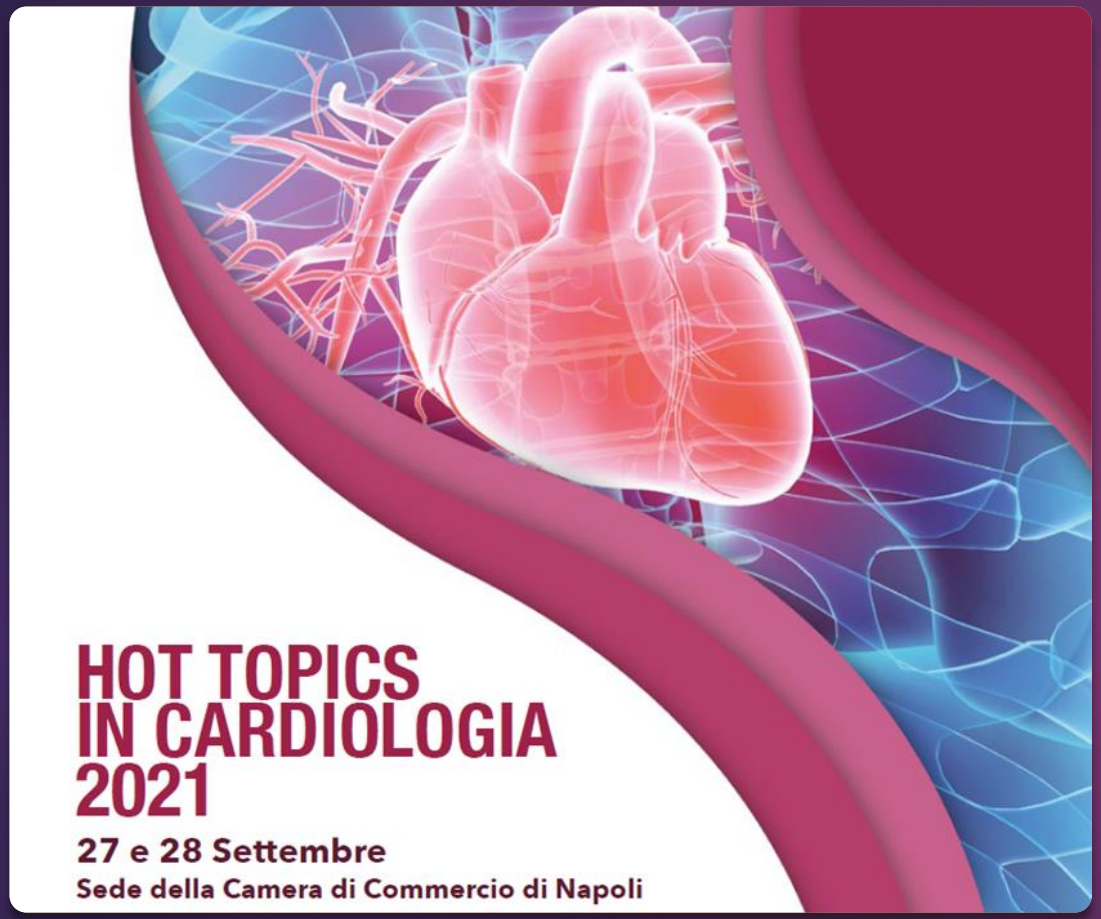
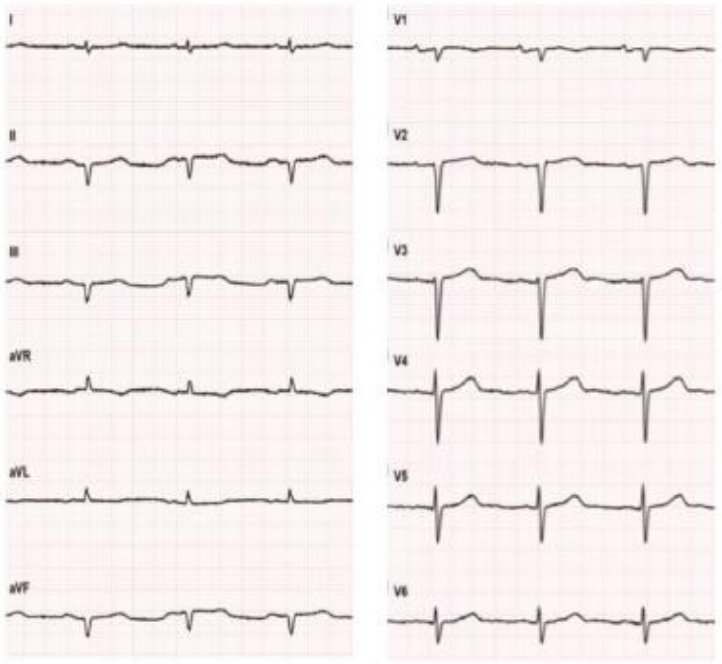


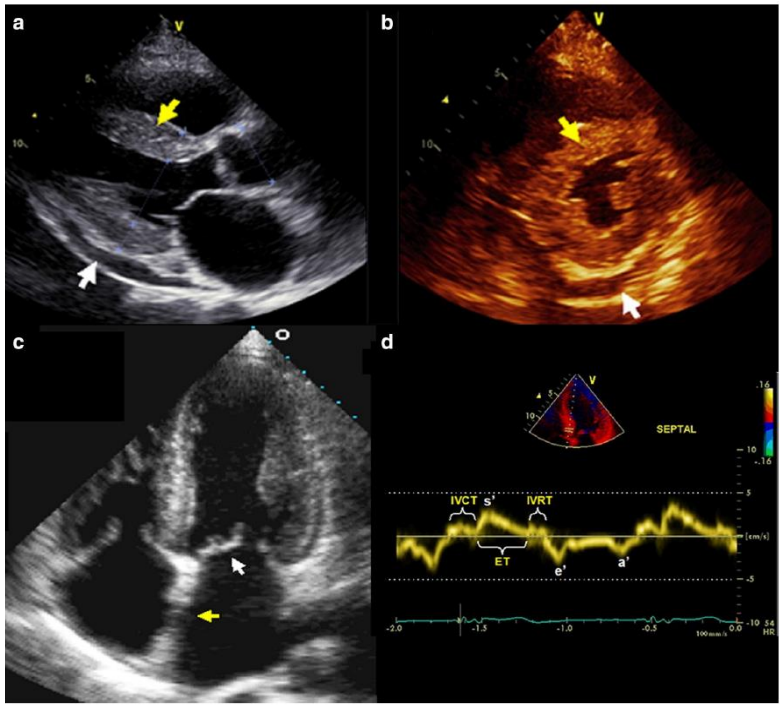
Amiloidosi cardiaca: ruolo della Medicina Nucleare

dott.ssa Mara Catalano
UOC Medicina Nucleare
AORN A. Cardarelli Napoli

Transthyretin amyloid cardiomyopathy: An uncharted territory awaiting discovery

European Journal of Internal Medicine 2020





- Bassi voltaggi: QRS<1mVnelle precordiali
  <0.5mV nelle periferiche
- Pattern pseudo infartuale con onde Q o ritardata progressione R
- BAV o BBS
- FA

Diagnostics 2021

Sospetto diagnostico

Cardiac amyloidosis should be considered if, in addition to concentric LV wall thickening (≥ 12 mm)—in the absence of hypertensive heart disease—one of the following points is present
Age > 60 years, symptoms of heart failure and still normal-sized ventricles
Low voltage or detection of an AV block in the resting ECG
Evidence of pericardial effusion, interatrial thickening, an echo hyperintense myocardial texture, a wall thickening of the RV, a valve thickening, or an "apical sparing"
Pathognomonic macroglossia with notches in the lateral parts of the tongue
Periorbital purpura (typically after minor injuries)
Atraumatic biceps tendon rupture
Carpal tunnel syndrome (mostly on both sides)
Sensorimotor polyneuropathy, neuropathic pain of unknown origin
Spinal stenosis
Autonomic dysfunction as well as orthostatic hypotension and erectile dysfunction
Vitreous opacity and pathognomonic pupillary changes

Clinical Research in Cardiology 2021

Amiloidosi cardiaca

- PATOLOGIA RARA O SOTTODIAGNOSTICATA?
- ALGORITMO DIAGNOSTICO IDEALE
- DIAGNOSTICA NON INVASIVA VS INVASIVA
- NUOVE TERAPIE

Cardiomiopatie infiltrative

- Amiloidosi
- Sarcoidosi
- Emocromatosi

↓

Deposito sostanze anomale

↓

IVS
Pattern restrittivo

Genesi fibrille amiloide

Eccessiva produzione di catene leggere monoclonali da discrasia plasmatica → **AL Amiloidosi**

Proteina di trasporto omotetramerica prodotta dal fegato che si disgrega e riassembla in maniera casuale → **Transtiretina Amiloidosi : ereditaria e Wild-type**

Amiloidosi ATTR

- Variante acquisita wildtype (ATTR wt)

  -sesso maschile

  -età avanzata

  -cardiomiopatia ipertrofica restrittiva ad insorgenza tardiva

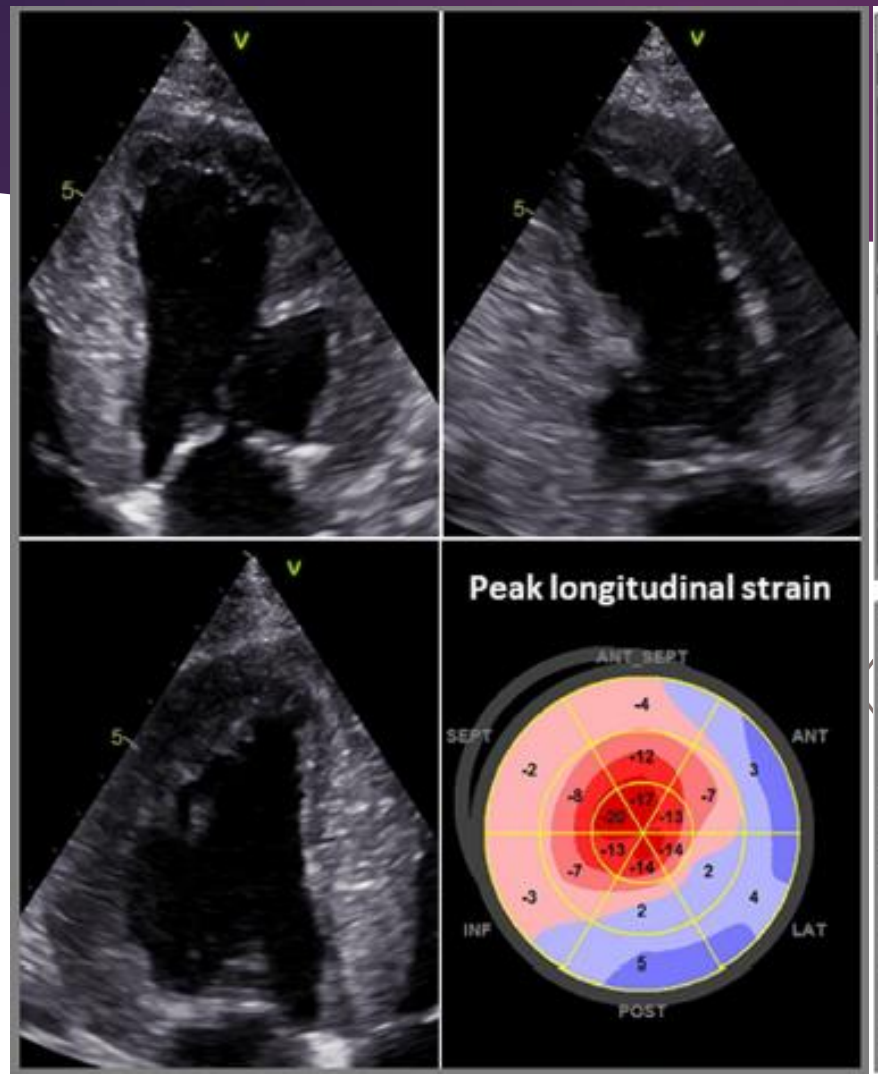
- Variante da mutazione ereditaria (ATTRm)

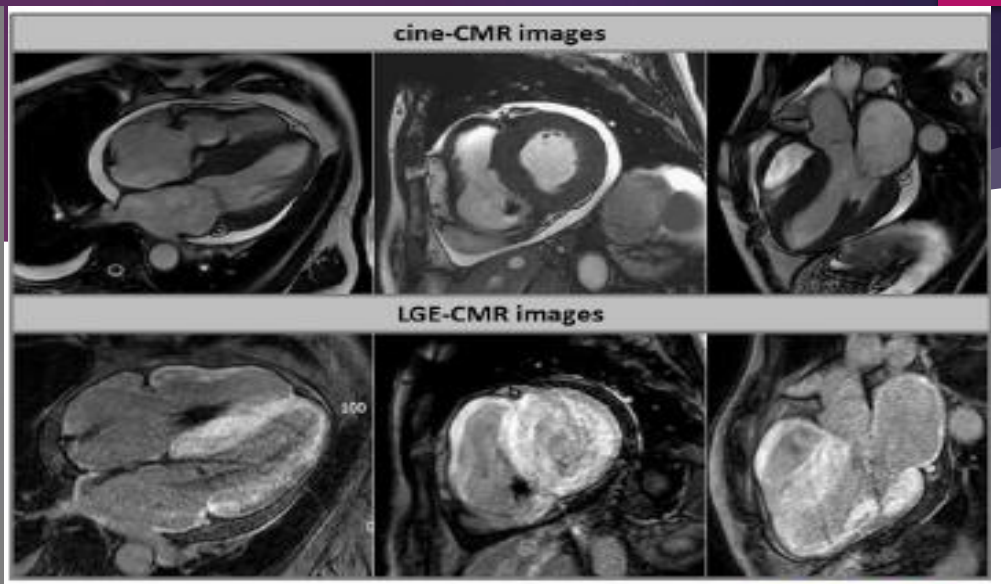
  -mutazioni di uno o più tratti del gene TTR

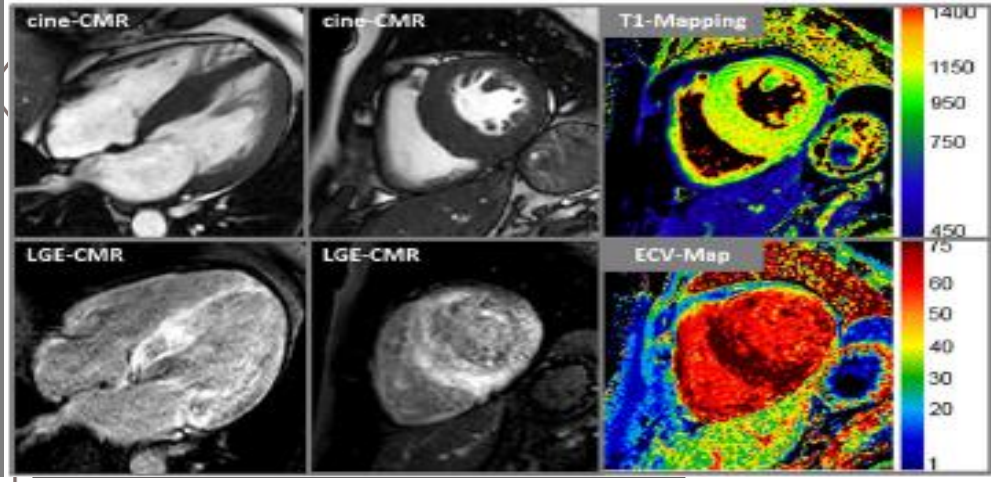
  -polineuropatia o più raramente cardiomiopatia o entrambe

DD: Test mutazione gene TTR

Sospetto clinico







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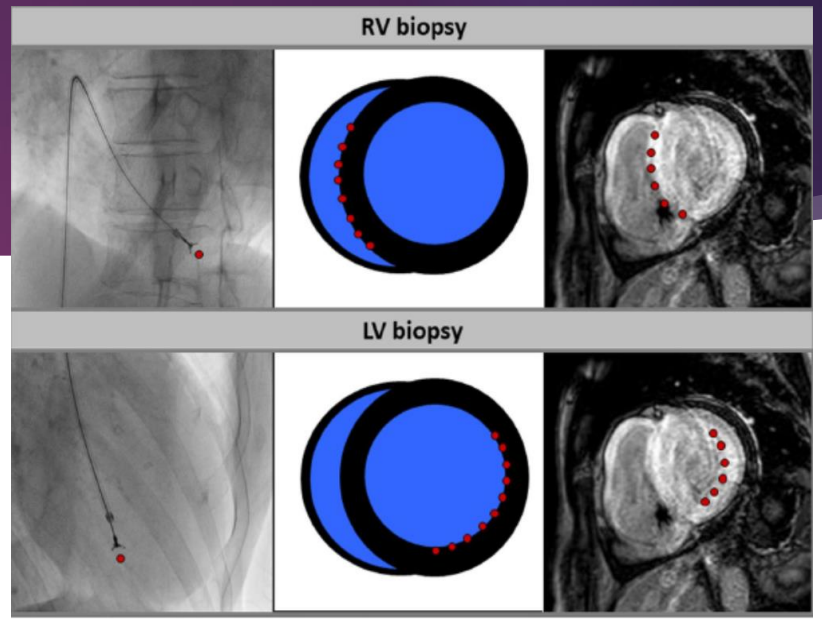
DIAGNOSI



Biopsia miocardica
-100% sensibilità
-Invasiva/Complicanze

-Caratterizzazione fenotipica
-IHC

Imaging non invasivo con RF a tropismo osseo

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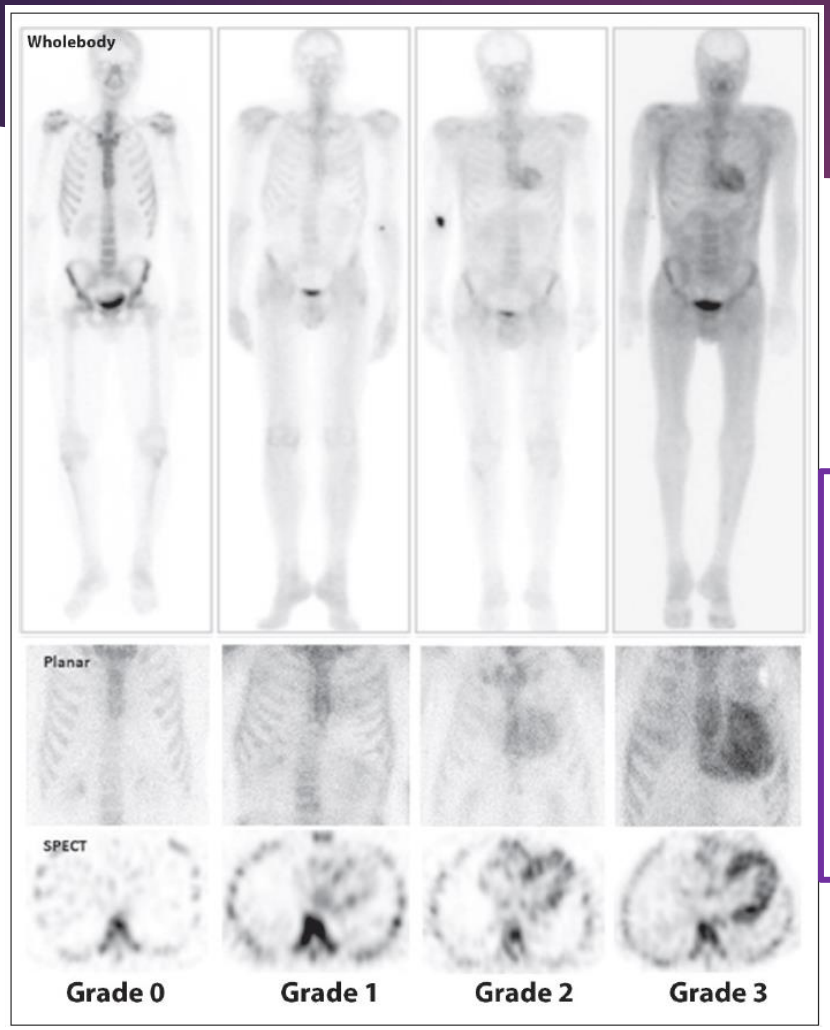
RF a tropismo osseo

- 99mTc-DPD e 99m-HMDP(extra-USA)
- 99mTc-PYP (USA)

Assenza di studi di comparazione

Scintigrafia ossea



Assente Focale Diffuso Focale su diffuso

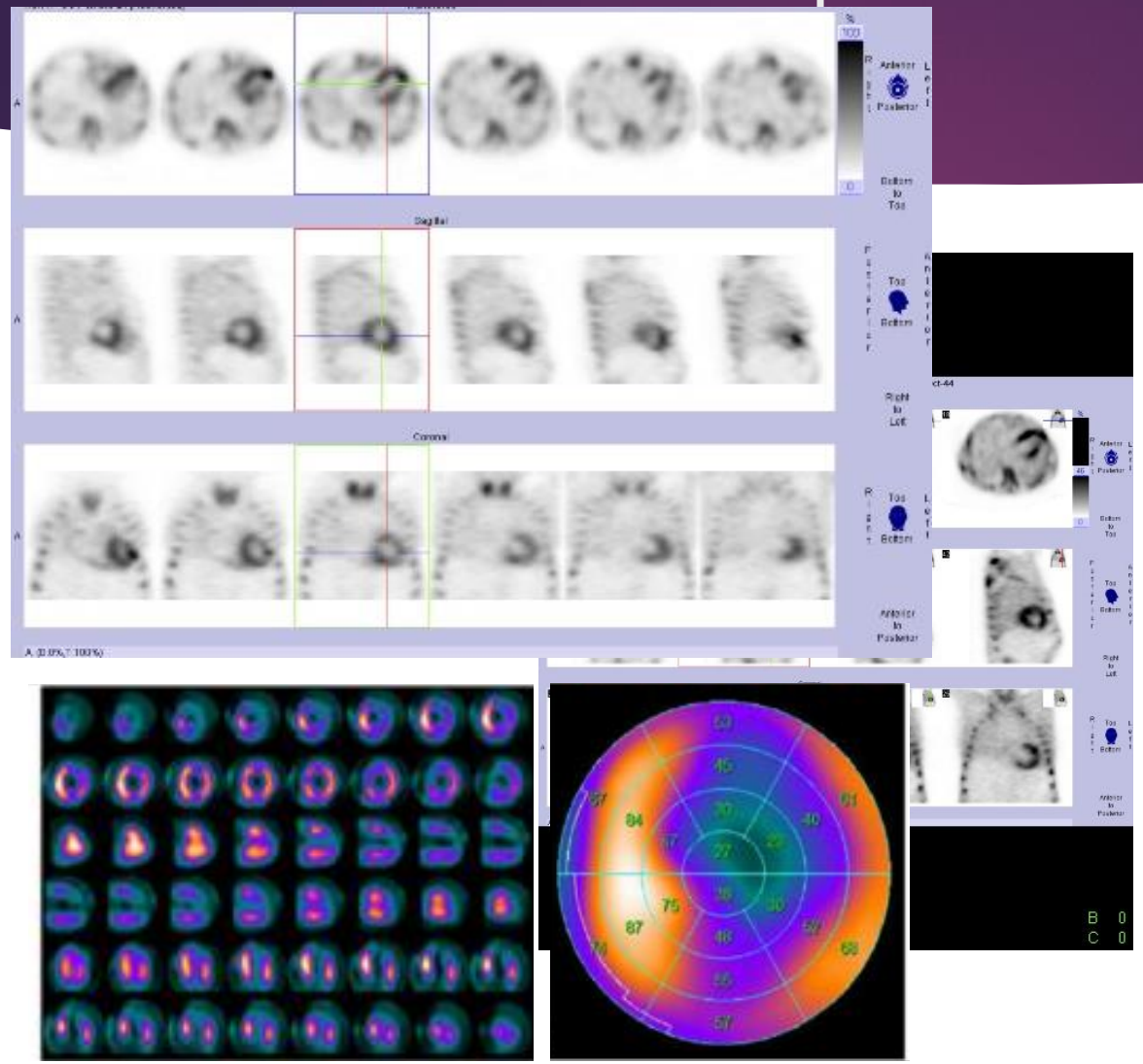
Perugini score

ATTR + ≥ grade 2

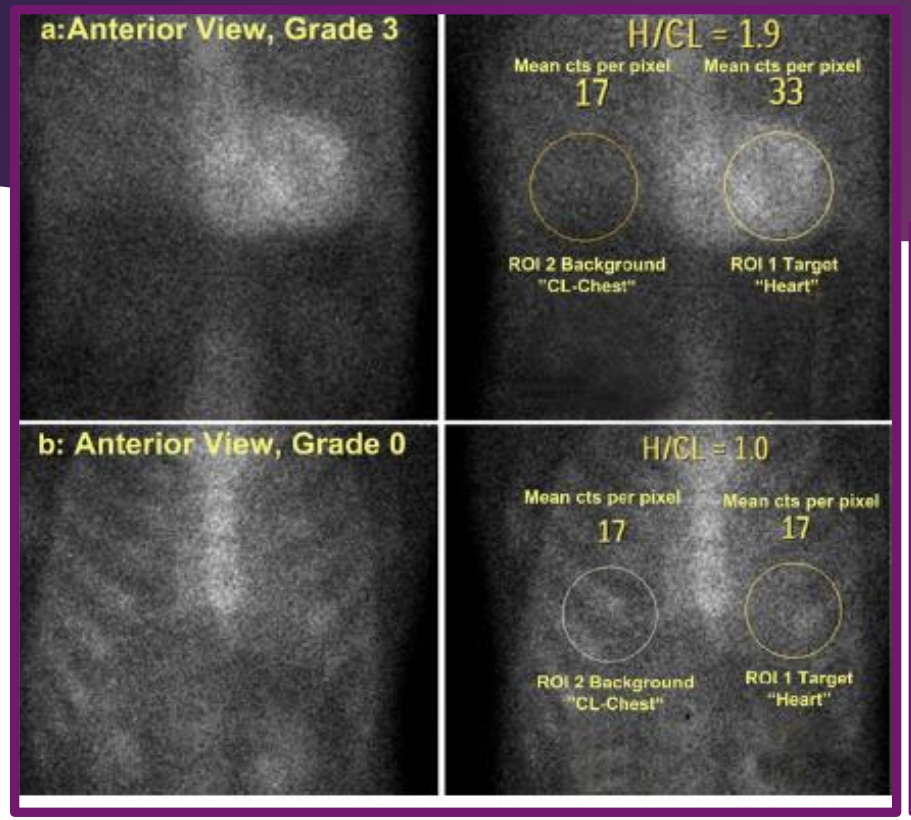
Table 2. Semi-quantitative Visual Grading of Myocardial ^{99m}Tc-DPD/HMDP Uptake by Comparison to Bone (rib) Uptake

Grade	Myocardial ^{99m}Tc-DPD/HMDP Uptake
Grade 0	no uptake and normal rib 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

SPEC
T



Analisi semiquantitativa



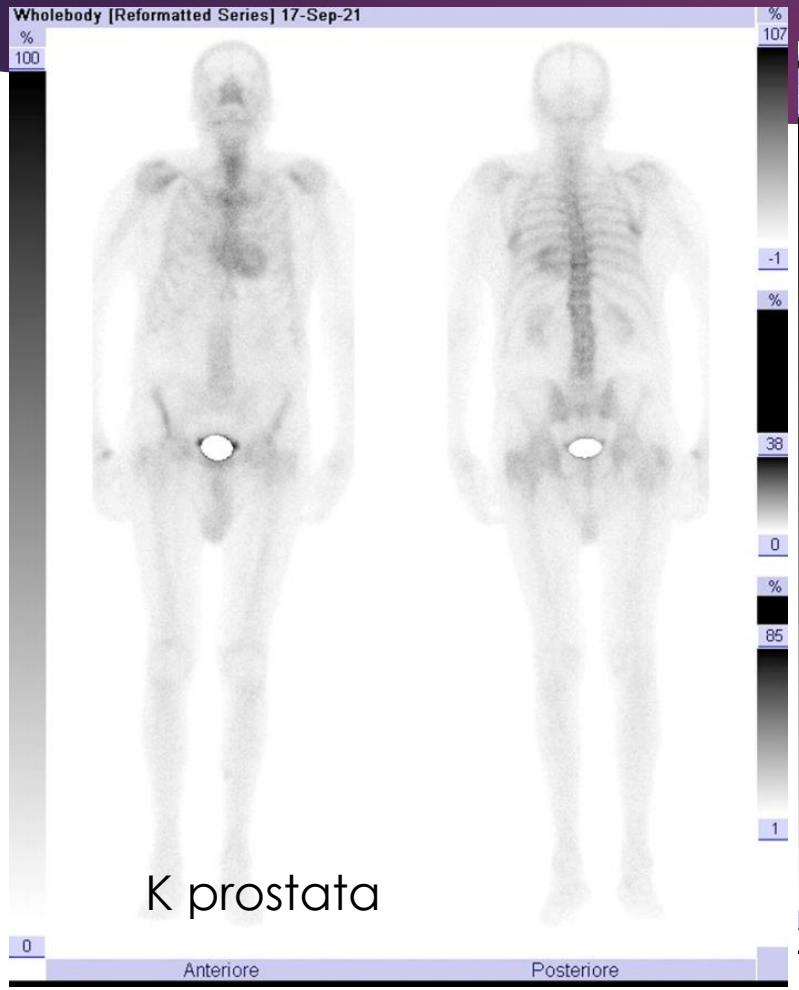
Analisi semiquantitativa

- H/CL (heart/controlateral lung)
- HR (heart tracer retention)
- WBR (whole body tracer retention)
- SR (skull retention)
- H/WB (heart/whole body uptake)
- H/S (heart/skull uptake)

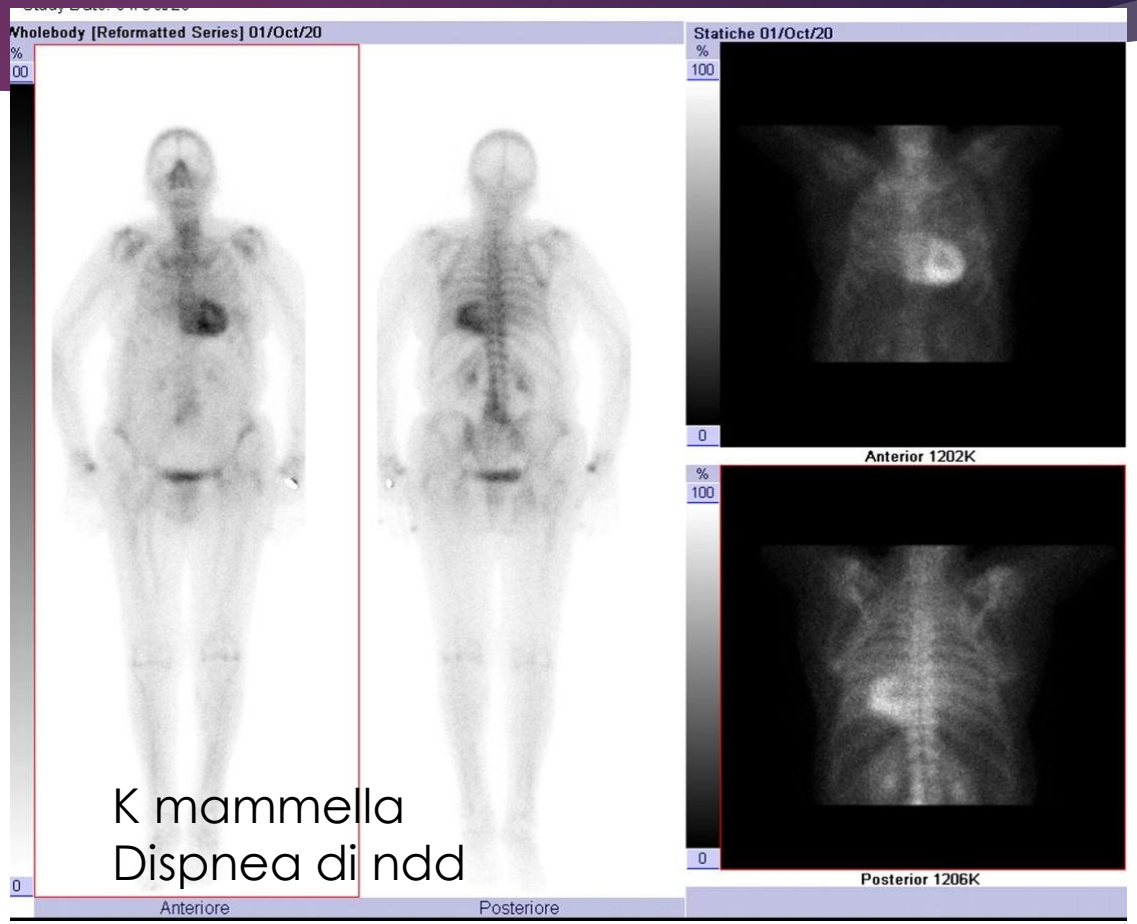
- Sensibilità ATTRwt vs ATTRm (influenza profilo genetico su bone scan)

J Nucl Cardiology 2019

Incidentalomi



K prostata



K mammella
Dispnea di ndd

Accuratezza diagnostica

Table 3 Accuracy of scintigraphy for the diagnosis of cardiac ATTR

Reference	Reference standard	True-positive	False-positive	True-negative	False-negative	Sensitivity (%)	Specificity (%)
[47]ª	Biopsy and genotyping/ immunohistochemistry	36	0	46	3	94	100
[48]ª	Biopsy and genotyping/ immunohistochemistry	13	1	7	0	100	88
[41]	Biopsy and genotyping/ immunohistochemistry	106	6	44	15	88	88
[49]ª	Biopsy and genotyping/ immunohistochemistry	238	15	98	23	91	87
[42]	Biopsy and genotyping/ immunohistochemistry	39	0	51	8	83	100
[50]ª	Biopsy combined with clinical and laboratory data	6	2	4	0	100	66.7
[43]	Biopsy and genotyping/ immunohistochemistry combined with clinical and laboratory data	159	1	56	19	89	98
[44]	Biopsy and genotyping/ immunohistochemistry	32	2	10	1	97	83
[51]ª	Biopsy and genotyping/ immunohistochemistry	8	0	11	0	100	100
[45]	Biopsy and genotyping/ immunohistochemistry	45	6	43	0	100	88
[46]	Biopsy and genotyping/ immunohistochemistry	15	0	20	0	100	100
[52]ª	Biopsy and genotyping/ immunohistochemistry	8	0	10	0	100	100
Pooled analysis						92.2 (95% CI 89–95)	95.4 (95% CI 77–99)

A visual grading score of ≥2 was considered positive for ATTR

ª Included in the meta-analysis; 95% CI 95% confidence interval

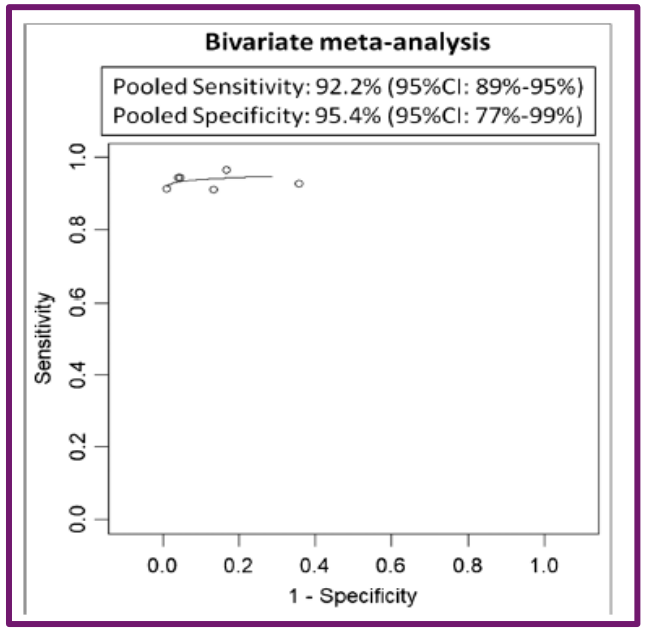
Eur J Nucl Med Mol Imaging 2018

Table 2 Technical aspects of bone scintigraphy in the included studies

Reference	Radiotracer	Injected activity	Time between radiotracer injection and image acquisition	Type of scintigraphic acquisition	Image analysis
[47]	^{99m}Tc-HMDP	700–740 MBq	150 min	Planar (WB)	Visual and semiquantitative (HR, WBR, H/WB)
[48]	^{99m}Tc-DPD	700–800 MBq	5 min and 3 h	Planar (WB) and SPECT/CT thorax	Visual and semiquantitative (HR, WBR, H/WB)
[41]	^{99m}Tc-PYP	370–925 MBq	1 h or 3 h	Planar (thorax)	Visual and semiquantitative (H/CL)
[49]	^{99m}Tc-DPD, ^{99m}Tc-PYP, ^{99m}Tc-HMDP	NR	1 h or 3 h	Planar (WB)	Visual
[42]	^{99m}Tc-HMDP	10 MBq/kg	10 min and 3 h	Planar (WB)	Visual and semiquantitative (HR, WBR, SR, H/WB, H/S)
[50]	^{99m}Tc-PYP	555–925 MBq	1 h, 2 h and/or 3 h	Planar (thorax) and SPECT (thorax)	Visual and semiquantitative (H/CL)
[43]	^{99m}Tc-DPD	700 MBq	3 h	Planar (WB) and SPECT/CT (thorax)	Visual
[44]	^{99m}Tc-PYP	555–925 MBq	1 h	Planar (thorax) and SPECT (thorax)	Visual and semiquantitative (H/CL)
[51]	^{99m}Tc-DPD	740 MBq	3 h	Planar (WB) and SPECT (thorax)	Visual
[45]	^{99m}Tc-DPD	740 MBq	5 min and 3 h	Planar (WB) and SPECT (thorax)	Visual and semiquantitative (HR, WBR, H/WB)
[46]	^{99m}Tc-DPD	740 MBq	5 min and 3 h	Planar (WB) and SPECT (thorax)	Visual and semiquantitative (HR, WBR, H/WB)
[52]	^{99m}Tc-DPD	550–650 MBq	5 min and 3 h	Planar (WB) and SPECT (thorax)	Visual and semiquantitative (HR, WBR, H/WB)

Eterogeneità studi

100% Analisi qualitativa
75 % Analisi semiquantitativa



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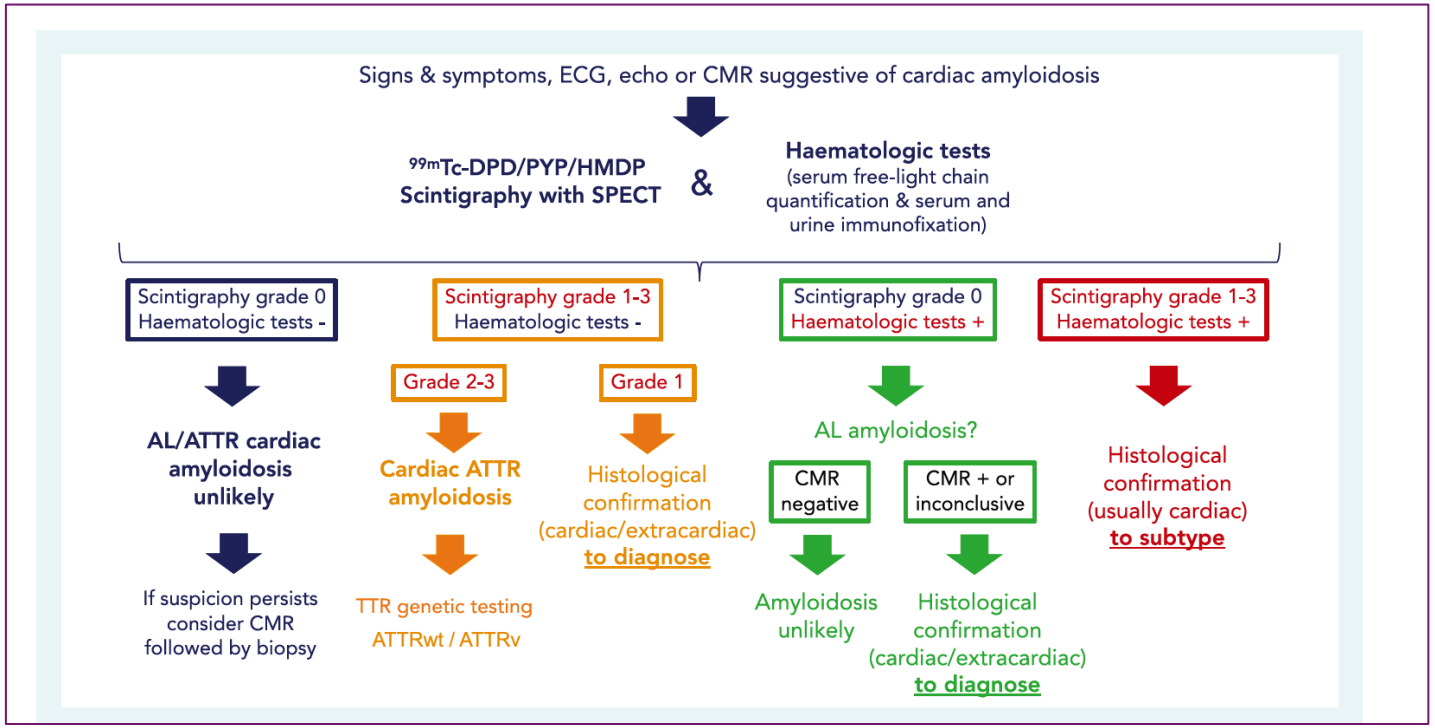
ESC algoritmo diagnostico



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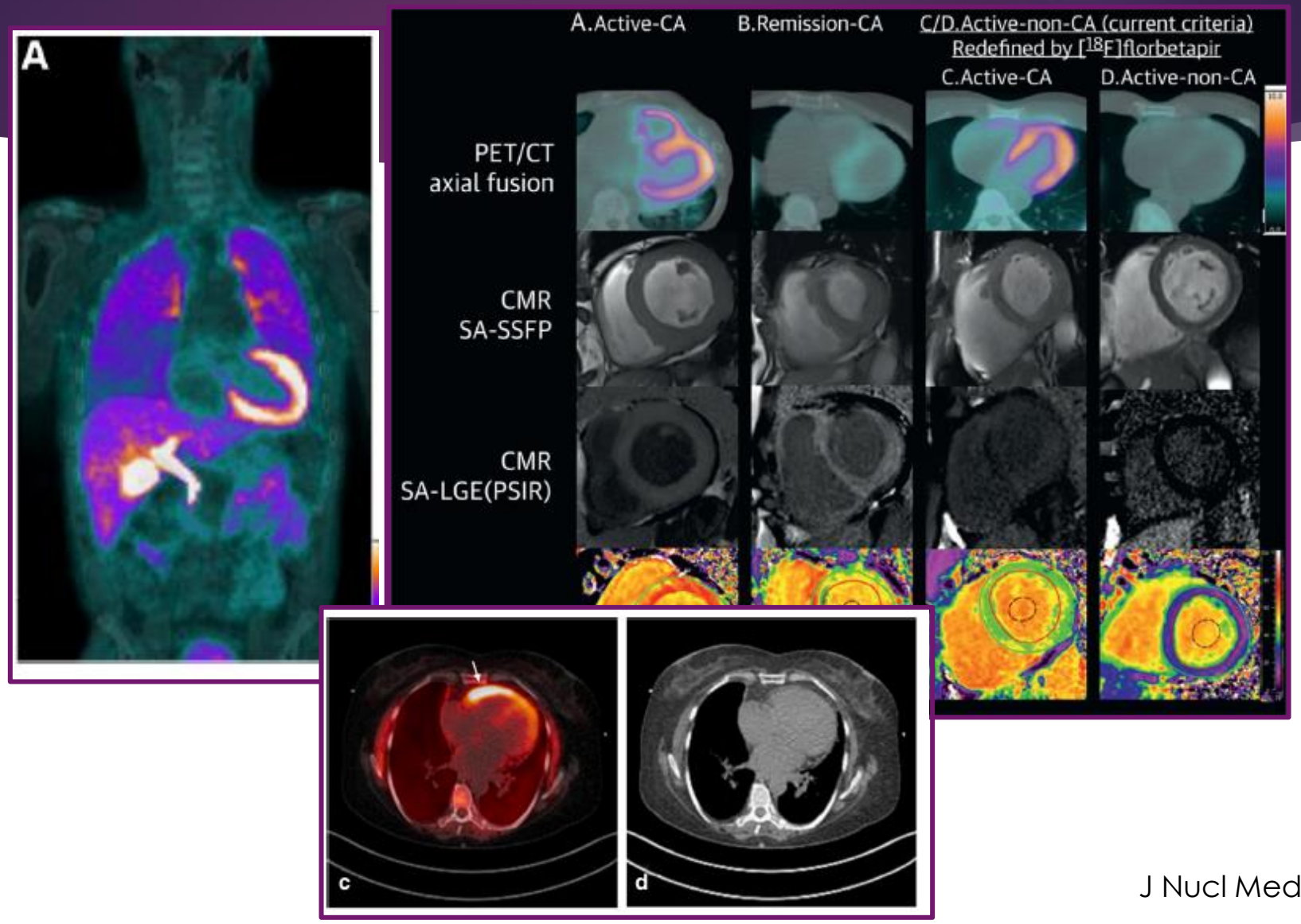
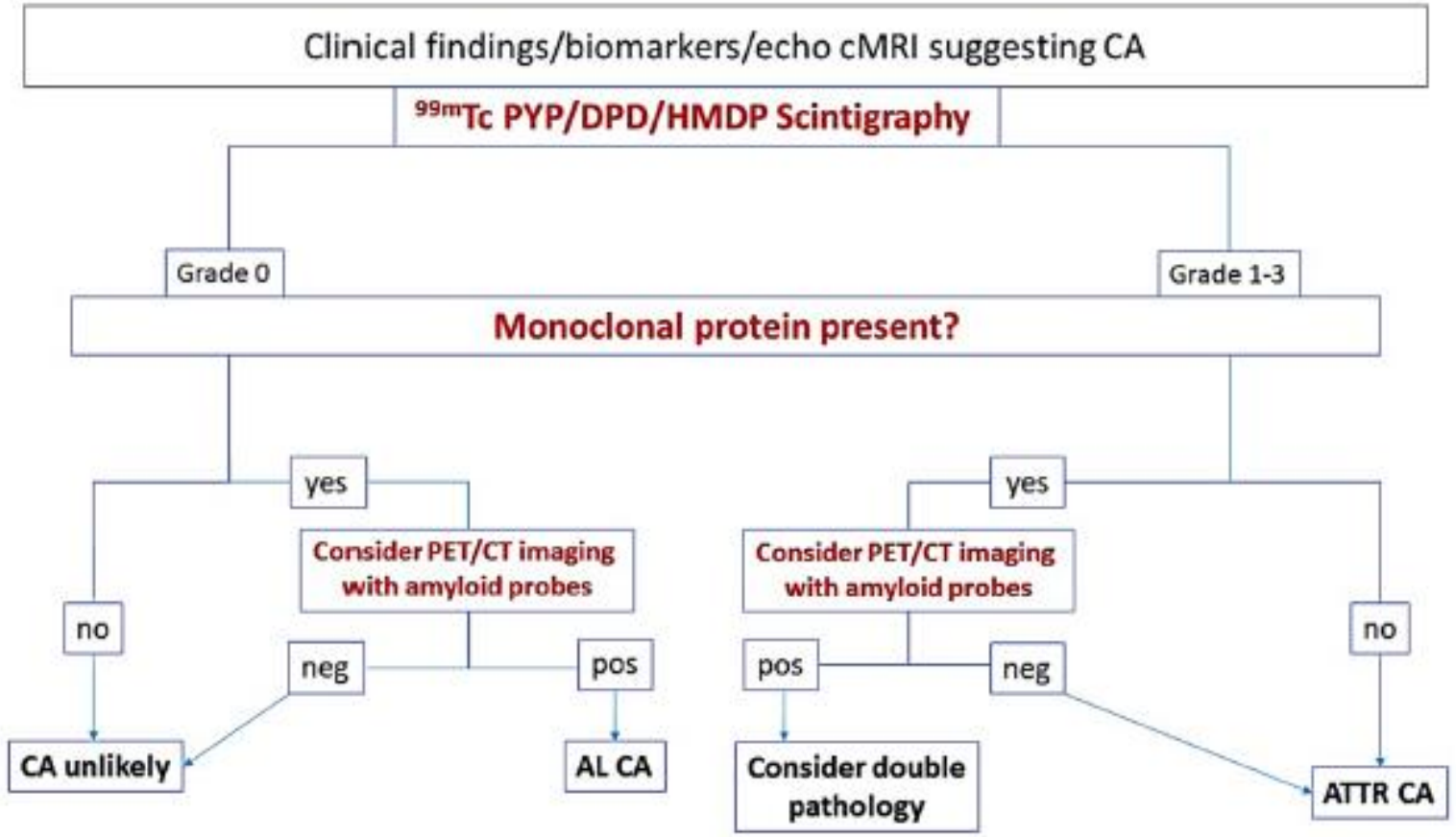
Amiloidosi AL: PET-TC con RF per amiloide



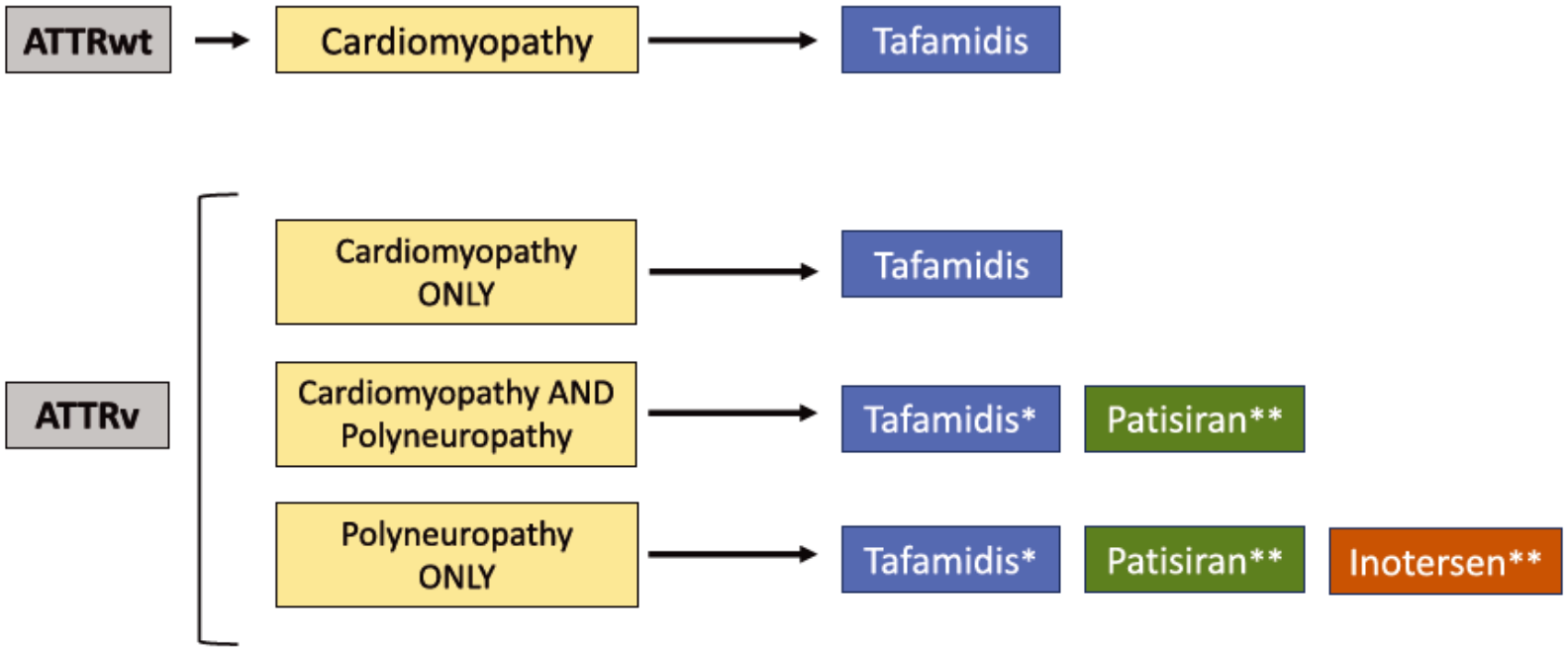
J Nucl Med 2019

Dual isotopes nuclear procedure: Bone scintigraphy/PET imaging



Clinical and Translational Imaging 2019

Terapia



* Polyneuropathy Stage 1
** Polyneuropathy Stage 1 & 2

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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.

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Grey Zones

Table 4
Grey zones and knowledge gaps in the current management of TTR-AC.

Reasonably indicated treatments and grey zones	
Anti-neurohormonal therapy	No survival benefit is demonstrated in TTR-AC. Beta-blockers and ACE-i/ARB can be poorly tolerated, especially in advanced stages due to vasodilatation and reduced CO.
Atrial fibrillation and anticoagulation	Anticoagulation with VKAs and DOACs should be administered based on the usual indications and contraindications. Patients with TTR-AC in sinus rhythm can harbour thrombi in the left atrial appendage, especially when atrial function is severely impaired. Therefore, TEE should be routinely performed before a planned cardioversion.
Atrial fibrillation, rate or rhythm control and catheter ablation	There is no specific recommended strategy for the management of arrhythmias. Digoxin should be avoided or used at low dosages due to concerns about potential enhanced toxicity caused by binding to amyloid fibrils. Drugs with a negative inotropic effect should be avoided (i.e. verapamil and diltiazem). The efficacy of catheter ablation seems limited, but future studies are required.
Transcatheter aortic valve implantation	Percutaneous or surgical aortic valve replacement should not be denied only because of coexistent AC. Definitive PM implantation may be required due to a higher risk of persistent AV blocks.
Ventricular arrhythmias and implantable cardioverter defibrillator	Sudden death is not infrequent in patients with advanced HF, but it is generally due to electromechanical dissociation. The role of ICD for the purpose of: - primary prevention is currently limited; - secondary prevention can be considered in select non-advanced cases with sustained VT/VF.
Cardiac resynchronization therapy	Very limited data are available on this topic. CRT should be considered in patients eligible for PM implantation with an estimated time of RV pacing >40%.
Heart transplantation	Highly selected HF patients with TTRwt or TTRv and predominant cardiac phenotype without extra-cardiac organ damage could be eligible. Combined heart and liver transplantation could be considered in very selected cases with mixed phenotype and limited neurological involvement.

Eur. J Nucl. Med. 2020

Follow-up

Table 7 Proposed follow-up scheme in cardiac amyloidosis

	AL	ATTR
Patient with cardiac amyloidosis	**Every month** (during initial haematological treatment): • Complete blood count, basic biochemistry, NT-proBNP and troponin • Serum free light chain quantification • Clinical evaluation by Haematology • Evaluation by Cardiology if clinically indicated **Every 3–4 months** (after completing initial haematological treatment): • Complete blood count, basic biochemistry, NT-proBNP and troponin • Serum free light chain quantification • Clinical evaluation by Haematology **Every 6 months:** • ECG • Echocardiography/CMR • Evaluation by Cardiology **Every 12 months:** • 24 h Holter ECG	**Every 6 months:** • ECG • Blood tests including NT-proBNP and troponin • Neurological evaluation (if ATTRv) • 6MWD (optional) • KCCQ (optional) **Every 12 months:** • Echocardiography/CMR • 24 h Holter ECG • Ophthalmological evaluation (if ATTRv)
ATTRv asymptomatic genetic carriers[a]		**Yearly:** • ECG • Blood tests including NT-proBNP and troponin • Echocardiography • Neurological and ophthalmological evaluation **Every 2 years:** • Holter ECG **Every 3 years or if any of above complementary test is abnormal:** • Scintigraphy • CMR

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Future direzioni

- Understanding the real prevalence of ATTR amyloidosis, particularly with the cardiac phenotype, in the various clinical scenarios and differentiating indolent cardiac accumulation of the 'senile' form from the authentic infiltrative disease;
- The use of diphosphonate single photon emission computed tomography to better characterize patients with Perugini score 1 (by detecting localized but intense amyloid deposition, thus allowing an early diagnosis [42]) and possibly to quantify the amyloid burden;
- Investigating the potential role of PET imaging with amyloid tracers (alone or in combination with bone tracer scintigraphy) for the differential diagnosis between AL and ATTR amyloidosis [43];
- Defining the minimal disease threshold to justify the initiation of novel treatments with high costs and potential side effects;
- Defining the degree of cardiac involvement to be considered so advanced that no significant benefit is expected from the administration of disease-modifying drugs;
- Identifying the most appropriate tool to quantify the global amyloid burden and to monitor its changes under specific treatment;
- Defining baseline and early on treatment criteria to identify 'responders' and 'non-responders' to disease-modifying therapies in order to guide the decision to discontinue, change or possibly associate drugs;
- Defining potential parameters at baseline to predict response to treatment and consequently identifying criteria to discontinue current drugs in favour of other medications or to start on combination therapy.

Eur J Internal Medicine 2020

Take home message

Scintigrafia ossea suggestiva di ATTR in:

- 13% pz >60 anni con spessore parietale ventricolare≥12mm ricoverati per HF con FE conservata
- 5% pz con cardiomiopatia ipertrofica
- 16% pz con stenosi aortica con basso flusso/basso gradiente paradosso

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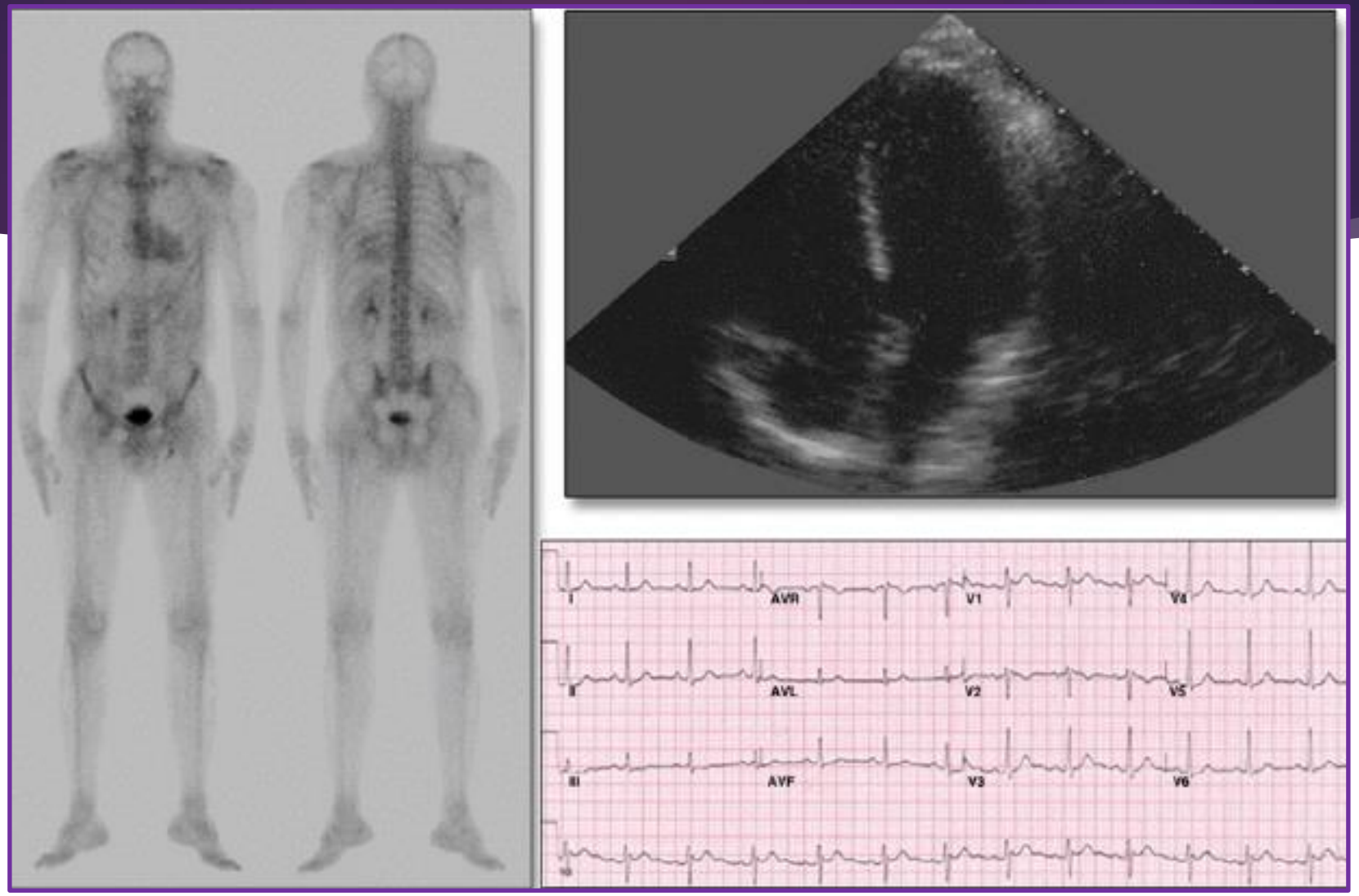

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