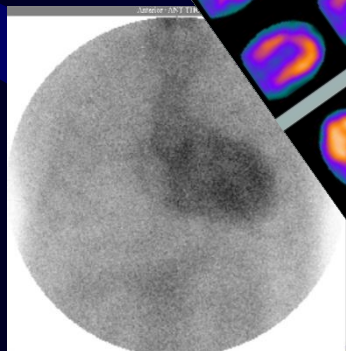
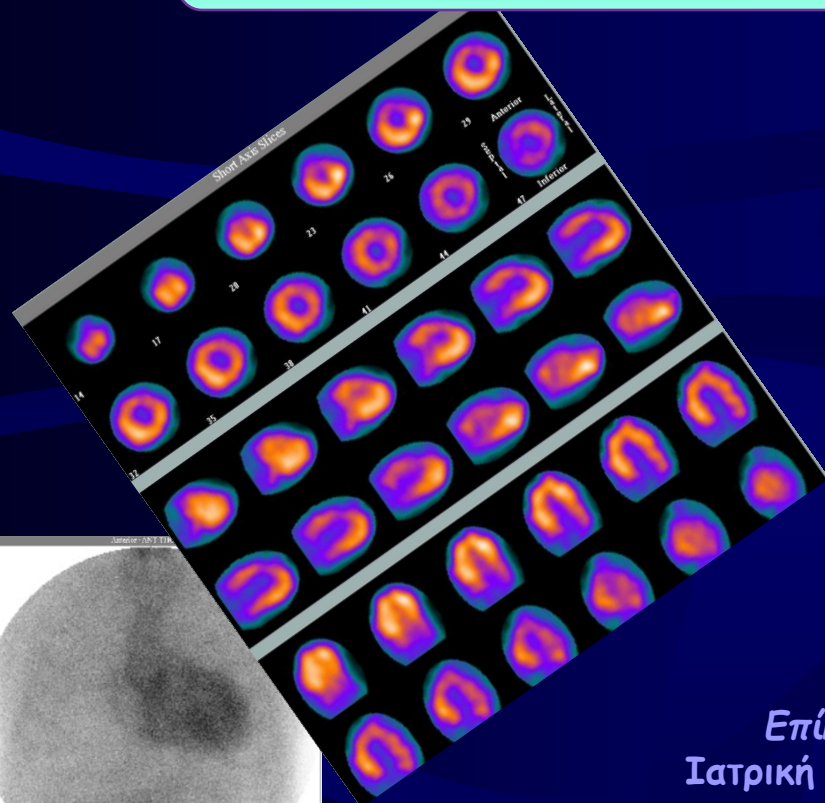
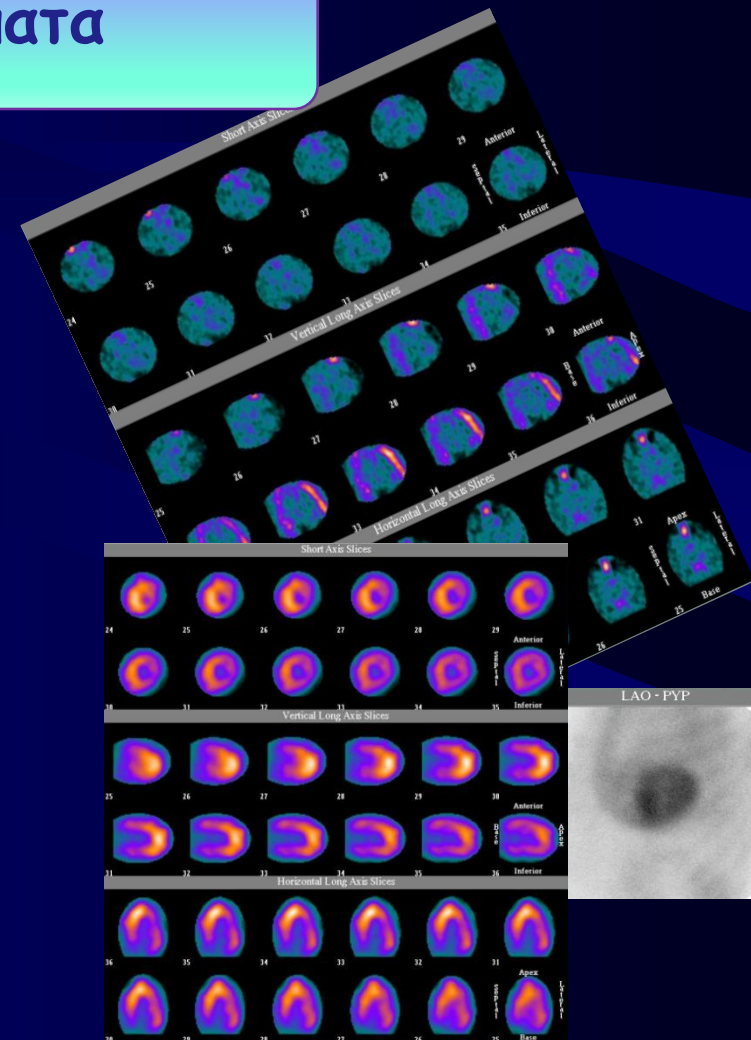




Απεικόνιση στην αμυλοείδωση - Παραδείγματα



Δρ. Πιπίτσα Ν. Βαλσαμάκη
Πυρηνική Ιατρός, MD, PhD
Επίκουρη Καθηγήτρια Πυρηνικής Ιατρικής
Ιατρική Σχολή, Δημοκρίτειο Πανεπιστήμιο Θράκης
Τμήμα Πυρηνικής Ιατρικής,
Πανεπιστημιακό Νοσοκομείο Αλεξανδρούπολης



Clarification Points

● Conflicts Of Interest with regard to this presentation

Honorarium from Pfizer: 2019, 2020, 2021, 2022, 2023

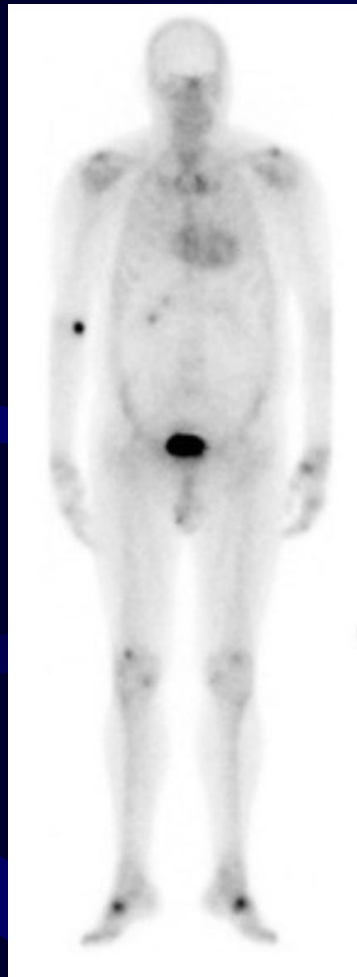
Διάγνωση καρδιακής ATTR με scan μυοκαρδίου με οστεόφιλους ιχνηθέτες χωρίς την ανάγκη βιοψίας: Standards and Pitfalls

Ποσοτικοποίηση και Ανταπόκριση στη Θεραπεία

PET-ιχνηθέτες αμυλοειδούς

Κατευθυντήριες Οδηγίες

Cardiac amyloidosis (CA) Τυχαίο εύρημα σε scan οστών...παλαιόθεν!



^{99m}Tc -DPD 3h pi
66 γ Μ, διερεύνηση
βλάβης στην ΑΡ
κνήμη

Έντονη πρόσληψη ρφ στο
μυοκάρδιο
χωρίς ωστόσο να έχει
ταυτοποιηθεί ο υπότυπος μέχρι
πριν περίπου μια εικοσαετία

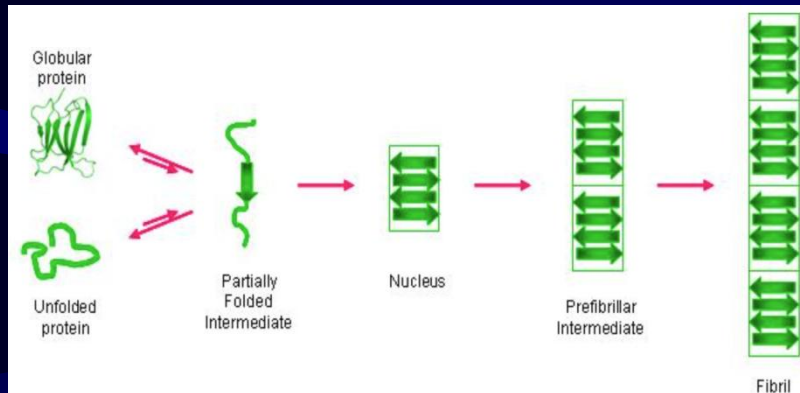


^{99m}Tc -HMDP 3h pi
94 γ Μ, διερεύνηση
↑PSA επί χ/θέντος
Ca προστάτη
Οστικές μεταστάσεις
ΣΣ

Cardiac amyloidosis (CA) or "stiff heart syndrome"

(CA) although known since 1867 [1], has recently drawn a revived interest in medical practice.

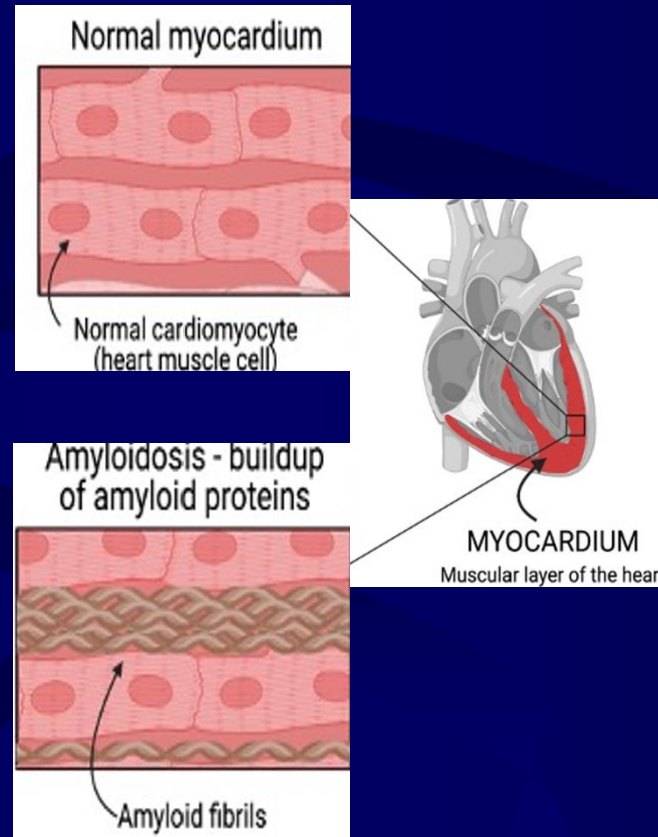
Υποεκτιμημένο και
υποδιαγνωσμένο
αίτιο καρδιακής ανεπάρκειας



Προοδευτική διαταραχή που
προκαλείται από εναποθέσεις
μιας διαταραγμένης
εξωκυττάριας πρωτεΐνης,
ήτοι ινιδίων αμυλοειδούς,
στον μυοκαρδιακό ιστό,
οδηγώντας σε πρώιμη
κατάληξη λόγω ΣΚΑ &
αρρυθμιών

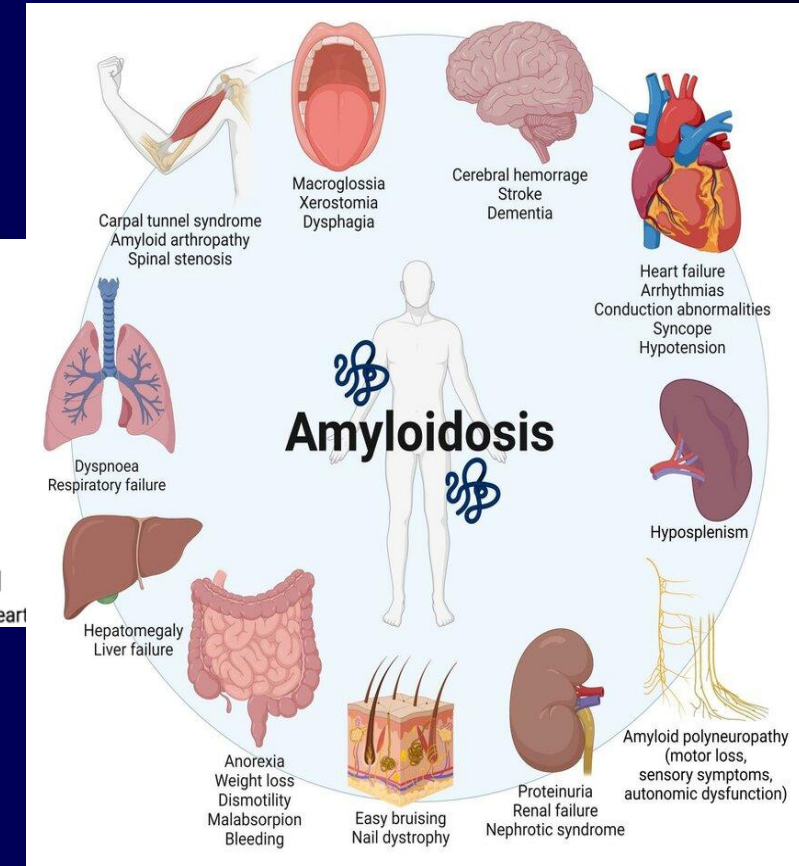
amorphous and hyaline change in tissue

the iodine-staining reaction of this material that resembles that of starch-



Epidemiology

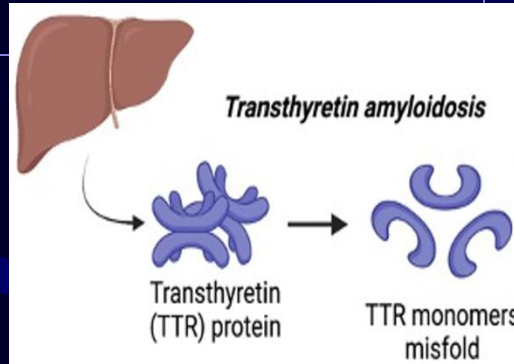
- ✓ more common in men > women
- ✓ rare in people < 40 yrs



Η εναπόθεση αμυλοειδούς μπορεί να
συμβεί σε πολλαπλά όργανα
προκαλώντας ποικιλία κλινικών
εκδηλώσεων

Παθοφυσιολογικό υπόβαθρο CA

- ❖ **ATTR:** fibrils consist of monomers or dimers of the normally tetrameric structure of TTR

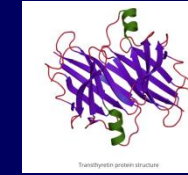


ATTR variant:
mutation in the TTR gene:
κυρίως
νευροπάθεια &
συχνά καρδιακή
συμμετοχή

ATTR wild type:
TTR unstable
with age
κυρίως καρδιακή
νόσος &
το μοναδικό σημαντικό
εξωκαρδιακό
χαρακτηριστικό είναι
ένα ιστορικό συ.
καρπιαίου σωλήνα, το
οποίο συχνά
προηγείται της ΚΑ
κατά 3-5 χρόνια

- ✓ Many different proteins may form amyloid fibrils under specific conditions
- ✓ sporadic or hereditary

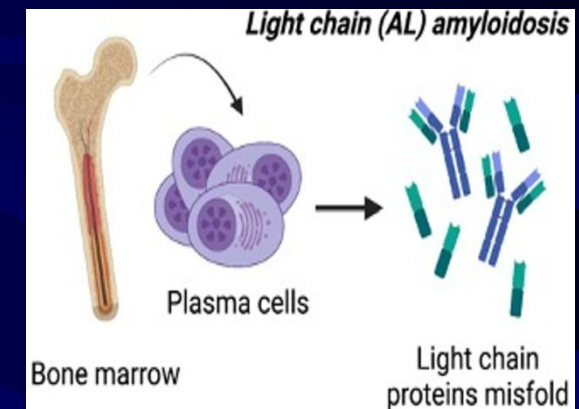
with different clinical course & treatment



Amyloid Type	Precursor Protein	Typical Decade of Presentation	Cardiac Involvement	Other Organ Involvement	Treatment	Prognosis (Median Survival)
Primary (AL) amyloidosis	Monoclonal light chain	6th or 7th decade (but can be any)	40% to 50%	Renal, liver, soft tissue, neuropathy	Chemotherapy or peripheral blood stem cell transplantation	48 mo but 8 mo for advanced-stage disease
Transthyretin amyloidosis						
ATTR (V30M)	Variant transthyretin	3rd or 4th decade (but geographical variation)	Uncommon (but can occur in older patients)	Peripheral and autonomic neuropathy	Liver transplantation (younger cases) not proven in others	Good with liver transplantation for V30M progressive disease
ATTR (T60 A)	Variant transthyretin	6th decade	Up to 90% by diagnosis	Peripheral and autonomic neuropathy	Liver transplantation possible in selected patients	Variable with liver transplantation
Wild-type ATTR	Wild-type transthyretin	70 y (but remains a consideration after 50 y)	Almost all cases	Carpal tunnel syndrome	Supportive	7 to 8 y
ATTR Ile 122	Variant transthyretin	6th decade or older	Almost all cases	Carpal tunnel syndrome	Supportive	7 to 8 y
Apolipoprotein A1 (ApoA1)	Variant apolipoprotein	6th decade or older	Rare	Predominantly renal	Renal (±liver) transplantation	Usually slowly progressive (y)
Secondary (AA) amyloidosis	Serum amyloid A (SAA)	Any	Rare	Renal, liver	Treat underlying inflammatory condition	Good
Atrial natriuretic peptide (ANP)	ANP	70 y or older	All cases but significance uncertain	None reported	Not needed	-

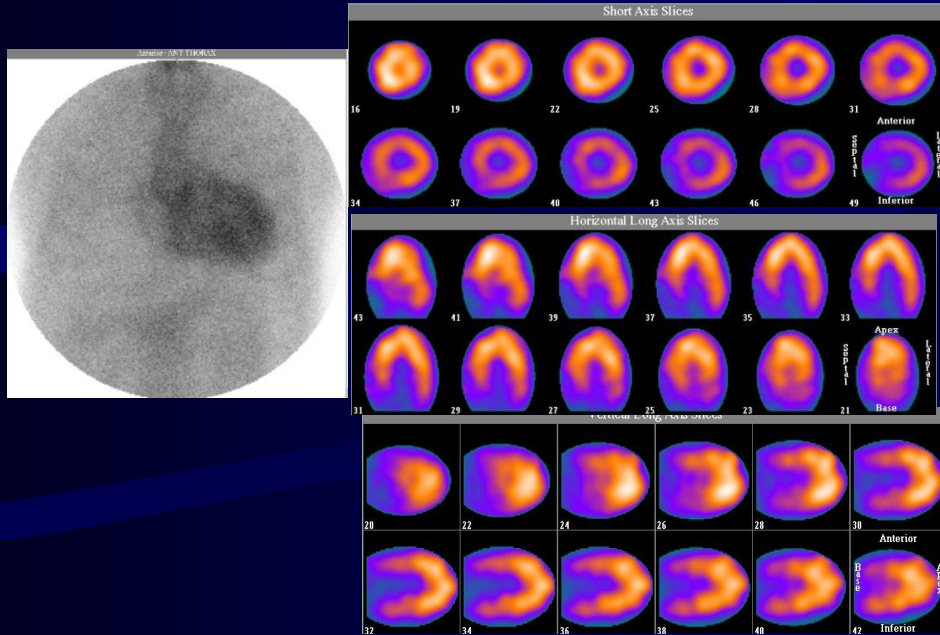
- ❖ **Primary light chain (AL) CA:** fibrils consist of light chain Igs produced by a clonal plasma cell population in the bm

καρδιακή συμμετοχή στο 50% των περιπτώσεων & μερικές φορές η μοναδική εκδήλωση



Και τα δύο είδη CA μοιράζονται κοινά χαρακτηριστικά ως προς την ηλικία & τις κλινικές εκδηλώσεις: **Κρίσιμη η δδ**

Αύξηση της ανίχνευσης της καρδιακής αμυλοείδωσης από τρανσθυρετίνη (επίκτητης & κληρονομικής) μετά το ~2013

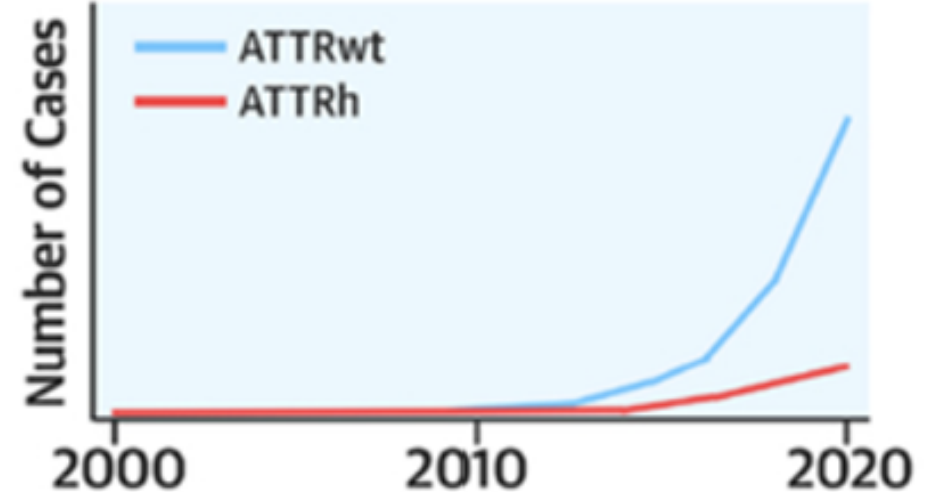


Papantoniou, Valsamaki et al. Imaging of cardiac amyloidosis by ^{99m}Tc -PYP scintigraphy, HJNM; 2015



Μία από τις ζωτικές εξελίξεις που οδήγησαν στην πρόοδο της διαχείρισης της **ATTR** ήταν η καθιέρωση του σπινθηρογραφήματος ως μη-επεμβατική μέθοδος διάγνωσης, **ιδίως σε ασθ χωρίς συνυπάρχουσα μονοκλωνική παραπρωτεΐναιμία**

Recognition of ATTR-CM

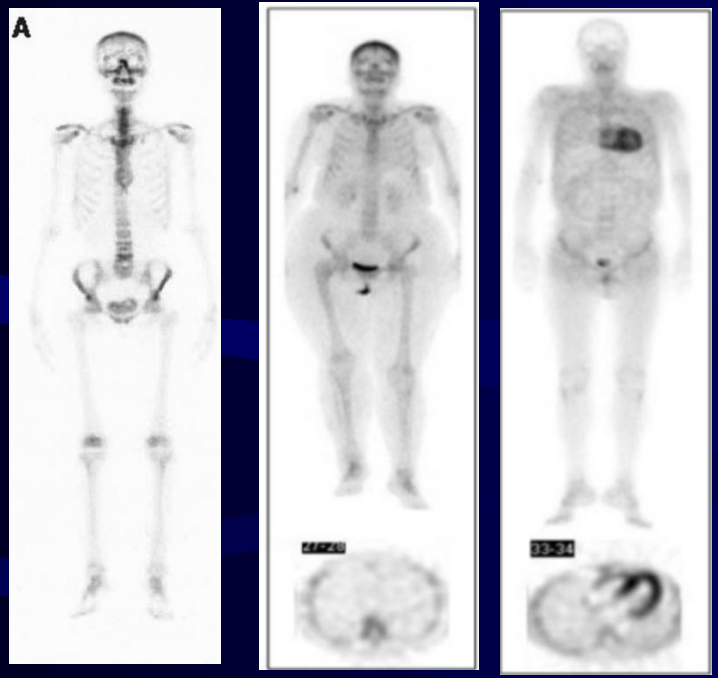


Ruberg FL, et al. J Am Coll Cardiol. 2019

Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

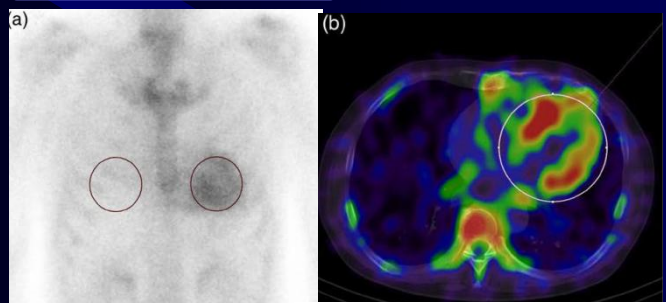
^{99m}Tc -DPD

AL **ATTR**



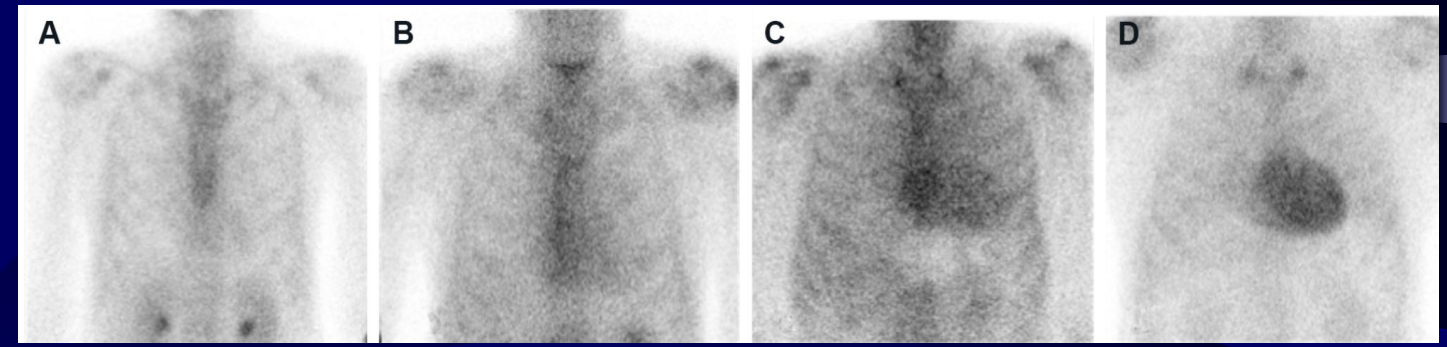
^{99m}Tc -HMDP

ATTR



^{99m}Tc -PYP

Multicentre study with direct clinical impact in detecting **ATTR**



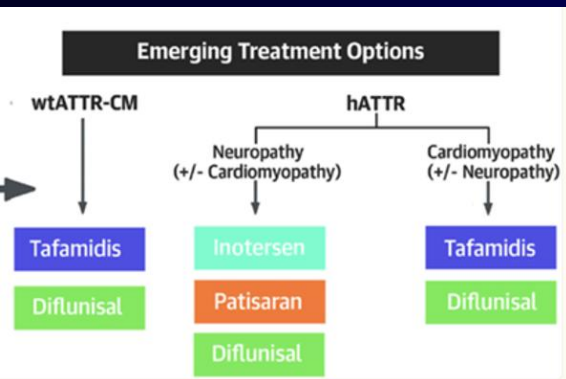
N= 857(/1217 suspected) pats with histologically proven amyloid (374 with EMB, rest with extracardiac histology + ECHO± CMR) & 360 pats subsequently confirmed to have non amyloid CMP

Myocardial radiotracer uptake on PYP scintigraphy was >99% sensitive & 86% specific for cardiac ATTR amyloid

'false positives' almost exclusively in cardiac AL amyloidosis

Table 5. Combined Radionuclide 'Bone' Scintigraphy and Monoclonal Protein Studies Compared With Amyloid Histology

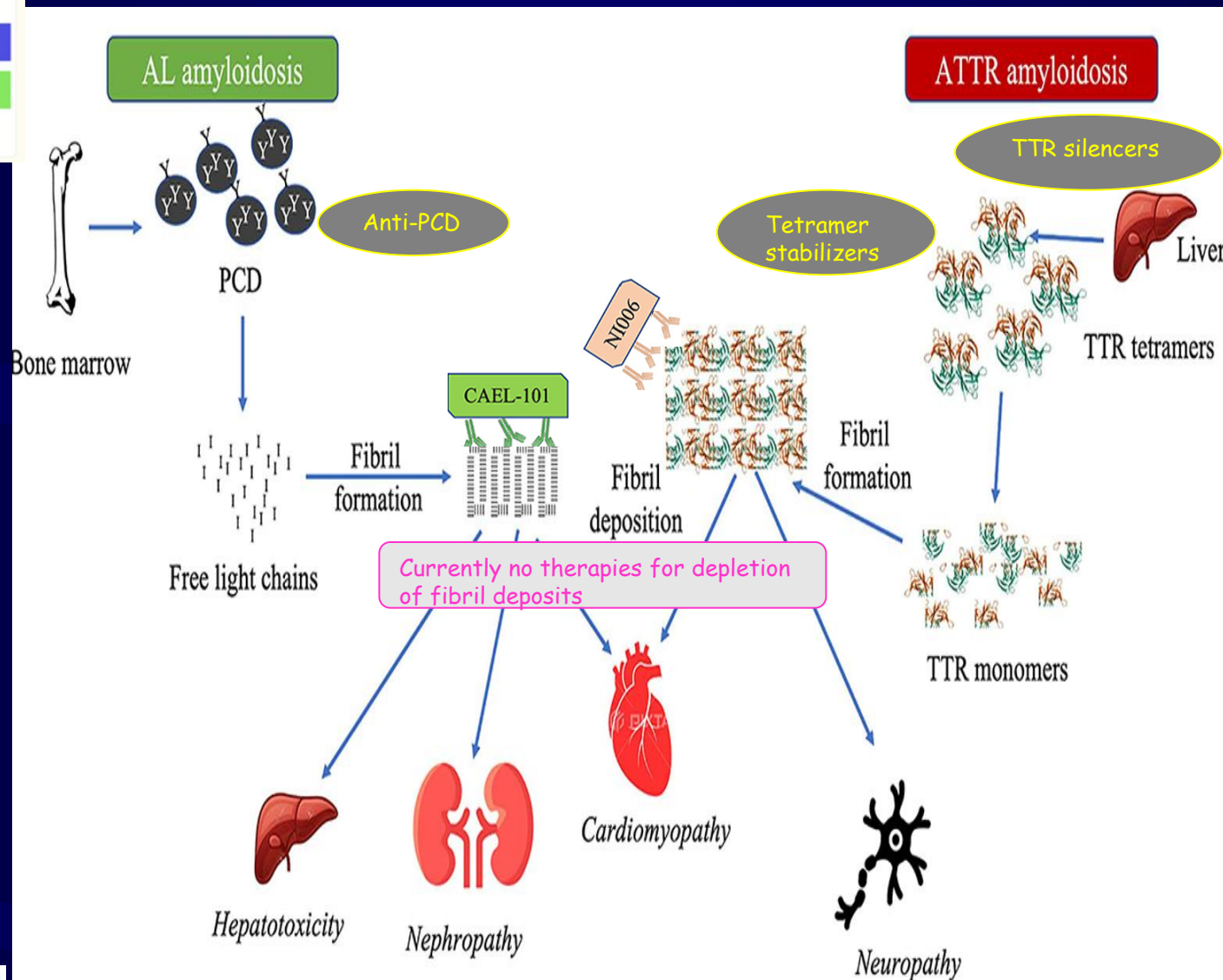
Grade 2 or 3 Radionuclide Scan+Absence of Clone vs ATTR Amyloid Deposits on Histology From Any Organ (n=1217)				
	Grade 2/3 Scan+No Clone, n	Grade 0/1 Scan or Clone, n	Sensitivity and Specificity (CI), %	PPV and NPV (CI), %
Cardiac ATTR amyloid	391	139	74 (70–77) sensitive*	NPV, 83 (80–86)
No cardiac ATTR amyloid	0	687	100 (99–100) specific	PPV, 100 (99–100)



Δεν υπάρχουν φάρμακα για την εξάλειψη των ιδίων των εναποθέσεων ινιδίων αμυλοειδούς

✓ The recent availability of new targeted treatments for ATTR has been increasingly evoking the interest among many different medical disciplines

Inhibition of new fibril production



❖ Νεωτεριστικά φάρμακα αναστέλλουν την παραγωγή ή σταθεροποιούν την TTR

Patisiran (iv 300μg/kg q3wk): RNA interference therapeutic agent

targets the common 3' untranslated region of TTR messenger RNA in the liver to **reduce circulating transthyretin levels** in both ATTRm & ATTRwt

Tafamidis (po 20mg/d): a transthyretin stabilizer: δεσμεύεται στην TTR στις θέσεις δέσμησης της θυροξίνης & has been shown to **reduce disease progression and mortality significantly**

for cardiomyopathy and peripheral neuropathy due to ATTR

Outline: diagnosis & typing of CA: ATTR?

commonly suspected in pats with:
➤ unexplained symptoms of HF
(restrictive pattern)

➤ typical, yet non-specific findings:

Biomarkers

↑TnT
NT-proBNP

ECG

LBBB in 40% of wtATTR
vs 4% in AL
low QRS voltages in
40% wtATTR vs 60% in AL
ST-T abnormalities,
AV block, poor R progression



Cardiac MR T1-mapping

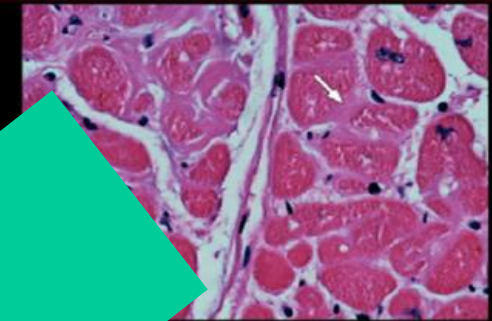
no dd ATTR vs AL
(late gadolinium enhancement)!
is esp. useful in patients with
other causes of LV hypertrophy
because it can differentiate
amyloidosis from HT,
which may not be possible by routine
Echo



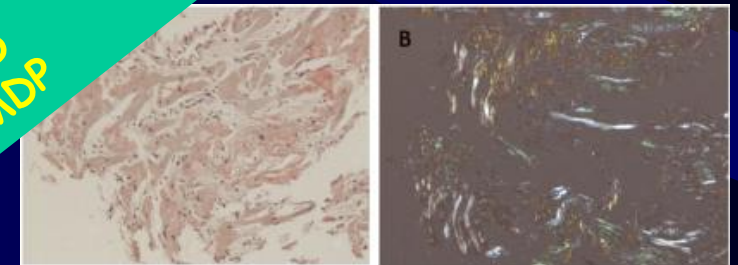
SPET bone-seeking tracers
99mTc-PYP
99mTc-DPD
99mTc-HMDP

EMB with IHC or
mass spectroscopy

Amyloid Deposits in the Heart



K. B. Shah, et al. Archives of Internal Medicine. 2006.



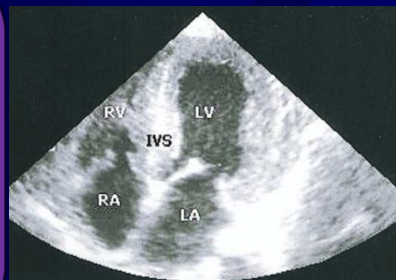
Cardiac AL stained as:
(A) Congo red only; (B) Apple-green
birefringence under polarized light

Falk et al. *Circ Cardiovasc Imaging*. 2015

Banyersad et al. *Circ Cardiovasc Img* 2013
Fontana et al. *JACC Cardiovasc Img* 2014

2D TTEchocard

concentric LV
& RV thickening
(without history of HT)
normal/near-normal EF
diastolic dysfunction
speckled or granular
myocardial appearance



Is there a gold standard for the noninvasive diagnosis of CA?

Table 1 Diagnostic sensitivity of fat pad fine needle aspiration in different cardiac amyloidoses

Amyloid type	n	Number positive by Congo red staining	Diagnostic sensitivity (CI)
Systemic AL amyloidosis	216	181	84% (78–88%)
ATTRm	113	51	45% (36–54%)
<i>Val122Ile</i>	69	23	33%
<i>Thr60Ala</i>	21	14	67%
ATTRwt	271	42	15% (11–20%)

Systemic AL amyloidosis vs. ATTR amyloidosis, $P < 0.001$ (Chi square test). The combination of absence of amyloid on FPFNA and absence of a *TTR* mutation on gene sequencing, had a positive predictive value for ATTRwt in this series of 87% (CI 82–91%) and a negative predictive value of 81% (CI 75–86%).

Radionuclide techniques with specific binding on amyloid constituents can detect systemic amyloid deposits

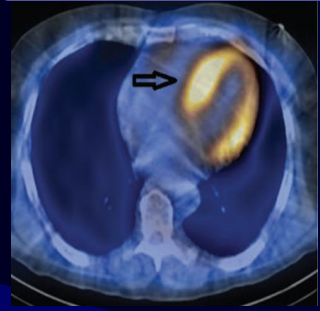
ATTR

✓ Several SPET & PET tracers have been used in imaging cardiac amyloidosis (CA)

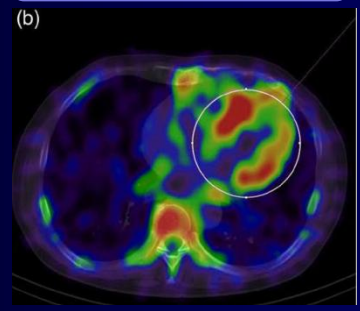
ATTR or AL?

^{11}C -PiB

$^{99\text{m}}\text{Tc}$ -DPD

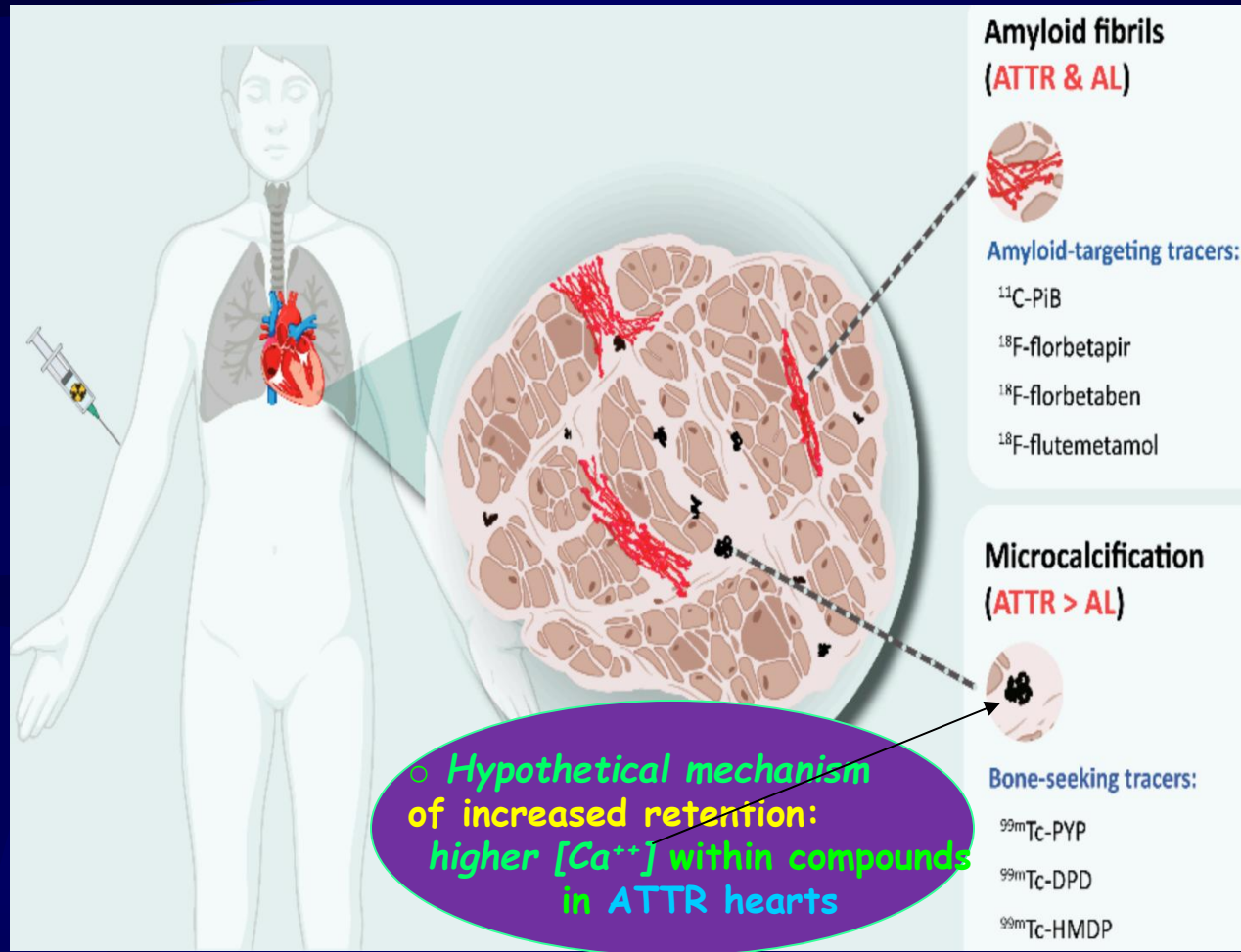
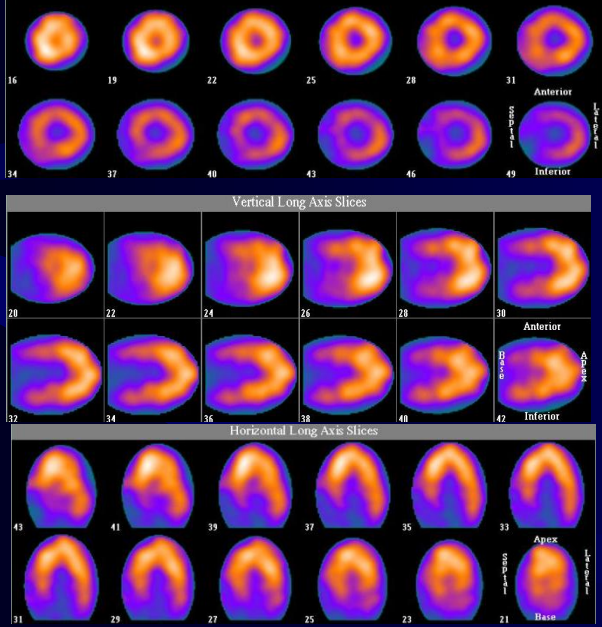


$^{99\text{m}}\text{Tc}$ -HMDP



Egi et al. Nuclear Medicine Communications 2025

$^{99\text{m}}\text{Tc}$ -PYP



✓ Cardiac scan with bone-seeking tracers is the cornerstone of an imaging-based diagnostic pathway for accurate, non-invasive confirmation of transthyretin CA (ATTR)

Σπινθηρογραφική ερμηνεία Ποιοτική και ημιποσοτική ανάλυση

Visual score	Degree of uptake	^{99m} Tc-DPD
0	Absent cardiac uptake and normal bone uptake	
1	Mild cardiac uptake, inferior to bone uptake	
2	Moderate cardiac uptake with attenuated bone uptake	
3	Strong cardiac uptake with mild/absent bone uptake	

Perugini et al. *J Am Coll Cardiol*. 2005 Sep 20;46(6):1076-84

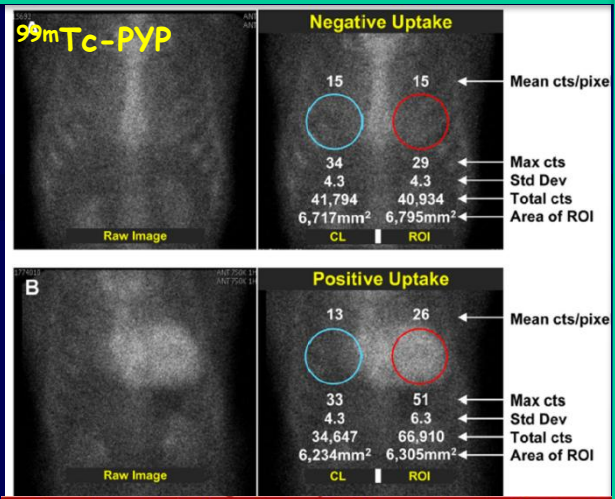
Table 2. Semi-quantitative Visual Grading of Myocardial ^{99m}Tc-PYP Uptake by Comparison to Bone(rib) Uptake

Grade	Myocardial ^{99m} Tc-PYP Uptake
Grade 0	no uptake and normal bone uptake
Grade 1	uptake less than rib uptake
Grade 2	uptake equal to rib uptake
Grade 3	uptake greater than rib uptake with mild/absent rib uptake

Perugini modified by Dorbala  **PRACTICE POINTS** 

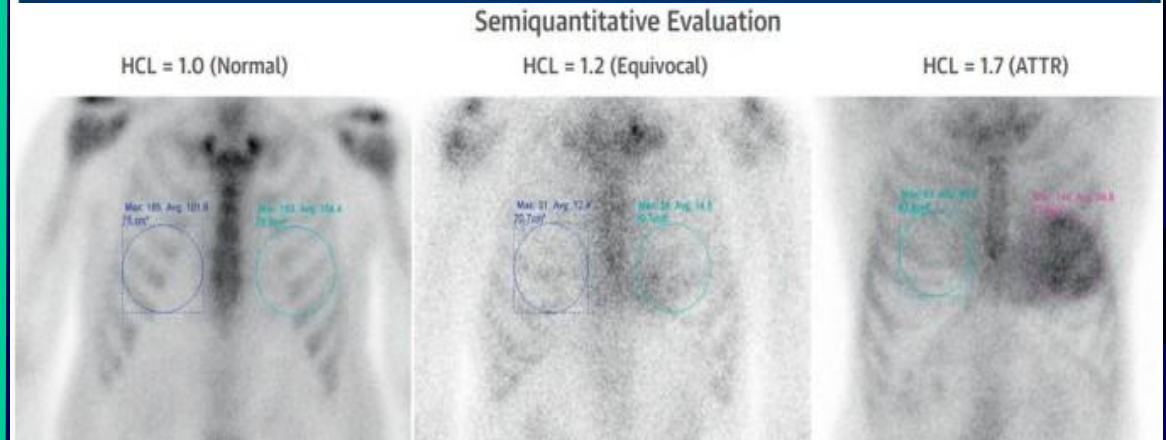
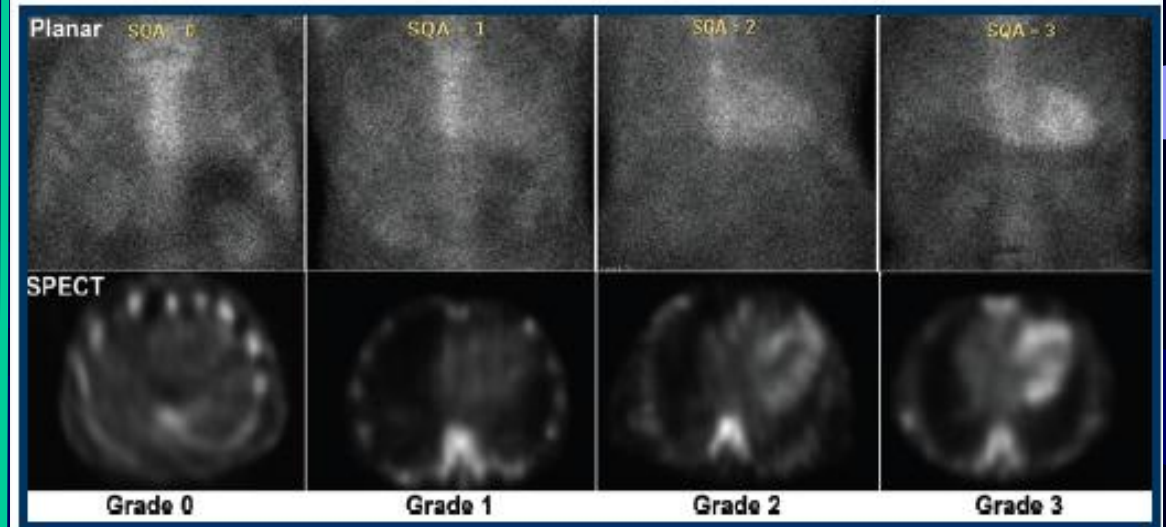
Dorbala et al. *J Nucl Cardiol* 2019

Bokhari S et al. *Circ Cardiovasc Imaging* 2013



Rather, the only independent variable associated with the H/CL ratio was ATTR versus AL amyloid (odds ratio, 9.8; 95% confidence interval, 2.6–37.5).

Figure 2. Grading ^{99m}Tc-PYP Uptake on Planar and SPECT Images



According to published ref standards,
a cut-off H/CL value of 1.5
best discriminates AL vs ATTR

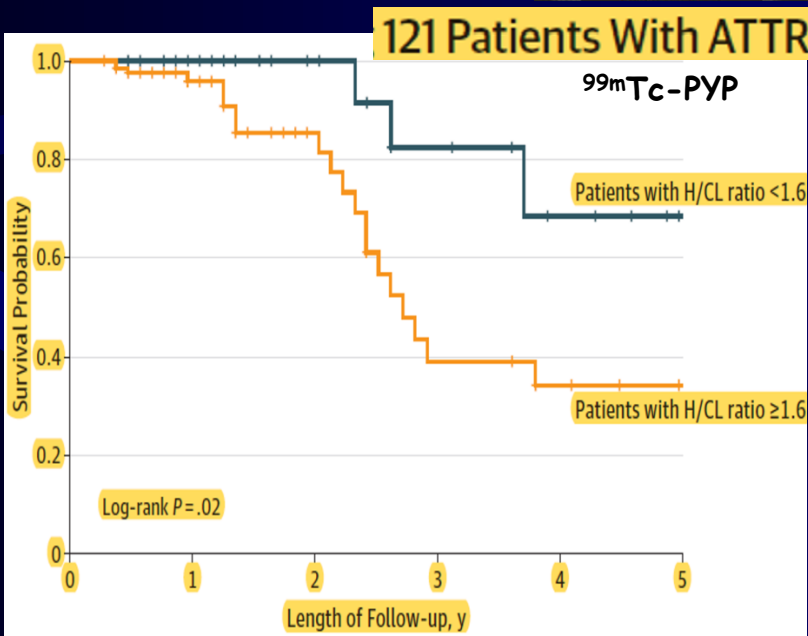
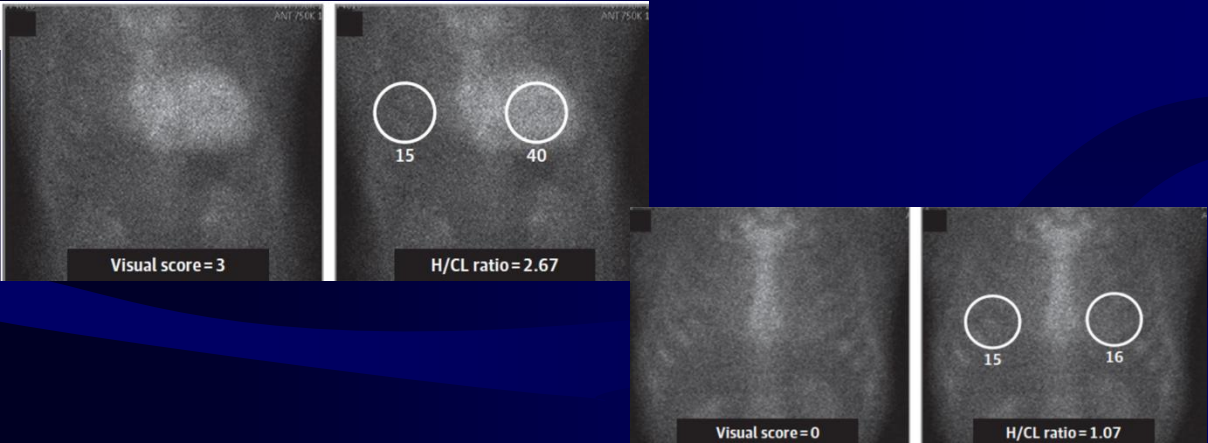
H/CL ratio ≥ 1.5 at one hour , > 1.3 at 3 hours

- (a) **Not suggestive:** A semi-quantitative visual Grade of 0
- (b) **Equivocal:** If diffuse myocardial uptake of ^{99m}Tc-PYP/DPD/HMDP is visually confirmed and the semi-quantitative visual grade is 1 or there is interpretive uncertainty of grade 1 versus grade 2 on visual grading
- (c) **Strongly suggestive:** If diffuse myocardial uptake of ^{99m}Tc-PYP/DPD/HMDP is visually confirmed, a semi-quantitative visual grade of 2 or 3

Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging

Predicting Survival for Patients With ATTR Cardiac Amyloidosis

✓ Συσχέτιση με πρόγνωση



Castano et al. JAMA Cardiol 2016

Prognostic utility of the Perugini grading of ^{99m}Tc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid

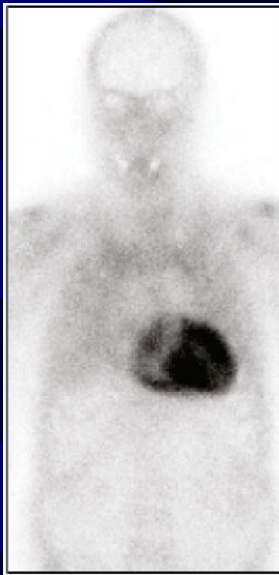
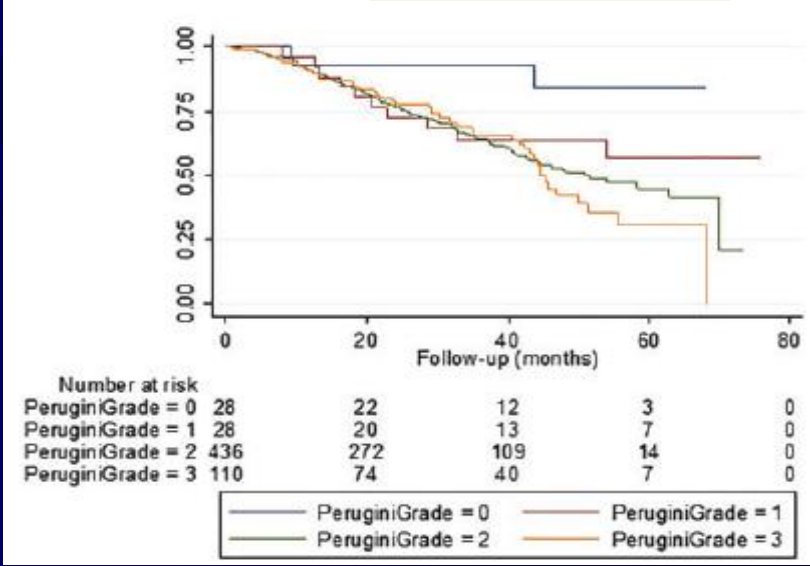
✓ Χωρίς συσχέτιση με πρόγνωση

^{99m}Tc-DPD scintigraphy is exquisitely sensitive for identification of cardiac ATTR amyloid, but stratification by Perugini grade of positivity at diagnosis has no prognostic significance.

There was no significant difference in survival between patients with a Perugini grade 1, 2, or 3 ^{99m}Tc-DPD scan

369 ATTRwt
151 ATTRv
(V122I & T60A)

(P = 0.39 for grade 1 vs. 2,
P = 0.19 for grade 1 vs. 3,
P = 0.51 for grade 2 vs. 3).



○ υψηλότερη αναλογία μαλακών ιστών/μηριαίου οστού σε υψηλού βαθμού 2-3 λόγω εναποθέσεων αμυλοειδούς

Hutt et al. Eur Heart Journal - Cardiovasc Imag 2017

Σπινθηρογραφικά πρωτόκολλα

Pharmacokinetics

1h pi: very high % skeletal uptake

Biphasic blood clearance:

$T_{1/2}$ 15min

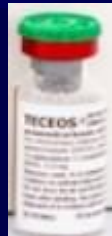
$T_{1/2}$ 100min

(blood pool)

1h pi: 40% in urine

Relatively often:
extracardiac uptake

^{99m}Tc -DPD,
 ^{99m}Tc - 3,3-diphosphone-
1,2-propan-dicarboxylic acid



^{99m}Tc -HMDP,
 ^{99m}Tc -hydroxymethylene
diphosphonate

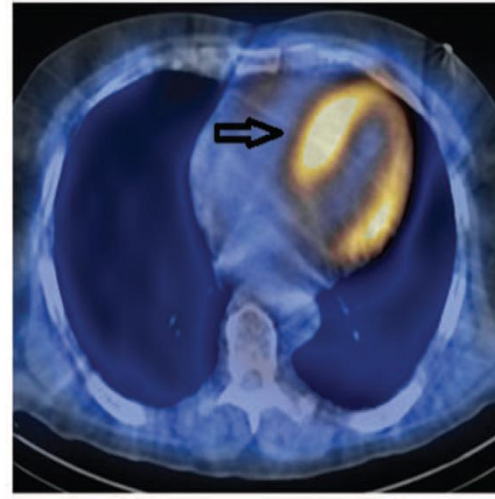


Kapeli et al.
Maika et al. 2020
Mattana et al. Vessel
Plus 2022

Banypersad SM et al.
J Am H Association 2012

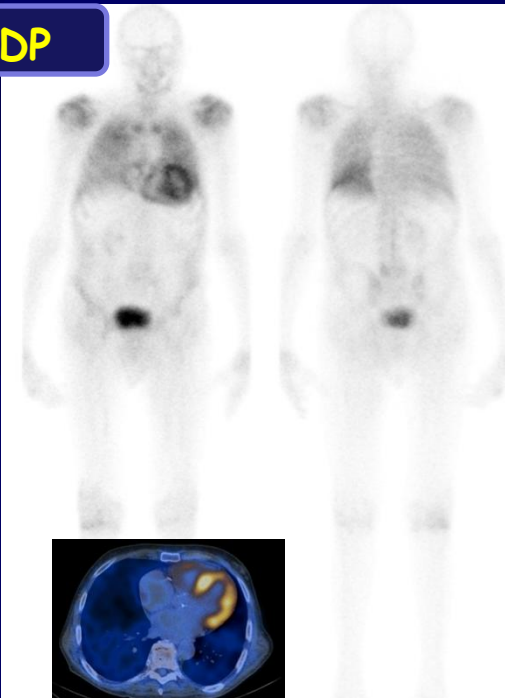
^{99m}Tc -DPD

ATTR



^{99m}Tc -HMDP

ATTR



✓ Απεικόνιση:
3h (2,5h για
HMDP)

Οπτική
αξιολόγηση
(Perugini)

ATTR σε εξωκαρδιακούς ιστούς:
πνεύμονες, μυς, τένοντες,
καρπιαίο σύνδεσμο, κοιλιακό λίπος:
↑ πρόσληψη DPD / HDP ανευρίσκεται
σχετικώς συχνά - **επικουρικό
κριτήριο**

DPD:

Εξωκαρδιακή πρόσληψη:

- σε 57 ασθ: στους
σκελετικούς μυς (>>>PYP)
- σε μυς, ώμο, θώρακα,
κοιλιακό τοίχωμα:
μμ/μηριαίο: score 0→3
(ίδιο για 2-3)
σε 563 ασθ

Perugini et al.
Rapezzi et al.



HMDP:

Εξωκαρδιακή πρόσληψη
(10min) σε 247 ασθ: 29%:
33% ATTRwt

20% ATTRv

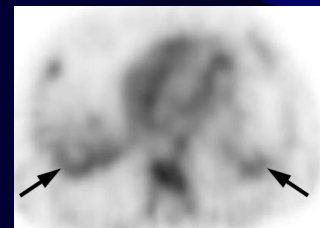
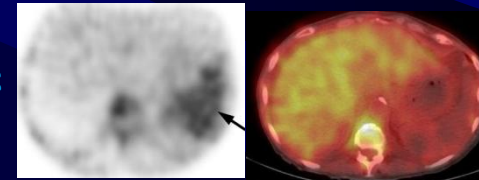
40% AL (ήπαρ & σπλήνας μόνο
σε AL)

Συχνότερη πρόσληψη: σε

πνεύμονες:

σε 82 ασθ: 60% ATTR

6% AL



Σπινθηρογραφικά πρωτόκολλα

Tc-99m-pyrophosphate (PYP) SPECT ^{99m}Tc-PYP SPECT

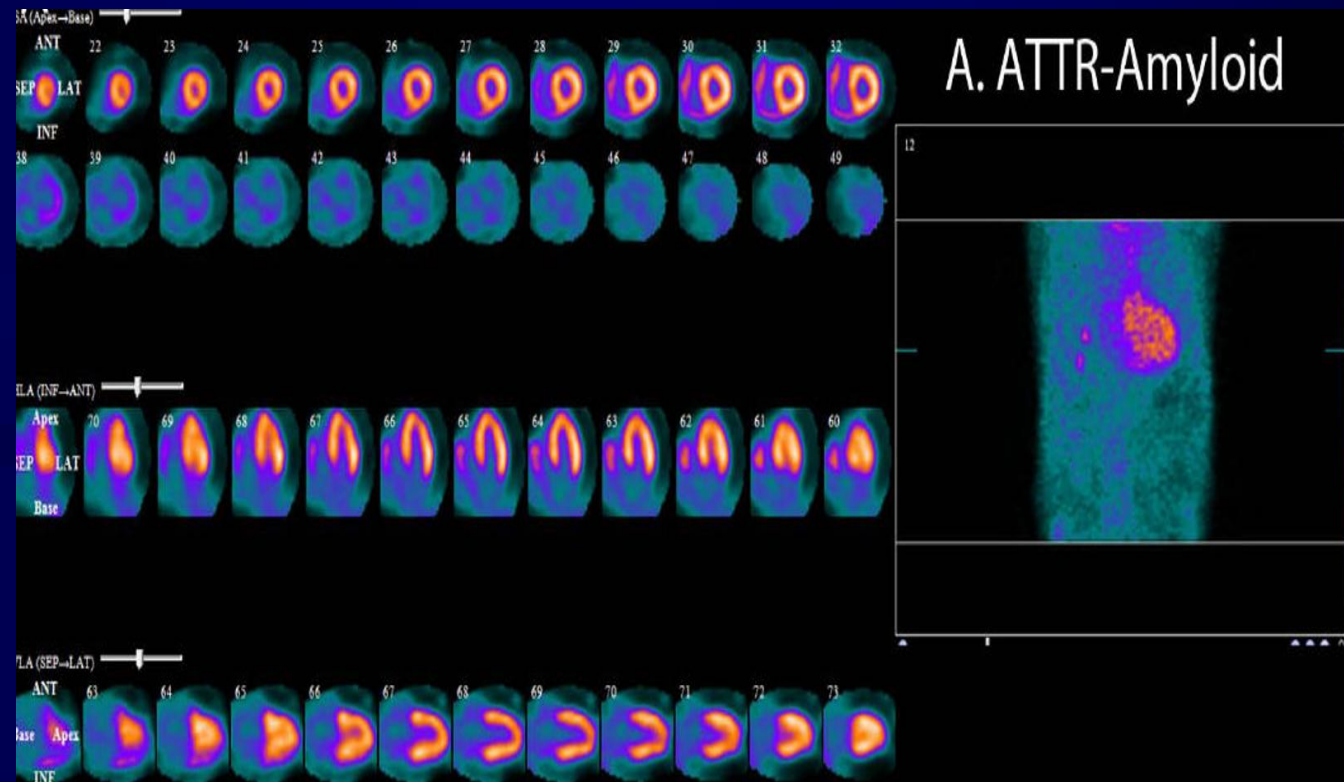
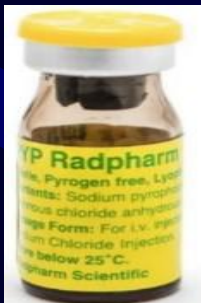
Pharmacokinetics

1-2 h pi: **40-50% skeletal uptake**
0.01-0.02%/gr
Acute MI: 24h-1wk/ max
48-72h

1 h pi: **10-11% blood pool**

24h pi: 2-3% blood pool
40% in urine

Rare: extracardiac uptake



At 1h
Higher optical sens (95% vs 58% uptake
↓heart/bone at 3h)
Χαμηλότερη ειδικότητα: 79%
(λόγω blood-pool)

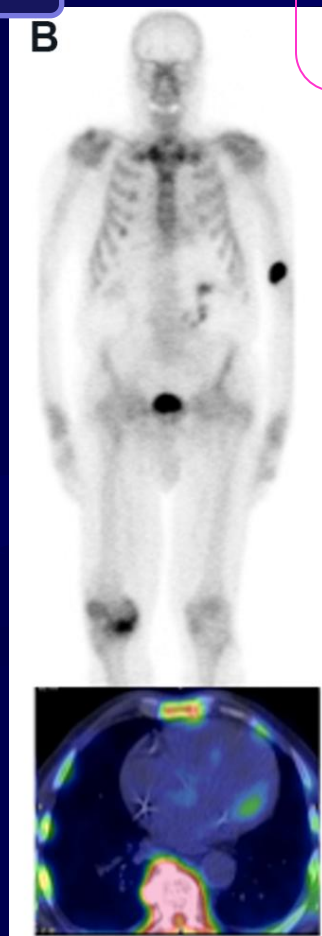
H/CL ≥ 1.5 @ 1 h with
Perugini gr ≥ 2
in the absence of
paraproteinemia:
Sens 97% Spec 100%
for ATTR

Tahara et al.. *ESC Heart Failure* 2022
Wehbe et al. *J Nucl Cardiol* 2021
Castano et al.. *JAMA Cardiol.* 2016

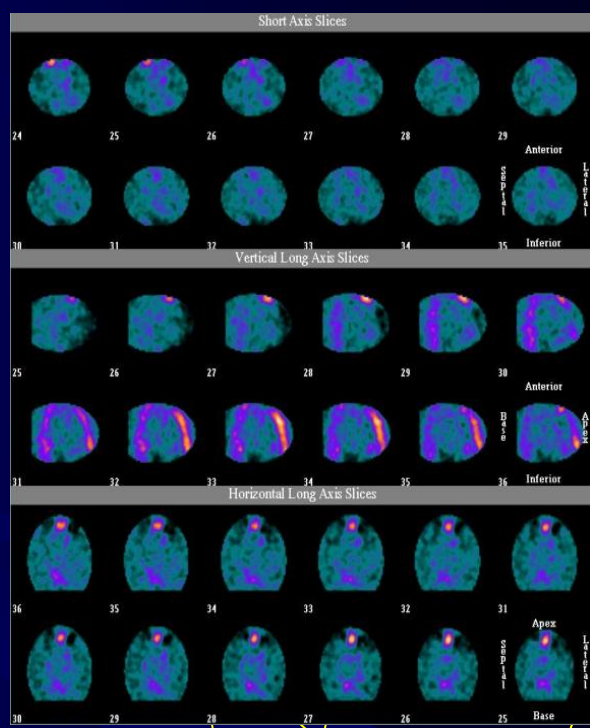
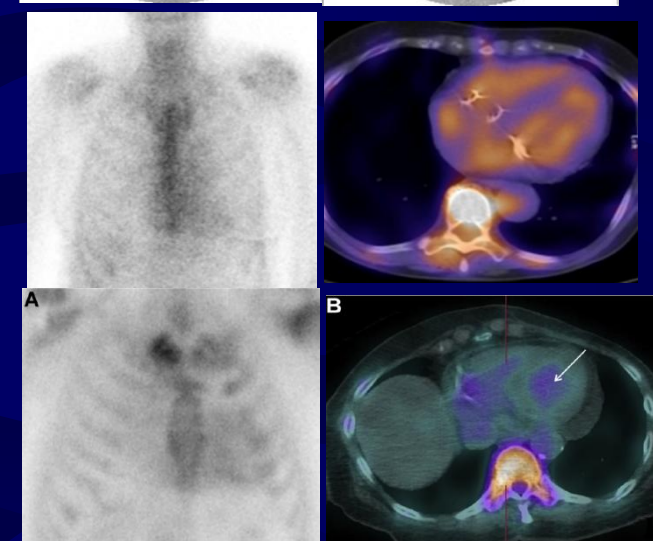
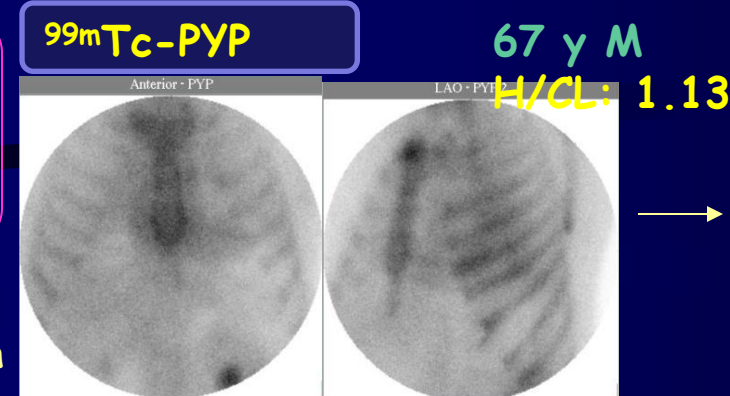
Falk et al. *Circ Cardiovasc Imaging* 2015



^{99m}Tc -DPD



Pitfalls
blood pool
19-23%
false (+)



○ At 3h
Spec 100%
(↓ blood pool)
Χρονοβόρα-
δυσχερής
συνεργασία

○ SPECT/
SPECT-CT
ή/ & LAO

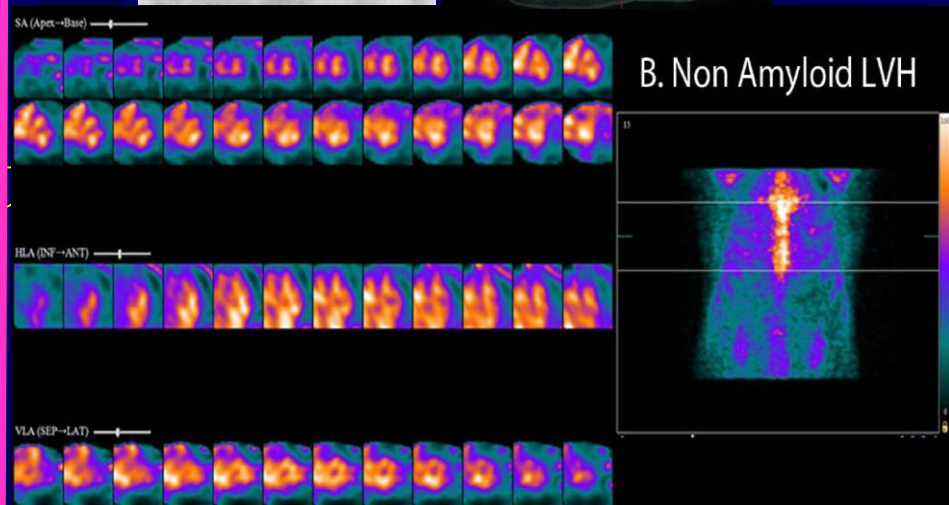
Tahara et al.. *ESC Heart Failure* 2022
Wehbe et al. *J Nucl Cardiol* 2021
Castano et al.. *JAMA Cardiol.* 2016
Falk et al. *Circ Cardiovasc Imaging* 2015

↑ πρόσληψη σε πνεύμονες, μυς ώμου, ισχίων & κοιλιακού τοιχώματος, με ↓ σε οστά. Χωρίς SPECT-CT, ανέφικτος ο προσδιορισμός καρδιακής πρόσληψης: Pitfall: false (-)

Wechalekar et al. *Nuclear Medicine Communications* 2024
Mattana et al. *Vessel Plus* 2022
Hanna M et al. *JACC* 2020

Visual gr 1 & corresponding SPECT-CT: blood pool

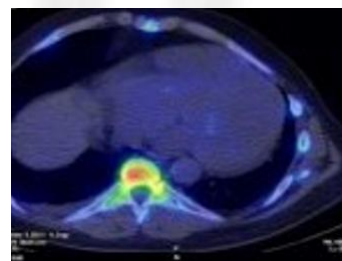
SPECT may also be used





Pitfalls: false (+)

Αίτια	Red flags	Επιβεβαίωση
AL	Abn Ser/Ur Prot Electroph, Ser FLCr	Ιστολογική
Blood pool	Πιθανή καρδιακή δυσλειτουργία	SPECT/ SPECT-CT
Υπερτροφική ΜΚΤ		
Τοξικότητα Υδροξυχλωροκίνης	Ιστορικό (PA, Sjögren κ.α.)	
AAροAI & II	Νεφροπάθεια	Γονιδιακός έλεγχος
ΑροAIV	Νεφροπάθεια	Ιστολογική
Ab2M	Νεφροπάθεια (αιμοκάθαρση >9χρ)	Ιστολογική
Πρόσφατο OEM (<4w)	Ιστορικό	SPECT/ SPECT-CT
Ενέσεις Fe	Ιστορικό	
Ραδιοχημική καθαρότητα	Τεχνικό σφάλμα	Repeat sc
Κατάγματα πλευρών, επασβεστωμένες βαλβίδες	Ιστορικό	SPECT/ SPECT-CT
Πλευριτική συλλογή/ παχυσαρκία	Ιστορικό	SPECT/ SPECT-CT



^{99m}Tc -DPD 3h pi
60 y M, υπερτροφική
ΜΚΤ -περκαρδιακή
συλλογή



a

^{99m}Tc -HMDP 3h pi
89 y M, ρχ
καθαρότητα

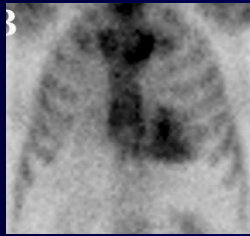


^{99m}Tc -HMDP 3h pi
82 y F, ενέσεις Fe

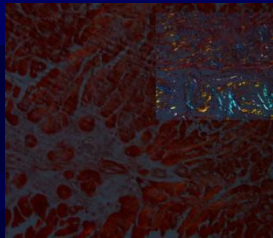
Pitfalls: false (+)



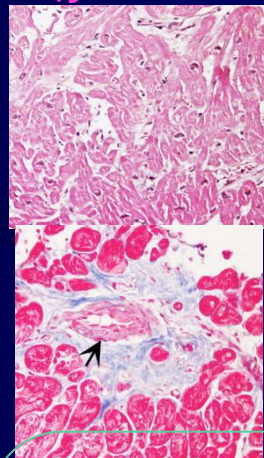
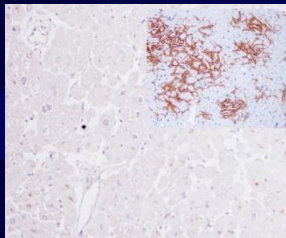
^{99m}Tc -HMDP, gr 3,
89y M, Υπερτροφική ΜΚΤ



ΕΜΒ: Υπερτροφία
κυττάρων, με στοιχεία
ίνωσης

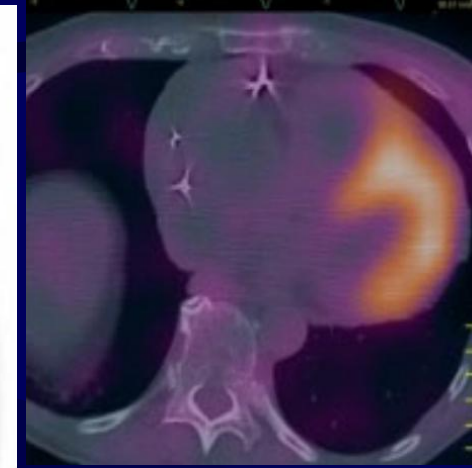
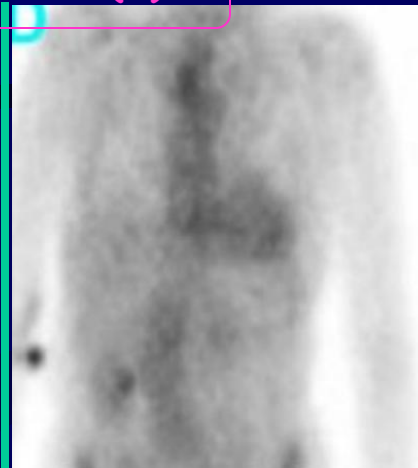


Congo-Red (-)
TTR
immunostaining (-)

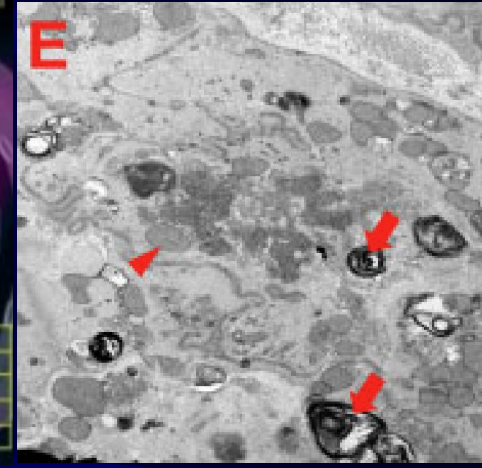


Πιθανοί υποκείμενοι μηχανισμοί:

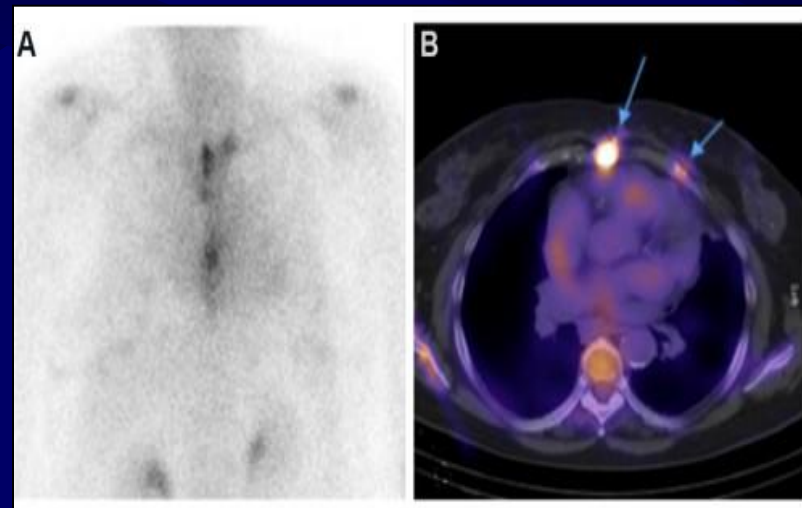
- $\uparrow[\text{Ca}^{++}]$ λόγω εστιακής κυτταρικής νέκρωσης (ασυμφωνία ζήτησης/παροχής O_2)
- Νόσος μικρών αγγείων
- Φλεγμονή



^{99m}Tc -PYP, gr 3,
70y F, με ΡΑ υπό
Υδροξυχλωροκίνη



Ε/Μ: Αποδιοργάνωση
μυοϊνιδίων, άφθονα
κενотόπια,
καμπυλόγραμμα
κυτταροπλασματικά
σωμάτια
(pathognomonic)

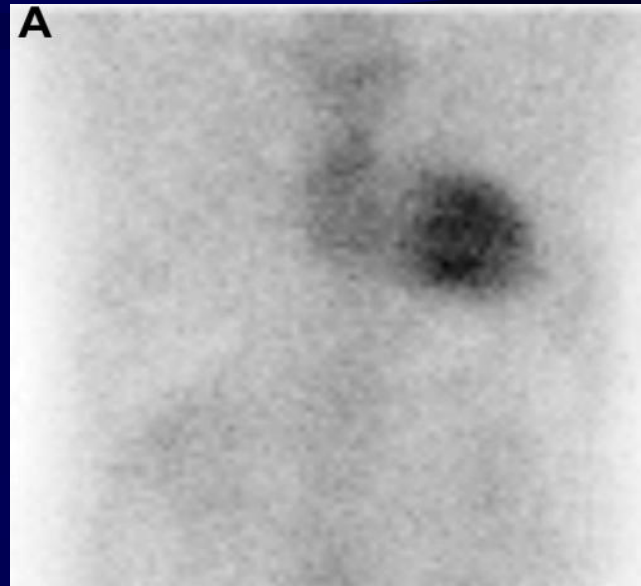


Pitfalls: false (+)

Typical Scan, Echo & CMR findings of CA
(EF: 55% mL V: 16mm, reduced GLS: -11% with apical sparing)

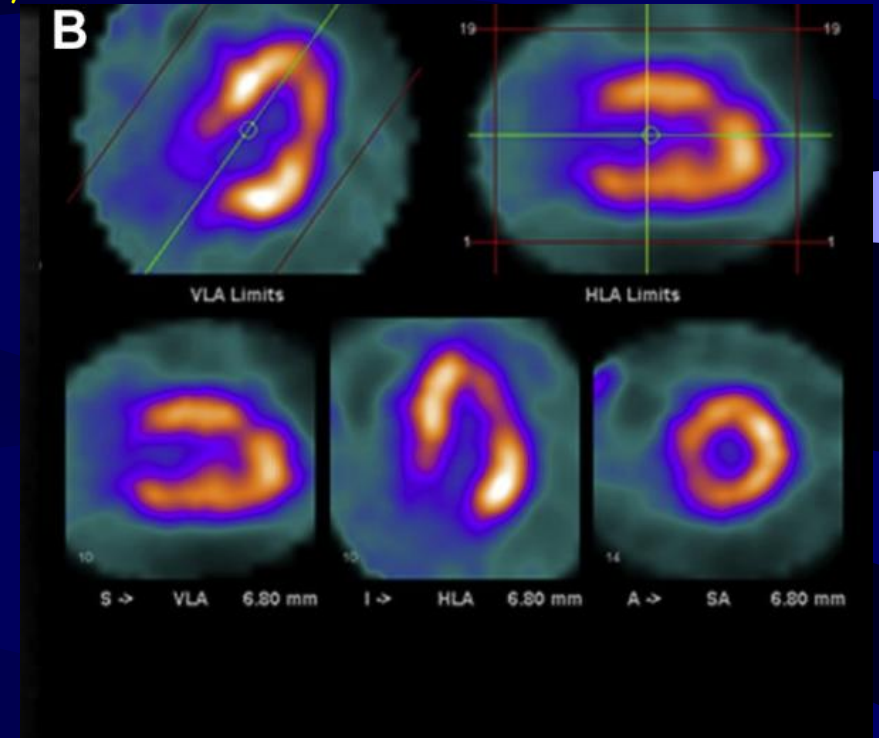
Serum Protein Electrophoresis: no monoclonal protein

Fat aspirate & bm: (-) for amyloid
Genetic testing revealed no TTR mutation



^{99m}Tc -PYP, gr 3,
66 y M

H/CL: 1.8



Initial dg: ATTRwt, tafamidis treatment

- In order to exclude AL, serum & urine IFE and serum free light chain (FLC) assay are required
- Subsequent:
serum k FLC of 2.83 mg/dl (0.33-1.94 mg/dl),
lambda FLC of 41.8 mg/dl (0.57-2.63 mg/dl), &
k/l ratio of 0.07 (0.25-1.65)
- Serum & urine protein IFE: an IgG lambda monoclonal protein

• Endomyocardial biopsy confirmed amyloid deposition, which was determined to be AL (lambda) by mass spectrometry

Error: Serum Protein Electrophoresis, without immunofixation electrophoresis!
Thus, AL was not excluded

Pitfalls: false (-)

Mutations & Pitfalls

Αίτια	Red flags	Επιβεβαίωση
ATTRv: Phe84Leu (89%) Val30Met Ser97Tyr Thr59Lys	Νευροπάθεια, Οικογενειακό ιστορικό	Γονιδιακός έλεγχος
Ήπια νόσος (μικρή ποσότητα αμυλοειδούς)		Ιστολογική
Εκτεταμένη νέκρωση (OEM)	Ιστορικό	SPECT /- CT
Καθυστερημένη ή πρώιμη λήψη	Τεχνικό σφάλμα	Repeat Sc

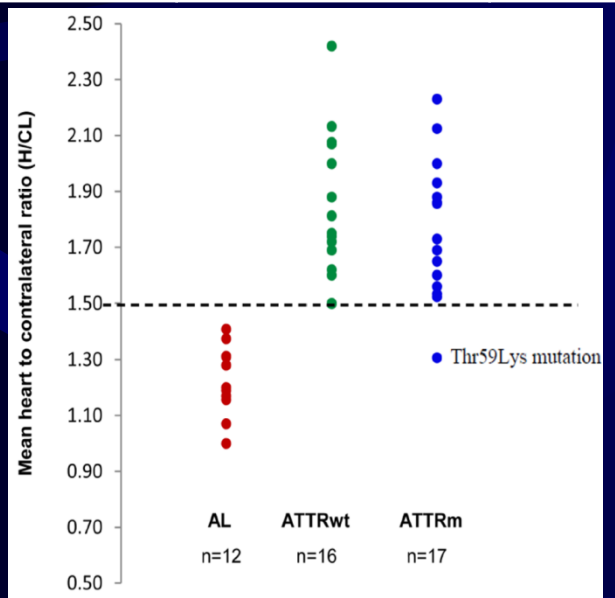


Table 1 TTR mutations Br Heart J 1993;70:111-115

Substitution	Normal residue	Clinical features	
		Predominant	Less significant
Arg 10	Cys	Neuro	
Met 30	Val	Neuro	Cardio
Ala 30	Val	Neuro	Cardio
Ile 33	Phe	Neuro	Vitreous
Leu 33	Phe	Neuro	Cardio
Pro 36	Ala	Neuro	Vitreous
Gly 42	Glu	Neuro	
Thr 45	Ala	Cardio	
Arg 47	Gly	Neuro	
Ala 47	Gly	Neuro	Cardio
Ala 49	Thr	Neuro	Vitreous
Arg 50	Ser	Neuro	
Pro 55	Leu	Neuro	Cardio
His 58	Leu	Neuro-ct	
Arg 58	Leu	Neuro-ct	
Ala 60	Thr	Cardio	Neuro-ct
Leu 64	Phe	Neuro	Cardio
His 69	Tyr	Vitreous	
Asn 70	Lys	Neuro-ct	Vitreous
Ala 71	Val	Neuro	Vitreous
Tyr 77	Ser	Neuro	Cardio
Ser 84	Ile	Neuro-ct	Vitreous
Asn 84	Ile	Vitreous	Cardio
Gln 89	Glu	Cardio	Neuro-ct
Asn 90	His	Cardio	Vitreous
Met 111	Leu	Cardio	
Cys 114	Tyr	Neuro	
Ile 122	Val	Cardio (black population)	

Neuro, neurological symptoms; Cardio, cardiac symptoms; ct, carpal tunnel syndrome; vitreous, ocular symptoms.

Specific ATTR mutations are (-)ve on scintigraphy

potential. mATTR is considered a rare disease, with currently estimated prevalence of 50,000 affected individuals worldwide [13]. It has a worldwide distribution

but it is endemic in areas of Portugal, northern Italy, Japan, Sweden and Cyprus [14]. mATTR is inherited in

an autosomal-dominant manner with variable penetrance. Over 120 mutations of TTR gene have been described with varying phenotypic expression depending on the mutation; not all mutations are amyloidogenic. Most common phenotypes are dominant neuropathic, dominant cardiomyopathic, or mixed. The most common mutation worldwide is V122I, which is detected in approximately 3-4% of African-Americans and is associated with predominantly cardiac manifestations [15, 16]; other cardiomyopathic TTR mutations are L111M and I68L.

A possible influence of the TTR genetic profile and ATTR amyloid fibril composition on scintigraphic findings has been hypothesized [23, 29]. Two different types of amyloid fibrils have been identified (type A and type B). Type B fibrils have been found predominantly in patients with early-onset ATTRm amyloidosis with V30M mutation and in patients carrying the Y114C mutation, whereas type A fibrils are noted in patients with all other mutations currently examined as well as in ATTRwt [29]. As demonstrated in some studies, bone scintigraphy can often be negative in patients with type B amyloid fibrils and usually positive in patients with type A amyloid fibrils [23, 29].

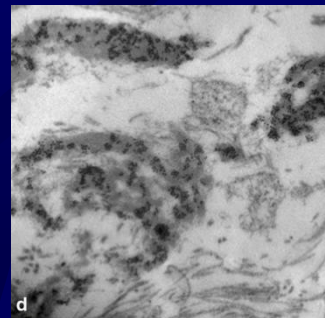
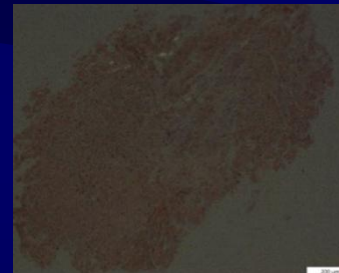
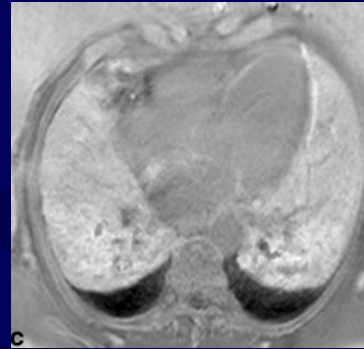
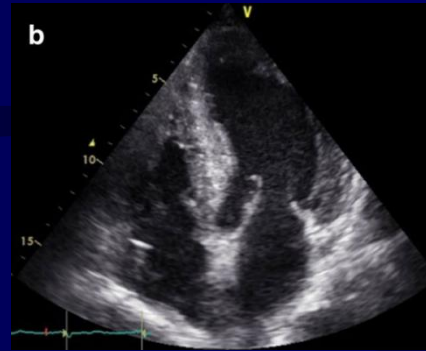
Treglia et al. EJNMMI 2018

Musumeci et al.

Pitfalls: false (-)

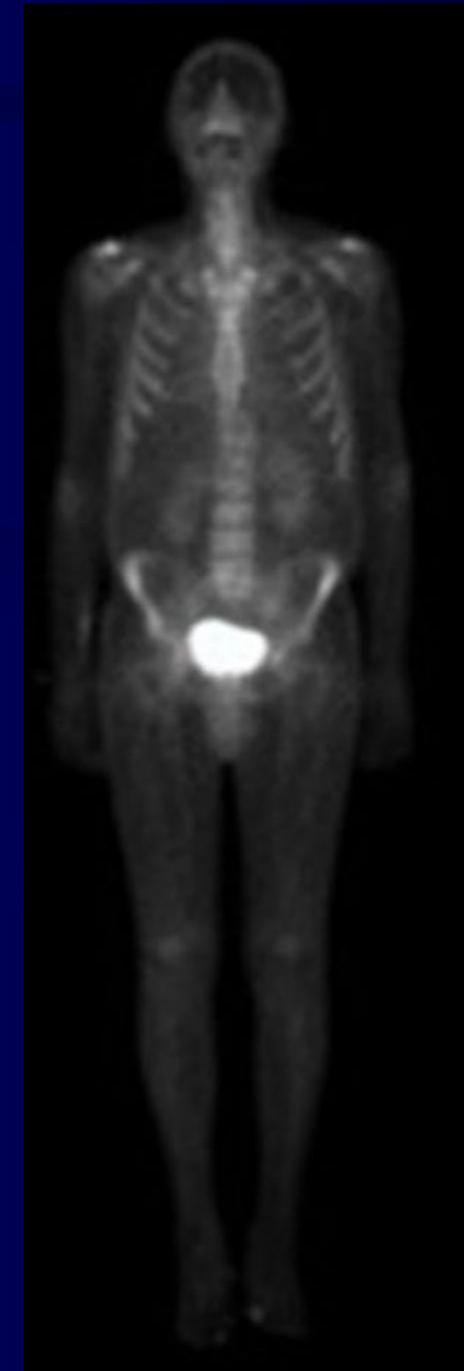
ΑΙ: OEM (PCI LAD)

- επιδείνωση ΚΑ
- ↑Trop & BNP
- Echo: αμφικοιλιακή υπερτροφία
- CMR: Υπερτρ. LV, με όψιμη ενίσχυση με Gadolinium findings suspicious for CA
- AL αποκλείστηκε (U & SPE & IFE)
- Βιοψία: Congo red (-) αλλά Immunoelectron microscopy για κ, λ και TTR: **ινίδια TTR** αμυλοειδούς 9μη στον εξωκυττάριο χώρο
- Γονιδιακός έλεγχος (-)



^{99m}Tc -DPD, gr 0,
67 y M

Ανεπαρκής ποσότητα
αμυλοειδούς



Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis

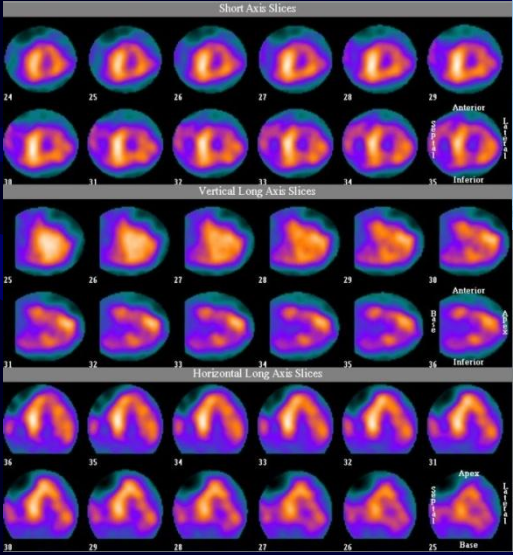
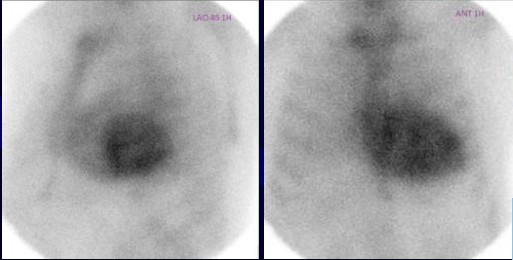
Bivariate meta-analysis

Pooled Sensitivity: 92.2% (95%CI: 89%-95%)
Pooled Specificity: 95.4% (95%CI: 77%-99%)

Bone tracers in Cardiac Amyloidosis

Planar scintigraphy and/or SPECT
ATTR more detectable than AL

79 y M



^{99m}Tc-PYP

Used in United States

Images are acquired at 60 and 80/180 minutes after administration, according to a specific protocol

Extremely little extra cardiac binding

Myocardial uptake in cardiotoxicity from hydroxychloroquine

^{99m}Tc-HMDP

Used in France

Images are acquired at 150/180 minutes after administration

Bind also skeletal muscle, lung and soft tissue

Appearance of lower myocardial uptake in ATTRwt compared to

^{99m}Tc-DPD

Used in Italy and England

Images are acquired at 180 minutes after administration

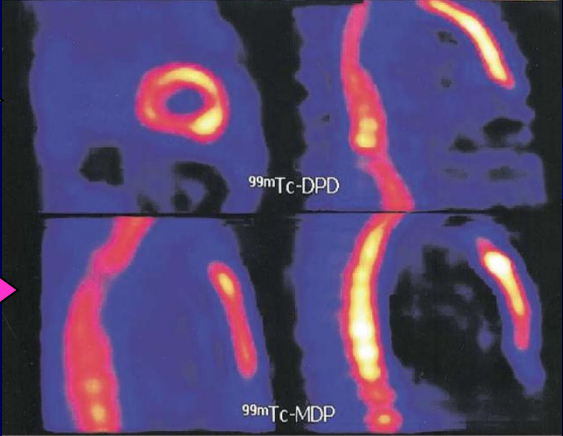
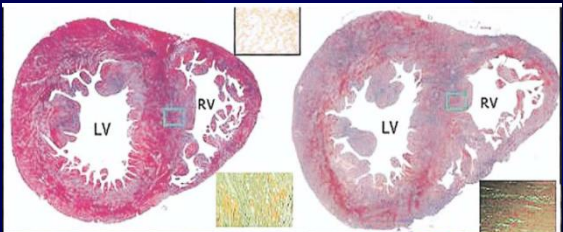
Bind also skeletal muscle, lung and soft tissue

ATTRv (Ser77Tyr) showed reduced uptake

Year	Country	Study design	Patients evaluated	Mean age (years)	Gender (% male)	Type of cardiac amyloidosis	Type of cardiac ATTR
2017	Italy	Retrospective two-centre	85	76	78	39 ATTR, 26 AL	16 ATTRm, 23 ATTRwt
2017	Australia	Prospective single-centre	21	65	90	13 ATTR, 8 AL	3 ATTRm, 8 ATTRwt
2016	USA	Retrospective multicentre	171	73	86	121 ATTR, 34 AL	37 ATTRm, 72 ATTRwt, 12 ATTRunknown
2016	Several	Retrospective multicentre	374	NR	NR	261 ATTR, 80 Other amyloidosis	NR
2015	France	Prospective single-centre	98	75	70	47 ATTR, 14 AL	26 ATTRm, 21 ATTRwt
2015	Greece	Retrospective two-centre	12	70.6	66.7	6 ATTR, 6 AL	NR
2014	UK	Retrospective single-centre	236	72	80	178 ATTR, 58 Other amyloidosis	46 ATTRm, 132 ATTRwt
2013	USA	Prospective single-centre	45	70	84	33 ATTR, 12 AL	17 ATTRm, 16 ATTRwt
2012	Spain	Retrospective single-centre	19	64.4	58	8 ATTR, 11 AL	3 ATTRm, 5 ATTRwt
2011	Italy	Retrospective single-centre	94	62	80	45 ATTR, 34 AL	28 ATTRm, 17 ATTRwt
2005	Italy	Retrospective single-centre	35	57.6	NR	15 ATTR, 10 AL	10 ATTRm, 5 ATTRwt
2002	Germany	Retrospective single-centre	18	54.4	50	8 ATTR	8 ATTRm

ATTR

AL



Pitfall

^{99m}Tc-MDP

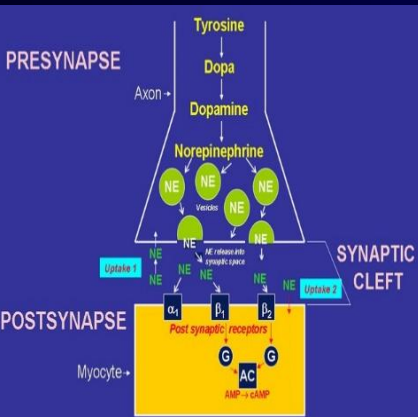
Not been validated in cardiac amyloidosis due to low sensitivity



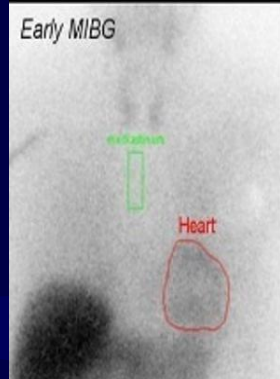
^{123}I -MIBG & ^{123}I -SAP: non-invasive dg of cardiac ATTR?

Metaiodobenzylguanidine:
χημικό ανάλογο της
NorEpi, οπότε υφίσταται
ενεργητική μεταφορά &
αποθήκευση στις
προσυναπτικές απολήξεις
των συμπαθητικών
νεύρων,

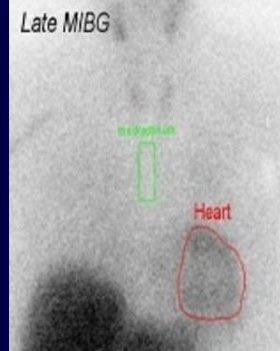
όπου και καθλώνεται,
καθώς δεν μεταβολίζεται
περαιτέρω



Planar images



heart to mediastinum ratio
HMR: $\text{HMP}_{20\text{min}} = \frac{\text{Heart}}{\text{Mediastinum}} > 1.6$



% έκπλυσης του ραδιοφαρμάκου
(washout) από την καρδιά στις 4h
 $\frac{\text{HMP}_{20\text{min}}}{\text{HMP}_{4\text{h}}} < 20\%$

MIBG SPECT

SA (APEX→BASE)

Early MIBG

Late MIBG

HLA (INF→ANT)

Early MIBG

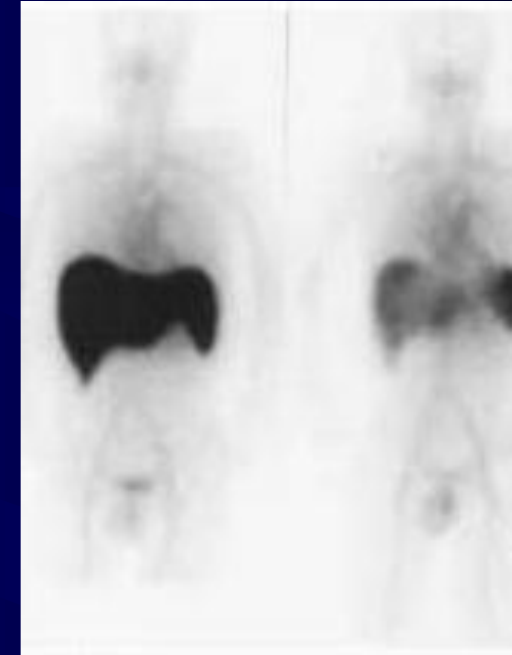
Late MIBG

VLA (SEP→LAT)

Early MIBG

Late MIBG

The specific amyloid tracer ^{123}I -SAP:
neither available
nor useful in imaging CA due to
blood-pool & ↓signal-to-noise ratio



Serum amyloid P component (SAP) is a normal blood protein, present in everybody, which is always present in amyloid deposits, in all types of amyloidosis because it binds strongly to amyloid fibrils of all types.

NATIONAL AMYLOIDOSIS CENTRE
Centre for Amyloidosis & Acute Phase Proteins
Division of Medicine (Royal Free Campus)
University College London
Royal Free Hospital
Rowland Hill Street, London NW3 2PF

Falk et al. *Circ Cardiovasc Imaging*.
2014

Delahaye N et al. *Eur J Nucl Med*. 1999
Tanaka M et al. *J Am Coll Cardiol*. 1997
Coutinho MC et al. *Circ Cardiovasc Imaging*. 2013
Sharp et al. *radiographics.rsna.org* 2016

^{123}I -MIBG για μελέτη αδρενεργικής νεύρωσης

✓ Myocardial sympathetic denervation:

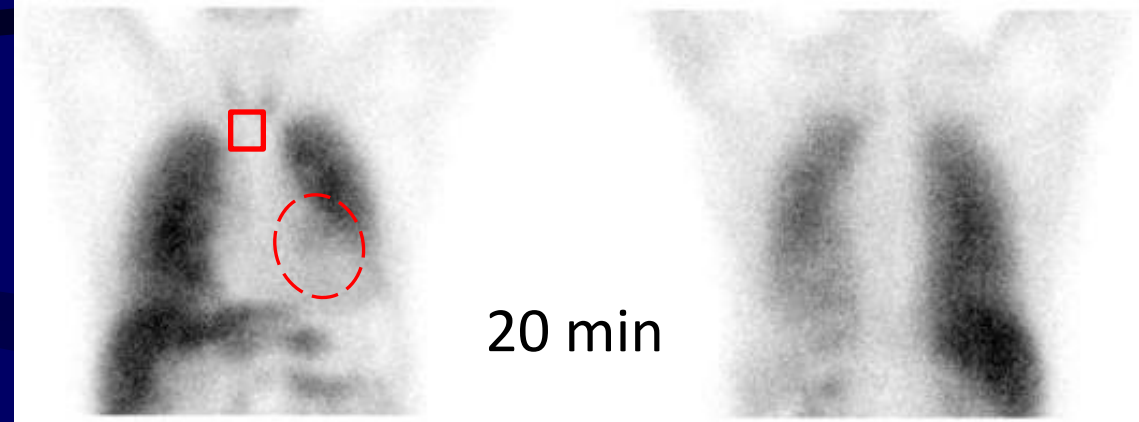
~early feature of cardiac involvement,
especially in individuals with TTR familial amyloid polyneuropathy:

AD with single-point mutations in the TTR gene who present with neuropathy/sensorimotor & autonomous, V30M with or without cardiac involvement or V122I solitary cardiac involvement

✓ In a study of 142 individuals with the FAP V30M variant:

a H-to-mediastinal uptake ratio < 1.6 vs ≥ 1.6 on ^{123}I -MIBG detected patients with high risk of mortality (HR 7.9, 95% CI, 3.38-15.2)prognostic indicator...but careful interpretation!

...may be affected by comorbidities, e.g., DM & neurodegenerative processes



20 min

heart to mediastinum rate -HMR
HMP_{20min}=1,27 HMR_{4ώρες}=1,18 ($\Phi T > 1,6$)



% έκπλυσης του ραδιοφαρμάκου (washout) από την καρδιά στις 4 ώρες $\geq 35\%$ (με $\Phi T < 20\%$)

ANT 1008K

POST 834K

Nonbiopsy diagnosis of Cardiac ATTR with cardiac scintigraphy using bone-seeking tracers: Standards and Pitfalls

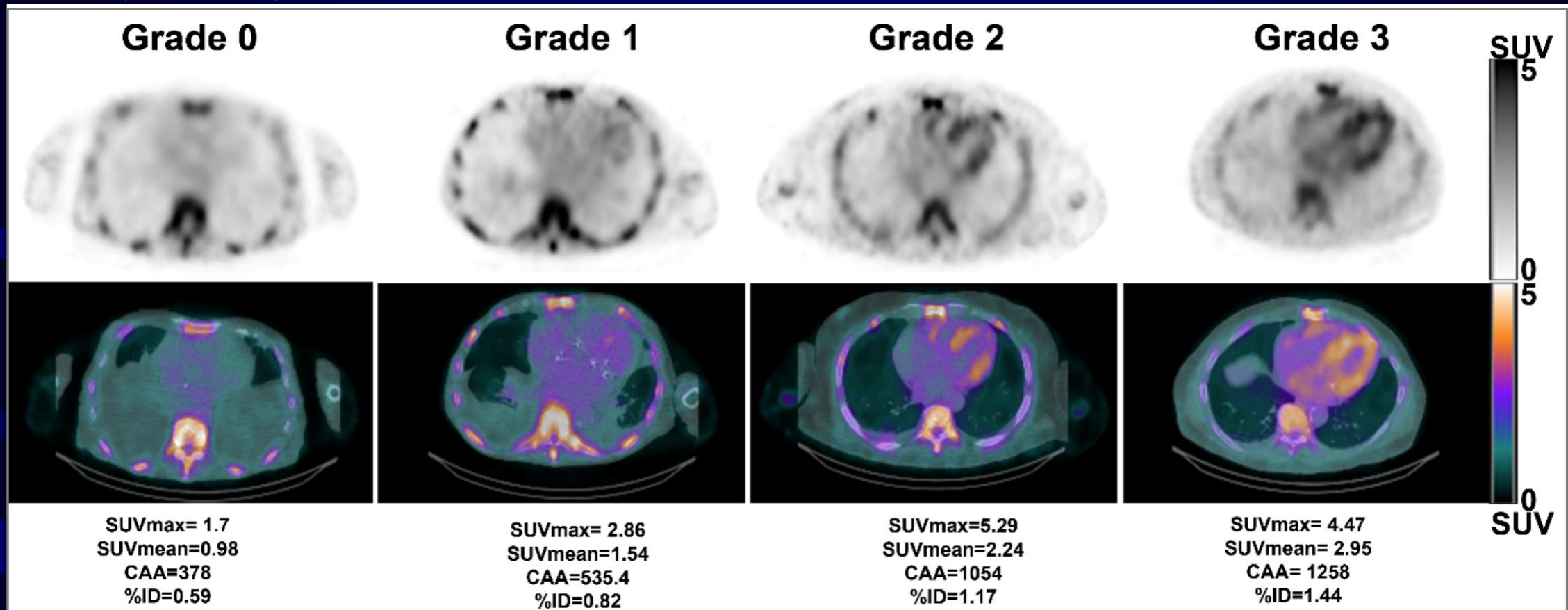
Quantification and Response to Treatment

PET amyloid-tracers

Recommendations

Absolute Quantitation of Cardiac ^{99m}Tc -pyrophosphate Using Cadmium Zinc Telluride-based SPECT/CT

Can myocardial amyloid burden be quantified?



In 72 known or suspected ATTR pats:
SUV max and mean, CAA (cardiac amyloid activity= SUVmean*LV volume), & %ID were moderately correlated with LV mass indexed to body surface area (echo-LVMI) and strongly correlated with extracellular volume (CMR-ECV)

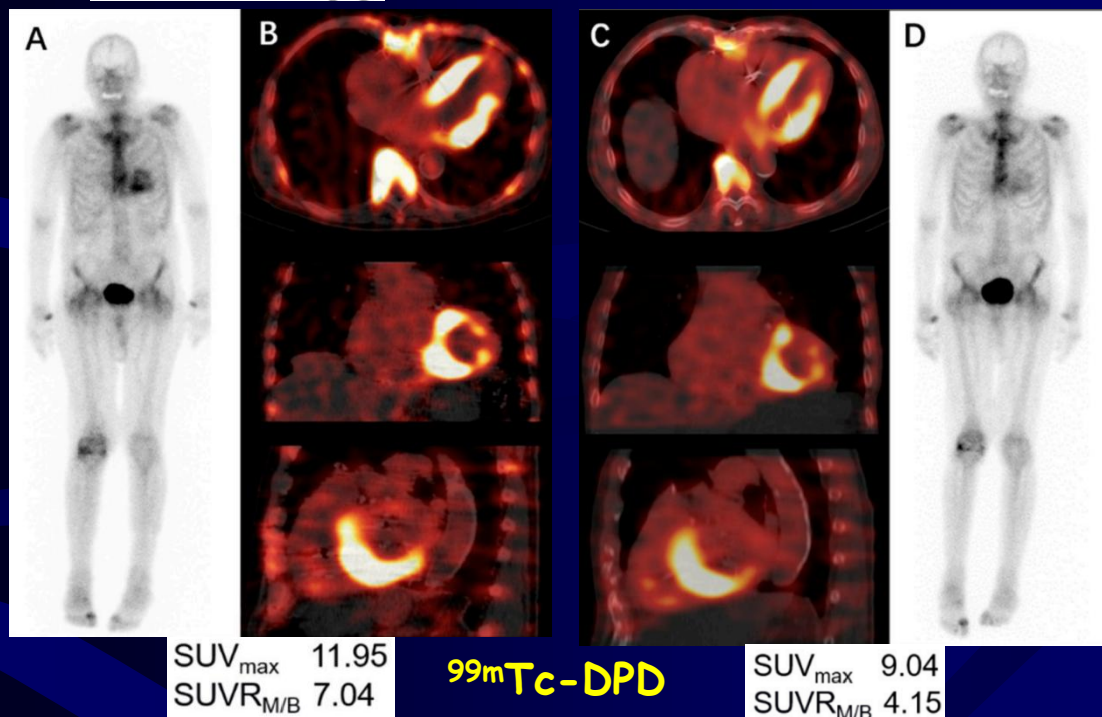
IMPLICATIONS FOR PATIENT CARE: Quantitative ^{99m}Tc -PYP SPECT/CT offers the potential for early detection, risk stratification, and monitoring of response to therapy in patients with cardiac amyloidosis.

Nuclear Molecular Imaging of Disease Burden and Response to Treatment for Cardiac Amyloidosis

ATTRwt: 6 mo on tafamidis

Pre-therapy

Post-therapy



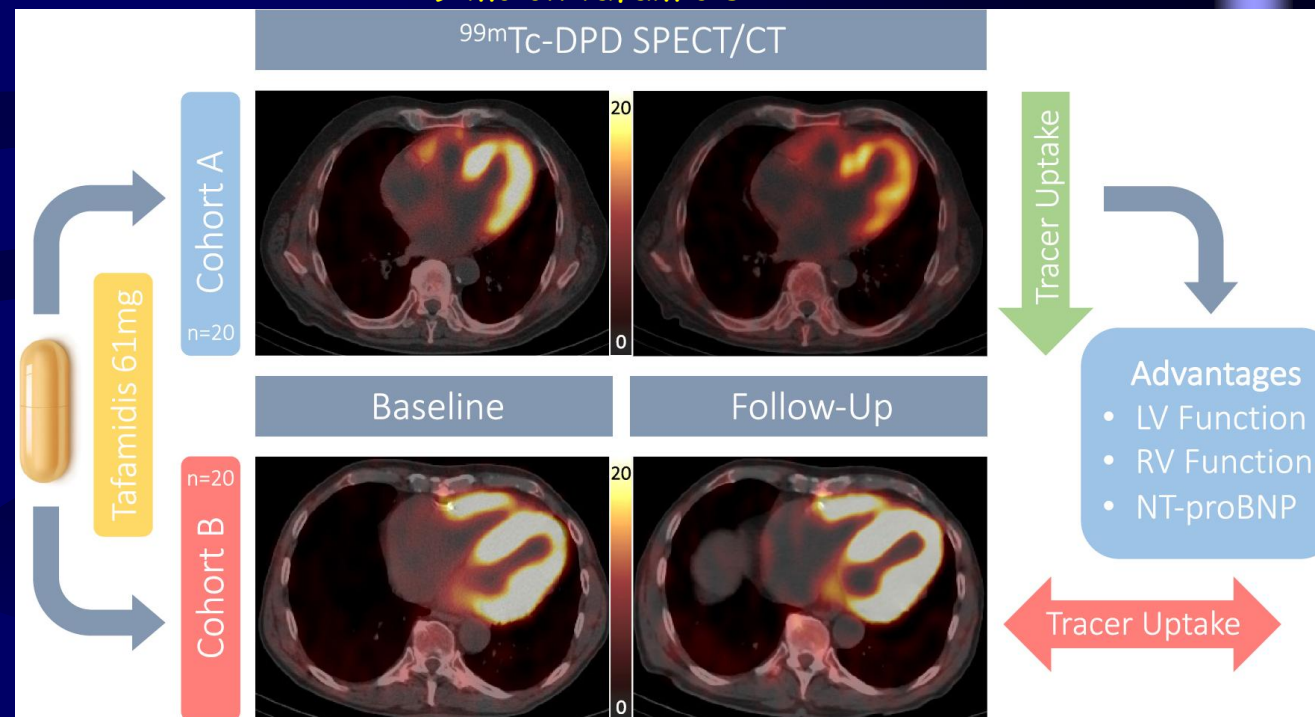
Quantitative SPECT/CT might be a promising tool for the assessment of **therapeutic response** and for managing the treatment of **ATTR**

$SUVR_{M/B} = SUV_{max}$ for myocardial/ background (blood pool)

Zhao et al. *Biology* 2022

Monitoring tafamidis treatment with quantitative SPECT/CT in transthyretin amyloid cardiomyopathy

40 ATTRwt: median
9 mo on tafamidis



Serial quantitative ^{99m}Tc-DPD SPECT/CT imaging with SUV may be a valid tool to quantify & monitor response to tafamidis treatment

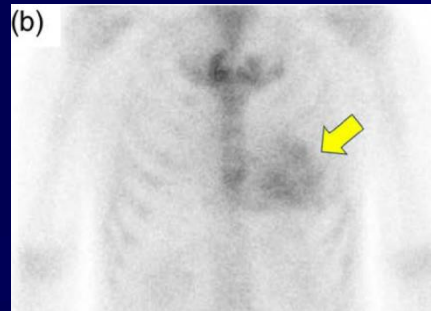
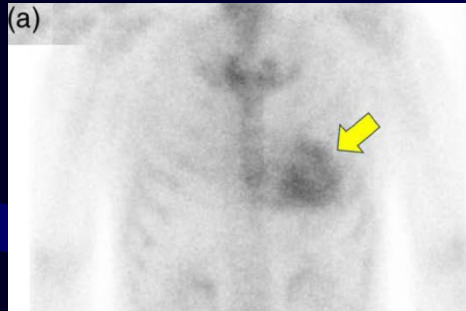
Retzl et al. *Eur Heart J - Cardiovasc Imag* 2023

Single-center analysis of cardiac amyloidosis using ^{99m}Tc -HMDP imaging for diagnosis and evaluation after tafamidis treatment

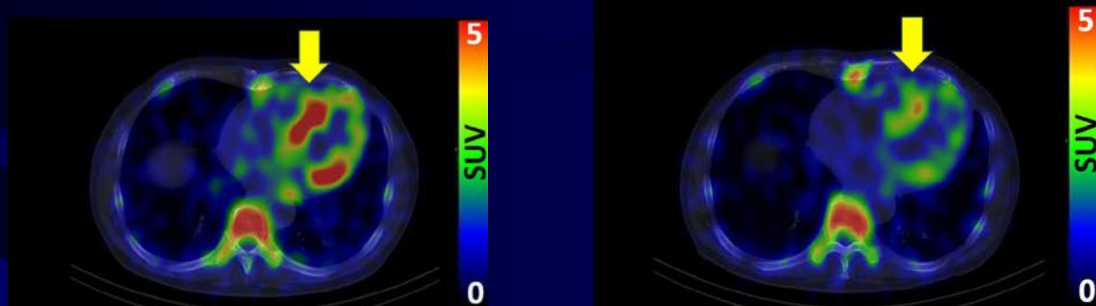
ATTRwt: 1 y on
tafamidis

Pre treatment

Post treatment



H/CL ratios before and after treatment were 2.19 and 2.12, respectively

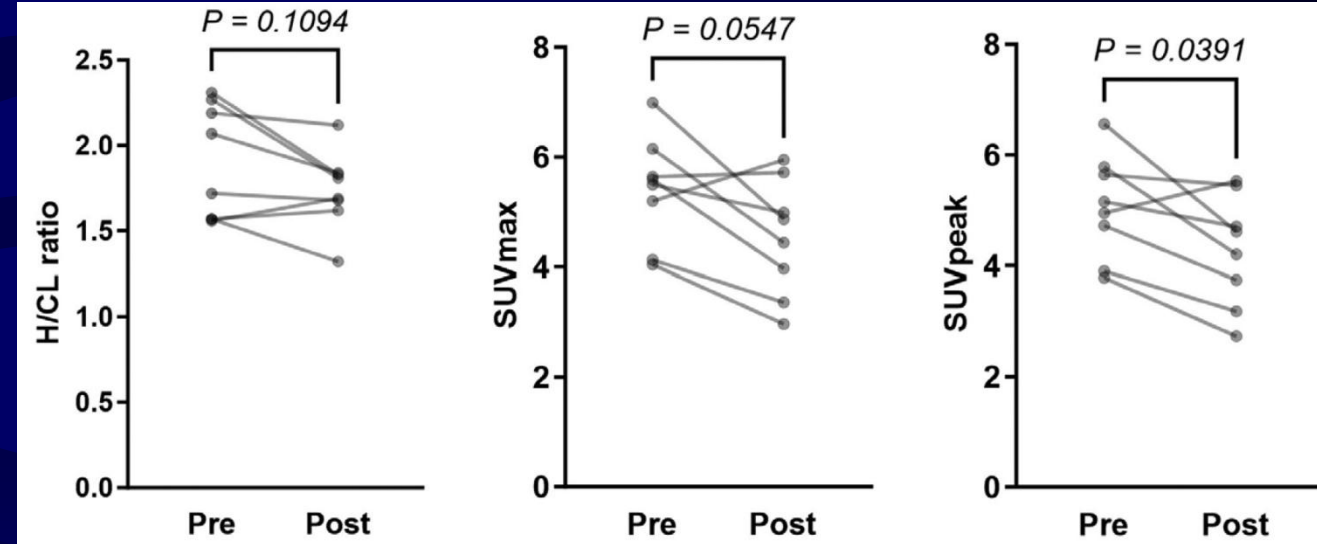


SUV_{max}
SUV_{peak}

6.99 and 4.87
6.52 and 4.61

H/CL ratio and
SUV_{max}/SUV_{peak} useful
for diagnosing cardiac
ATTR

Myocardial SUV_{peak} may
be useful for monitoring
changes in cardiac uptake
after tafamidis



There is also an ongoing clinical trial
(REMOD-TTR, NCT04535349)
designed to evaluate the effect
of 6 mo of tafamidis on quantitative
and semi-quantitative SPECT/CT
assessment of bone-seeking tracers

“ASSUMER” on PYP Scan for Cardiac Amyloid Typing and Origin: Case-Specific Corroborating Clinical Background and Genetic Analysis

❖ **Cardiac insufficiency:**
18mo

PTCA LAD 1 y earlier
Carpal tunnel sy: **bilat**
surgery: 6 y earlier
Vertebral canal stenosis
dg 12 mo earlier
Senile cataract surg 6 mo
earlier
Developmental dysplasia
of the left hip

Serum Cardiac Biomarker	Measurement in pg/mL	Normal Limits
troponin-T	55.83	< 14
NT-proBNP	2096.0	< 125

✓ **Meticulous investigation for underlying plasma cell dyscrasia/primary (AL) amyloidosis: (-)**

Specifically:
Serum electrophoresis & immunofixation: (-) for monoclonal paraprotein

Urine EP & IF: (-)

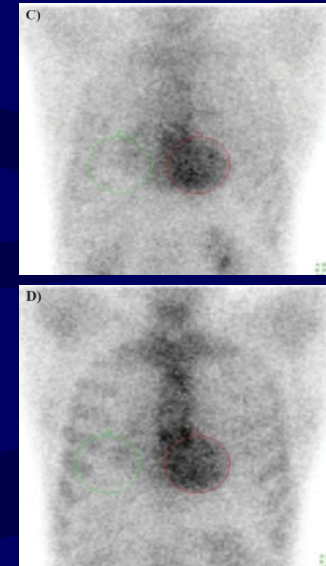
Serum Igs: wnl

➤ bm biopsy: wnl

➤ Fat (abd) aspirate: (-) for amyloid deposits

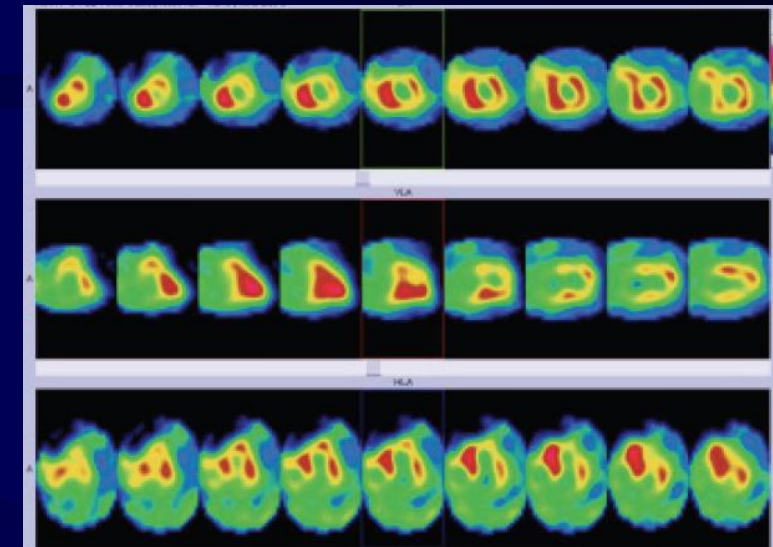
✓ Serum FLCs: wnl
κFLC: 10 mg/L (3.3-19.4)
λFLC: 11 mg/L (5.71-26.3)
κ/λ ratio: 0.91 (0.25-1.65)

79 y M



ATTRwt
Post-therapy with tafamidis
H/CL_{60min}: 1,64 vs 1,86
H/CL_{180min}: 1,41 vs 1,88

❑ **Genetic investigation for possible mutations in the TTR gene: (-)**



Diffuse intense biventricular myocardial tracer retention (grade 3) with Apical Sparing, Septal Uptake more marked and an associated myocardial Equivalent Retention, particularly H/CL ratio from 1 h to 3 h pi (“ASSUMER”) could be a hallmark of the amyloid fibril subtype and origin

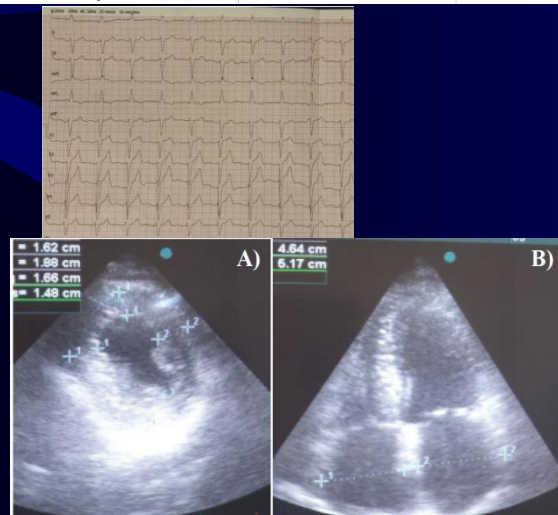


TABLE 1 Summary of Quantitative ^{99m}Tc-PYP/DPD/HMDP SPECT Metrics for Transthyretin Cardiac Amyloidosis

Definition		Units	Notes
SUV _{mean}	Tracer uptake in the VOI/(injected activity/patient weight) Mean value in the VOI	g/ml	1-6 Insensitive to early disease which may start focally
SUV _{max}	Tracer uptake in the VOI/(injected activity/patient weight) Maximal value in the VOI	g/ml	1-6 Represents a single voxel value Can be contaminated by spillover from bone
SUV _{peak}	Highest average SUV in a 1cm ³ sphere or average SUV of 1cm ³ centered on the voxel defined by SUV _{max}	g/ml	1-6 Affected by region selected Can be contaminated by spillover from bone
%ID	Product of mean activity concentration in the VOI and its volume normalized to injected dose	%	6 Independent of patient weight Considers myocardial volume
Retention index*	Ratio of average tissue activity within time range to integral of plasma activity from time of injection to midpoint of time range	min ⁻¹	Need early and dynamic images to quantify this measure Challenging with later imaging tracers
Target to background ratio	Heart to contralateral lung/whole-body activity ratio; Myocardium-to-blood pool activity or SUV ratio	Unitless	Simple to use Affected by activity in the background
Cardiac amyloid activity	Product of SUV _{mean} and volume	g	3, 6 Incorporates volume
Volume of amyloid	Volume of myocardium above defined threshold value	ml	6 May be insensitive to early disease

Harmonization of imaging protocols, such as the uptake period for a given tracer, and calibration are crucial for clinical adoption of quantitative SPECT metrics

Developing quantitative SPECT tracer-based measurements of amyloid burden is a crucial first step toward early diagnosis and cost-effective management of HFpEF from ATTR-CA

Nonbiopsy diagnosis of Cardiac ATTR with cardiac scintigraphy using bone-seeking tracers: Standards and Pitfalls

Quantification and Response to Treatment

PET amyloid-tracers

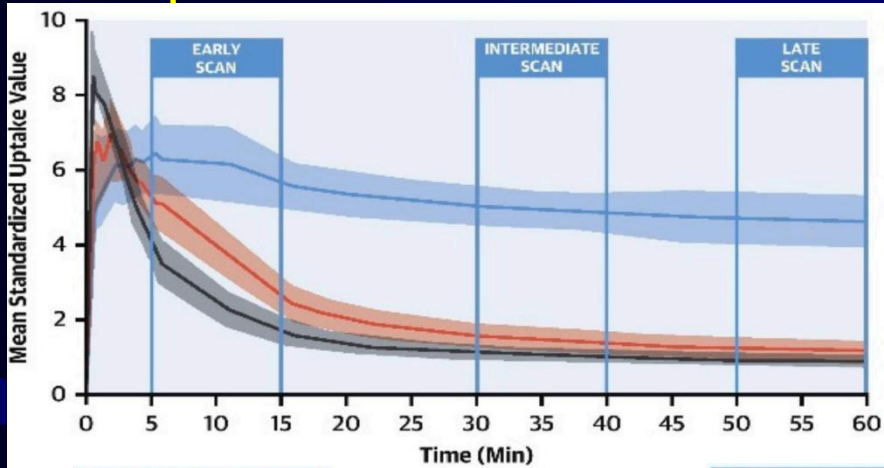
Recommendations



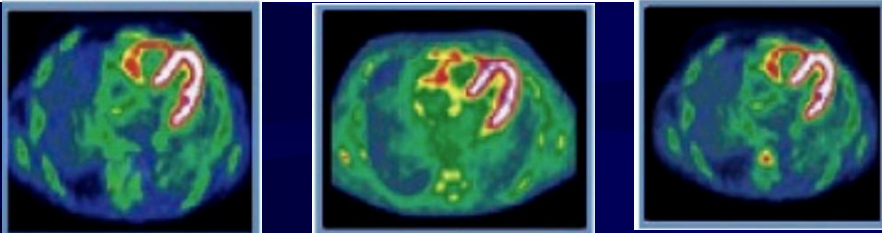
Pitfalls: Differential diagnosis of the subtype of cardiac amyloidosis is NOT effectuated by PET amyloid tracers...or?

under investigation

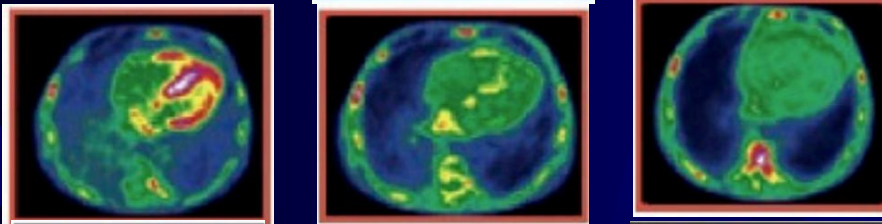
- ^{18}F -florbetapir
- ^{11}C -PiB
- ^{18}F -florbetaben
- ^{18}F -flutemetamol
- ^{124}I -evuzamitide



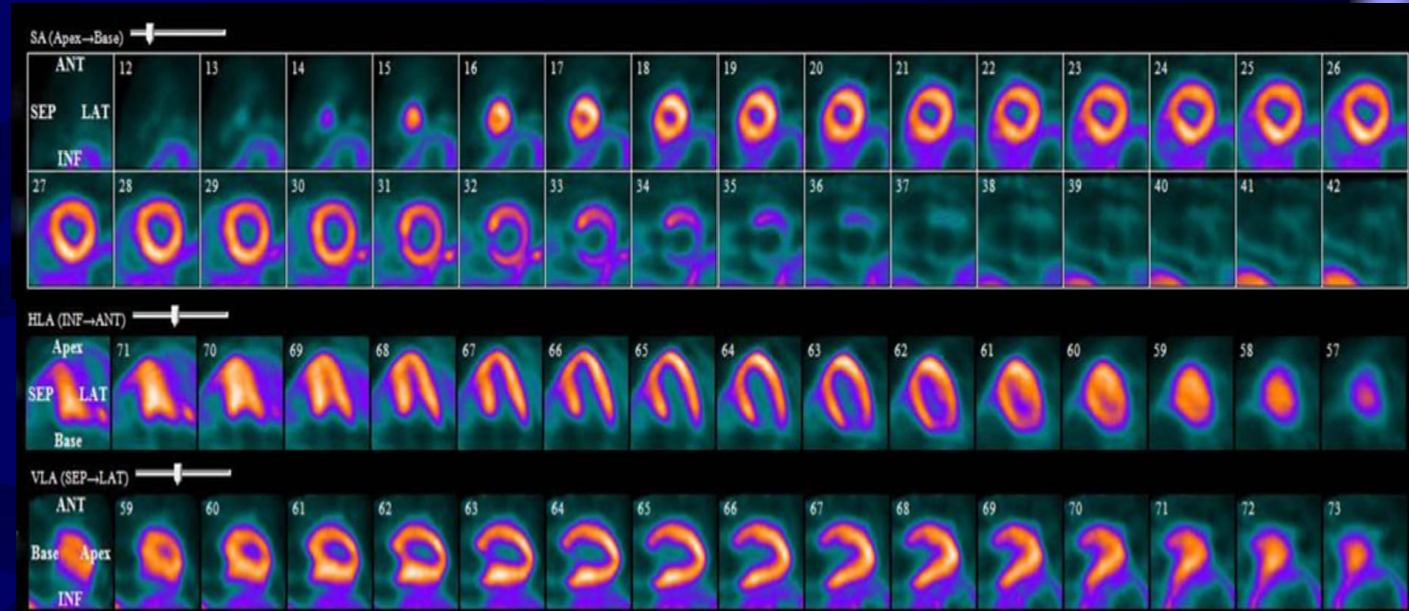
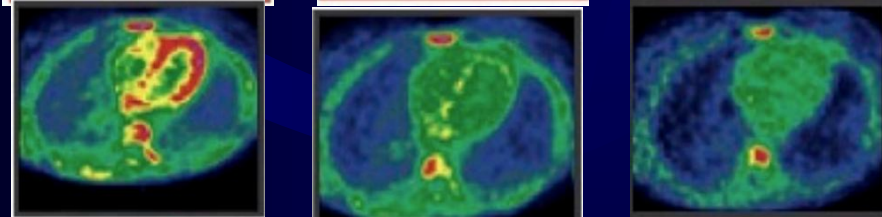
AL



ATTR



No CA



Rest ^{18}F -florbetapir in ATTR

- direct imaging of amyloid fibrils
- potential quantification of the amyloid burden
- detection of early cardiac involvement, prior to structural alterations

Antoni et al. J Nucl Med. 2013
Falk et al. Circ Cardiovasc Imaging. 2015
Genovesi et al. JACC Cardiovasc Imaging 2021

Non-invasive dg of cardiac ATTR: is FDG PET useful?

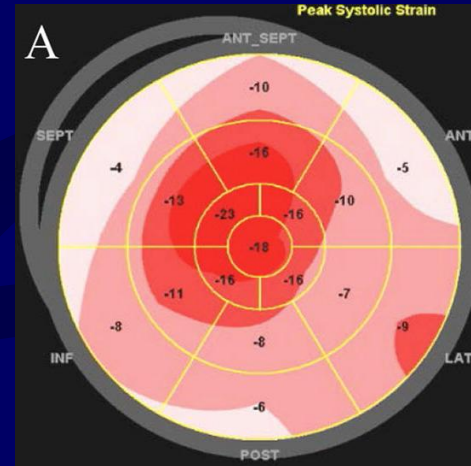
➤ PET tracers: ^{18}F -FDG/ ^{13}N -ammonia:

- is frequently utilized to evaluate cardiac sarcoidosis (CS) but findings can reflect other forms of myocardial inflammation or altered myocardial metabolic activity

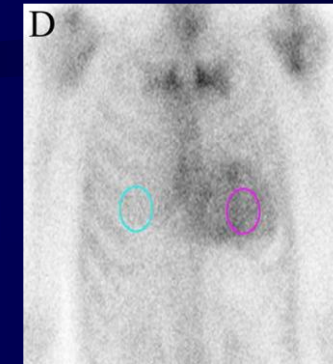
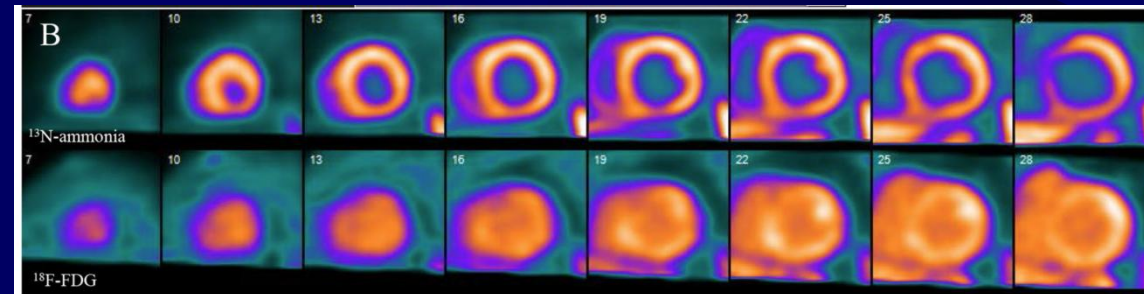
5 cases where cardiac PET findings suggested CS, but RV endomyocardial biopsy samples revealed ATTR-type cardiac amyloidosis

77-y-o man with history of bilateral carpal tunnel syndrome & spinal stenosis who presented with progressive dyspnea on exertion

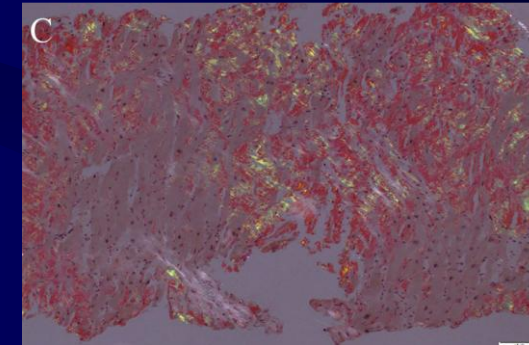
ECG sinus rhythm with 1st degree AV block multiple PVC, & q-waves in the inferior leads consistent with prior inferior MI



LV global longitudinal strain on TTE: abn at -12% (normal = more negative than -18%) with apical sparing, a pattern consistent with cardiac amyloidosis



PYP scan
H/CL 1.9
on 3-h
imaging



Representative EMB pathology sample with Congo red stain demonstrating green birefringence under cross-polarized light (100x original magnification).

Nonbiopsy diagnosis of Cardiac ATTR with cardiac scintigraphy using bone-seeking tracers: Standards and Pitfalls

Quantification and Response to Treatment

PET amyloid-tracers

Recommendations

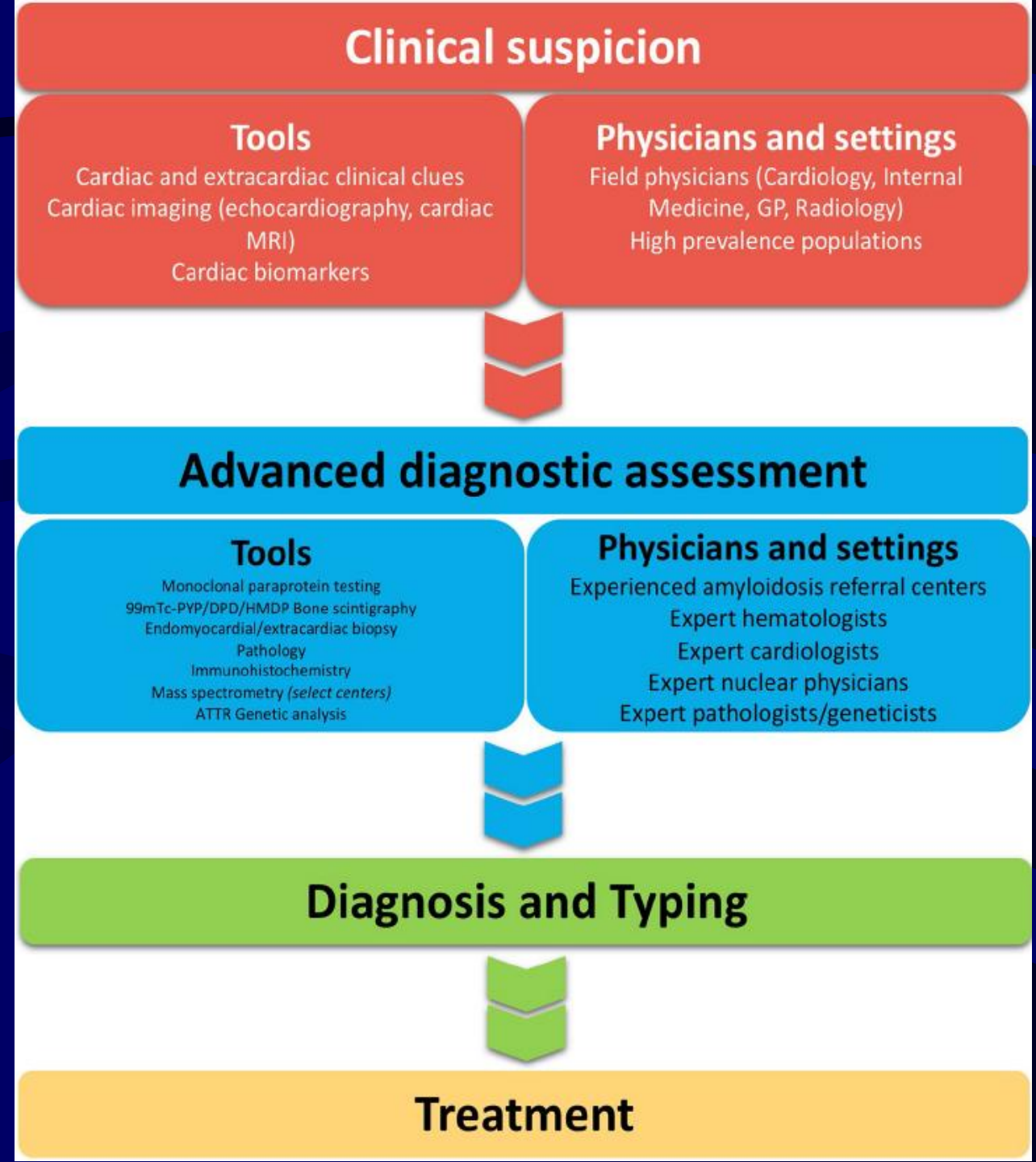
Heightened Index of Suspicion

- Increased wall thickness without obvious cause
- HFpEF with concomitant right heart failure (+JVP, hepatomegaly, edema)
- Discordance of wall thickness and electrocardiographic voltage
- History of carpal tunnel syndrome, lumbar spinal stenosis, or spontaneous biceps tendon rupture
- Low flow, low gradient aortic stenosis
- Diffuse late gadolinium enhancement or increased extracellular volume of cardiac MRI
- Apical longitudinal strain preservation
- Natriuretic peptides elevated out of proportion to clinical syndrome
- Persistently positive troponin in the absence of acute coronary syndrome

Ruberg FL, et al. J Am Coll Cardiol. 2019

Fig. 2 Proposed integrated diagnostic management strategy of patients with cardiac amyloidosis

Heart Failure Reviews Springer Nature 2021



Take home messages

^{99m}Tc-PYP/DPD/HMDP scan has been incorporated in multisocietal guidelines for the non-invasive dg of cardiac ATTR thus avoiding the need for biopsy

-Reference Centers: multidisciplinary approach

...with valuable implications in:
prognosis
treatment- incl. novel therapeutic choices:
tafamidis (stabilizes TTR)
patisiran (inhibits TTR synthesis)
genetic guidance

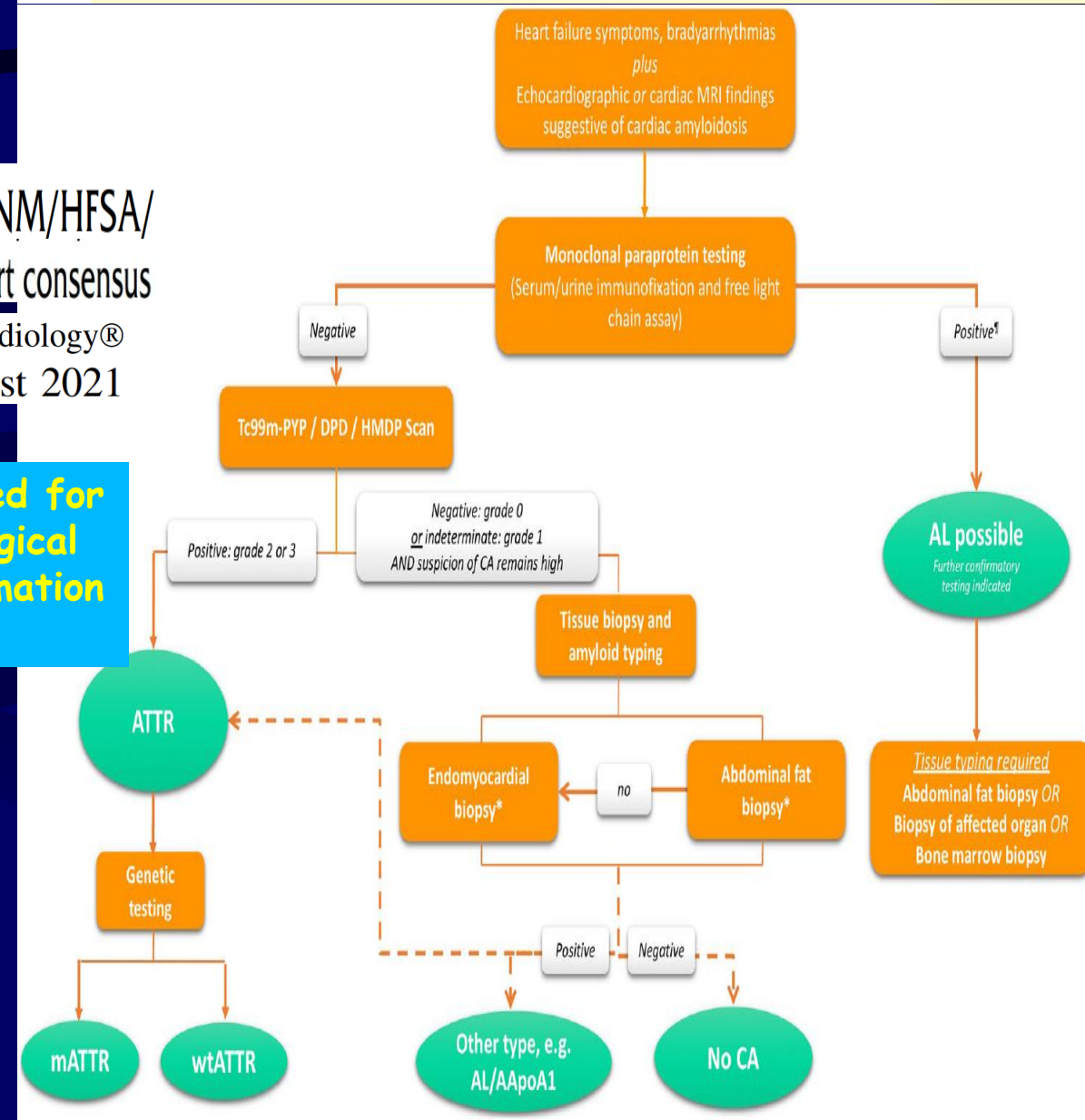
➤ ^{99m}Tc-PYP/DPD/HMDP scan
χρήσιμο σε ασυμπτωματικούς
ATTR με (-) ECHO/MRI:
ως screening test: grade 1 υποδεικνύει
αρχόμενη καρδιακή διήθηση

ASNC/AHA/ASE/EANM/HFSA/
ISA/SCMR/SNMMI expert consensus

Journal of Nuclear Cardiology®
July/August 2021

No need for histological confirmation

Fig. 3 Proposed algorithm for the diagnostic workup of patients with suspected cardiac amyloidosis



Potential Recommendations

Further uses

regarding disease progression/arrest:

follow-up

assessment of response to treatment

- incorporate **scan indices** (H/CL or SUV retention index) as part of a routine annual exam
- investigate **relationship between therapy-induced reduction in scan indices and outcome**

Could ^{99m}Tc -PYP/DPD/HMDP scan be utilized in the elderly as noninvasive screening test for cardiac ATTR disease?



Thank you for your attention