Strumenti diagnostici per la cardiopatia amiloidotica

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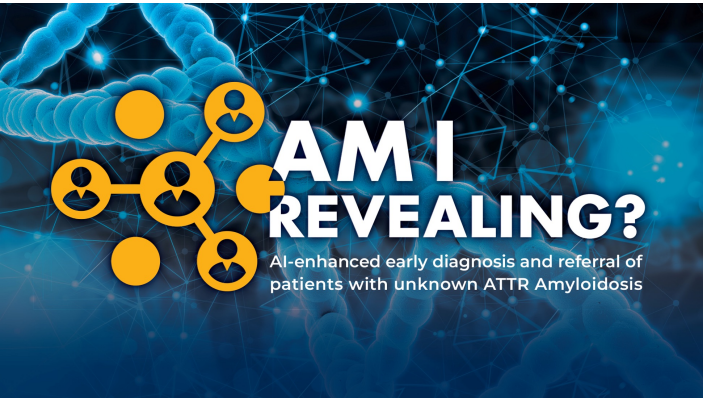
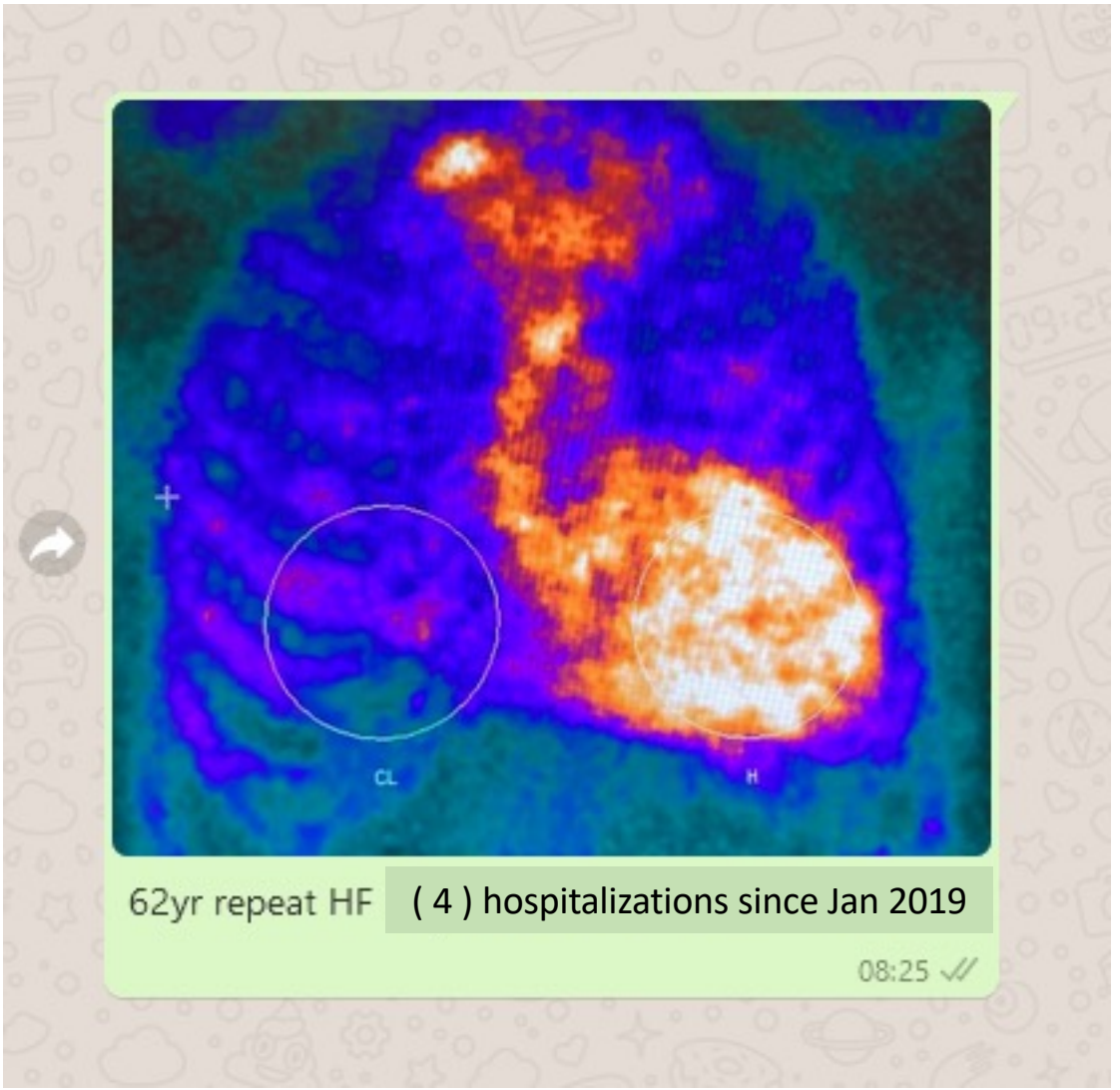
Artwork di
Ursula Ferrara



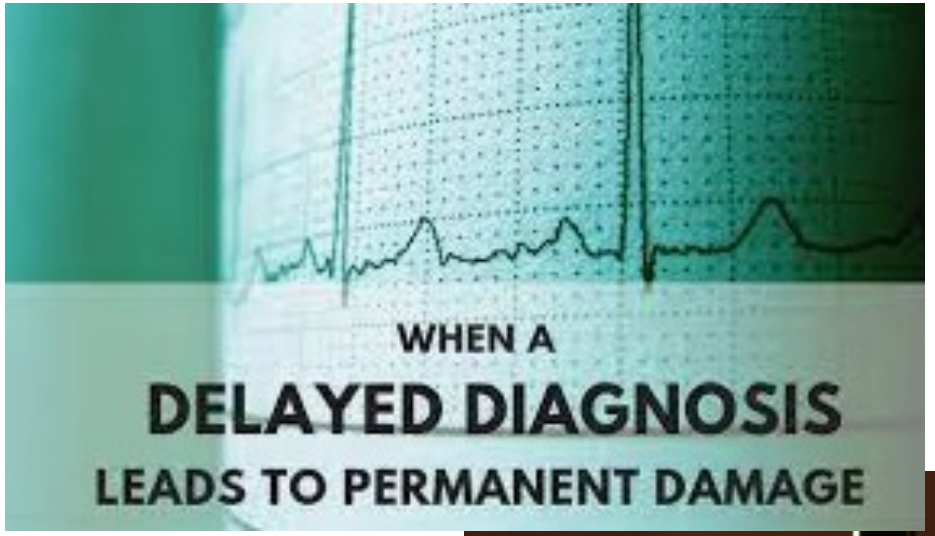
Fondazione Monasterio
la ricerca che cura



SCUOLA SUPERIORE SANT'ANNA
PISA

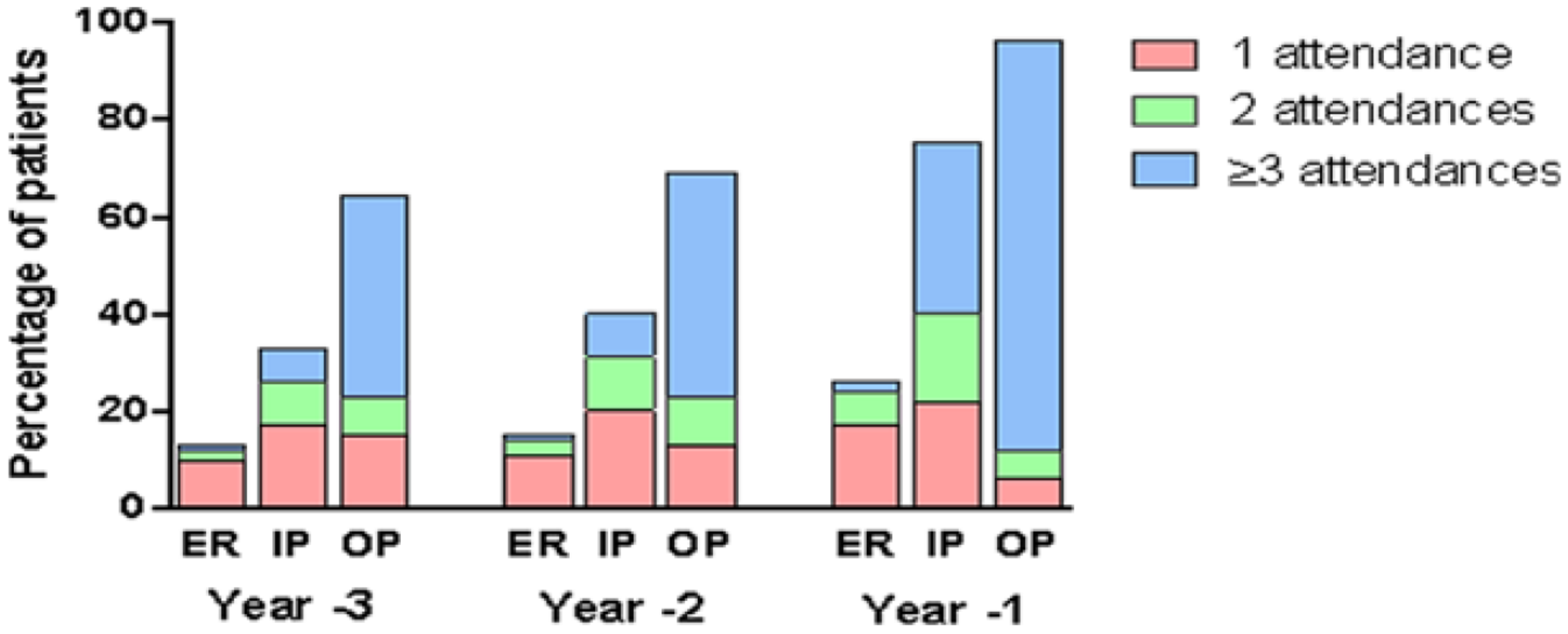
you find what you are looking for

you look for what you know



Delayed diagnosis

Hospital admissions *before* diagnosis



Lane T et al, 2019

CA: no time to be wasted

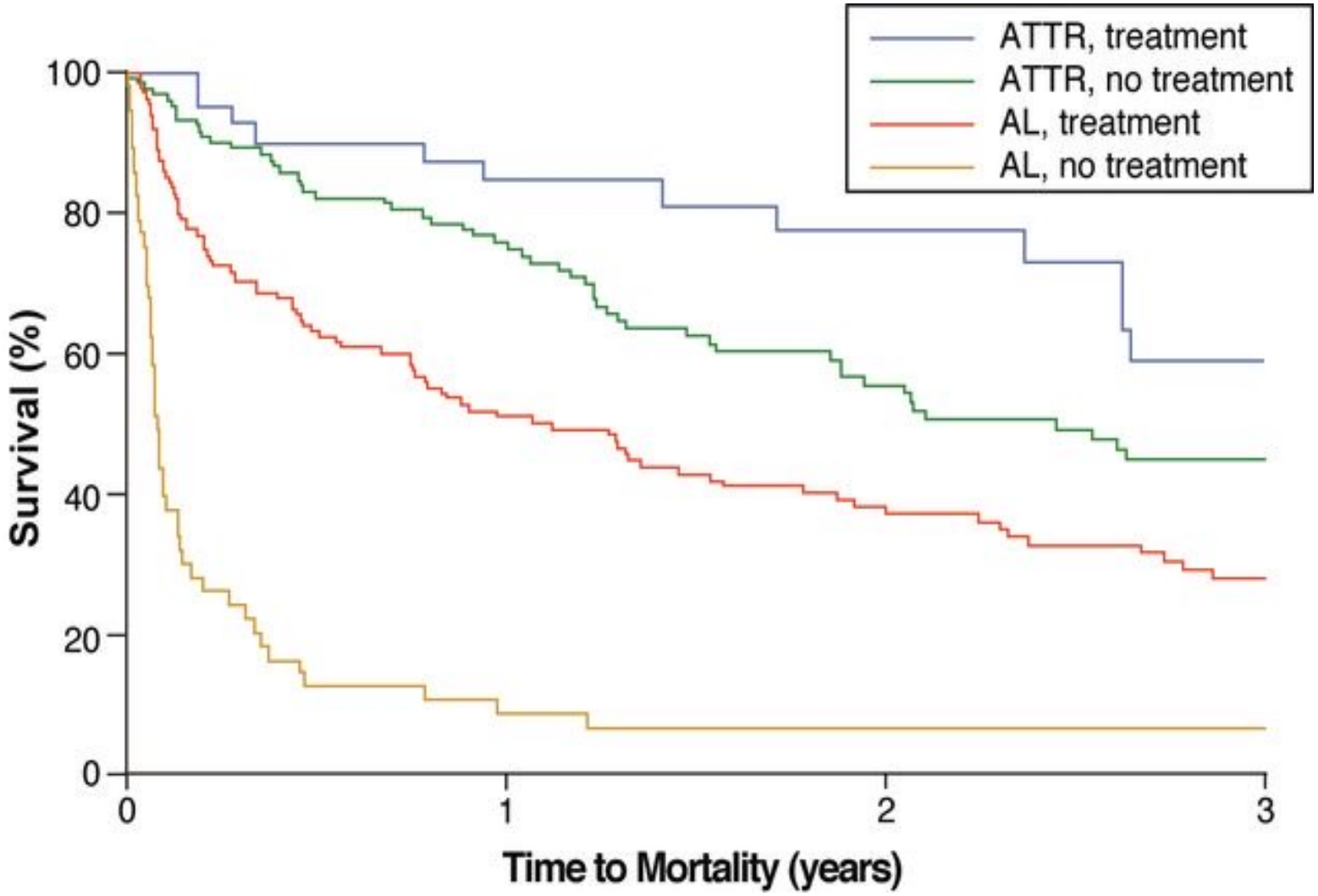
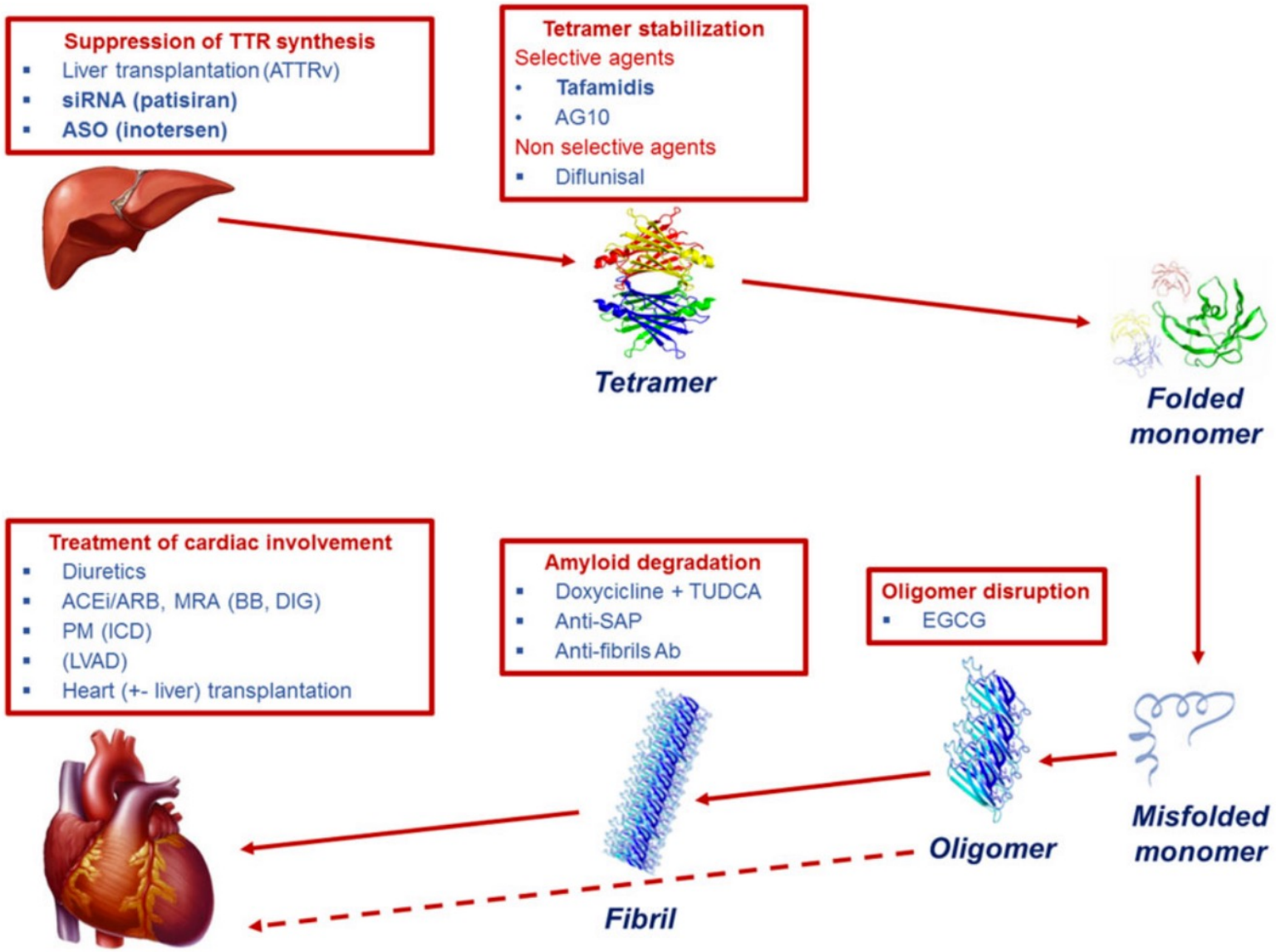


Figure from Sperry et al. 2016.[1]

AL, amyloid light-chain; ATTR, transthyretin-mediated amyloidosis; CA, cardiac amyloidosis.

1. Sperry BW, et al. *J Am Heart Assoc* 2016;5(3):e002877.



ESC European Society of Cardiology
European Heart Journal (2019) **0**, 1–10
doi:10.1093/eurheartj/ehz298

CLINICAL REVIEW
New drugs

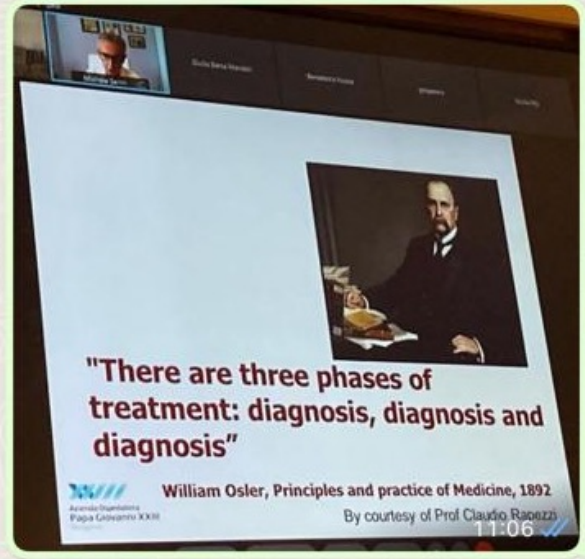
Treatment of cardiac transthyretin amyloidosis: an update

Michele Emdin[1,2*†], Alberto Aimo[3†], Claudio Rapezzi[4], Marianna Fontana[5,6], Federico Perfetto[7,8], Petar M. Seferović[9,10], Andrea Barison[1,2], Vincenzo Castiglione[1,3], Giuseppe Vergaro[1,2], Alberto Giannoni[1,2], Claudio Passino[1,2], and Giampaolo Merlini[11,12]

22 Rapezzi

va bene domani o giovedì fascia 13-15? 12:34

5 lug 2021



Poteva non ringraziarmi, il merito è di osler. Anche churchill e Stalin hanno alcuni aforismi utili che ti girerò 11:14

https://twitter.com/micheleemdin/status/1412004364936437762?s=24 13:05

Michele Emdin on Twitter

"Overture of the 2nd Master on "Heart Failure pathophysiology, Clinical features and management."
Lectio magistralis given by Michele Senni citing Claudio Rapezzi citing William Osler on the 3

First:
have the suspicion..

SUSPECT CA in the presence of 'red flag' clusters of symptoms

Left Ventricular Wall Thickness ≥ 12 mm

+ ≥1 of

- HF in pts ≥65 years
- Aortic stenosis pts ≥65 years
- Hypotension or normotensive, if previously hypertensive
- Sensory involvement, autonomic dysfunction
- Peripheral polyneuropathy
- Proteinuria
- Skin bruising
- Bilateral carpal tunnel
- Ruptured biceps tendon
- Subendocardial/transmural LGE or increased ECV
- Longitudinal strain with apical sparing
- Decreased QRS voltage to mass ratio
- Pseudo Q waves on ECG
- AV conduction disease
- Possible family history

Figure adapted from Garcia-Pavia et al. 2021.[1]

AV, atrio-ventricular; CA, cardiac amyloidosis; ECG, electrocardiogram; ECV, extracellular volume; HF, heart failure; LGE, late gadolinium enhancement; pts, patients.

1. Garcia-Pavia P, et al. *Eur J Heart Fail* 2021;23:512–526.

How to get a final differential diagnosis

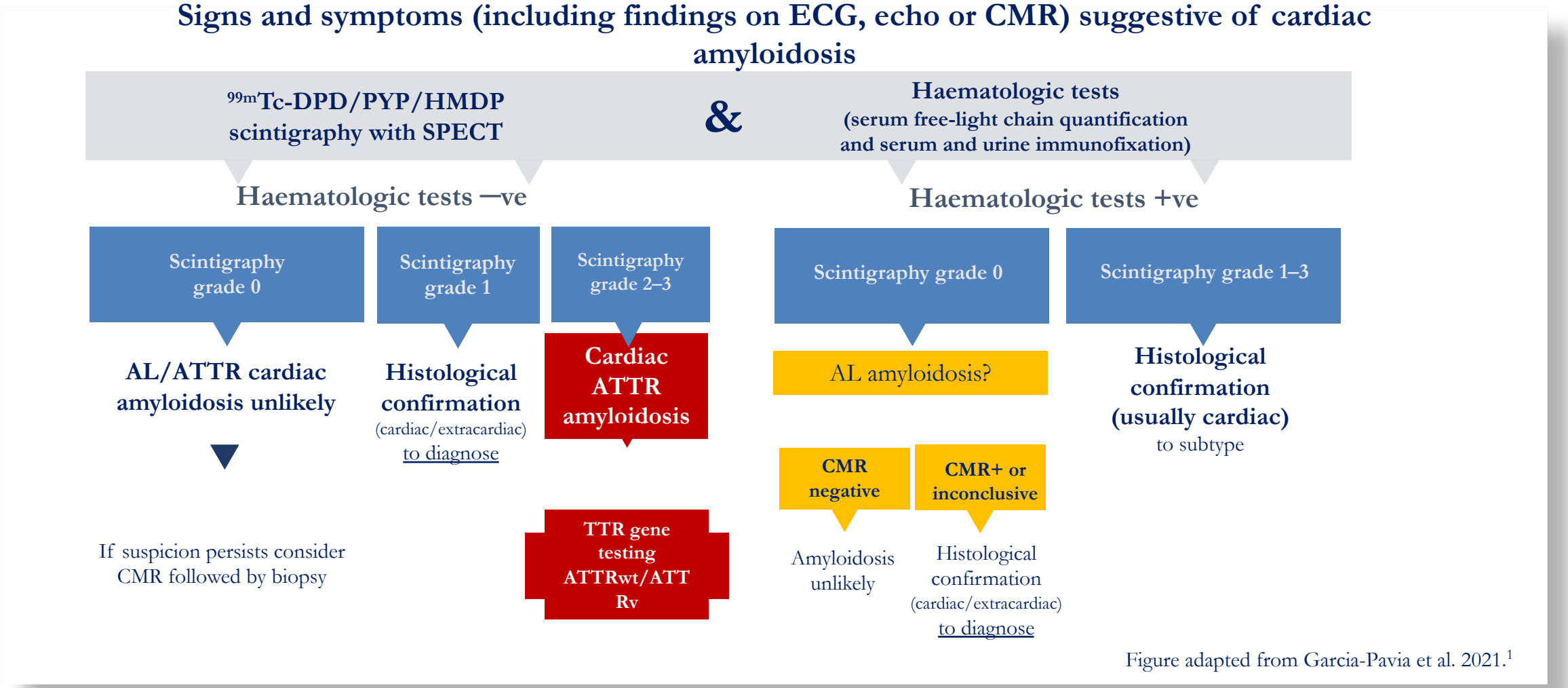
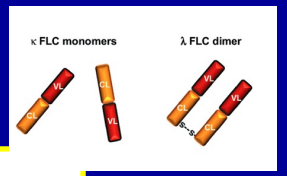


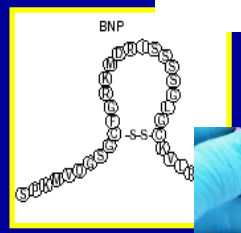
Figure adapted from Garcia-Pavia et al. 2021.[1]

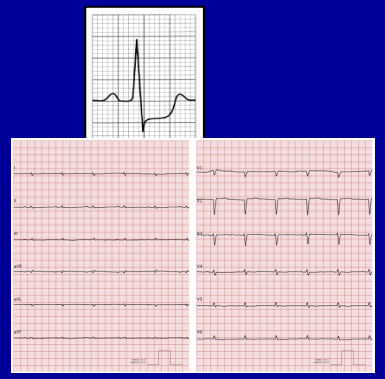
Position statement of the ESC Working Group on Myocardial and Pericardial Diseases.[1]

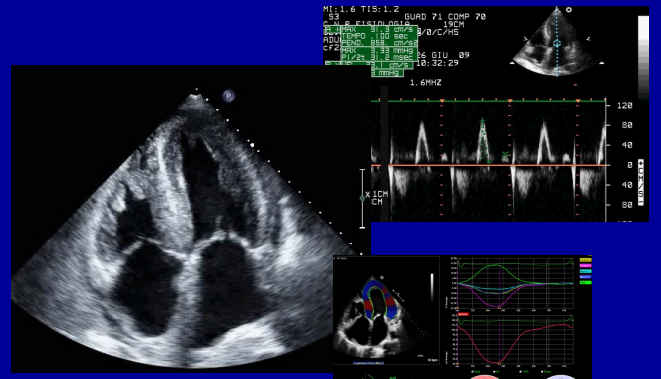
99mTc-DPD, DPD3,3-diphosphono-1,2-propanodicarboxylic acid; AL, amyloid light chain; ATTRv, hereditary transthyretin-mediated amyloidosis (v for variant); ATTRwt, wild-type transthyretin-mediated amyloidosis ; CMR, cardiac magnetic resonance; ECG, electrocardiogram; ESC, European Society of Cardiology; HMDP, hydroxymethylene diphosphonate; PYP, pyrophosphate; SPECT, single photon emission computed tomography.

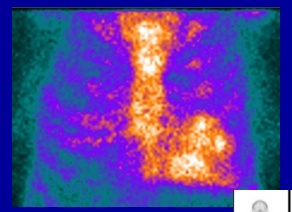
1. Garcia-Pavia P, et al. *Eur J Heart Fail* 2021;23:512–526.

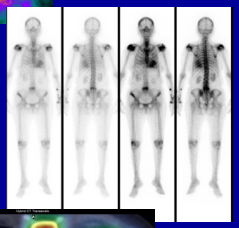


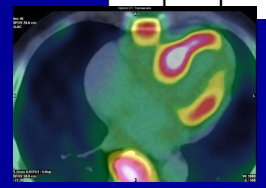


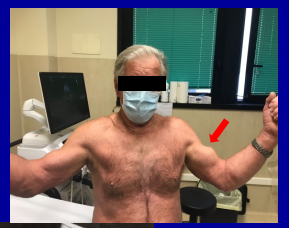


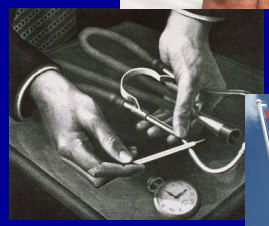


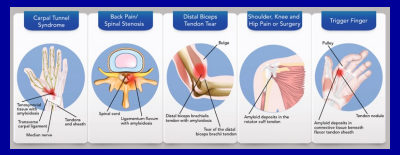




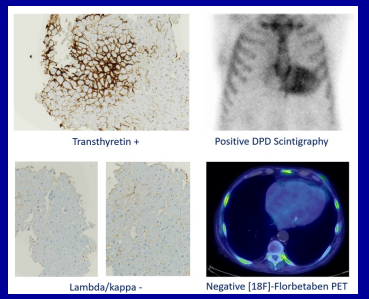


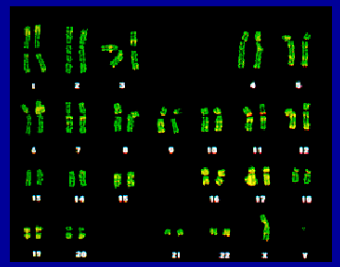


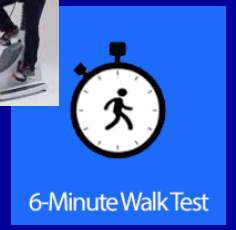


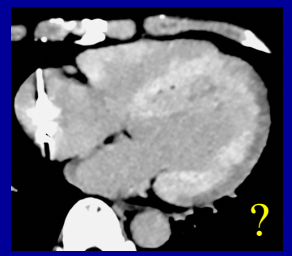


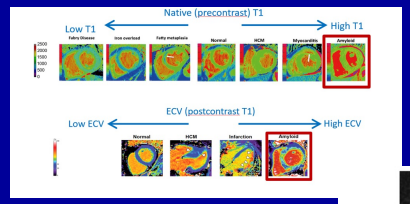
How to diagnose..

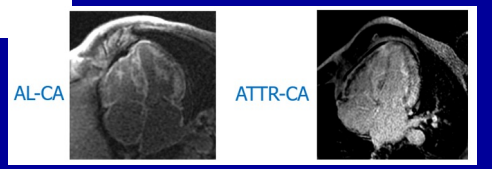


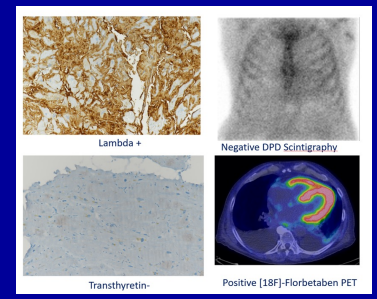




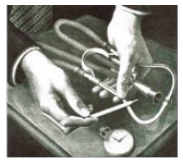
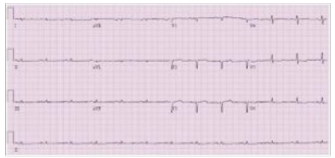
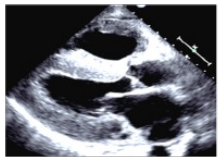








Cardiac biomarkers to diagnose CA

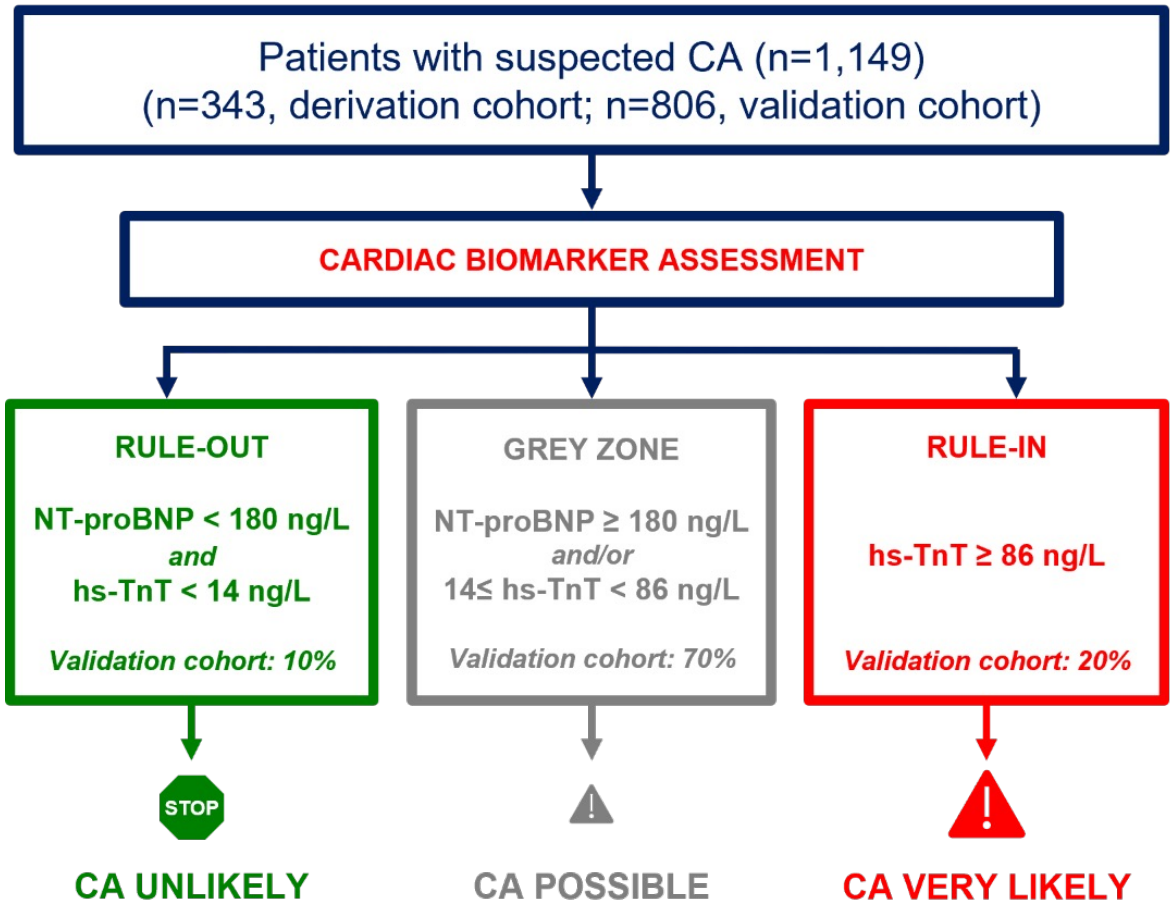


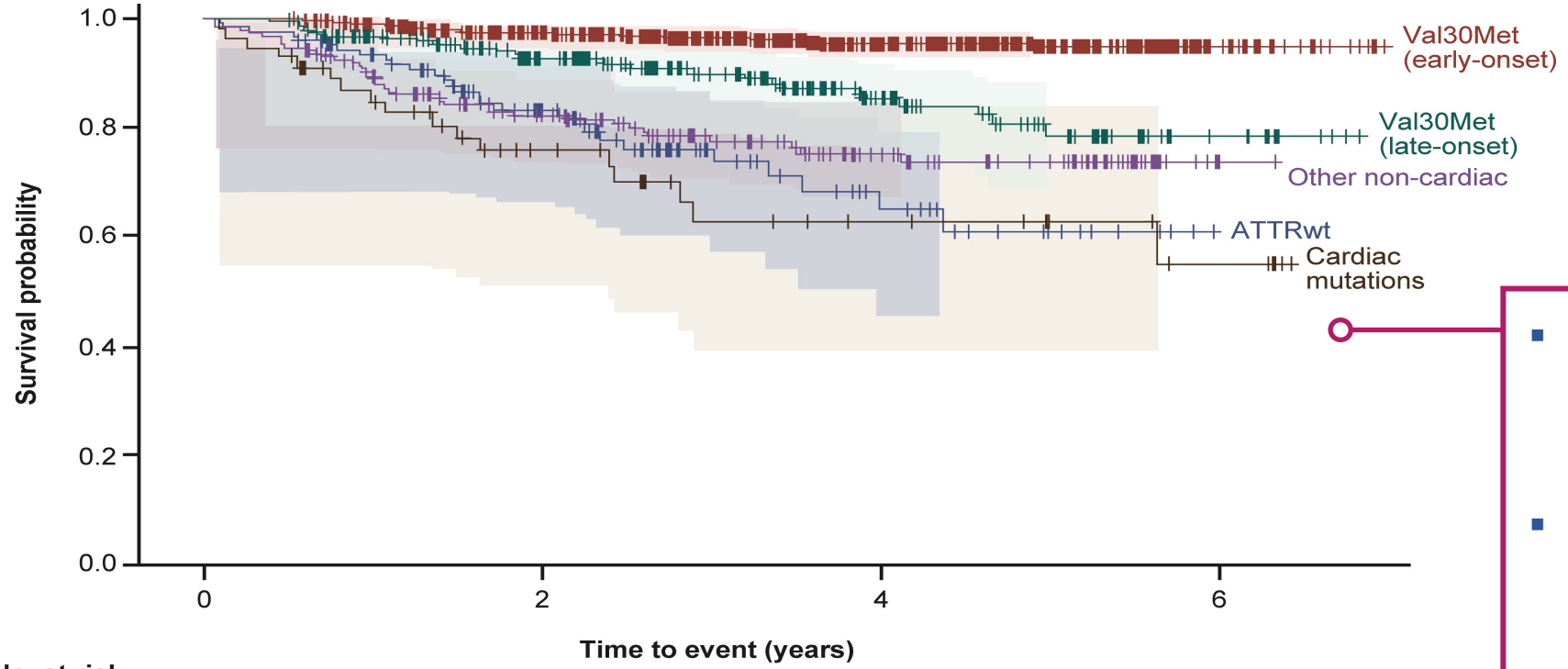
Figure from Vergaro G, et al 2023[1]

AL, amyloid light-chain; ATTR, transthyretin-mediated amyloidosis; BNP, B-type natriuretic peptide; CA, cardiac amyloidosis; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; (hs-)TnT/I, (high-sensitivity) troponin T/I; URL, upper reference limit.

1. Vergaro G. *Eur J Heart Fail* 2023;25(3):335–346.

The importance of genetic testing

Survival in ATTR-CA patients varies by genotype



No. at risk				
ATTRwt	122	66	21	0
Cardiac mutations	56	28	15	6
Val30Met (early-onset)	741	602	319	32
Val30Met (late-onset)	270	189	76	9
Other non-cardiac	186	121	58	2

- Patients with ATTRv amyloidosis have poorer prognosis (than ATTRwt)
- Differential diagnosis (genetic testing) is critical for the optimum management of patients and their families

n=1375 patients from THAOS

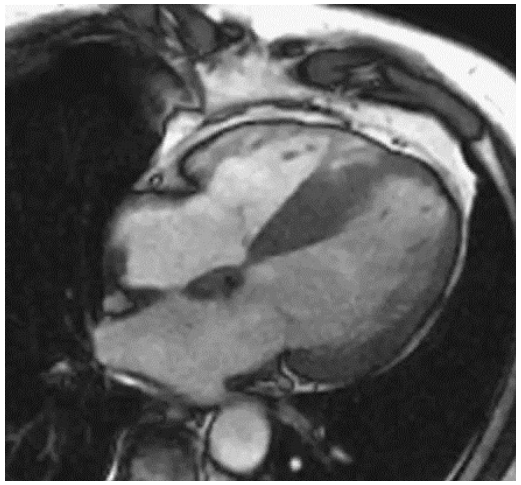
Figure from Damy et al. 2019.[1]

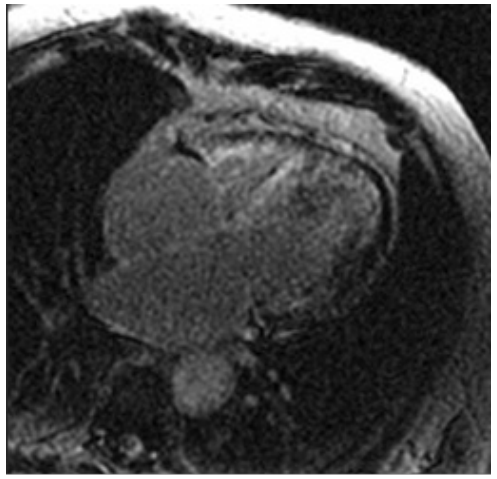
ATTR, transthyretin-mediated amyloidosis; CA, cardiac amyloidosis; ATTRv, hereditary transthyretin-mediated amyloidosis (v for variant); ATTRwt, wild-type transthyretin-mediated amyloidosis.

1. Damy T, et al. *Eur Heart J* 2019; 43(5):391–400.

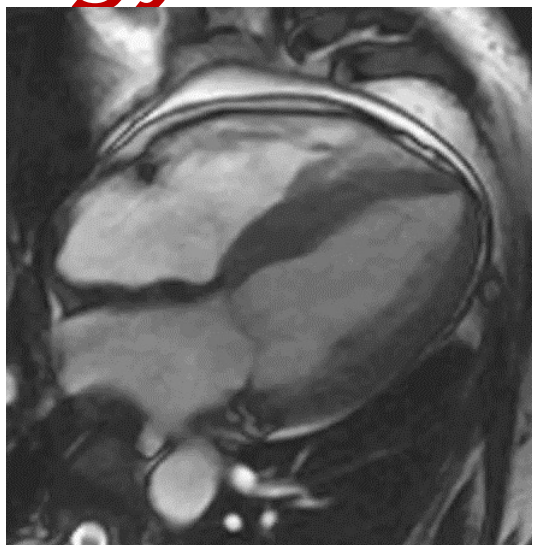
The importance of genetic testing

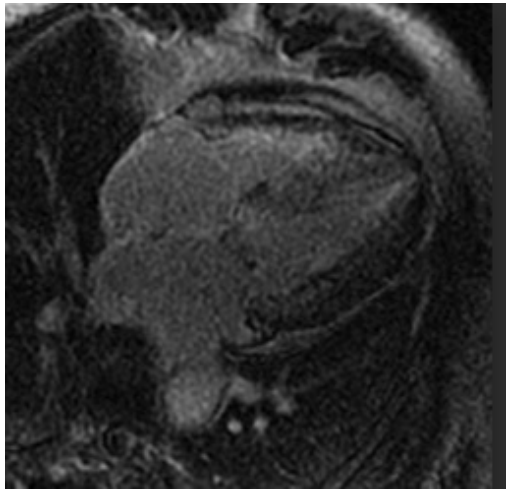
Double pathology exists.





M, 66 y, ATTRwt-CA,
sarcomeric CMP
MYBPC3 gene - Glu542Gln

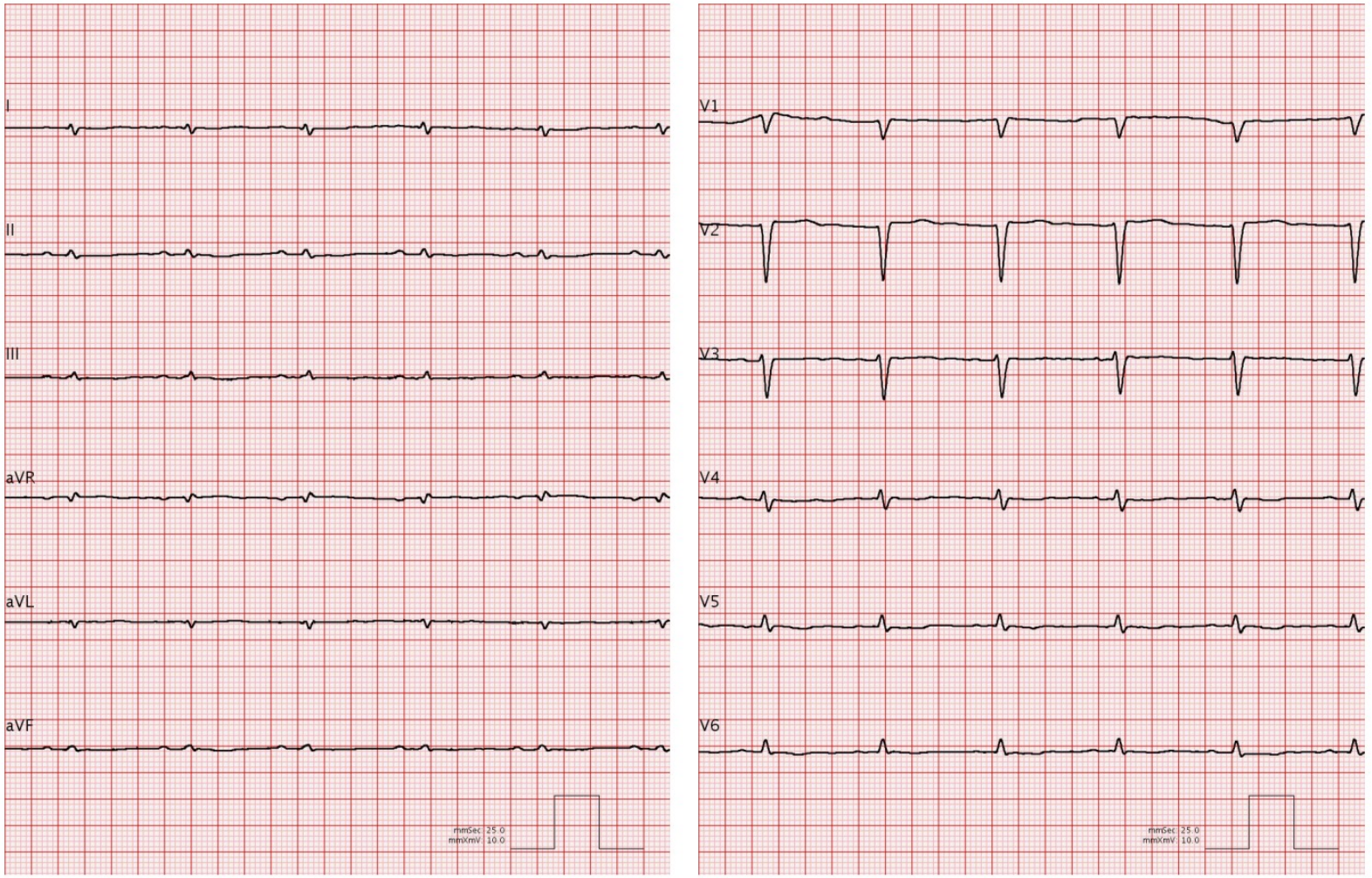




M, 65 y, CAD, «NSTEMI»,
ATTRv-CA
TTR gene - Ile88Leu

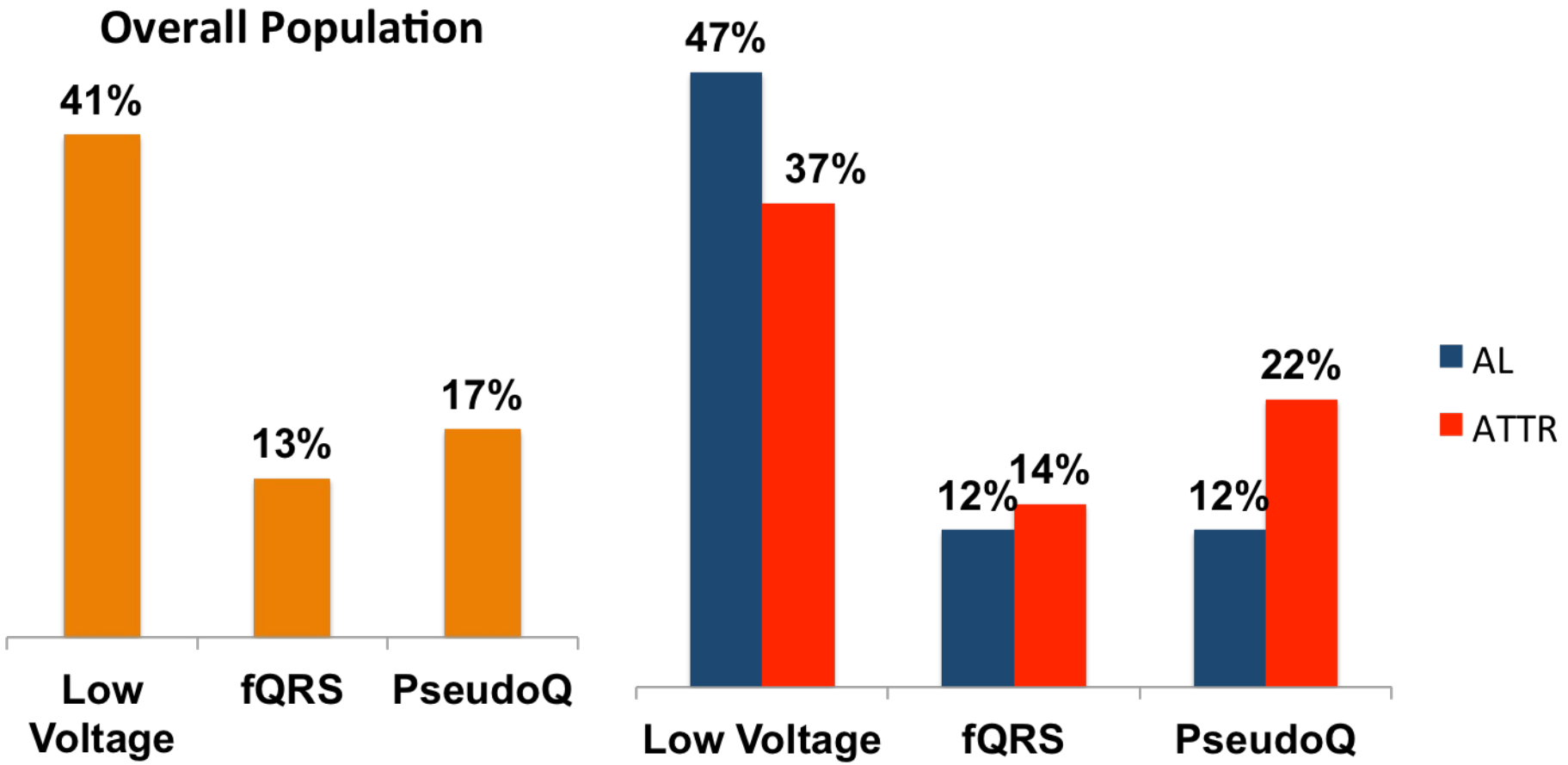
ATTRv, hereditary transthyretin-mediated amyloidosis (v for variant); ATTRwt, wild-type transthyretin-mediated amyloidosis CA, cardiac amyloidosis; CAD, coronary artery disease; CMP, cardiac myosin-binding protein C

D.A. Male, 69 yo – Diagnosed Jan 2019



Cardiac Amyloidosis: FTGM experience

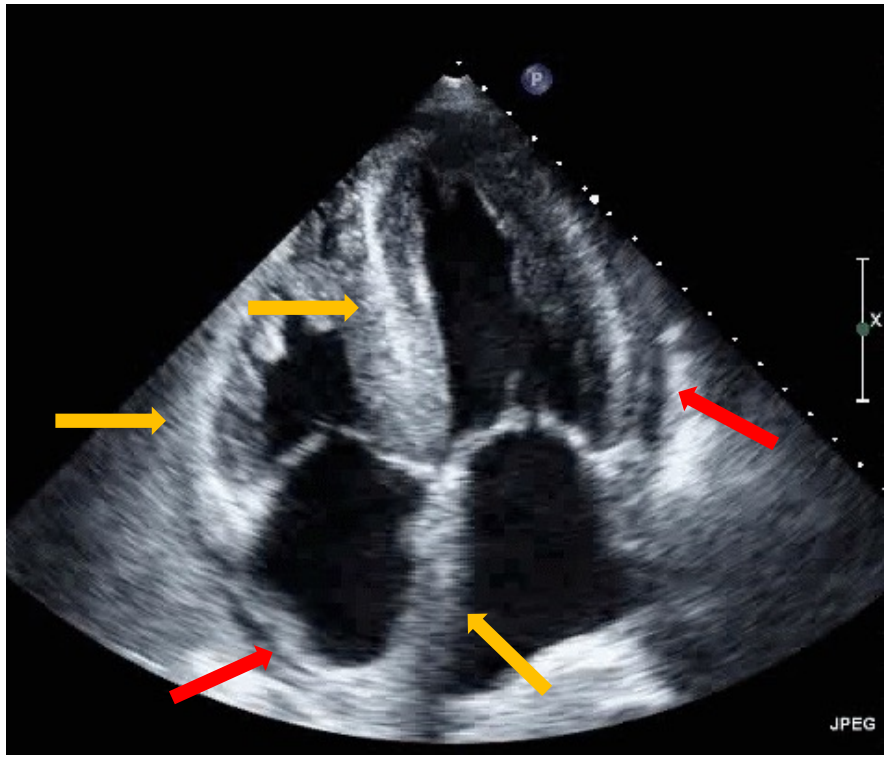
284 patients with cardiac amyloidosis (EBM/echo/DPD-CTPET/MRI proven +NT-proBNP)



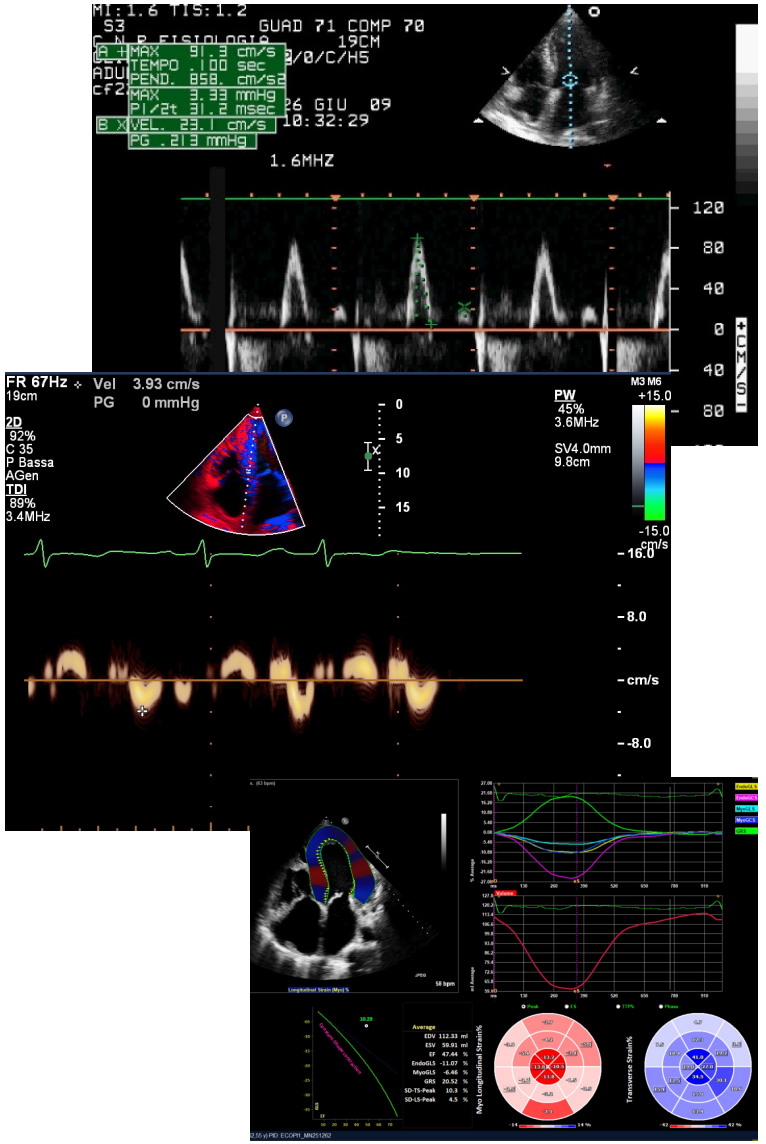
CA: insights from echo

Echocardiography

The high accessibility, the ability to describe both cardiac structure and function, makes echocardiography the first-line tool in CA assessment.



- Infiltrative cardiomyopathy
- LV & RV pseudohypertrophy
- Granular sparkling
- Biatrial dilatation
- Early LV diastolic dysfunction
- Delayed LC systolic dysgunction
- Apical sparing
- IA septum thickening
- Valve involvement
- Pericardial effusion



Courtesy of dr. Chubuchnyi

CA: 4-chamber strain evaluation

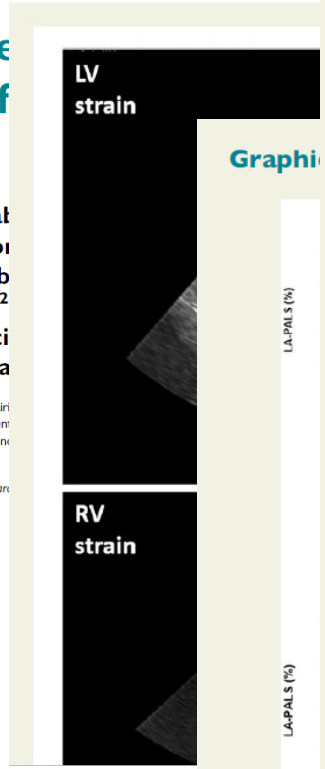
ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2022) **00**, 1–12
https://doi.org/10.1093/ehjci/jeac057

Multi-chamber spe
diagnostic value of
amyloidosis

Alberto Aimo [1,2*†], **Iacopo Fab**
Giulia Elena Mandoli[3], **Maria Cor**
Valentina Spini[2], **Vladyslav Chub**
Elisa Poggianti[2], **Claudia Taddei**[2]
Giorgia Panichella[1], **Carlotta Sci**
Claudio Passino [1,2], **Matteo Ca**

[1]Institute of Life Sciences, Scuola Superiore Sant'Anna, Piazza Martiri
Gabriele Monasterio, Pisa, Italy; [3]Division of Cardiology, Department
Sciences, King's College London, St. Thomas' Hospital Campus, Lon
Medicine, Athens, Greece

Received 27 July 2021; editorial decision 3 March 2022; accepted 4 Mar



Graphi

Keywo

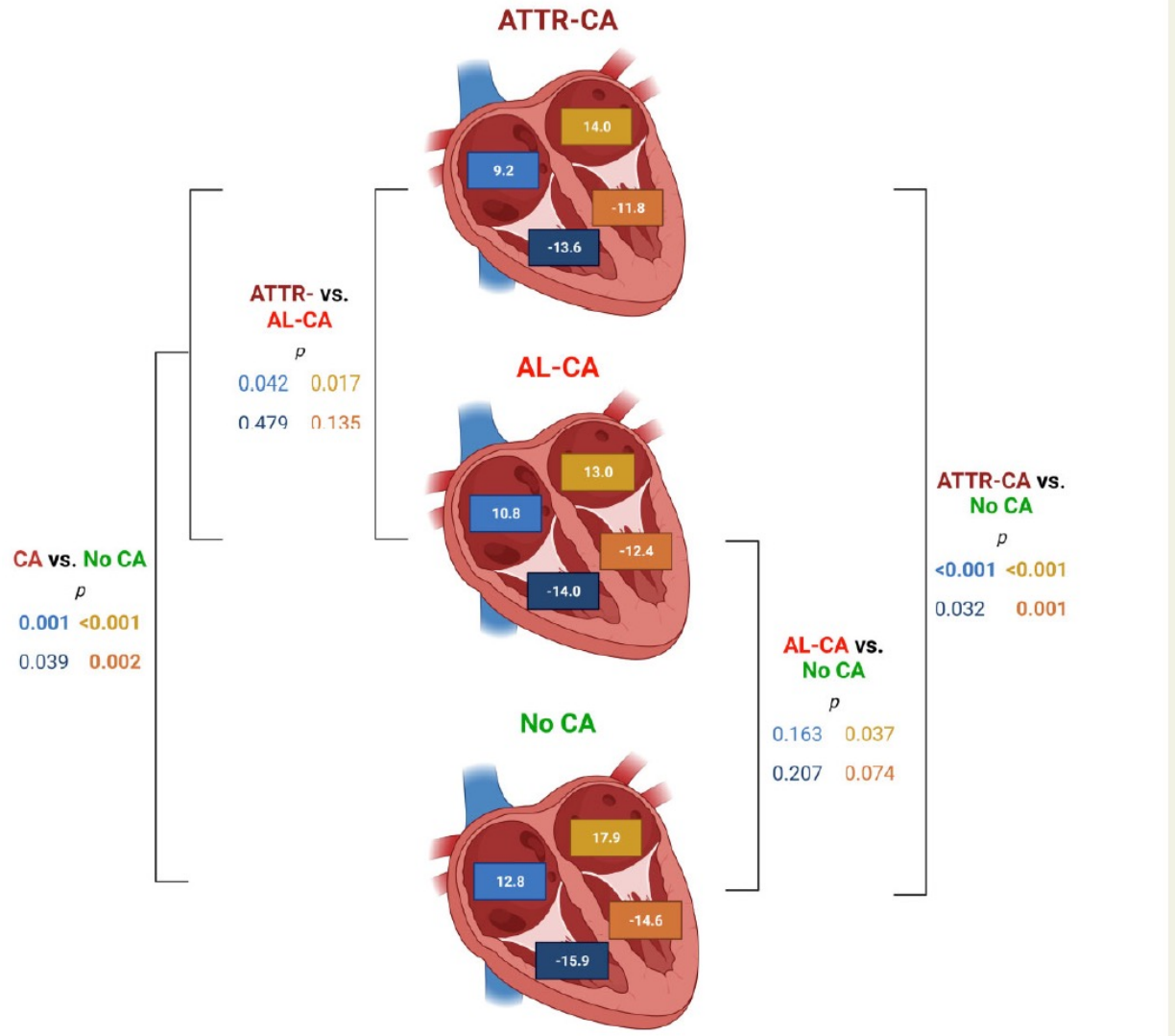


Figure 5 Comparison between strain values in the four chambers. Median values of left ventricular global longitudinal strain (GLS), peak left atrial longitudinal strain, peak right ventricular GLS, and peak right atrial longitudinal strain are reported. The Bonferroni correction was applied to account for multiple comparisons (n = 4); significant P-values (<0.0125) are highlighted in bold.

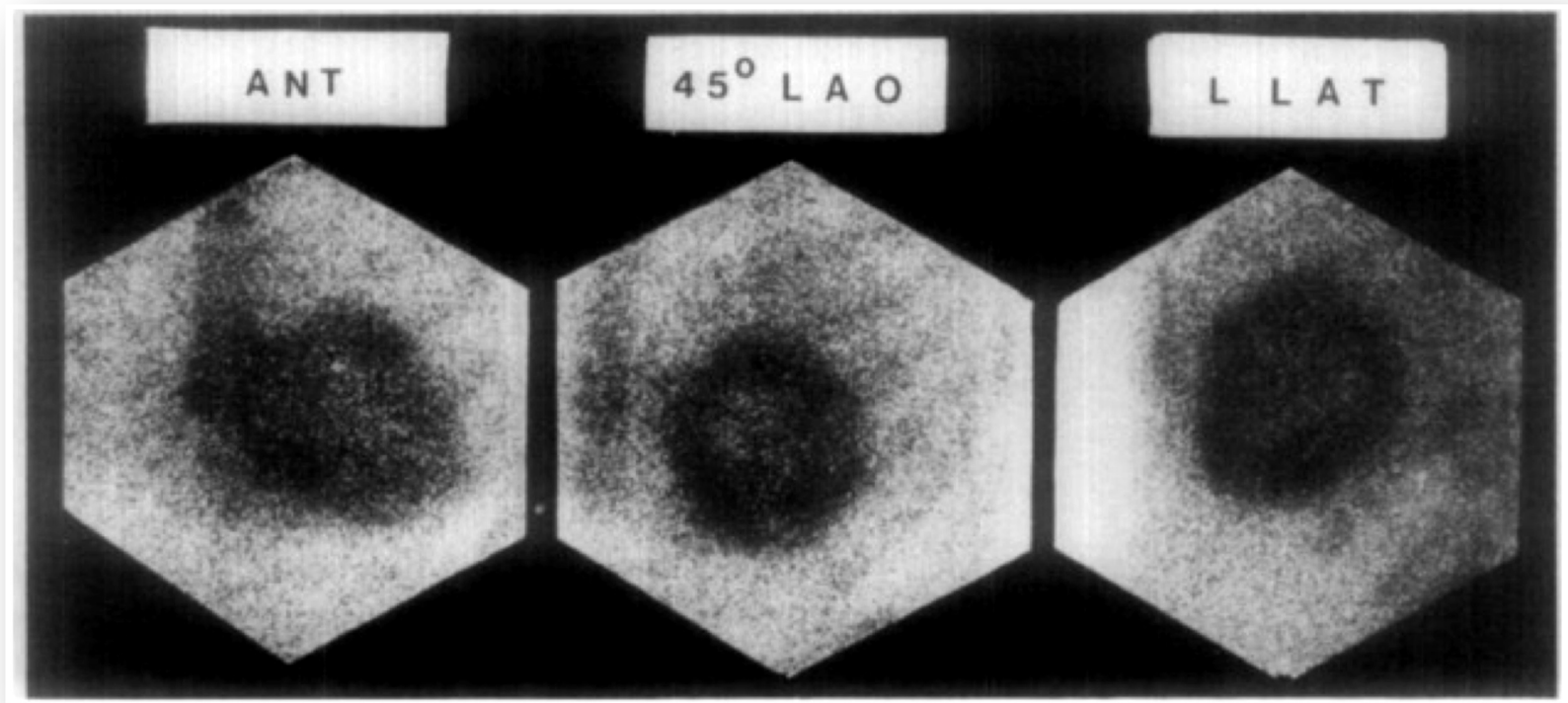
CA, cardiac amyloidosis.

1. Aimo A, et al. *Eur J Clin Invest* 2021;51(5):e13449.

Value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the noninvasive diagnosis of cardiac amyloidosis

Am Heart J. 1982

Theodore A. Wizenberg, M.D., Jaroslaw Muz, M.D., Young H. Sohn, M.D., Wolfram Samlowski, M.D., and Arnold M. Weissler, M.D. *Detroit, Mich.*



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

Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy.

Perugini E[1], Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, Leone O, Farsad M, Ciliberti P, Bacchi-Reggiani L, Fallani F, Branzi A, Rapezzi C.

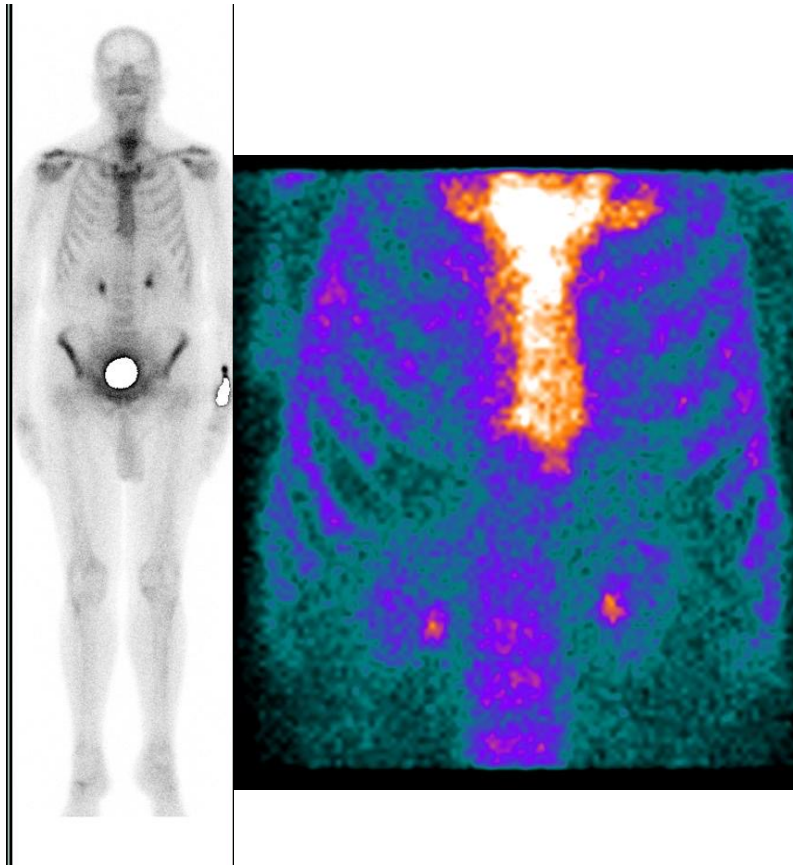
Score visivo di captazione planare:

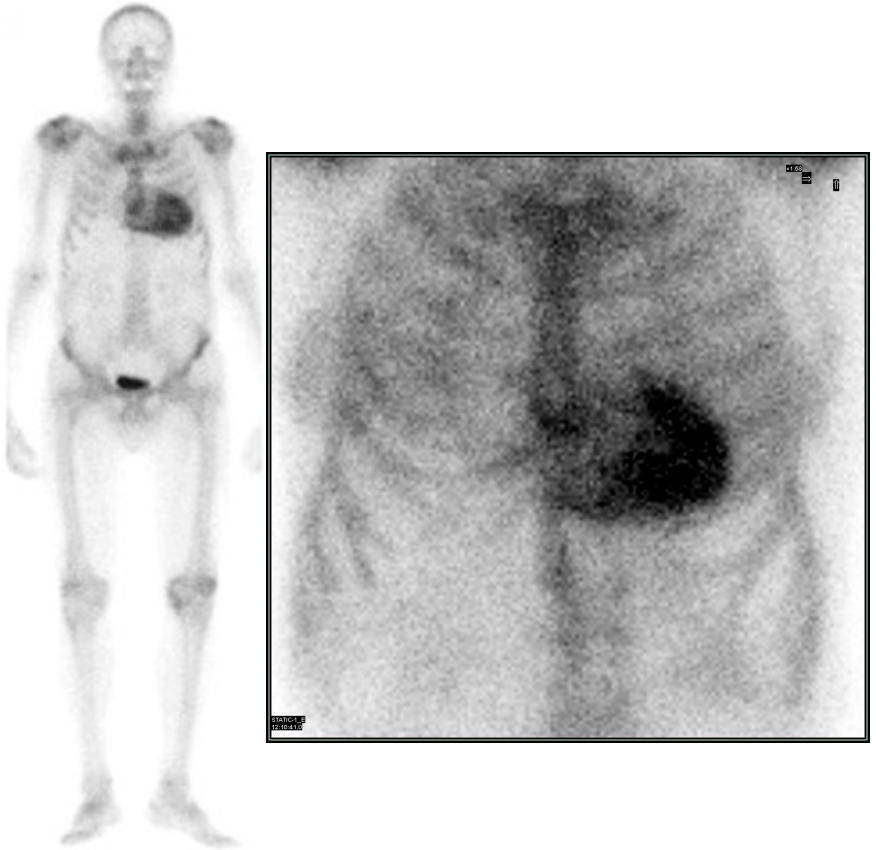
0 = assente captazione cardiaca e captazione ossea normale

1 = debole captazione cardiaca, di intensità inferiore a quella ossea

2 = moderata captazione cardiaca associata ad attenuata captazione ossea

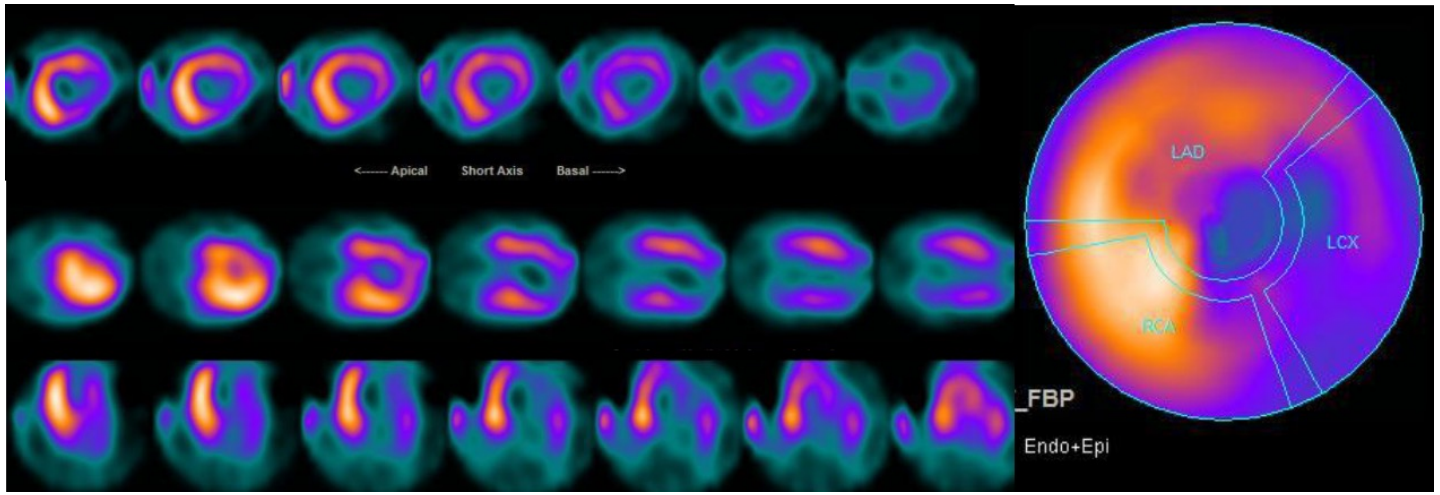
3 = intensa captazione cardiaca associata a ridotta o assente captazione ossea



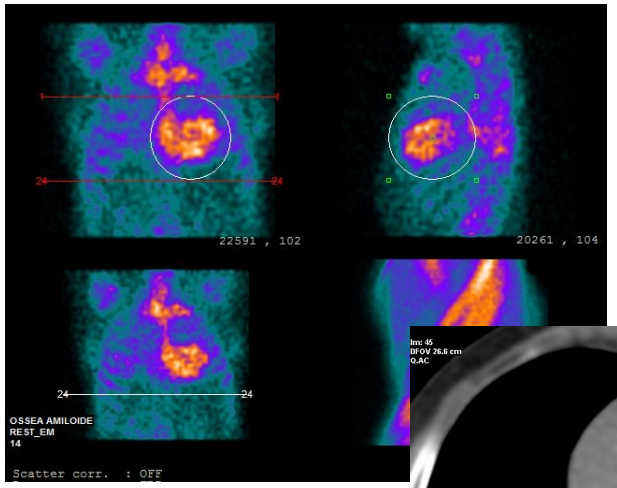


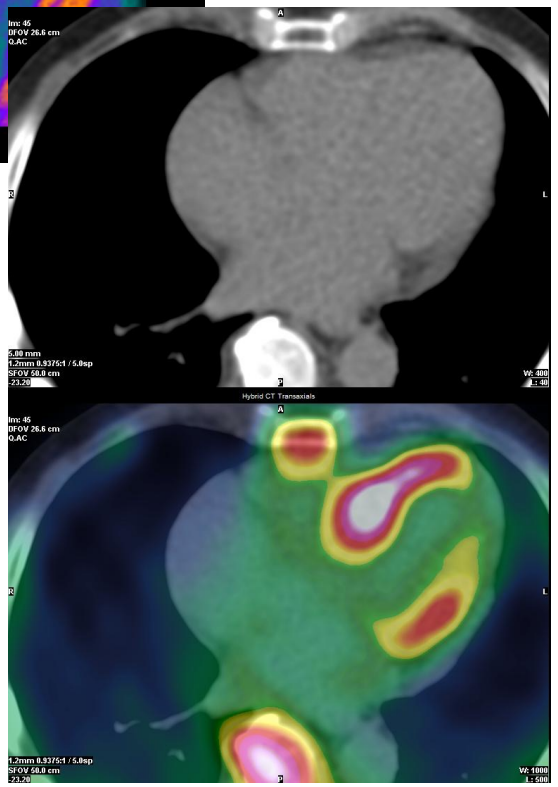
Beyond the "Perugini score": CZT detector + CT-SPECT

Discovery NM/CT 670 CZT



370 Mbq – 10 min/scan 2 hours after injection





CA, cardiac amyloidosis; CT, computerized tomography; CZT, cadmium zinc telluride; NT, nuchal translucency test; SPECT, single-photon emission computed tomography.

Towards a non-invasive diagnosis of AL-CA

^{18}F-Florbetaben PET/CT for AL-CA diagnosis

ORIGINAL RESEARCH

[18F]-Florbetaben PET/CT for Differential Diagnosis Among Cardiac Immunoglobulin Light Chain, Transthyretin Amyloidosis, and Mimicking Conditions

Dario Genovesi, MD,[a,*] Giuseppe Vergaro, MD, PhD,[b,c,*] Assuero Giorgetti, MD,[a,*] Paolo Marzullo, MD,[a] Michele Scipioni, EngD,[d] Maria Filomena Santarelli, EngD,[e] Angela Pucci, MD,[f] Gabriele Buda, MD,[g] Elisabetta Volpi, BSc, PhD,[h] Michele Emdin, MD, PhD[b,c]

ABSTRACT

OBJECTIVES This study aimed to test the diagnostic value of [18F]-florbetaben positron emission tomography (PET) in patients with suspicion of CA.

BACKGROUND Diagnosis of cardiac involvement in immuno transthyretin-related amyloidosis (ATTR), which holds major ir frequently delayed. Furthermore, although diphosphonate rad stration of cardiac amyloidosis (CA) in AL may require endomy

METHODS Forty patients with biopsy-proven diagnoses of C initial clinical suspicion and later diagnosed with non-CA pathol with a 60-min dynamic [18F]-florbetaben PET acquisition, anc radiotracer injection.

RESULTS Visual qualitative assessment showed intense early high, persistent cardiac uptake in all the static scans, whereas uptake decrease soon after the early scan. Semiquantitative as value (SUV_{mean}) in patients with AL, sustained over the whole a [IQR]: 4.00 to 7.43; vs. delayed SUV_{mean}: 3.50; IQR: 2.32 to 6 SUV_{mean}: 2.55; IQR: 1.80 to 2.97; vs. delayed SUV_{mean}: 1.25; IQ (early SUV_{mean}: 3.50; IQR: 1.60 to 3.37; vs. delayed SUV_{mean}: found comparing heart-to-background ratio and molecular vol

CONCLUSIONS Delayed [18F]-florbetaben cardiac uptake m mimicking conditions. [18F]-florbetaben PET/computed tomog diagnosis of AL amyloidosis, which is still often challenging anc II Explorative Study on Evaluation of Diagnostic Efficacy of the Cardiac Amyloidosis [FLORAMICAR2]; EudraCT number: 2017-

Genovesi D et al. 2021[1]

JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2020

EDITORIAL COMMENT

^{18}F-Florbetaben and PET/CT Holds Promise for the Identification and Differentiation Among Cardiac Amyloidosis Entities*

Thomas H. Schindler, MD, PhD,[a] Vijay Sharma, PhD,[a] Alessio Imperiale, MD, PhD[b]

Cardiac amyloidosis caused by aberrant deposi-tions of immunoglobulin light chains (AL) or liver-generated protein transthyretin (TTR) may clinically manifest in a restrictive form of cardiomyopathy, leading to progressive heart failure and worse clinical outcome (1,2). Because the clinical heart failure manifestation of restrictive cardiomyopathy with preserved left ventricular ejection fraction is a nonspecific feature shared with other cardiovascular disease entities, cardiac amyloidosis is frequently missed. In view of novel and emerging treatment options of cardiac depositions AL and TTR (3–5), which likely improve symptoms and importantly prognosis in these patients, it is imperative to identify and differentiate these different forms of cardiac amyloidosis in the early stage of disease manifestation (6,7). Clinical presentation, electrocardiogram, echocardiography, and/or cardiac magnetic resonance commonly raise the suspicion or differential for cardiac amyloidosis and endomyocardial biopsy for definite diagnosis may ensue (1). Conversely, endomyocardial biopsy is invasive and associated with some sampling error, and it may not be applied in a wider range of patients with suspicion for cardiac amyloidosis. Thus, there is a definite need for a noninvasive diagnostic approach for the identification and differentiation of cardiac amyloidosis. In this respect, positron emission radiotracers such as ^{11}C-Pittsburgh B compound (^{11}C-PiB) or ^{18}F-florbetapir in concert with positron emission tomography (PET) have been demonstrated to noninvasively identify cardiac amyloidosis but without being able to reliably differentiate between AL and TTR with reported protocols (8,9). Conversely, myocardial scintigraphy with planar and/or single-photon emission computed tomography acquisitions in conjunction with bone-seeking agents such as technetium Tc 99m (^{99m}Tc)-pyrophosphate and (^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid provide a high sensitivity and specificity (99% and 86%, respectively) for the diagnosis of cardiac TTR (6). Notably, in the absence of a monoclonal protein in serum or urine, a positive ^{99m}Tc-pyrophosphate scan yields a specificity and positive predictive value for cardiac ATTR amyloidosis of 100% (10). Thus, the endeavor is now more geared toward the noninvasive identification of cardiac AL with ^{11}C-PiB and fluorodeoxyglucose F18 (^{18}F)-labeled radiotracers such as ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-flutemetamol and PET imaging (1). These different PET radiotracers connect to fibrils but in a predominant nonspecific fashion so that no definite separation between cardiac AL and TTR so far was reported. Because treatment options between AL and TTR are quite different, however, a more comprehensive and specific diagnostic approach that can identify and differentiate among cardiac amyloid disease entities is highly desirable.

In this issue of *JACC*, Genovesi et al. (1) report that serial and delayed PET/computed tomography (CT) acquisitions of cardiac ^{18}F-florbetaben uptake hold promise to identify and in particular to differentiate between cardiac AL and TTR, respectively.

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University in St. Louis School of Medicine, St. Louis, Missouri, and the [b]Biophysics and Nuclear Medicine, University Hospitals of Strasbourg, Strasbourg, France. Supported by the departmental fund from Washington University (No. ID 3273-03128). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.06.017

Schindler T et al. 2021[2]

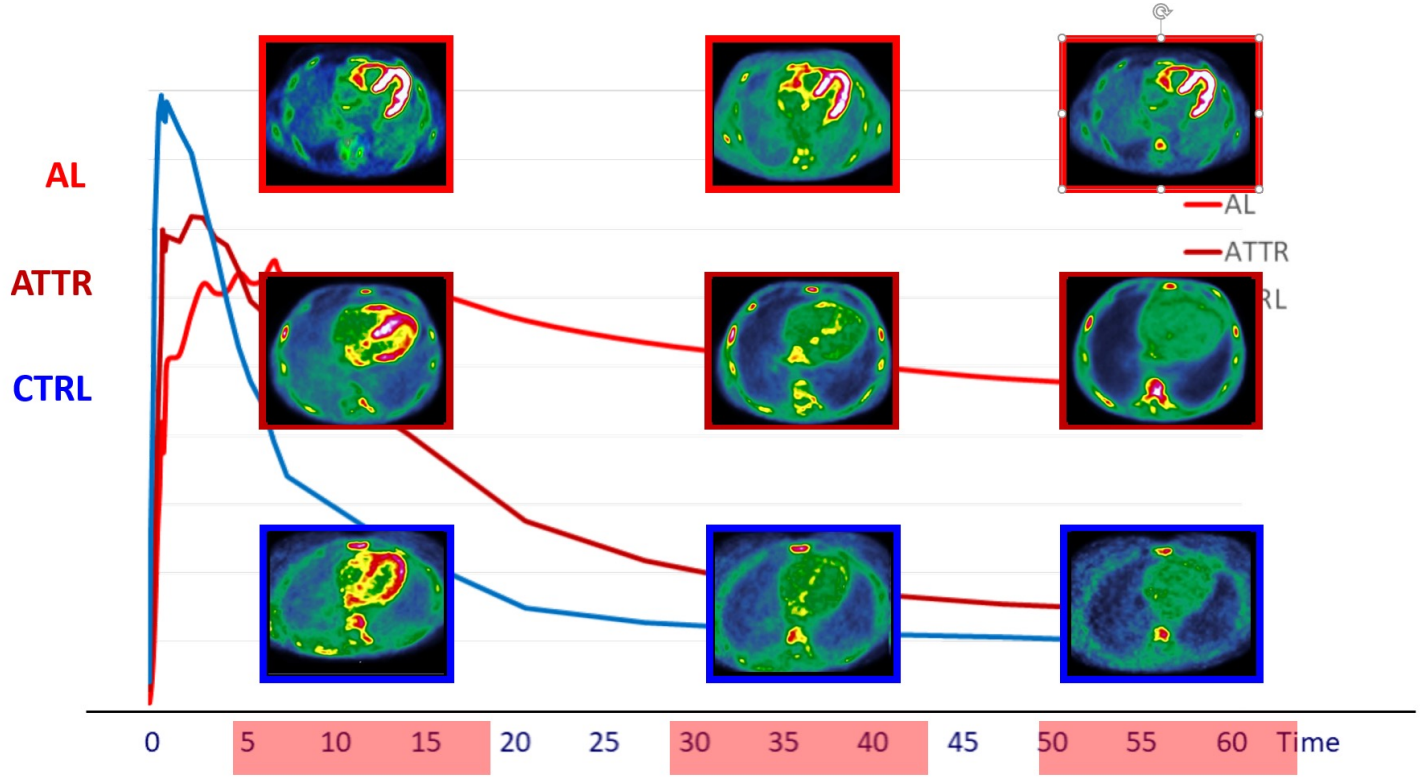


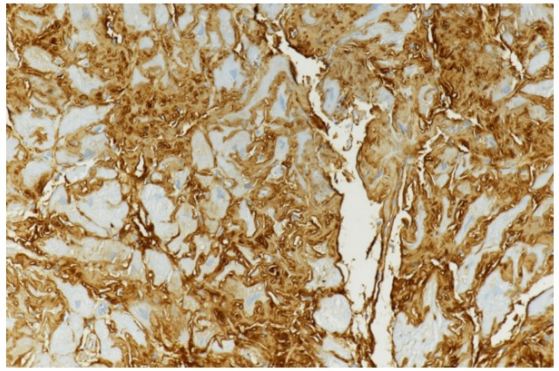
Image adapted from Genovesi et al. 2021.[1]

AL, immunoglobulin light-chain amyloidosis; CA, cardiac amyloidosis; CT, computerized tomography; PET, positron emission tomography.

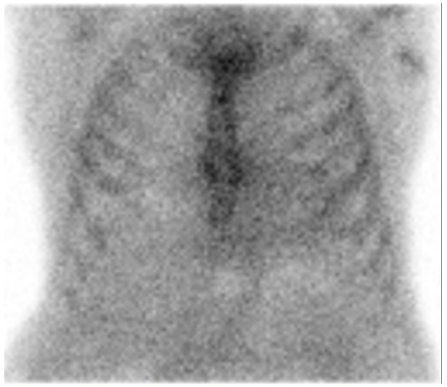
1. Genovesi D, et al. *JACC Cardiovasc Imaging* 2021;14(1):246–255; 2. Schindler T, et al. *JACC Cardiovasc Imaging* 2021;14(1):256–258.

^{18}F-Florbetaben PET/CT for AL-CA diagnosis

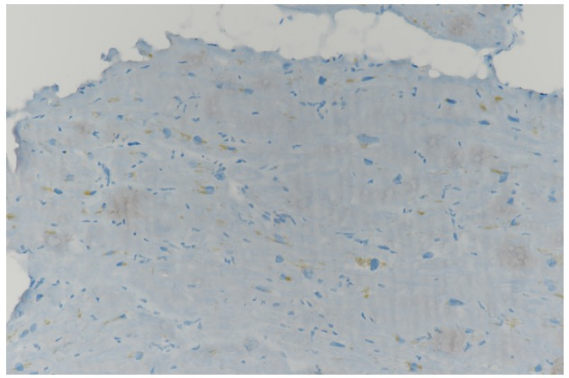
AL-CA



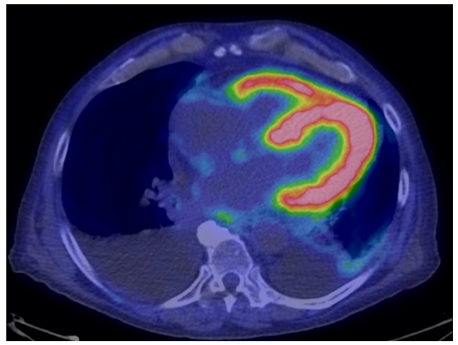
Lambda +



Negative DPD Scintigraphy

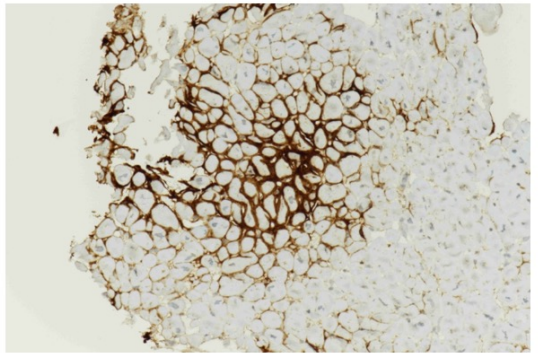


Transthyretin-

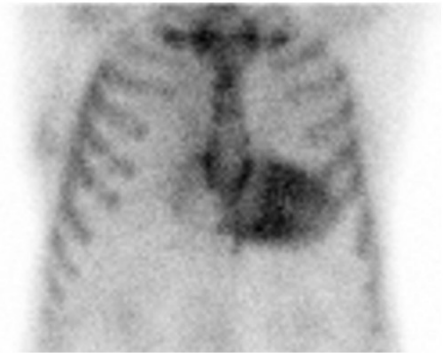


Positive [18F]-Florbetaben PET

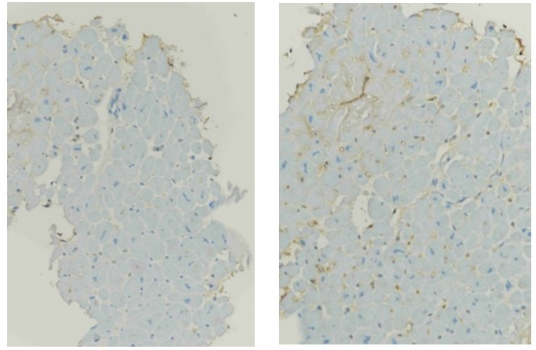
ATTR-CA



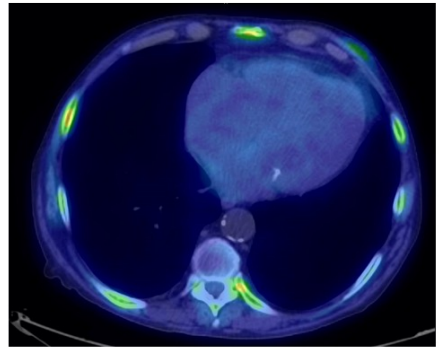
Transthyretin +



Positive DPD Scintigraphy



Lambda/kappa -



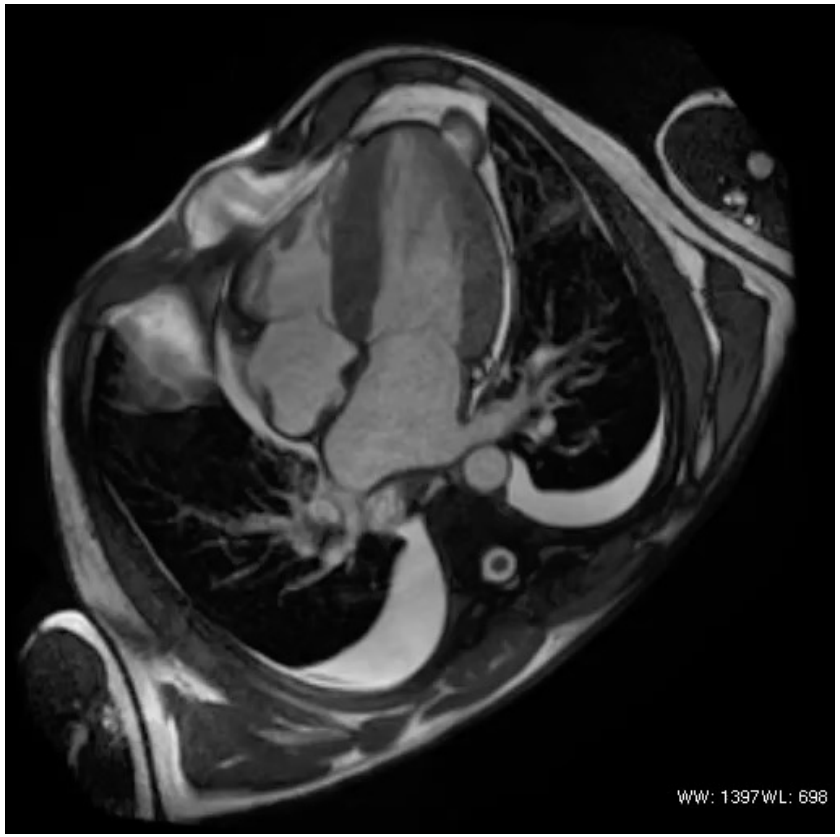
Negative [18F]-Florbetaben PET

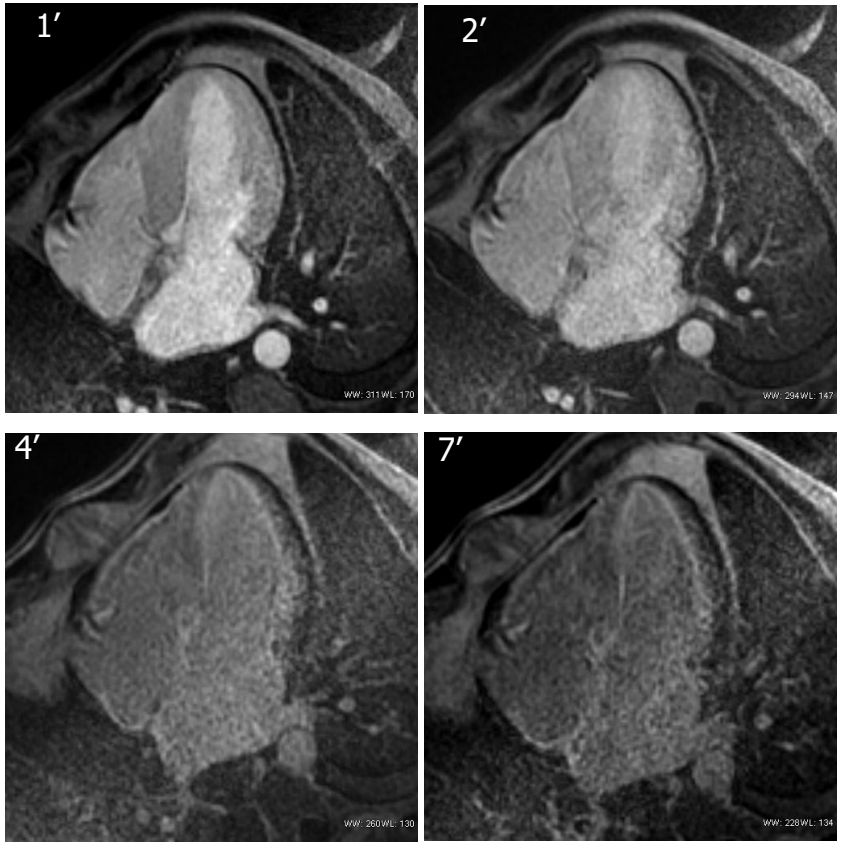
Images provided presenter.

AL, amyloid light-chain; CA, cardiac amyloidosis; ATTR, transthyretin-mediated amyloidosis; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid scan; PET, positron emission tomography.

AL amyloidosis: CMR findings

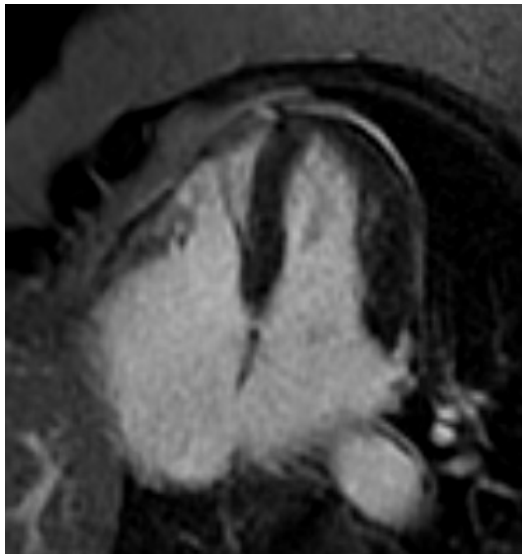
- *Pseudo-hypertrophy*
- *Thickened LA wall*
- *Pericardial effusion*
- *Early darkening of LV cavity*
- *Diffuse subendocardial LGE*
- *Nulling defect*



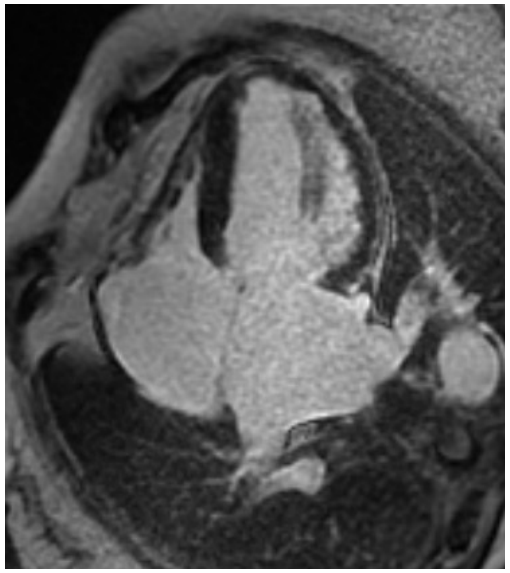


LGE IN AMYLOIDOSIS

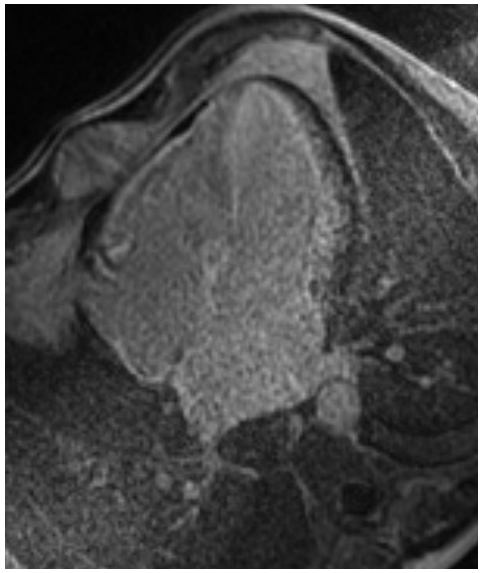
control



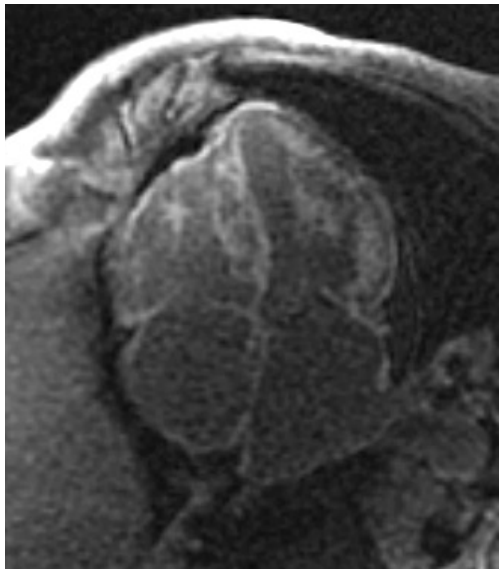
Early AL Amyloidosis



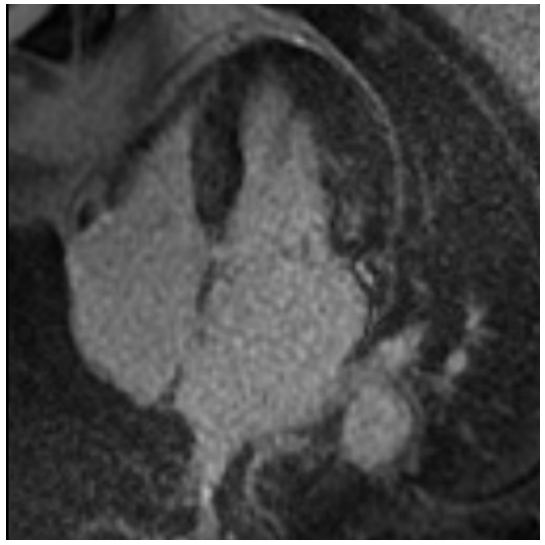
Intermediate AL Amyloidosis



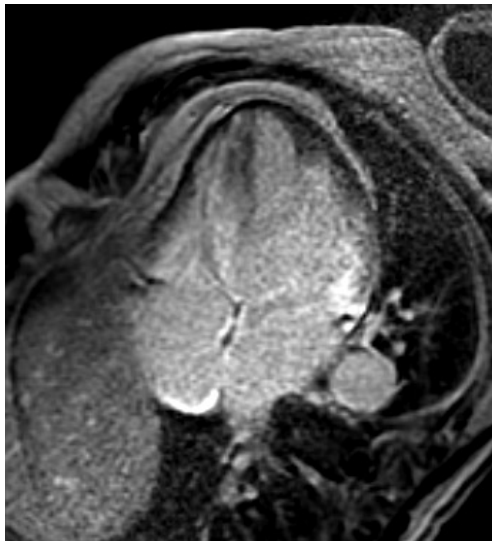
Late AL Amyloidosis



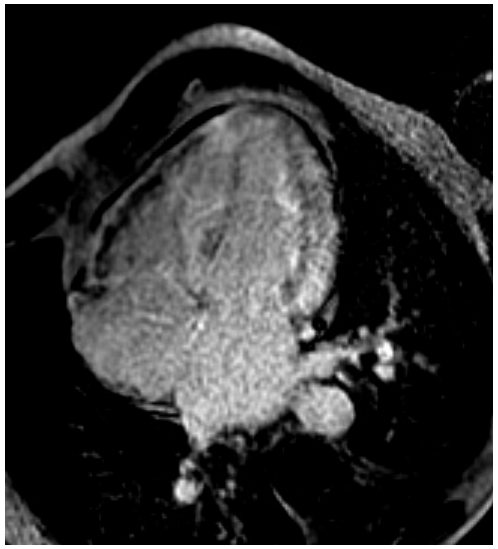
Early (senile) TTR amyloidosis



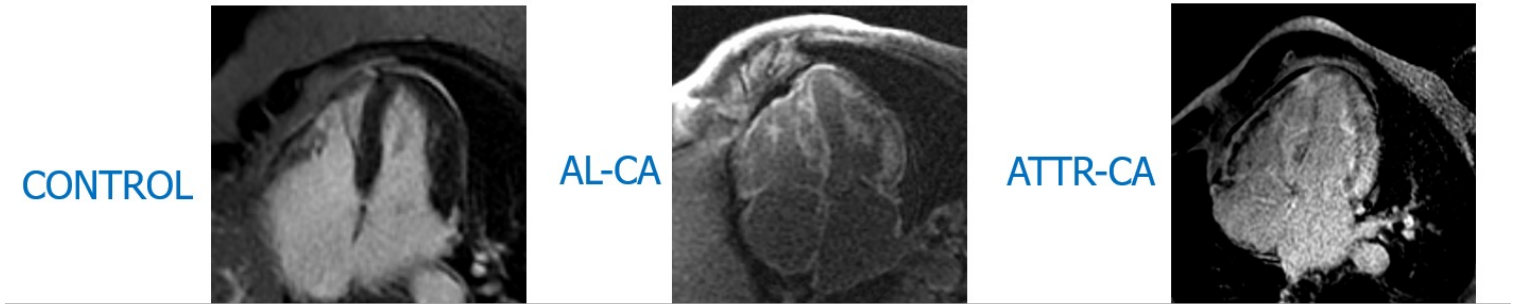
Intermediate (senile) TTR amyloidosis

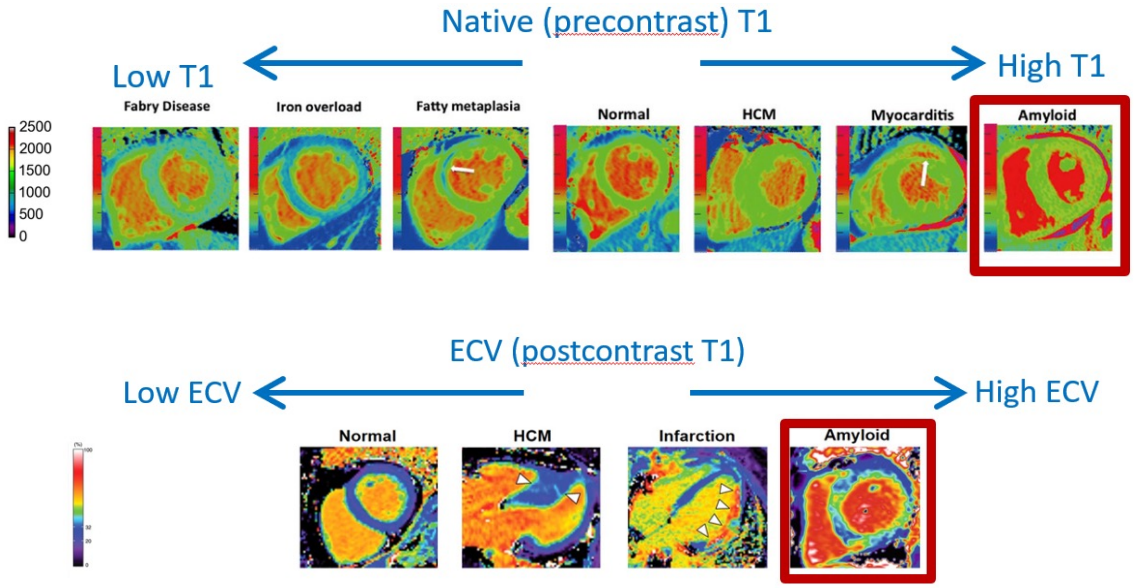


Late (mutated) TTR amyloidosis



ATTR-CA: insight from CMR



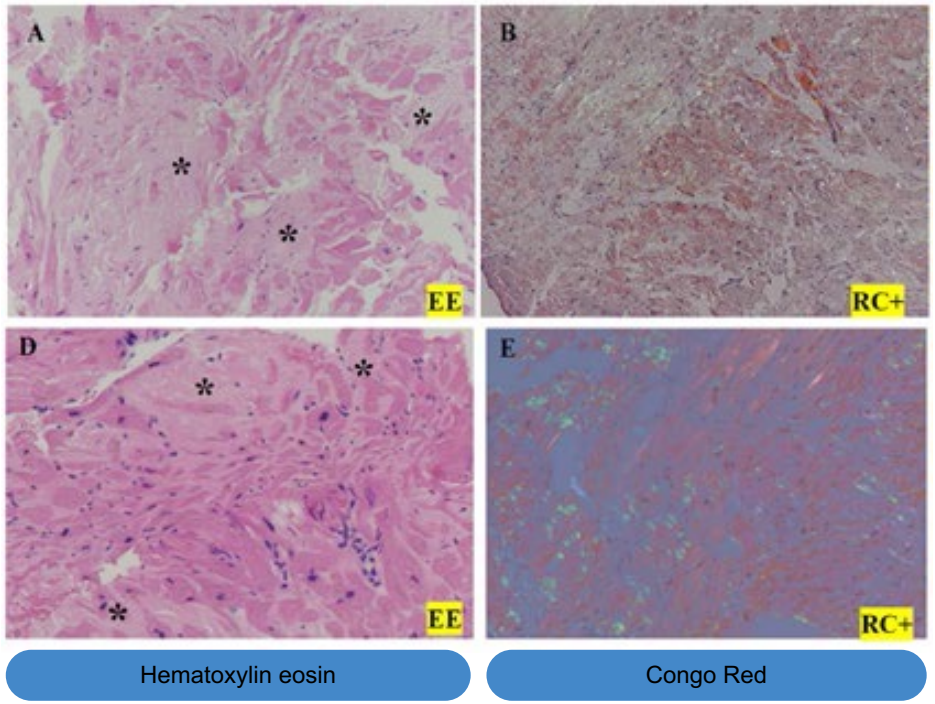


- Pseudo-hypertrophy
- Thickened LA wall
- Pleuro-pericardial effusion
- Early darkening of LV cavity (> in AL-CA)
- Nulling defect
- Subendocardial vs diffuse LGE for diagnosis and prognosis
- Precontrast T1 Mapping
- Precontrast T2 mapping (> in AL-CA)
- Postcontrast T1 Mapping
- ECV (extracellular volume) for diagnosis and prognosis

AL, amyloid light-chain; ATTR, transthyretin-mediated amyloidosis; CA, cardiac amyloidosis; ECV, extracellular volume; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle.

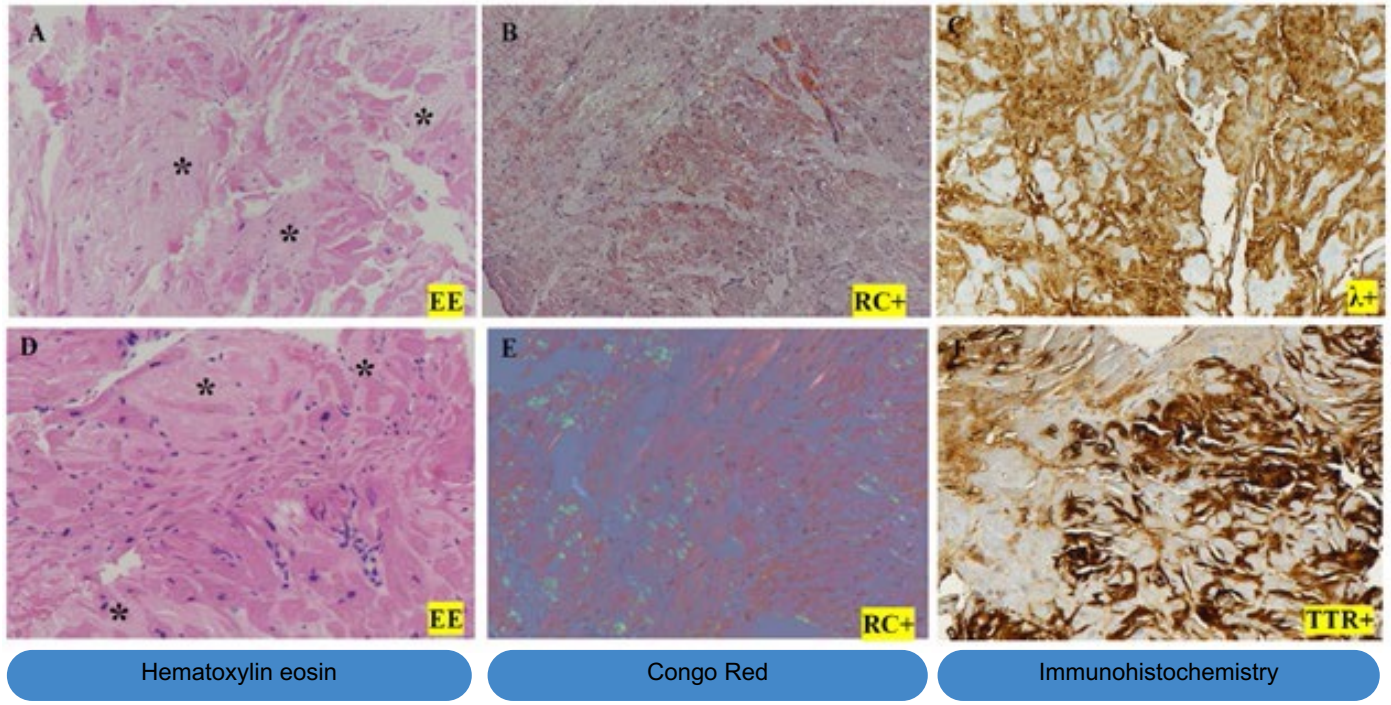
1. Razvi Y, et al. *Front Cardiovasc Med* 2021;8:751293; 2. Chatzantonis G, et al. *Clin Res Cardiol* 2021;110:555.

Amyloid detection



Courtesy of Dr. A. Pucci

Amyloid typing



Courtesy of Dr. A. Pucci

Beyond amyloidosis; fibrosis as a target in CA

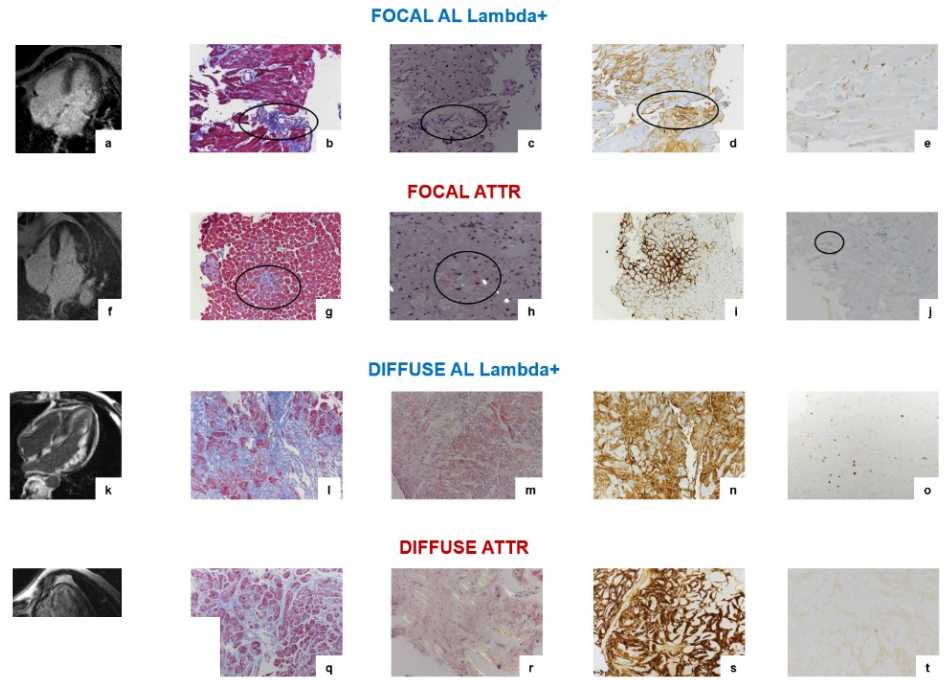
American Heart Association.

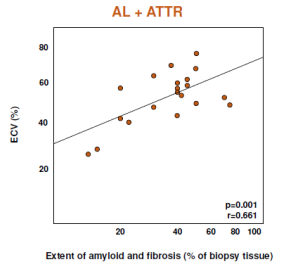
JAHA

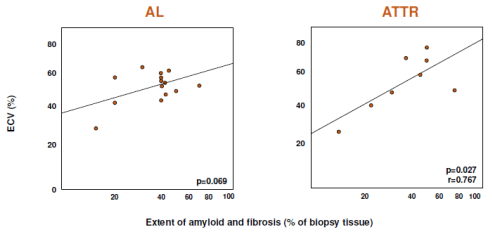
Amyloid Deposits and Fibrosis on Left Ventricular Endomyocardial Biopsy Correlate with Extracellular Volume in Cardiac Amyloidosis

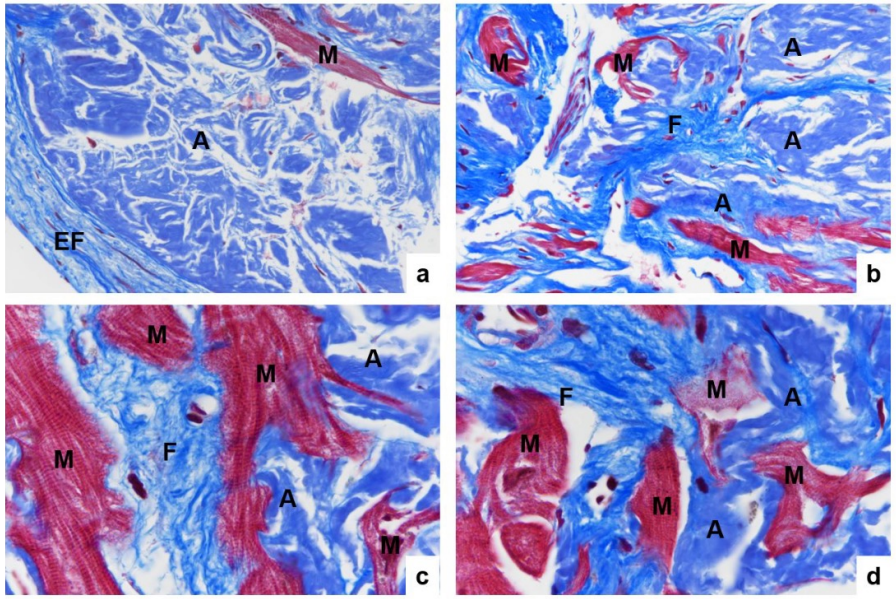
Running title: *Pucci et al.; Amyloid and fibrosis in left ventricular biopsies*

Angela Pucci, MD[1*], Alberto Aimo, MD[1,2*], Veronica Musetti, BSc[2,3], Andrea Barison, MD, Giuseppe Vergaro, MD, PhD[2,3], Dario Genovesi, MD[3], Assuero Giorgetti, MD[3], Silvia Mas PhD[2], Chiara Arzilli, MD[1], Concetta Prontera, BSc[3], Luigi Emilio Pastormerlo, MD, PhD[3], M Alessandro Coceani, MD[3], Marco Ciardetti, MD[3], Nicola Martini, PhD[3], Cataldo Palmieri, M Claudio Passino, MD[2,3], Claudio Rapezzi, MD[4,5], Michele Emdin, MD, PhD[2,3]

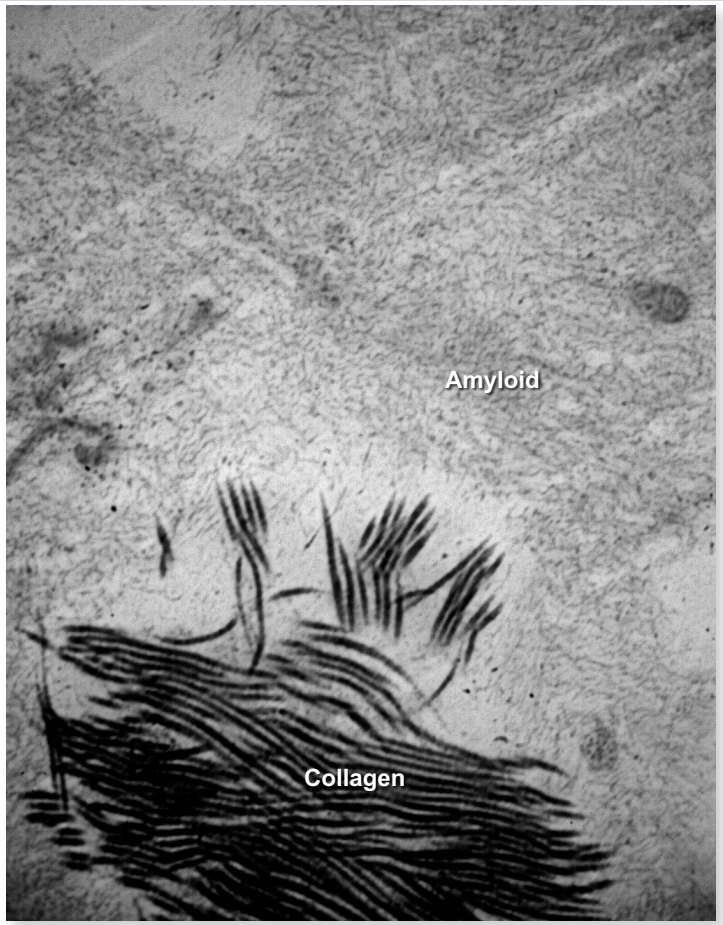


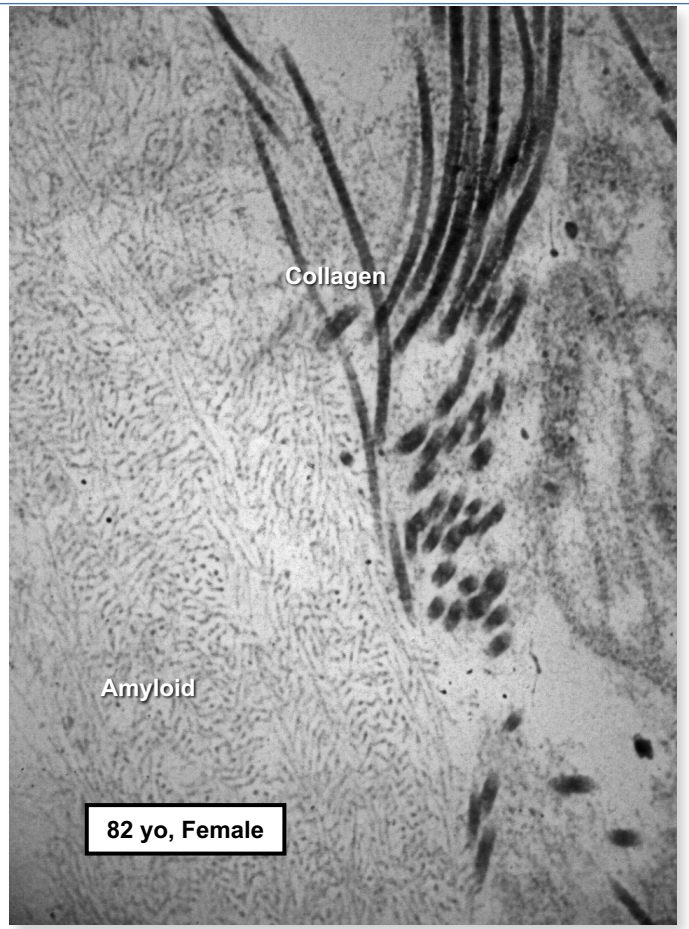






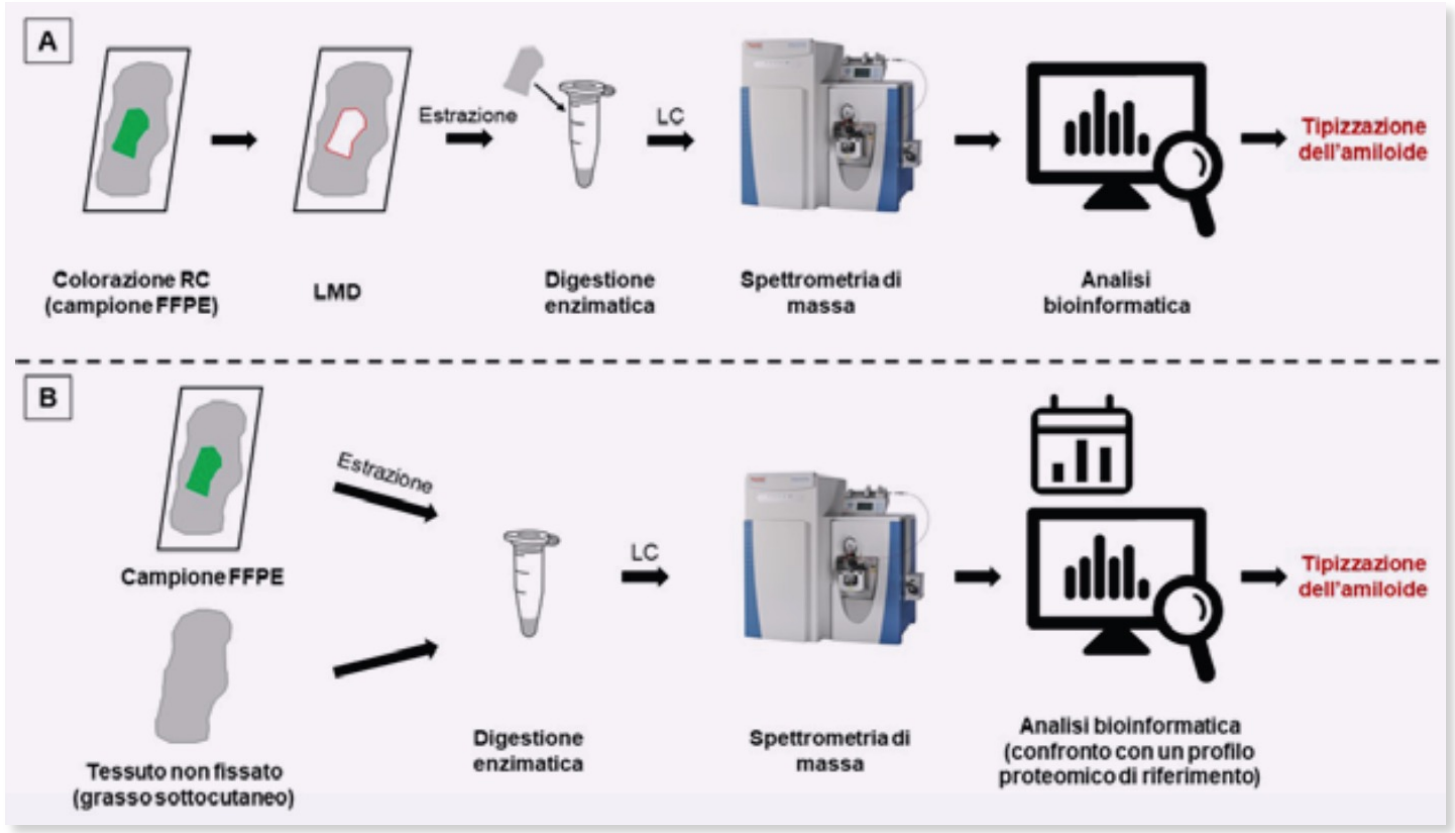
Electron Microscopy





Courtesy of Dr. A. Pucci

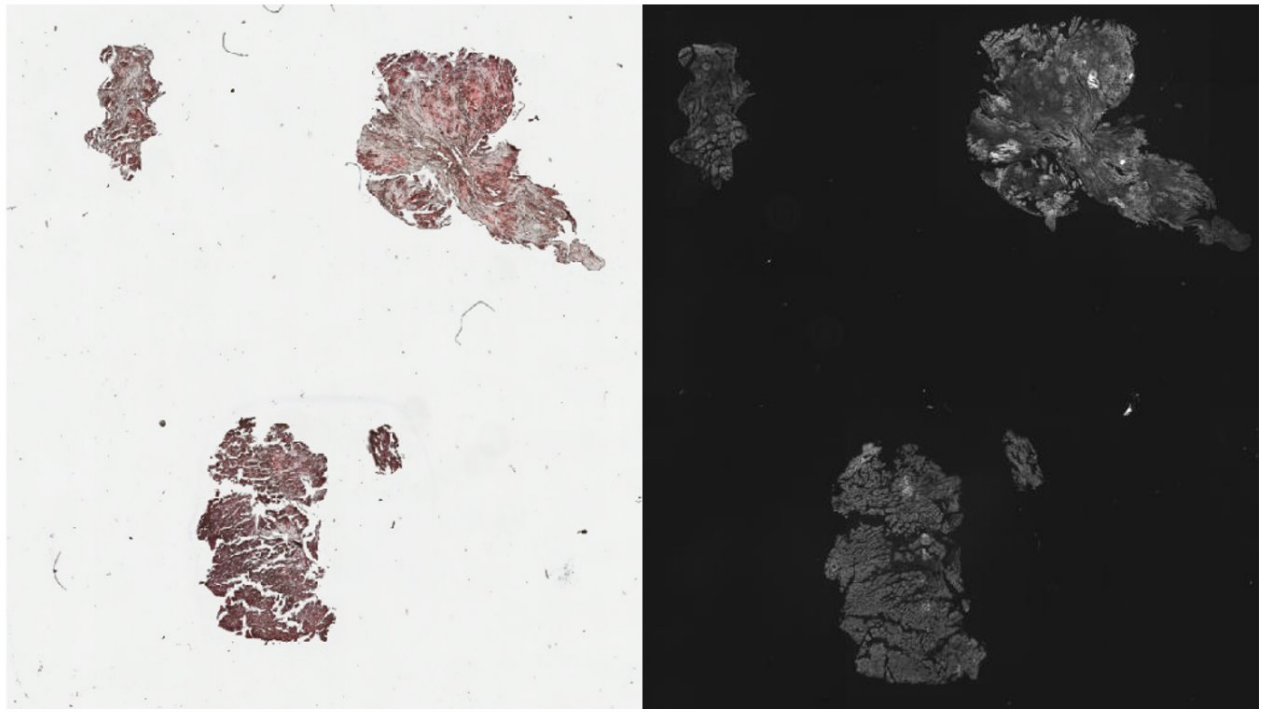
Mass Spectrometry



From Emdin M, Vergaro G, Passino C, Edt.
Amiloidosi Cardiaca. Come si diagnostica, come di cura.
2020

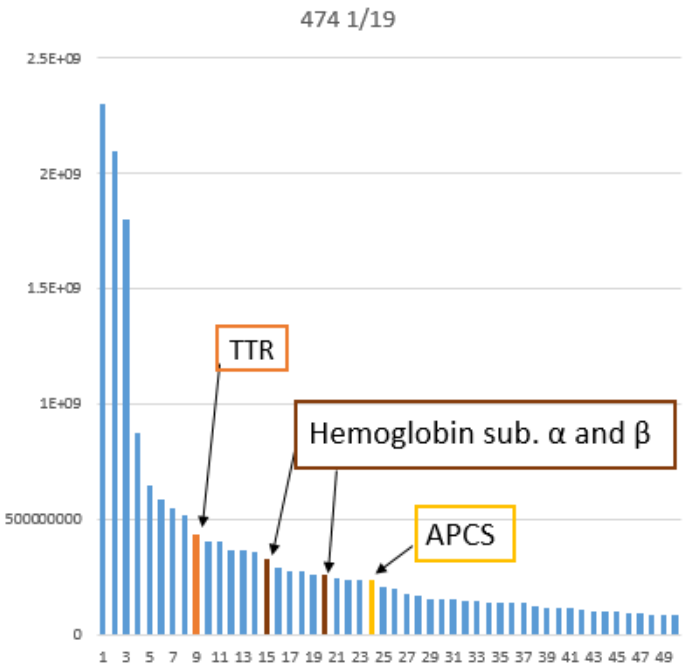
Case 2 – 474 1/19

Cardiac amyloidosis, heart tissue sample (FFPE) , Bright Field (Congo Red) and Fluorescence (exc. 479 nm, 43 DsRed filter).



Case 2 – 474 1/19

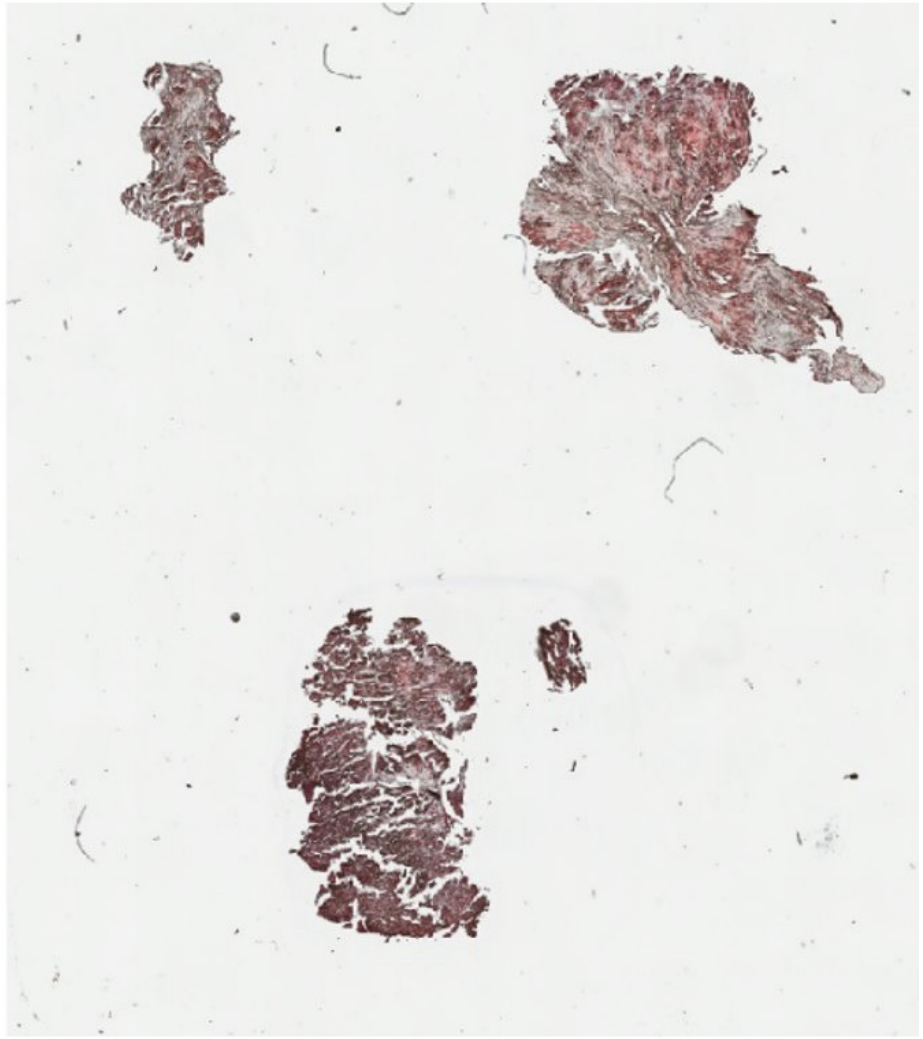
Rank	Accession	Description	Coverage	# Peptides	# PSMs	# Unique	# Protein	Area: F10:emPAI	Score Seq	# Peptides Sequest HT
1	P12883	Myosin-7 OS=Homo sapiens OX=9606 GN=MYH7 PE=1 SV=5	64	158	784	57	1	2.3E+09	1880,524	2838	158
2	P08590	Myosin light chain 3 OS=Homo sapiens OX=9606 GN=MYL3 PE=1 SV=3	67	15	63	12	1	2.1E+09	141,51	192	15
3	P17661	Desmin OS=Homo sapiens OX=9606 GN=DES PE=1 SV=3	79	42	171	38	1	1.8E+09	180,161	595	42
4	P68032	Actin, alpha cardiac muscle 1 OS=Homo sapiens OX=9606 GN=ACTC1 PE=1 SV=	71	22	163	2	1	8.8E+08	222,872	561	22
5	P06576	ATP synthase subunit beta, mitochondrial OS=Homo sapiens OX=9606 GN=AT	55	22	85	22	1	6.5E+08	33,145	285	22
6	P04264	Keratin, type II cytoskeletal 1 OS=Homo sapiens OX=9606 GN=KRT1 PE=1 SV=	56	36	84	31	1	5.9E+08	53,362	286,99295	36
7	P25705	ATP synthase subunit alpha, mitochondrial OS=Homo sapiens OX=9606 GN=A	47,377938	21	73	21	1	5.5E+08	16,783	245	21
8	P10916	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform OS=Hom	87	17	82	17	1	5.2E+08	3980,072	275	17
9	P02766	Transthyretin OS=Homo sapiens OX=9606 GN=TTR PE=1 SV=1	65	9	29	9	1	4.4E+08	463,159	123	9
10	P35609	Alpha-actinin-2 OS=Homo sapiens OX=9606 GN=ACTN2 PE=1 SV=1	65	49	139	38	1	4.1E+08	39,471	474	49
11	P09493	Tropomyosin alpha-1 chain OS=Homo sapiens OX=9606 GN=TPM1 PE=1 SV=2	59	28	77	10	1	4.1E+08	864,964	246	28
12	P68133	Actin, alpha skeletal muscle OS=Homo sapiens OX=9606 GN=ACTA1 PE=1 SV=	71	22	166	2	1	3.7E+08	250,189	571	22
13	P02679	Fibrinogen gamma chain OS=Homo sapiens OX=9606 GN=FGG PE=1 SV=3	51	17	52	17	1	3.7E+08	11,915	175	17
14	P02671	Fibrinogen alpha chain OS=Homo sapiens OX=9606 GN=FGA PE=1 SV=2	33	26	75	26	1	3.6E+08	15,681	250	26
15	P69905	Hemoglobin subunit alpha OS=Homo sapiens OX=9606 GN=HBA1 PE=1 SV=2	63	7	21	7	1	3.3E+08	41,17	67	7
16	Q8WZ42	Titin OS=Homo sapiens OX=9606 GN=TTN PE=1 SV=4	25	657	907	657	1	2.9E+08	1,798	2893	657
17	Q14896	Myosin-binding protein C, cardiac-type OS=Homo sapiens OX=9606 GN=MYB	46	43	97	43	1	2.8E+08	10,906	322	43
18	P02144	Myoglobin OS=Homo sapiens OX=9606 GN=MB PE=1 SV=2	33	4	14	4	1	2.8E+08	12,335	54	4
19	P17540	Creatine kinase S-type, mitochondrial OS=Homo sapiens OX=9606 GN=CKMT	43	15	43	15	1	2.6E+08	13,125	150	15
20	P68871	Hemoglobin subunit beta OS=Homo sapiens OX=9606 GN=HBB PE=1 SV=2	76	5	33	5	1	2.6E+08	42,288	109	5
21	P19429	Troponin I, cardiac muscle OS=Homo sapiens OX=9606 GN=TNNI3 PE=1 SV=3	31	7	35	7	1	2.5E+08	73,989	94	7
22	P45379	Troponin T, cardiac muscle OS=Homo sapiens OX=9606 GN=TNNT2 PE=1 SV=3	42	16	31	16	1	2.4E+08	99	83	16
23	P02675	Fibrinogen beta chain OS=Homo sapiens OX=9606 GN=FGB PE=1 SV=2	52	21	58	21	1	2.4E+08	13,678	207	21
24	P02743	Serum amyloid P-component OS=Homo sapiens OX=9606 GN=APCS PE=1 SV=	23	5	12	5	1	2.4E+08	4,012	34	5
25	P12235	ADP/ATP translocase 1 OS=Homo sapiens OX=9606 GN=SLC25A4 PE=1 SV=4	40	12	19	4	1	2.1E+08	5,31	52	12
26	P00403	Cytochrome c oxidase subunit 2 OS=Homo sapiens OX=9606 GN=MT-CO2 PE=	14	3	6	3	1	2E+08	1,783	14	3
27	P06732	Creatine kinase M-type OS=Homo sapiens OX=9606 GN=CKM PE=1 SV=2	43	13	32	13	1	1.8E+08	7,962	121	13
28	P04792	Heat shock protein beta-1 OS=Homo sapiens OX=9606 GN=HSPB1 PE=1 SV=2	46	8	17	8	1	1.7E+08	10,938	63	8
29	P35333	Myosin-6 OS=Homo sapiens OX=9606 GN=MYH6 PE=1 SV=5	41	99	492	6	1	1.6E+08	96,789	1760	99
30	Q99798	Aconitate hydratase, mitochondrial OS=Homo sapiens OX=9606 GN=ACO2 PE	44	32	57	32	1	1.6E+08	18,475	201	32
31	P63316	Troponin C, slow skeletal and cardiac muscles OS=Homo sapiens OX=9606 GN	47	8	19	8	1	1.6E+08	99	73	8
32	P40926	Malate dehydrogenase, mitochondrial OS=Homo sapiens OX=9606 GN=MDH2	48	12	24	12	1	1.5E+08	7,031	83,073136	12
33	P12829	Myosin light chain 4 OS=Homo sapiens OX=9606 GN=MYL4 PE=1 SV=3	61	11	16	10	1	1.5E+08	13,251	53	11
34	O75112	LIM domain-binding protein 3 OS=Homo sapiens OX=9606 GN=LDB3 PE=1 SV=	34	16	44	16	1	1.4E+08	9,798	142	16
35	P05505	Aspartate aminotransferase, mitochondrial OS=Homo sapiens OX=9606 GN=(	35	14	21	14	1	1.4E+08	4,878	58	14
36	P05413	Fatty acid-binding protein, heart OS=Homo sapiens OX=9606 GN=FABP3 PE=1	53	8	15	8	1	1.4E+08	9	44	8
37	P04406	Glyceraldehyde-3-phosphate dehydrogenase OS=Homo sapiens OX=9606 GN	45	12	26	12	1	1.4E+08	15,681	91	12
38	P02511	Alpha-crystallin B chain OS=Homo sapiens OX=9606 GN=CRYAB PE=1 SV=2	60	11	23	11	1	1.3E+08	27,48	74	11
39	P08123	Collagen alpha-2(I) chain OS=Homo sapiens OX=9606 GN=COL1A2 PE=1 SV=7	6,1493411	7	15	7	1	1.2E+08	0,334	51	7
40	O75390	Citrate synthase, mitochondrial OS=Homo sapiens OX=9606 GN=CS PE=1 SV=	22	9	15	9	1	1.2E+08	2,511	39	9
41	Q03825	Phosphate carrier protein, mitochondrial OS=Homo sapiens OX=9606 GN=SLC	23	9	11	9	1	1.2E+08	2,162	26,504213	9
42	P12111	Collagen alpha-3(VI) chain OS=Homo sapiens OX=9606 GN=COL6A3 PE=1 SV=	22	59	97	59	1	1.1E+08	2,079	314	59
43	P48047	ATP synthase subunit O, mitochondrial OS=Homo sapiens OX=9606 GN=ATPS	62	10	18	10	1	1E+08	16,783	60	10
44	Q9NPC6	Myozenin-2 OS=Homo sapiens OX=9606 GN=MYOZ2 PE=1 SV=1	57	12	20	12	1	1E+08	10,548	62	12
45	P06753	Tropomyosin alpha-3 chain OS=Homo sapiens OX=9606 GN=TPM3 PE=1 SV=2	42	16	38	4	1	1E+08	41,17	126	16
46	O94875	Sorbin and SH3 domain-containing protein 2 OS=Homo sapiens OX=9606 GN=	15	16	23	16	1	970000000	1,154	68	16
47	Q14315	Filamin-C OS=Homo sapiens OX=9606 GN=FLNC PE=1 SV=3	39	76	126	69	1	930000000	3,959	429	76
48	Q13642	Four and a half LIM domains protein 1 OS=Homo sapiens OX=9606 GN=FHL1 P	7	2	4	2	1	910000000	0,468	12	2
49	P12109	Collagen alpha-1(VI) chain OS=Homo sapiens OX=9606 GN=COL6A1 PE=1 SV=	19	14	27	14	1	890000000	1,384	84,740827	14
50	P04908	Histone H2A type 1-B/E OS=Homo sapiens OX=9606 GN=HIST1H2AB PE=1 SV=	21	2	3	2	1	880000000	2,981	12	2



Case 2 – 474 1/19

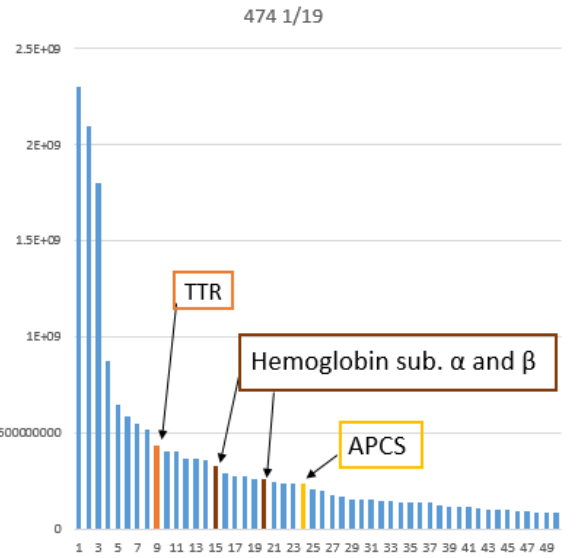
Proteomics form EMBs

Cardiac amyloidosis, heart tissue sample (FFPE) , Bright Field (Congo Red) and Fluorescence (exc. 479 nm, 43 DsRed filter).

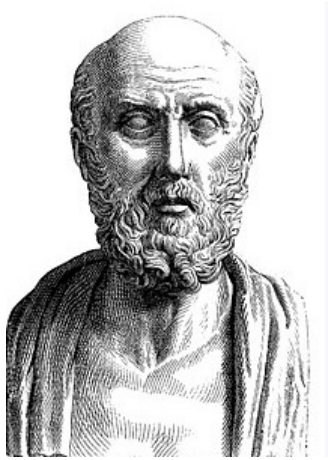


Case 2 – 474 1/19

Rank	Accession	Description	Coverage	# Peptide	# PSMs	# Unique	# Protein	Area: F10: emPAI	Score Seq	# Peptides Sequest HT
1	P12883	Myosin-7 OS=Homo sapiens OX=9606 GN=MYH7 PE=1 SV=5	64	158	784	57	1	2.3E+09	1880,524	2838	158
2	P08590	Myosin light chain 3 OS=Homo sapiens OX=9606 GN=MYL3 PE=1 SV=3	67	15	63	12	1	2.1E+09	141,51	192	15
3	P17661	Desmin OS=Homo sapiens OX=9606 GN=DES PE=1 SV=3	79	42	171	38	1	1.8E+09	180,161	595	42
4	P68032	Actin, alpha cardiac muscle 1 OS=Homo sapiens OX=9606 GN=ACTC1 PE=1 SV=	73	22	163	2	1	8.8E+08	222,872	561	22
5	P06576	ATP synthase subunit beta, mitochondrial OS=Homo sapiens OX=9606 GN=A1	55	22	85	22	1	6.5E+08	33,145	285	22
6	P04264	Keratin, type II cytoskeletal 1 OS=Homo sapiens OX=9606 GN=KRT1 PE=1 SV=	56	36	84	31	1	5.9E+08	53,362	286,99295	36
7	P25705	ATP synthase subunit alpha, mitochondrial OS=Homo sapiens OX=9606 GN=A	47,377938	21	73	21	1	5.5E+08	16,783	245	21
8	P10916	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform OS=Hom	87	17	82	17	1	5.2E+08	9980,072	275	17
9	P02766	Transthyretin OS=Homo sapiens OX=9606 GN=TTR PE=1 SV=1	65	9	29	9	1	4.4E+08	463,159	123	9
10	P35609	Alpha-actinin-2 OS=Homo sapiens OX=9606 GN=ACTN2 PE=1 SV=1	65	49	139	38	1	4.1E+08	39,471	474	49
11	P09493	Tropomyosin alpha-1 chain OS=Homo sapiens OX=9606 GN=TPM1 PE=1 SV=2	59	28	77	10	1	4.1E+08	864,984	246	28
12	P68133	Actin, alpha skeletal muscle OS=Homo sapiens OX=9606 GN=ACTA1 PE=1 SV=	71	22	166	2	1	3.7E+08	250,189	571	22
13	P02679	Fibrinogen gamma chain OS=Homo sapiens OX=9606 GN=FGG PE=1 SV=3	51	17	52	17	1	3.7E+08	11,915	175	17
14	P02671	Fibrinogen alpha chain OS=Homo sapiens OX=9606 GN=FGA PE=1 SV=2	33	26	75	26	1	3.6E+08	15,681	250	26
15	P69905	Hemoglobin subunit alpha OS=Homo sapiens OX=9606 GN=HBA1 PE=1 SV=2	63	7	23	7	1	3.3E+08	43,17	67	7
16	Q8WZ42	Titin OS=Homo sapiens OX=9606 GN=TTN PE=1 SV=4	25	657	907	657	1	2.9E+08	1,798	2893	657
17	Q14896	Myosin-binding protein C, cardiac-type OS=Homo sapiens OX=9606 GN=MYB	46	43	97	43	1	2.8E+08	10,906	322	43
18	P02144	Myoglobin OS=Homo sapiens OX=9606 GN=MB PE=1 SV=2	33	4	14	4	1	2.8E+08	12,335	54	4
19	P17540	Creatine kinase S-type, mitochondrial OS=Homo sapiens OX=9606 GN=CKMT	43	15	43	15	1	2.6E+08	13,125	150	15
20	P68871	Hemoglobin subunit beta OS=Homo sapiens OX=9606 GN=HBB PE=1 SV=2	76	9	33	5	1	2.6E+08	42,288	109	9
21	P19429	Troponin I, cardiac muscle OS=Homo sapiens OX=9606 GN=TNNI3 PE=1 SV=3	31	7	35	7	1	2.5E+08	73,989	94	7
22	P45379	Troponin T, cardiac muscle OS=Homo sapiens OX=9606 GN=TNNT2 PE=1 SV=3	42	16	31	16	1	2.4E+08	99	83	16
23	P02675	Fibrinogen beta chain OS=Homo sapiens OX=9606 GN=FGB PE=1 SV=2	52	21	58	21	1	2.4E+08	13,678	207	21
24	P02743	Serum amyloid P-component OS=Homo sapiens OX=9606 GN=APCS PE=1 SV=	23	5	12	5	1	2.4E+08	4,012	34	5
25	P12235	ADP/ATP translocase 1 OS=Homo sapiens OX=9606 GN=SLC25A4 PE=1 SV=4	40	12	19	4	1	2.1E+08	5,31	52	12
26	P00403	Cytochrome c oxidase subunit 2 OS=Homo sapiens OX=9606 GN=MT-CO2 PE=	14	3	6	3	1	2E+08	1,783	14	3
27	P06732	Creatine kinase M-type OS=Homo sapiens OX=9606 GN=CKM PE=1 SV=2	43	13	32	13	1	1.8E+08	7,962	121	13
28	P04792	Heat shock protein beta-1 OS=Homo sapiens OX=9606 GN=HSPB1 PE=1 SV=2	46	8	17	8	1	1.7E+08	10,938	63	8
29	P13533	Myosin-6 OS=Homo sapiens OX=9606 GN=MYH6 PE=1 SV=5	41	99	492	6	1	1.6E+08	96,789	1760	99
30	Q99798	Aconitate hydratase, mitochondrial OS=Homo sapiens OX=9606 GN=ACO2 PE	44	32	57	32	1	1.6E+08	18,475	201	32
31	P63316	Troponin C, slow skeletal and cardiac muscles OS=Homo sapiens OX=9606 GN	47	8	19	8	1	1.6E+08	99	73	8
32	P40926	Malate dehydrogenase, mitochondrial OS=Homo sapiens OX=9606 GN=MDH2	48	12	24	12	1	1.5E+08	7,031	83,0731386	12
33	P12829	Myosin light chain 4 OS=Homo sapiens OX=9606 GN=MYL4 PE=1 SV=3	61	11	16	10	1	1.5E+08	13,251	53	11
34	O75112	LIM domain-binding protein 3 OS=Homo sapiens OX=9606 GN=LDB3 PE=1 SV=	34	16	44	16	1	1.4E+08	9,798	142	16
35	P00505	Aspartate aminotransferase, mitochondrial OS=Homo sapiens OX=9606 GN=	35	14	21	14	1	1.4E+08	4,878	58	14
36	P05413	Fatty acid-binding protein, heart OS=Homo sapiens OX=9606 GN=FABP3 PE=	53	8	15	8	1	1.4E+08	9	44	8
37	P04406	Glyceraldehyde-3-phosphate dehydrogenase OS=Homo sapiens OX=9606 GN	45	12	26	12	1	1.4E+08	15,681	91	12
38	P02511	Alpha-crystallin B chain OS=Homo sapiens OX=9606 GN=CRYAB PE=1 SV=2	60	11	23	11	1	1.3E+08	27,48	74	11
39	P08123	Collagen alpha-2(I) chain OS=Homo sapiens OX=9606 GN=COL1A2 PE=1 SV=7	6,3493411	7	15	7	1	1.2E+08	0,334	51	7
40	O75390	Citrate synthase, mitochondrial OS=Homo sapiens OX=9606 GN=CS PE=1 SV=	22	9	15	9	1	1.2E+08	2,511	39	9
41	Q03825	Phosphate carrier protein, mitochondrial OS=Homo sapiens OX=9606 GN=SLC	23	9	11	9	1	1.2E+08	2,162	26,504213	9
42	P12111	Collagen alpha-3(VI) chain OS=Homo sapiens OX=9606 GN=COL6A3 PE=1 SV=	22	59	97	59	1	1.1E+08	2,079	314	59
43	P48047	ATP synthase subunit O, mitochondrial OS=Homo sapiens OX=9606 GN=ATP5	62	10	18	10	1	1E+08	16,783	60	10
44	Q9NPC6	Myozenin-2 OS=Homo sapiens OX=9606 GN=MYOZ2 PE=1 SV=1	57	12	20	12	1	1E+08	10,548	62	12
45	P06753	Tropomyosin alpha-3 chain OS=Homo sapiens OX=9606 GN=TPM3 PE=1 SV=2	42	16	38	4	1	1E+08	41,17	126	16
46	O94875	Sorbin and SH3 domain-containing protein 2 OS=Homo sapiens OX=9606 GN=	15	16	23	16	1	97000000	1,154	68	16
47	Q14315	Filamin-C OS=Homo sapiens OX=9606 GN=FLNC PE=1 SV=3	39	76	126	69	1	93000000	3,959	429	76
48	Q13642	Four and a half LIM domains protein 1 OS=Homo sapiens OX=9606 GN=FHL1 P	7	2	4	2	1	91000000	0,468	12	2
49	P12109	Collagen alpha-1(VI) chain OS=Homo sapiens OX=9606 GN=COL6A1 PE=1 SV=	19	14	27	14	1	89000000	1,384	84,740327	14
50	P04908	Histone H2A type 1-B/E OS=Homo sapiens OX=9606 GN=HIST1H2AB PE=1 SV=	23	2	3	2	1	88000000	2,981	12	2



Prognosis..



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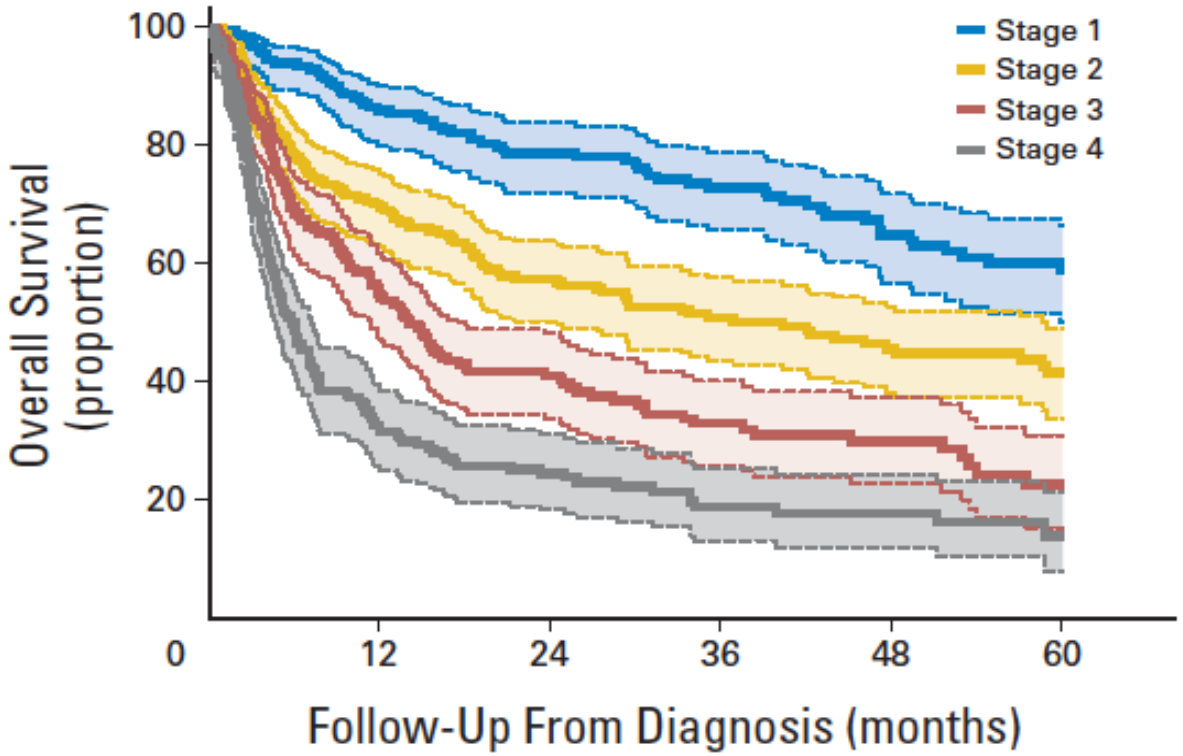
460 -377 B.C

Biomarkers: NPs, Hs-Tn, FLC

JOURNAL OF CLINICAL ONCOLOGY

Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements

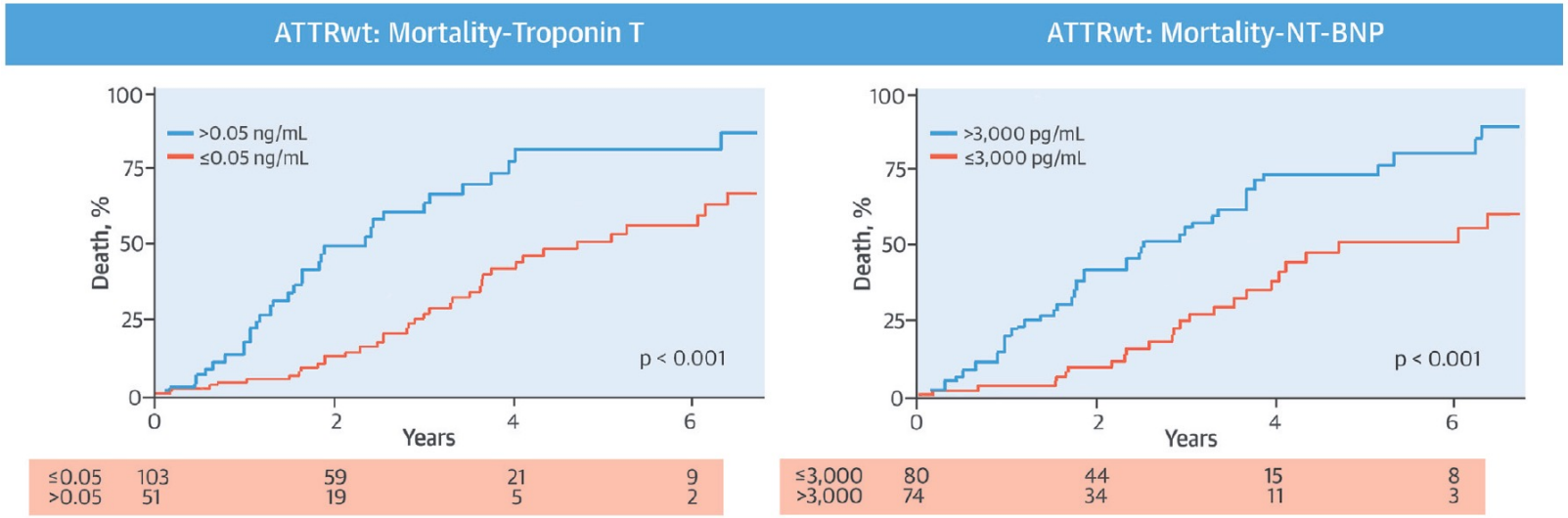


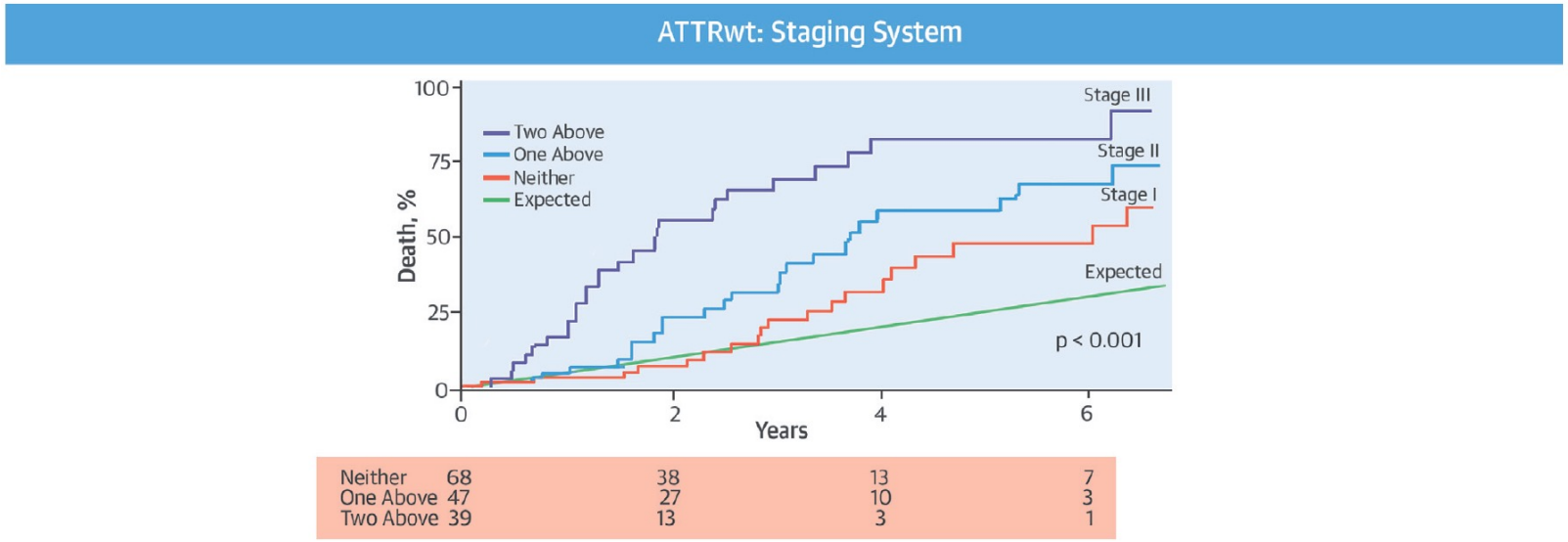
Multivariable model (810 newly diagnosed patients with AL amyloidosis)

-FLC-diff (c.o. 18 mg/dl)
-cTnT (c.o. 25 ng/l)
-NT-proBNP (c.o. 1,800 ng/l)

Kumar S et al, 2012

Cardiac biomarkers and outcome in ATTRwt





Grogan M et al, 2016

Prognostic s… …TR amyloidosis

Kumar et al.[15] (Mayo) AL

Staging parameters:
FLC-diff ≥18 mg/dL
Troponin T ≥0.025 ng/mL
NT-proBNP ≥1800 pg/mL

Stage	5-year survival
Stage I (0 parameters)	68%
Stage II (1 parameter)	60%
Stage III (2 parameters)	28%
Stage IV (3 parameters)	14%

Lillenes et al.[16] (BU) AL

Staging parameters:
Troponin I > 0.1 ng/mL
BNP > 81 pg/mL

Stage	Me… su…
Stage I (0 parameters)	No…
Stage II (1 parameter)	11…
Stage III (2 parameters)	51…
Stage IIIb (2 parameters and BNP > 700 pg/mL)	12…

Grogan et al.[17] (Mayo) ATTRwt

Staging parameters:
Troponin T > 0.05 ng/mL
NT-proBNP >3000 pg/mL

Stage	4-year survival/ median survival
Stage I (0 parameters)	57% 66 months
Stage II (1 parameter)	42% 40 months
Stage III (2 parameters)	18% 20 months

…e et al.[18] (NAC) …& ATTRwt

…parameters:
…45 mL/min/1.73 m²
…NP > 3000 pg/mL

Median survival	Score	Median survival
69.2 months	Score 1–3	90.5 months
46.7 months	Score 4–6	38.5 months (Mayo) 36 months (NAC)
24.1 months	Score 7–9	20.3 months (Mayo) 19.8 months (NAC)

Cheng et al.[19] ATTRv & ATTRwt

Scoring parameters:
Mayo or NAC score (0 to 2 points)
Daily dose of Furosemide or equivalent:
0 mg/kg (0 points), >0–0.5 mg/kg (1 point), >0.5–1 mg/kg (2 points), and >1 mg/kg (3 points)
NYHA class I–IV (1 to 4 points)

ESC European Society of Cardiology — European Journal of Heart Failure (2021) doi:10.1002/ejhf.2140 — POSITION PAPER

Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Pablo Garcia-Pavia[1,2,3*], Claudio Rapezzi[4,5], Yehuda Adler[6], Michael Arad[7], Cristina Basso[3,8], Antonio Brucato[9], Ivana Burazor[10], Alida L.P. Caforio[3,11], Thibaud Damy[12], Urs Eriksson[13], Marianna Fontana[14], Julian D. Gillmore[14], Esther Gonzalez-Lopez[1,3], Martha Grogan[15], Stephane Heymans[16,17,18], Massimo Imazio[19], Ingrid Kindermann[20], Arnt V. Kristen[21,22], Mathew S. Maurer[23], Giampaolo Merlini[24,25], Antonis Pantazis[26], Sabine Pankuweit[27], Angelos G. Rigopoulos[28], and Ales Linhart[29]

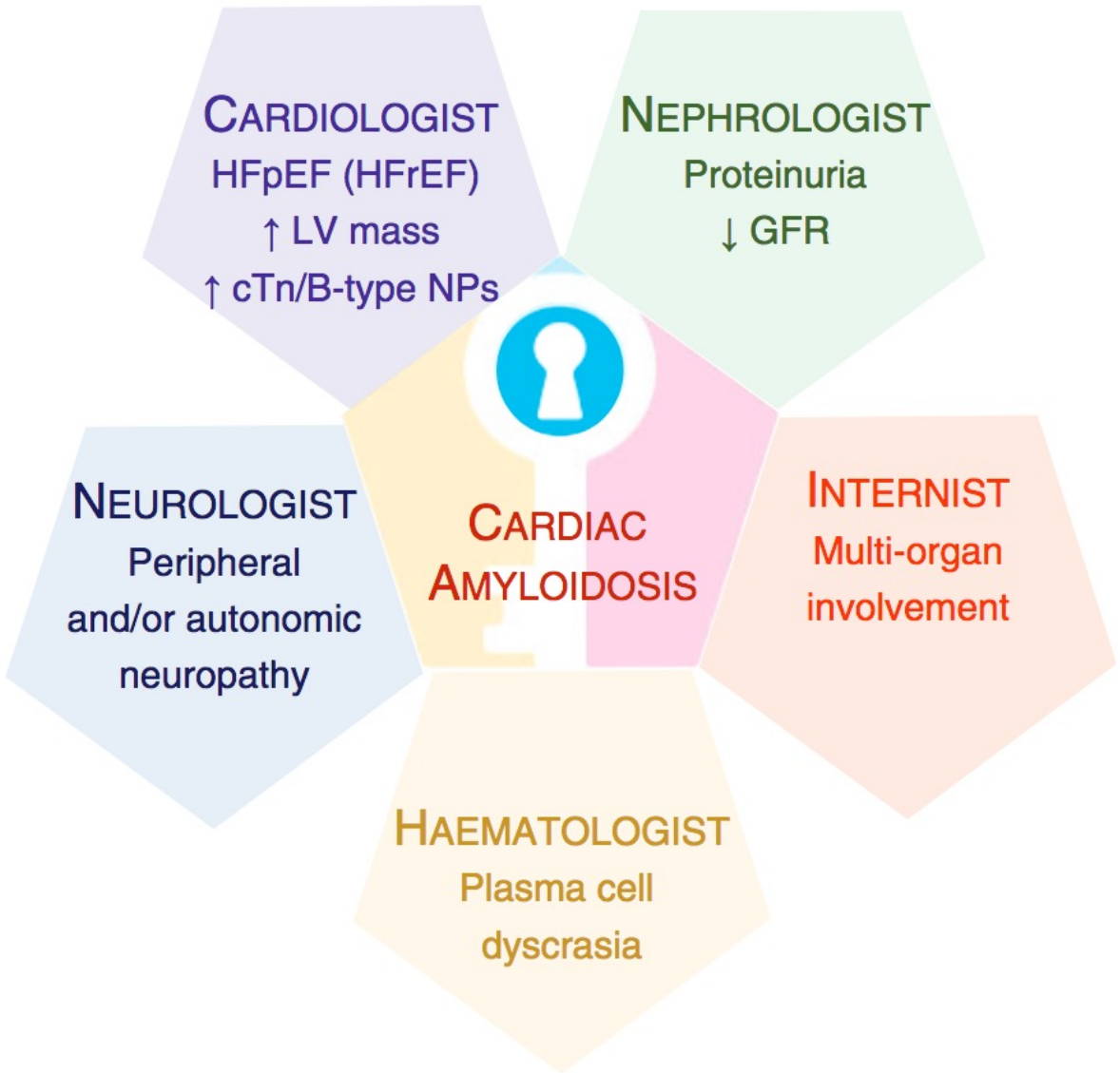
Proposed follow-up scheme

	AL-CA	ATTR-CA
• Serum free light chain quantification • Clinical evaluation by Haematology	**Every month** (during initial haematological treatment) **Every 3–4 months** (after completing initial haematological treatment)	-
• Complete blood count • Basic biochemistry • NT-proBNP • Troponin	**Every month** (during initial haematological treatment) **Every 3–4 months** (after completing initial haematological treatment)	**Every 6 months**
• Evaluation by Cardiology • ECG • Echocardiography/CMR	**Every 6 months**	**Every 6 months**
• 24 h Holter ECG	**Every 12 months**	**Every 12 months**
• 6MWD (optional) • KCCQ (optional)	**Every 6 months**	**Every 6 months**
• Neurological evaluation (if ATTRv)	-	**Every 6 months**
• Ophthalmological evaluation (if ATTRv)		**Every 12 months**

6MWD, 6-minute walk distance; AL, amyloid light-chain; ATTR, transthyretin-mediated amyloidosis; ATTRv, hereditary transthyretin-mediated amyloidosis (v for variant); CA, cardiac amyloidosis; CMR, cardiovascular magnetic resonance; ECG, echocardiogram; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide.

1. Garcia-Pavia P, et al. *Eur J Heart Fail* 2021;23(4):512–526.

Never work alone..



for updates

European Journal of Preventive Cardiology

ESC European Society of Cardiology

Review

European Journal of Preventive Cardiology
0(00) 1–10

DOI: 10.1177/2047487319877708
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SAGE

Keys to early diagnosis of cardiac amyloidosis: red flags from clinical, laboratory and imaging findings

Giuseppe Vergaro[1,2], Alberto Aimo[1], Andrea Barison[1,2], Dario Genovesi[2], Gabriele Buda[3], Claudio Passino[1,2] and Michele Emdin[1,2]

Vergaro G et al, 2019

AmyLab

Prof. Michele Emdin, Dr. Giuseppe Vergaro

Dr. Alberto Aimo
Dr. Vincenzo Castiglione
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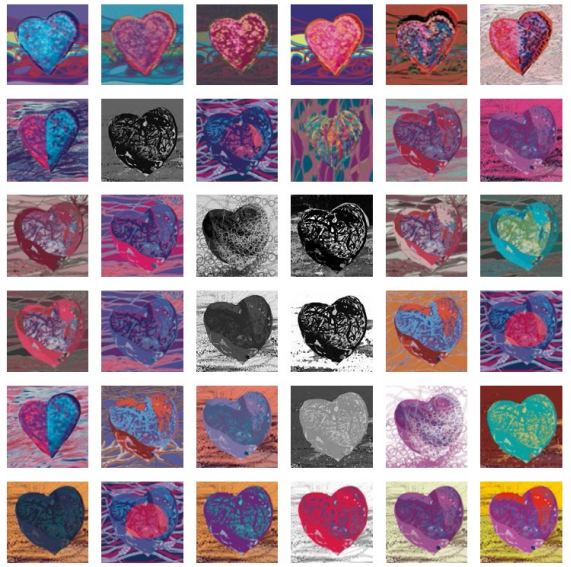

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Strumenti diagnostici per la cardiopatia amiloidotica

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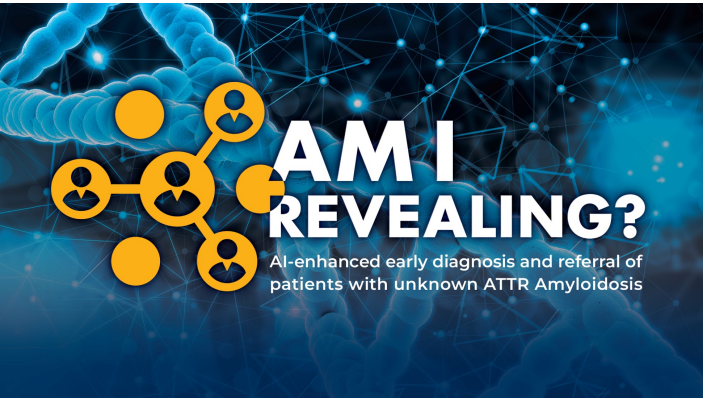

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