤΕ τη νόσο !!!

Υπάρχει και ακριβής μέθοδος διάγνωσης.

&

Εξατομικευμένη θεραπεία



ΕΥΧΑΡΙΣΤΩ