AMILOIDOSI CARDIACA

Dott. Walter Grosso Marra

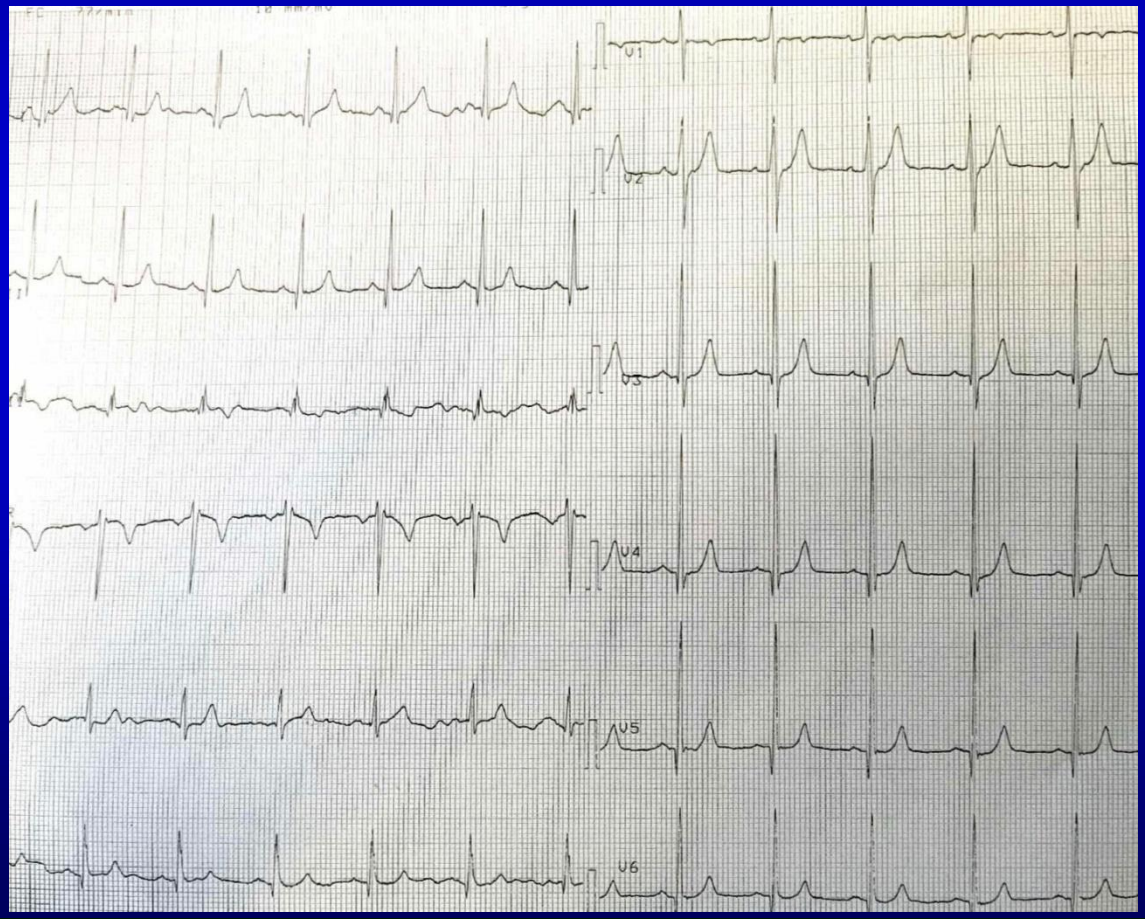
Cardiologia Universitaria Città della Salute, Torino

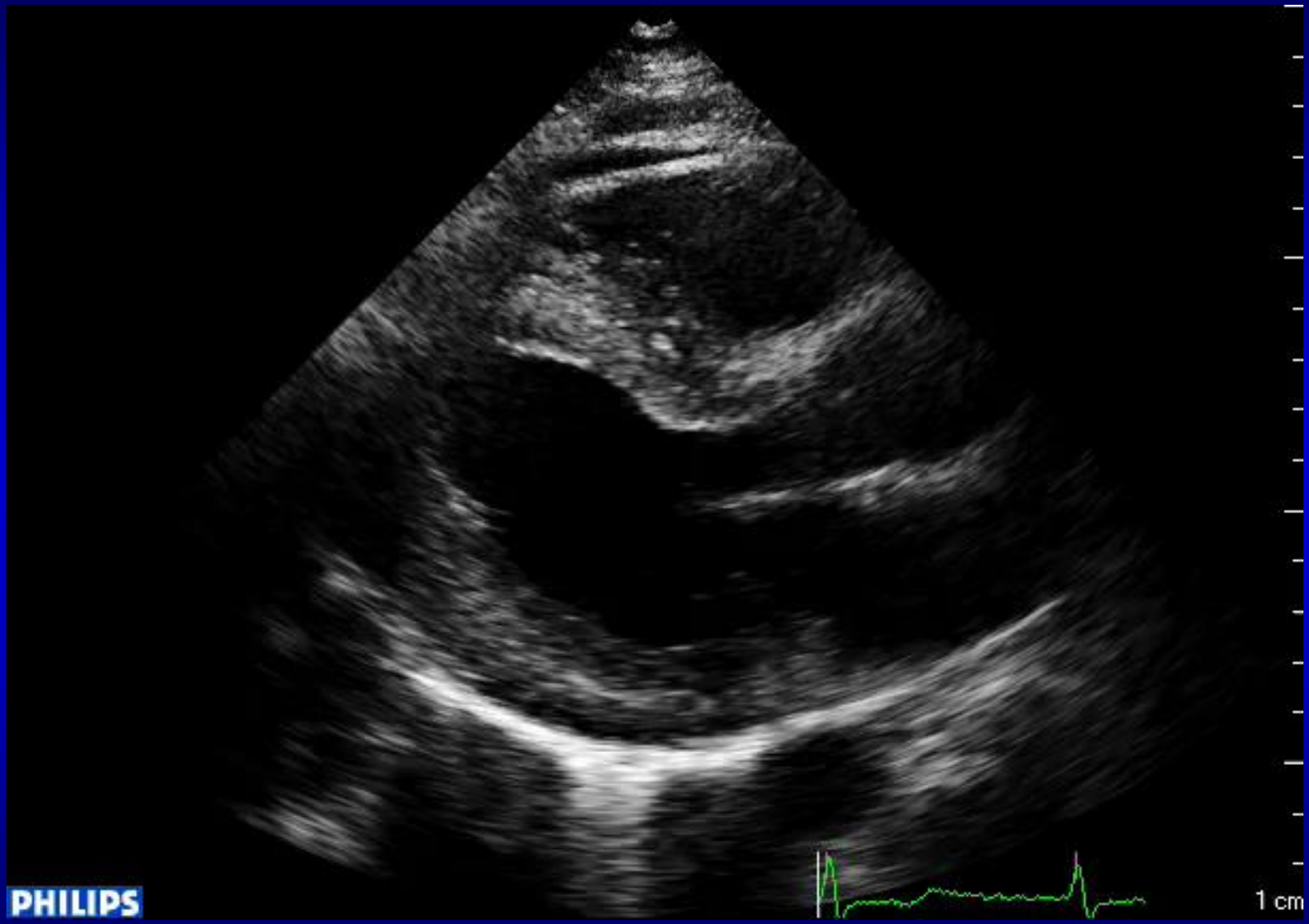
Dipartimento Cardiovascolare

D. G.

- Uomo di 50 anni
- Non fattori di rischio cardiovascolare. Forte familiarità per SCD materna.
- Da anni sintomatico per dispnea per sforzi moderati (NYHA II)
- Ictus criptogenetico nel 2014 senza reliquati.Anomalia corneale non definita
- Agli ematochimici riscontro di microalbuminura, funzione renale lievemente ridotta

- ECG:

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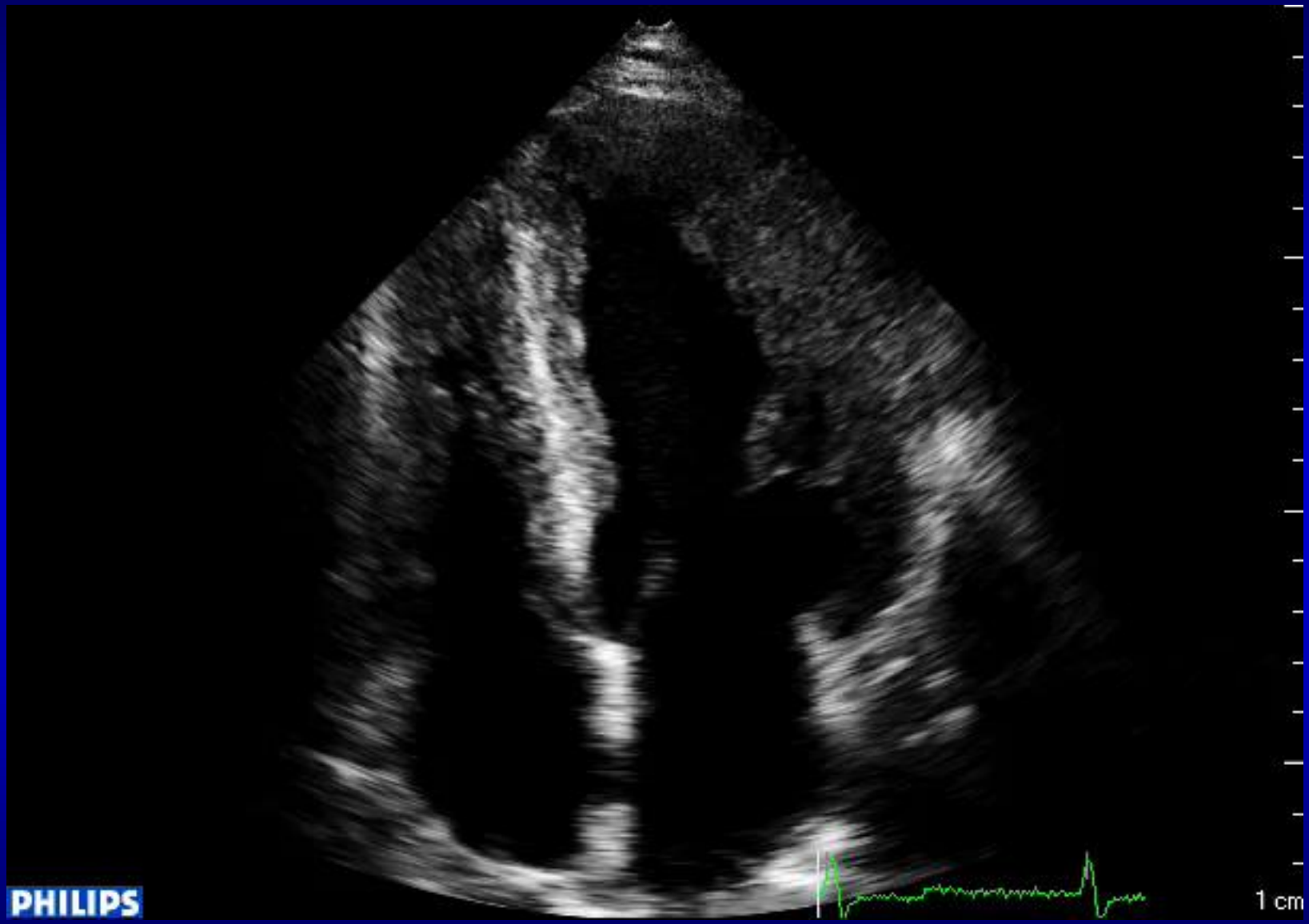
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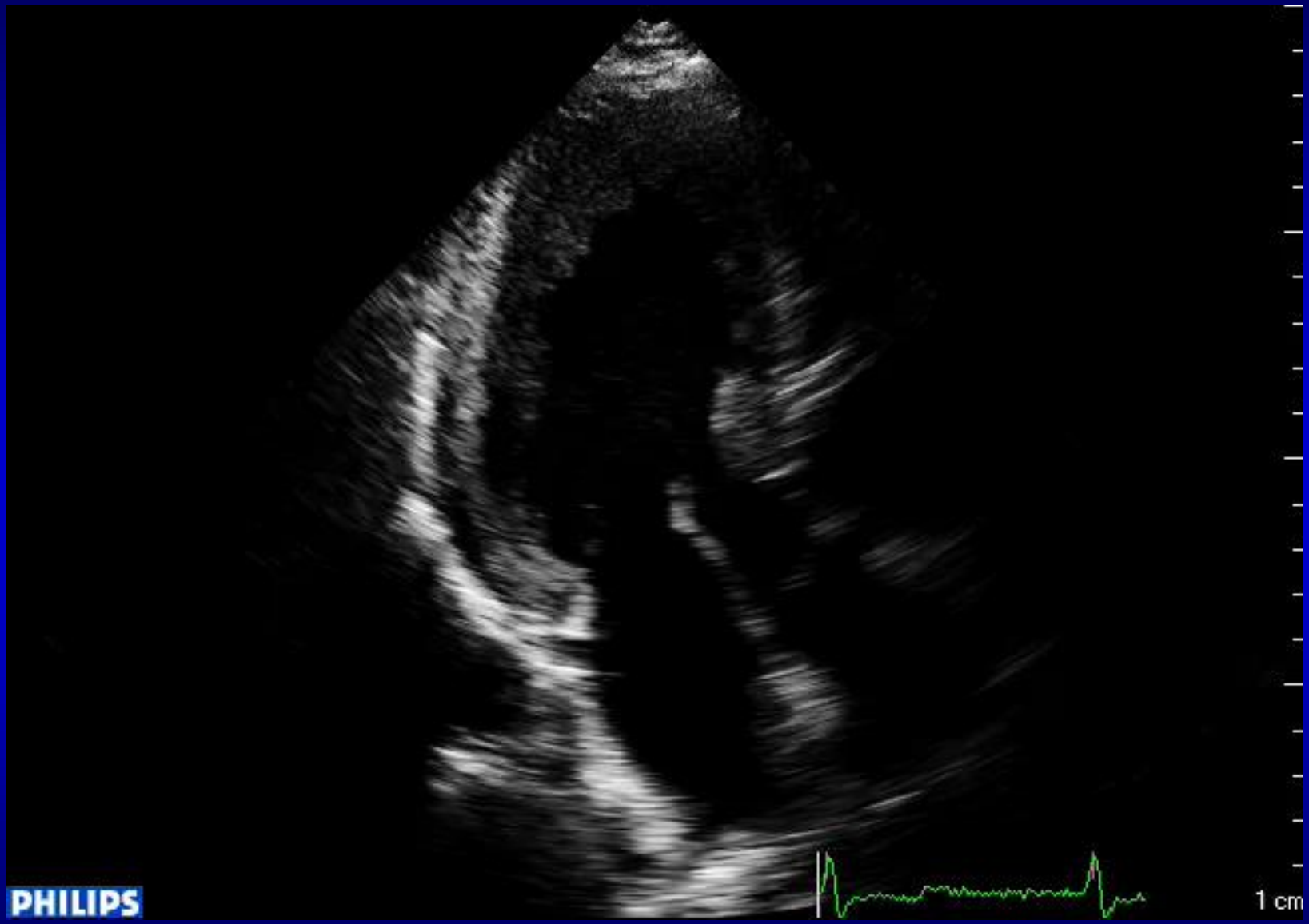
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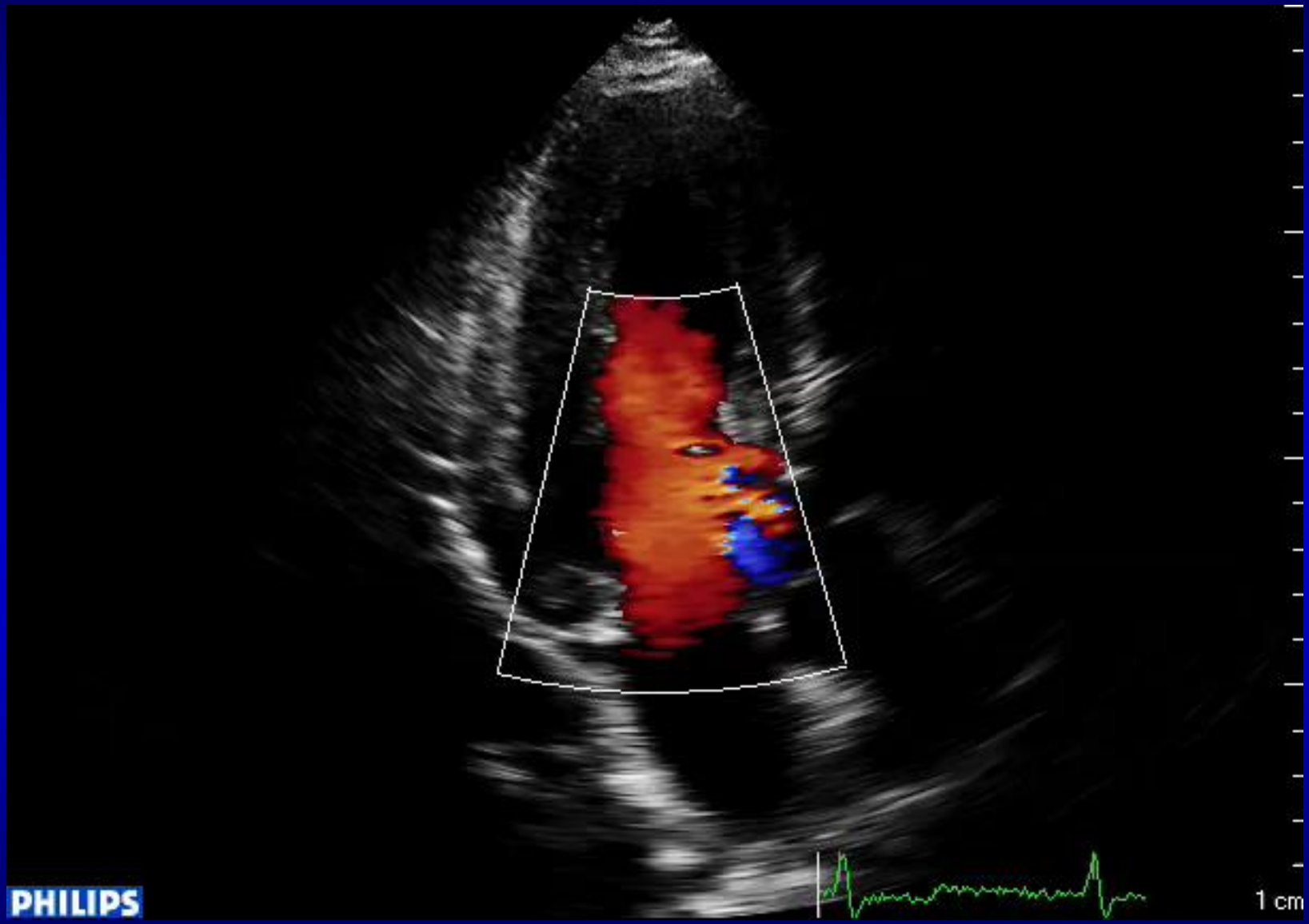
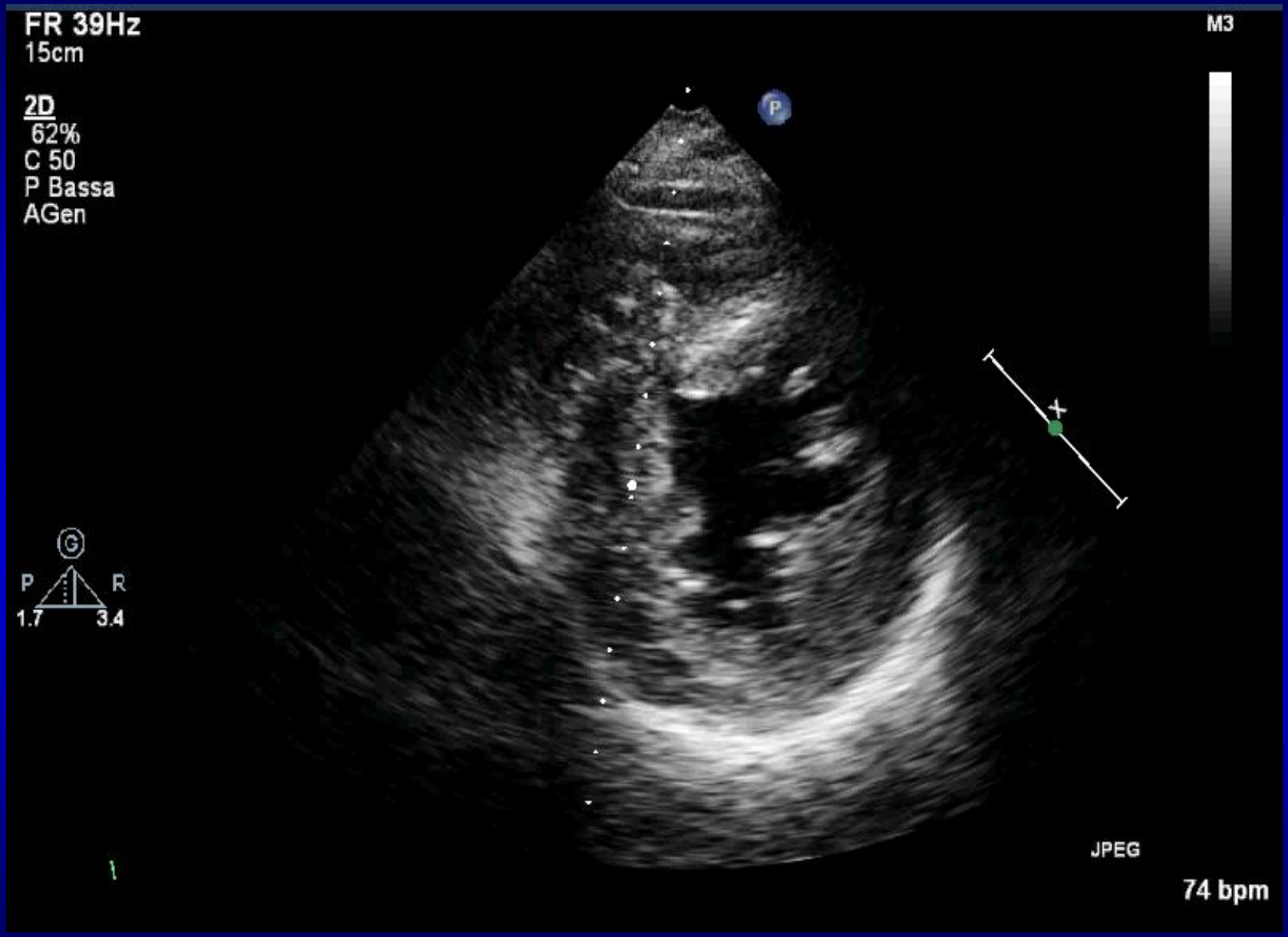

PHILIPS
1 cm

L. M.

- Donna di 68 anni
- Insufficienza renale cronica in trattamento dialitico
- NYHA II-III e cardiopalmo
- Familiarità per malattia di Fabry (figlio)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2D
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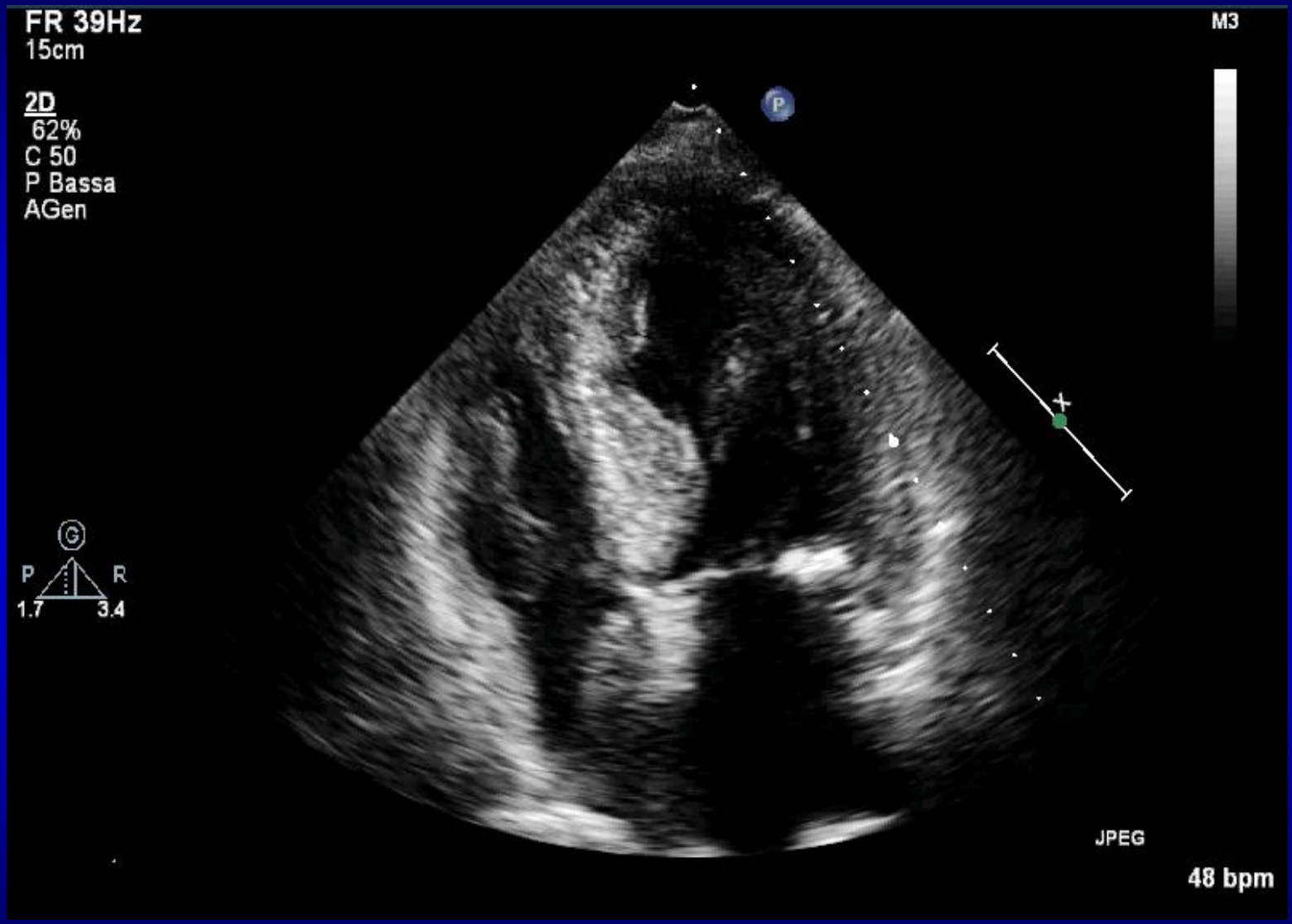
C 50
P Bassa
AGen
M3
P
G
P
R
1.7
3.4
JPEG
74 bpm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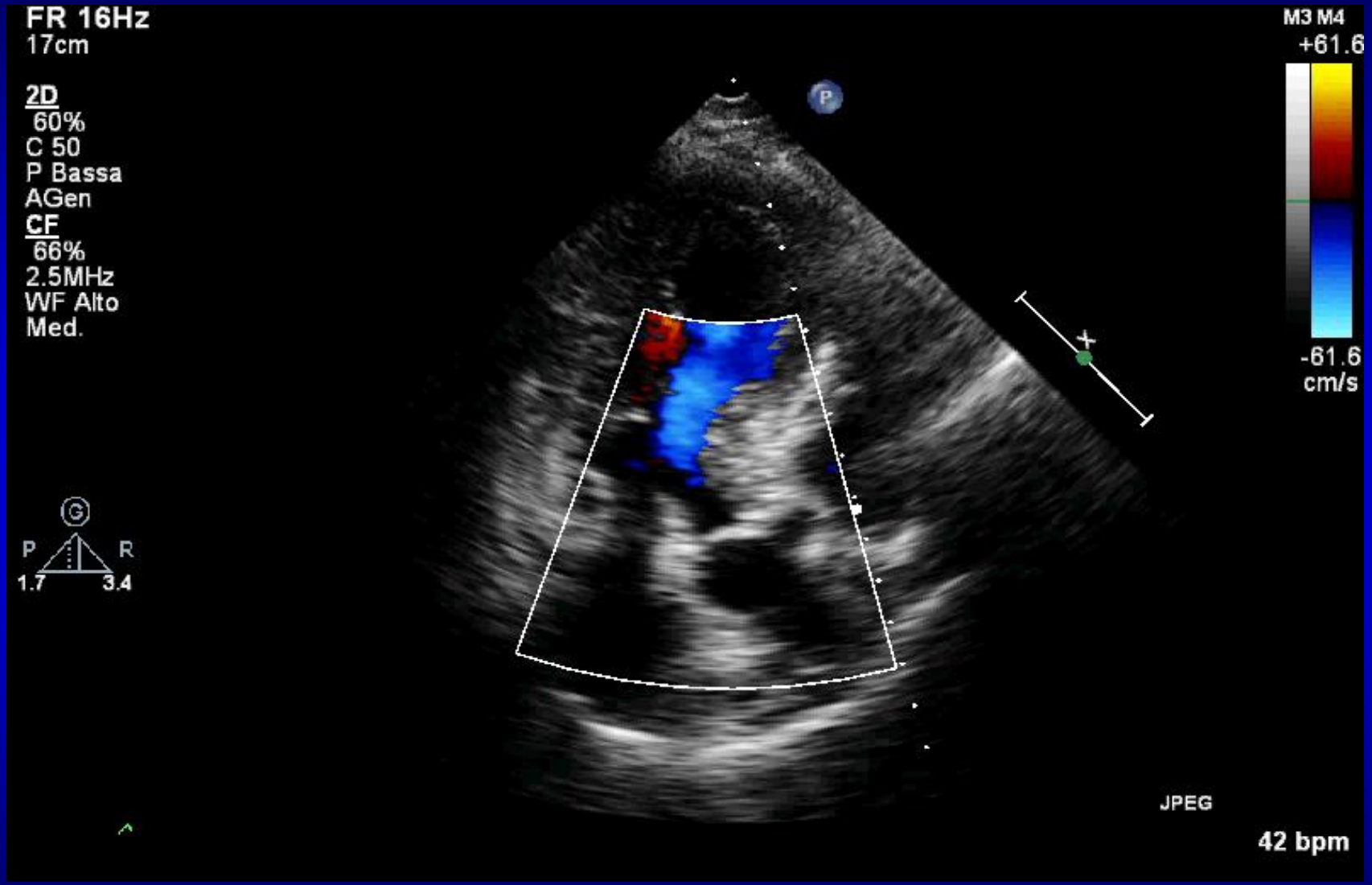
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2D
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CF
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WF Alto
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M3 M4
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cm/s
P
R
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3.4
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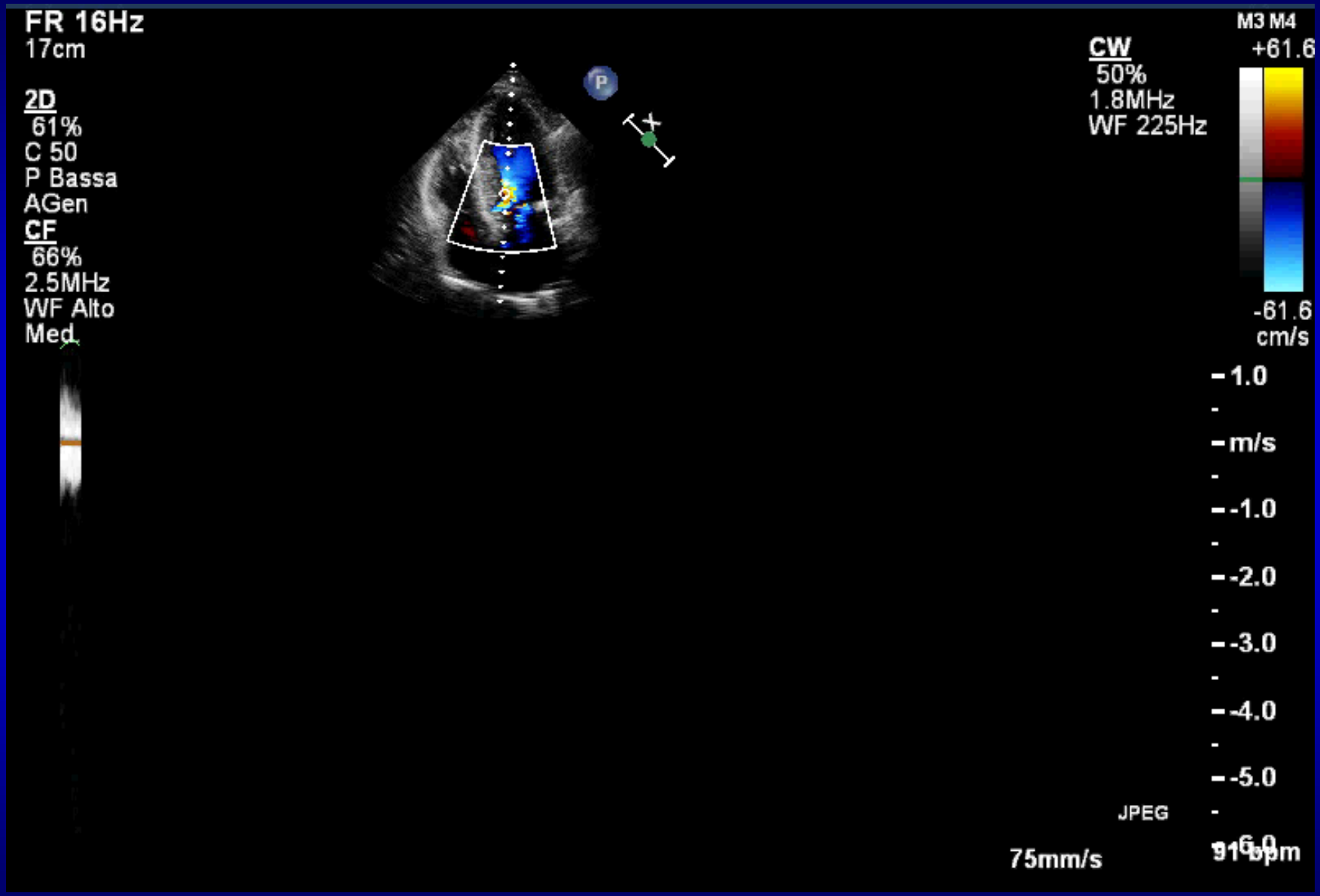
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2D
61%
C 50
P Bassa
AGen
CF
66%
2.5MHz
WF Alto
Med
CW
50%
1.8MHz
WF 225Hz
M3 M4
+61.6
-61.6
cm/s
1.0
m/s
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
JPEG
75mm/s
91 bpm

Caso clinico

Donna di 52 anni, ex fumatrice.

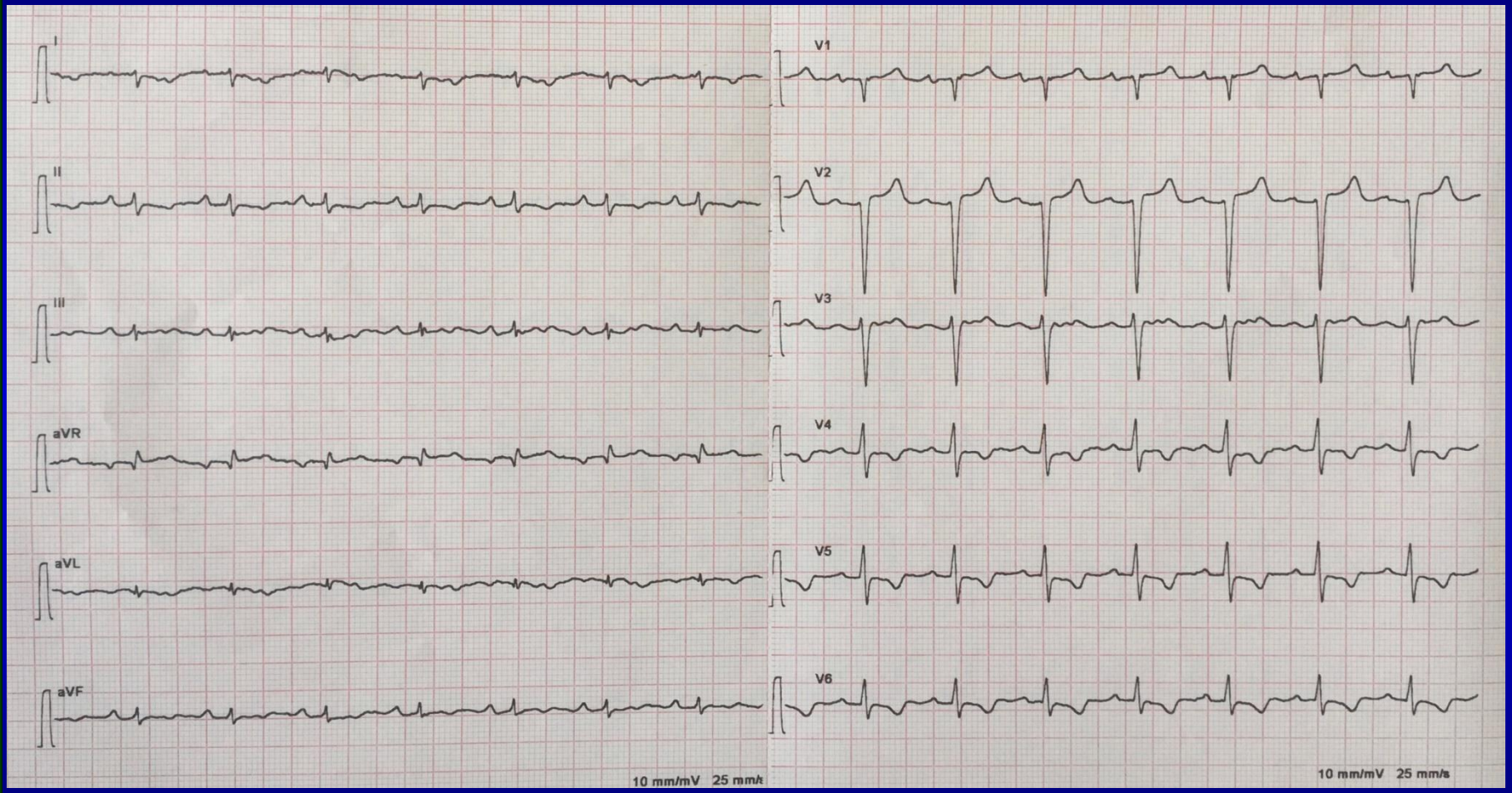
Anamnesi patologia remota:

- pregresso ipotiroidismo sottoposto a trattamento sostitutivo
- A gennaio 2016 posizionamento di impianti dentari con utilizzo di antibioticoterapia e FANS
- A febbraio 2016 sindrome influenzale trattata con Amoxicillina

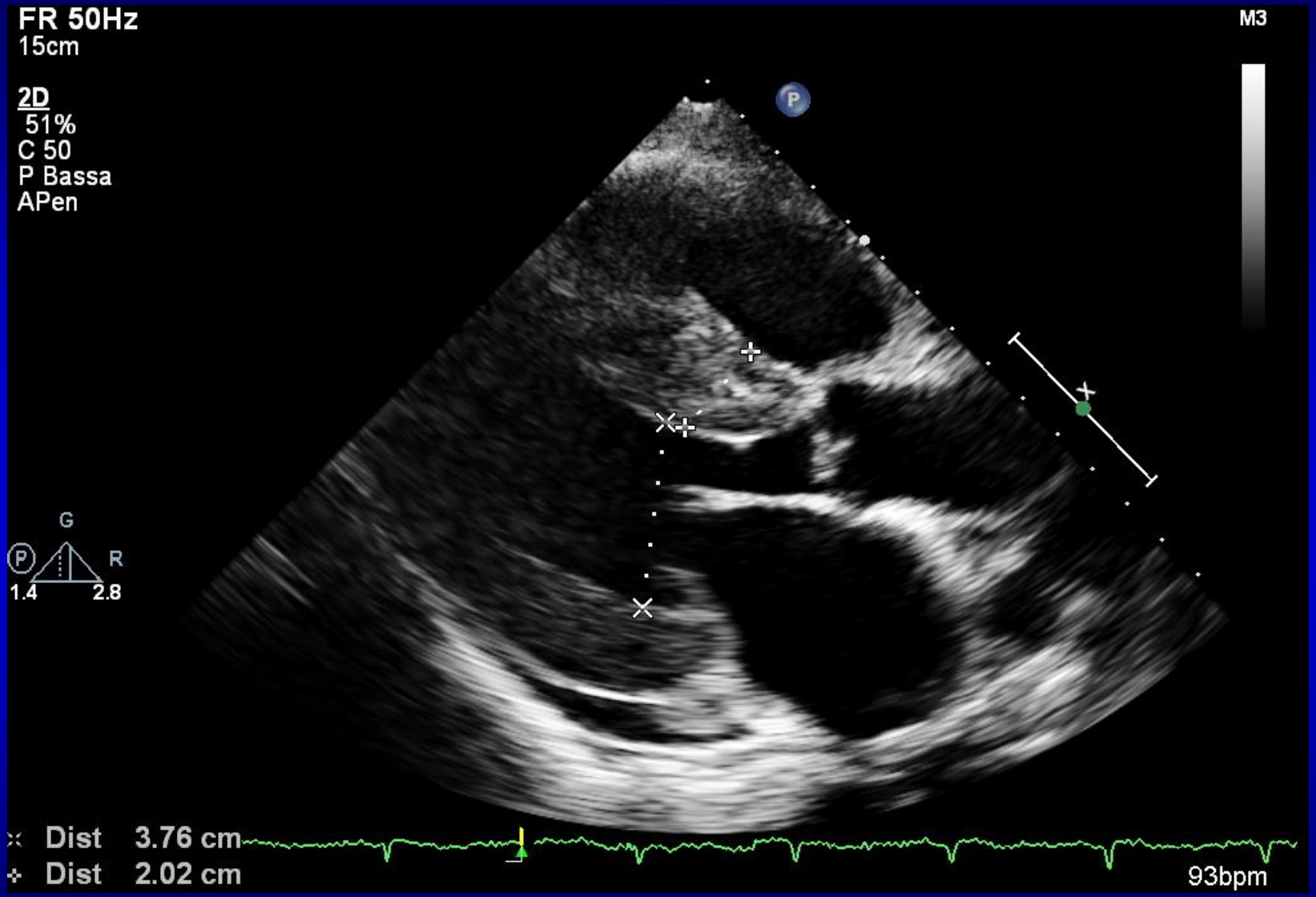
Accesso in DEA per comparsa da circa 15 giorni di dispnea per sforzi lievi (NYHA III) ed edemi declivi

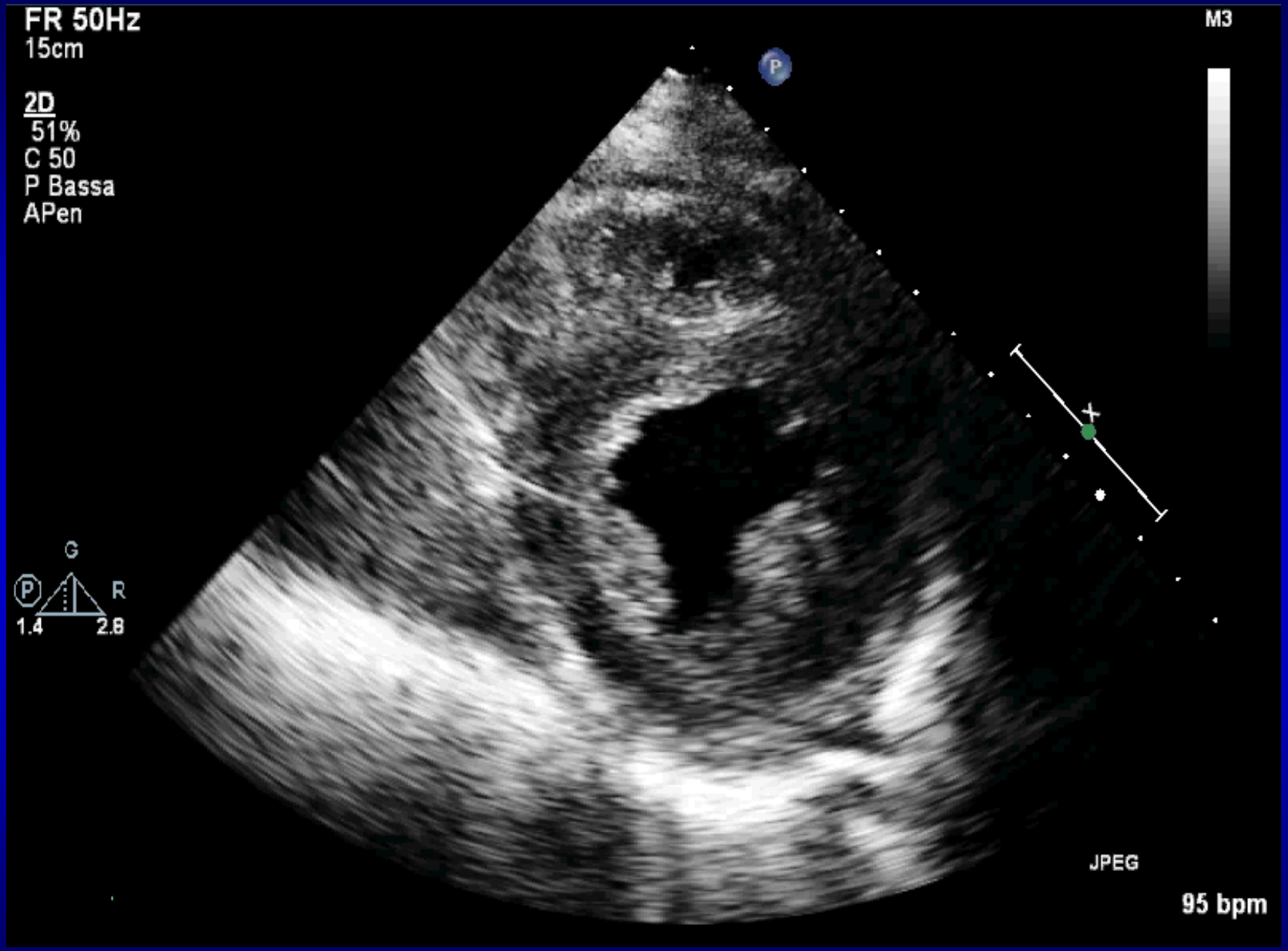
- Parametri vitali nella norma
- Lab: creatinina 7.45 ml/dl, K+ 6.8 mmol/l, TnT 0.216 mcg/L, NT-proBNP 43425 npg/mL
- EGA A in AA: acidosi metabolica compensata (pH 7.35, pO2 70 mmHg, pCO2 25 mmHg, HCO3- 13.8 mmol/l, lattati 0.8 mmol L)
- Rx torace: Versamento pleurico basale bilaterale > dx, congestione ombre ilari.

Elettrocardiogramma



Ecocardiogramma

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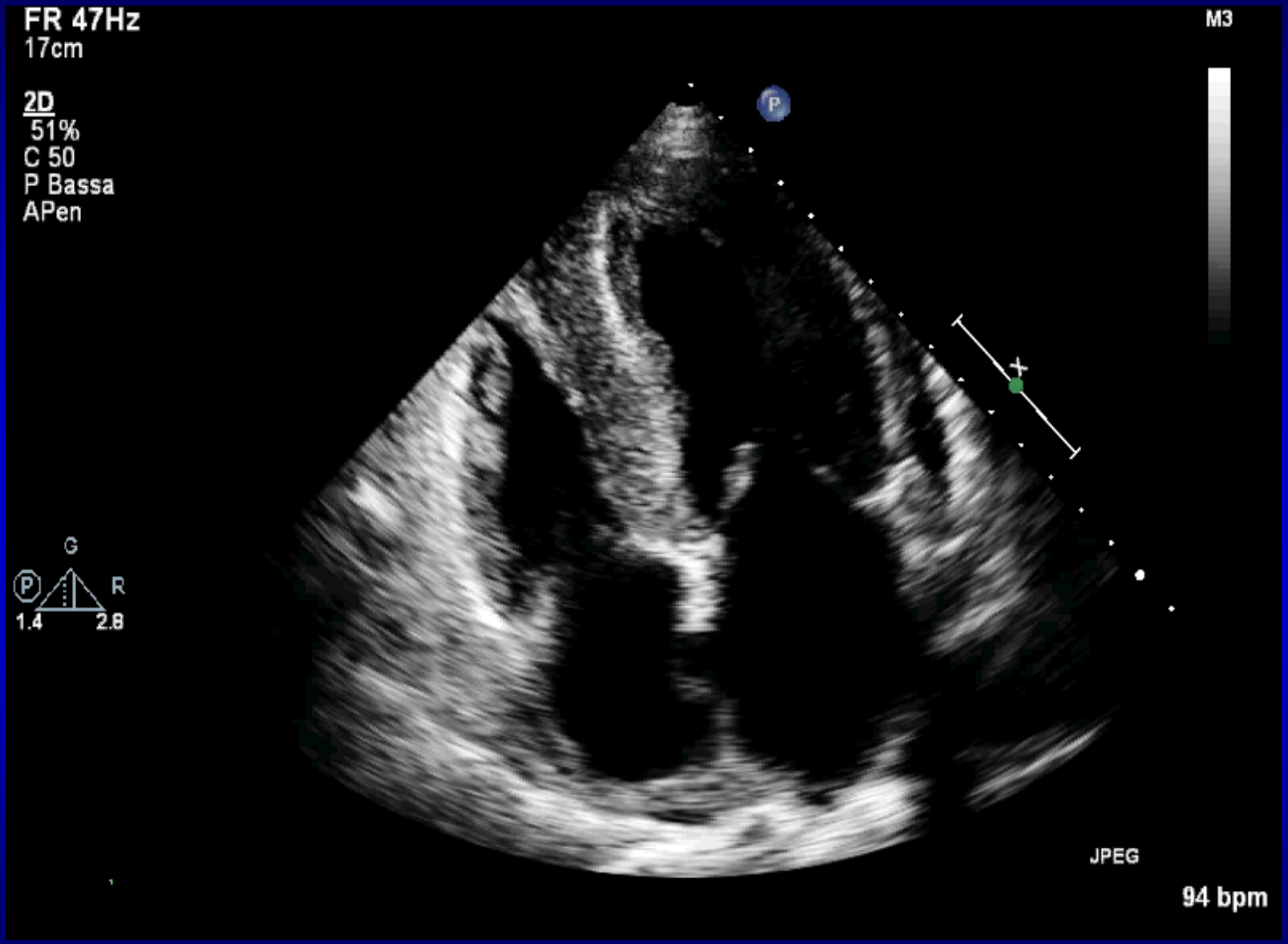
2D
51%
C 50
P Bassa
APen
M3
G
P
R
1.4
2.8
JPEG
95 bpm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C 50
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APen
M3
G
P
R
1.4
2.8
JPEG
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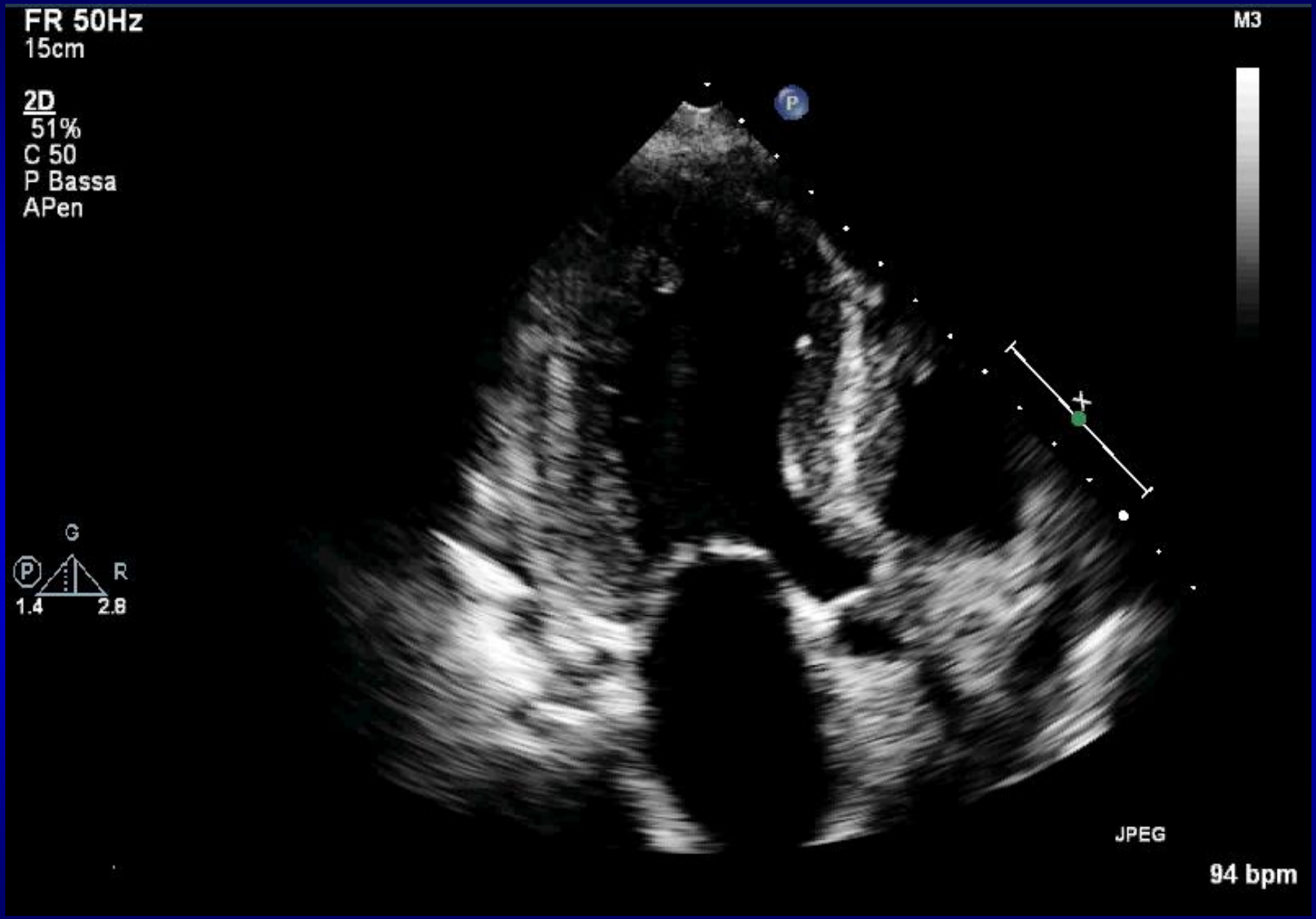
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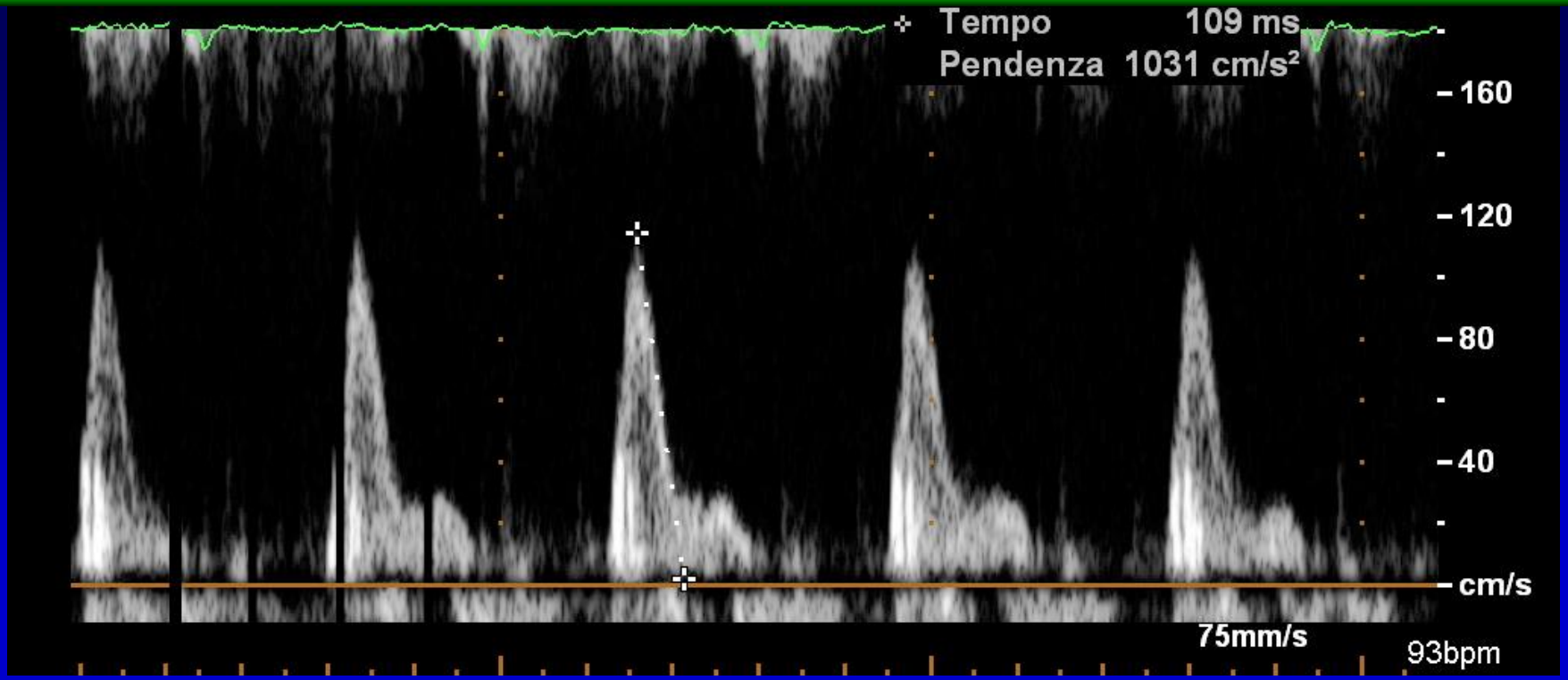
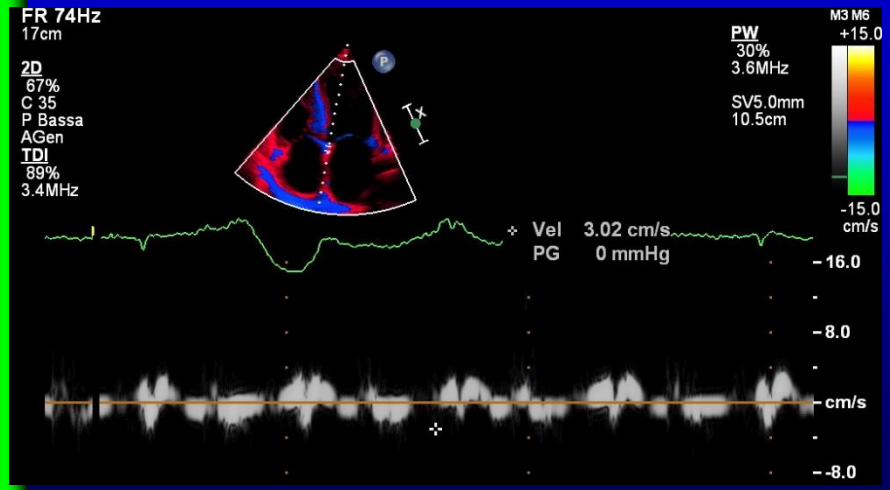
15cm
2D
51%
C 50
P Bassa
APen
M3
G
P
R
1.4
2.8
JPEG
94 bpm


Tempo 109 ms
Pendenza 1031 cm/s²
160
120
80
40
cm/s
75mm/s
93bpm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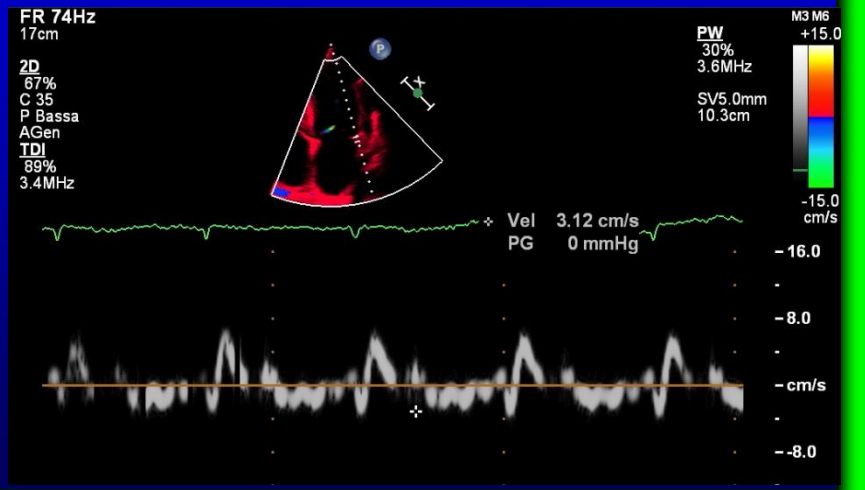
17cm
2D
67%
C 35
P Bassa
AGen
TDI
89%
3.4MHz
PW
30%
3.6MHz
SV5.0mm
10.5cm
M3 M6
+15.0
-15.0
cm/s
Vel 3.02 cm/s
PG 0 mmHg
16.0
8.0
cm/s
-8.0


FR 74Hz
17cm
2D
67%
C 35
P Bassa
AGen
TDI
89%
3.4MHz
PW
30%
3.6MHz
SV5.0mm
10.3cm
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cm/s
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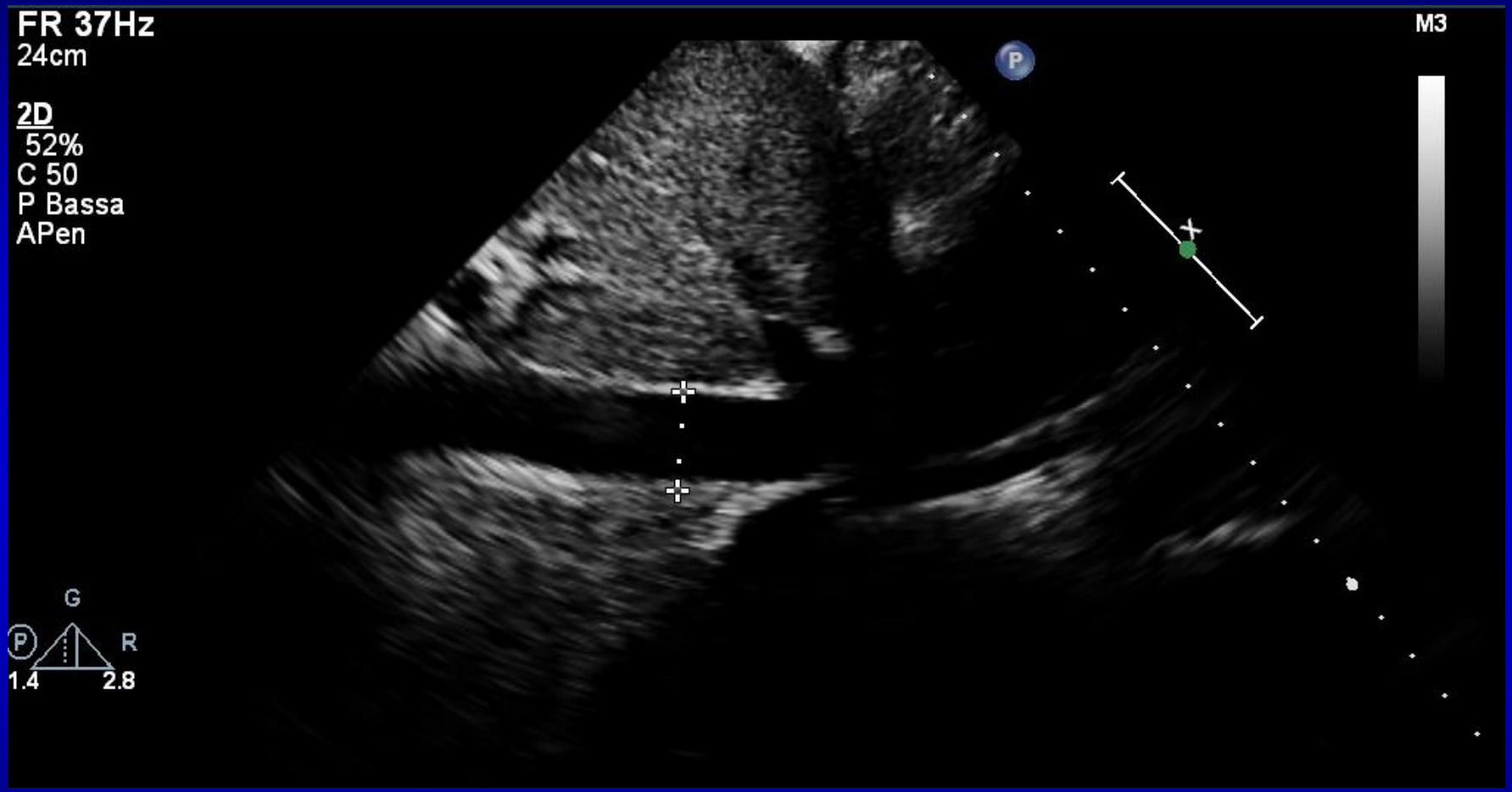
PG 0 mmHg
16.0
8.0
cm/s
-8.0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G
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R
1.4
2.8

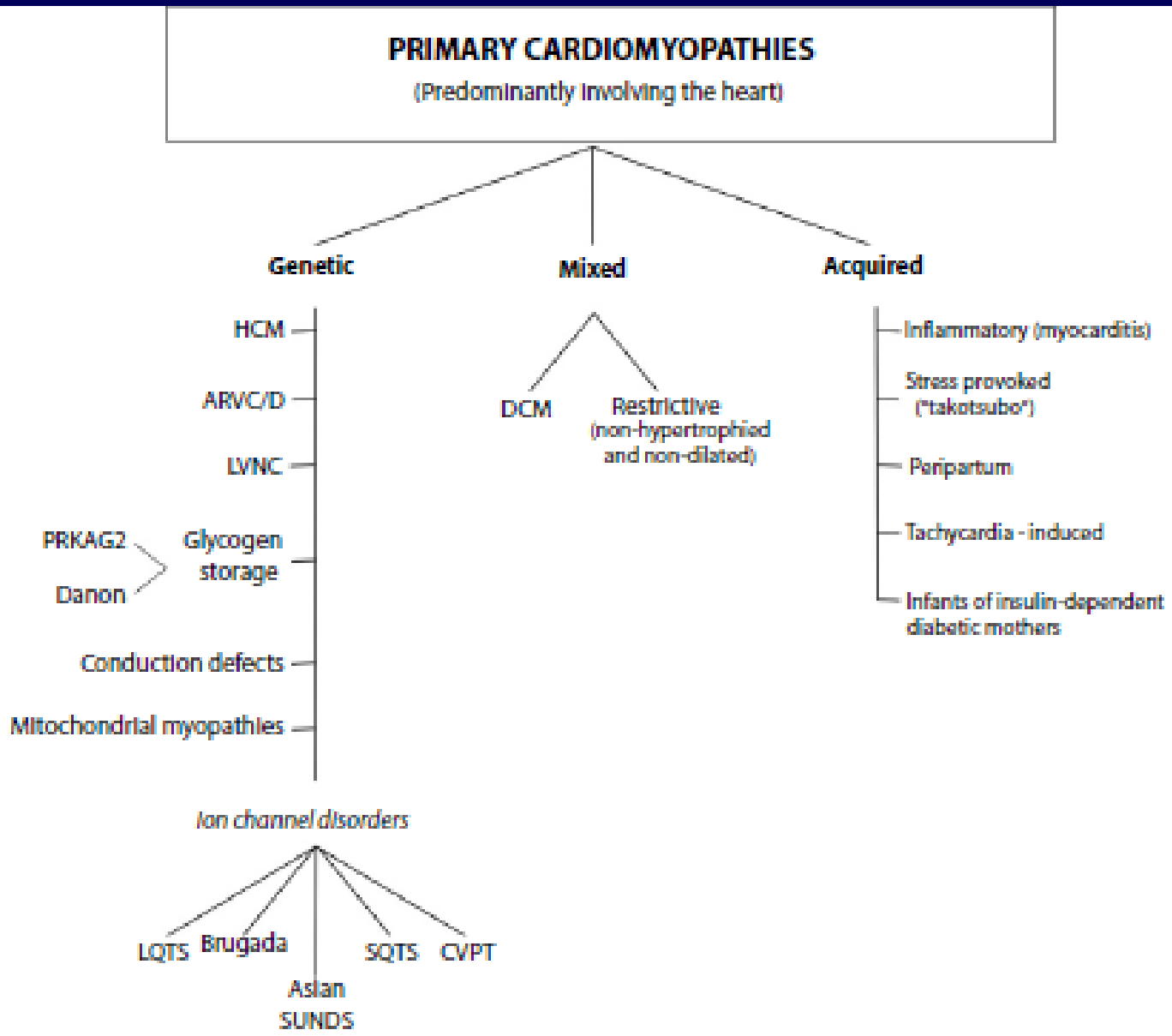


Figure 1. Classification of the cardiomyopathies – American Heart Association. Modified from [7].

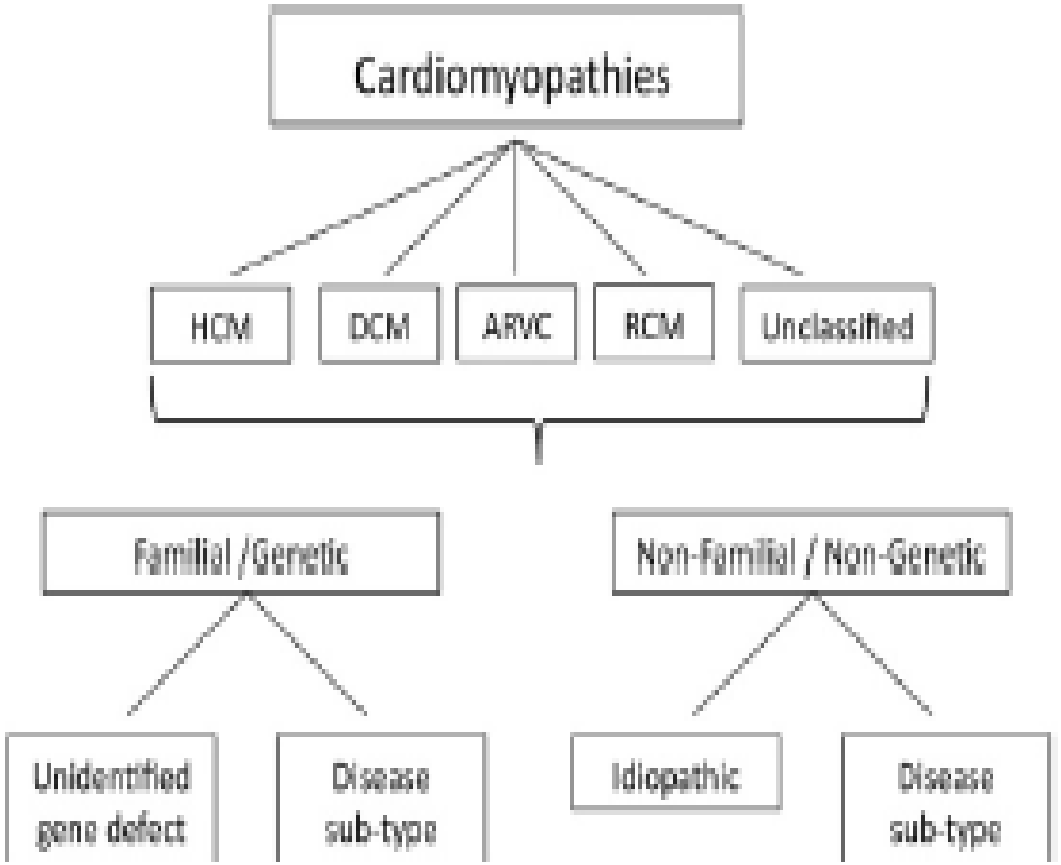


Figure 2. Classification of the cardiomyopathies – European Society of Cardiology. Modified from [8].

Table 1. Hypertrophic cardiomyopathy.

FAMILIAL	Unknown gene
	Sarcomeric protein disease ß myosin heavy chain, Cardiac myosin binding protein C Cardiac troponin I, T and C, a-tropomyosin, Essential myosin light chain, Regulatory myosin light chain, Cardiac actin, a- myosin heavy chain, Titin
	Glycogen storage diseases (e.g. GSD II (Pompe's disease); GSD III (Forbes' disease), AMP kinase (WPW, HCM, conduction disease)
	Lysosomal storage diseases (e.g. Anderson-Fabry disease, Hurler's syndrome)
	Disorders of Fatty Acid Metabolism Camitine, Phosphorylase B kinase deficiency
	Mitochondrial cytopathies (e.g. MELAS, MERFF, LHON)
	Syndromic HCM Noonan's syndrome, LEOPARD syndrome, Friedreich's ataxia, Beckwith-Wiedemann syndrome; Swyer's syndrome (pure gonadal dysgenesis)
	Other: Muscle LIM protein Phospholamban promoter Familial Amyloid
NON-FAMILIAL	
	Obesity; Infants of diabetic mothers; Athletic training; Amyloid (AL / prealbumin)

Table 3. Restrictive cardiomyopathy.

FAMILIAL, unknown gene

- **Sarcomeric protein mutations:** Troponin I (RCM +/– HCM), Essential myosin light chain
- **Familial Amyloidosis** Transthyretin (RCM + neuropathy)
  Apolipoprotein (RCM + nephropathy)
- **Desminopathy**
- **Pseuxanthoma elasticum**
- **Haemochromatosis**
- **Anderson-Fabry disease**
- **Glycogen storage disease**
- **Endomyocardial fibrosis (Familial)** (Fusion FIP1-like-1 / PDGFRA genes)

NON FAMILIAL

- **Amyloid (AL/prealbumin)**
- **Scleroderma**
- **Endomyocardial fibrosis**
  Hypereosinophilic syndrome, Idiopathic chromosomal cause
- **Drugs**: serotonin, methysergide, ergotamine, mercurial agents, busulfan, anthracyclines
- **Carcinoid heart disease, Metastatic cancers, Radiation**

Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

Table 6 Echocardiographic clues to diagnosis grouped according to main morphological phenotype

Main cardiac phenotype	Finding	Specific diseases to be considered
HCM	Increased interatrial septum thickness	Amyloidosis
	Increased atrioventricular valve thickness	Amyloidosis; Anderson–Fabry disease
	Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson–Fabry disease
	Mild–moderate pericardial effusion	Amyloidosis, myocarditis
	Ground-glass appearance of ventricular myocardium	Amyloidosis
	Concentric LVH	Glycogenosis, Anderson–Fabry disease
	Extreme concentric LVH	Danon disease, Pompe disease
	Global hypokinesia (with/without LV dilatation)	Anderson– Fabry; mitochondrial disease; TTR-related amyloidosis; PRKAG2 mutations; Danon disease; myocarditis; end-stage sarcomeric HCM

Rapezzi, European Heart Journal (2013) 34, 1448–1458

Diagnosi Differenziale

Infiltrative Cardiovascular Diseases

Cardiomyopathies That Look Alike

James B. Seward, MD,* Grace Casaclang-Verzosa, MD†

Condition	Age at Presentation	History and Clinical Presentation	Echocardiography	ECG Profile	CMR LGE	Biopsy
Cardiac amyloid	>30 yrs	Heart failure symptoms, nephrotic syndrome, idiopathic peripheral neuropathy, unexplained hepatomegaly	Symmetrical increase in LV and RV wall thickness, dilated LA and RA, granular appearance of myocardium, pericardial effusion, decreased EF in advanced cases	Decreased or normal QRS complex voltage, pseudoinfarction in inferolateral leads	Global, diffuse, pronounced in subendocardium; RV and LV walls	Myocyte atrophy, amyloid replaces normal cardiac tissue
Fabry disease	Male: 11 ± 7 yrs;	Neuropathic pain, impaired	Symmetrical increase in LV and	Increased or normal QRS complex	Focal, midwall, inferolateral	Enlarged myocytes with

Table 2 Conditions With Dilated LV and Infarct Pattern

Condition	Age at Presentation	History	Echocardiography	ECG	CMR LGE	Cardiac Biopsy
Sarcoidosis	Young adults	Congestive heart failure	Variable wall thickness, focal or global hypokinesis, LV aneurysm	Infrahisian block, atypical infarction pattern	Patchy, basal and lateral LV walls	Noncaseating, multinucleated giant cell granuloma surrounded by band of dense collagen fibers
Wegener disease	Young adults	Chronic upper and lower respiratory tract infections	Regional hypokinesis, pericardial effusion, mild MR, LV systolic dysfunction	Atrial fibrillation, atrioventricular block, atypical infarction pattern	Diffuse, midwall	Vasculitis with necrotizing granulomatous inflammation
Hemochromatosis	Hereditary hemochromatosis: >30 yrs in men, older in women; secondary hemochromatosis: any age	Hereditary hemochromatosis: liver function abnormalities, weakness and lethargy, skin hyperpigmentation, diabetes mellitus, arthralgia, impotence in men; secondary hemochromatosis: hemolytic anemia, multiple blood transfusions	Dilated LV with global systolic dysfunction	Supraventricular arrhythmia, ventricular conduction abnormality is rare		Iron deposits within the myocyte
		mental development, skeletal deformities, corneal clouding, hepatosplenomegaly	aortic valve stenosis or insufficiency, normal EF	arrhythmia		accumulation of mucopolysaccharides within lysosomes
Differential diagnosis						
Hypertrophic cardiomyopathy	17–18 yrs	Maybe asymptomatic, dyspnea, angina, syncope, sudden death	Asymmetrical hypertrophy, small LV cavity, LVOT obstruction, normal EF	Increased QRS complex voltage, pseudo–delta wave, giant T-wave inversion	Patchy, midwall, junctions of the ventricular septum and RV	Myocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis
Hypertensive heart disease	Adults	History of hypertension	Symmetrical increase in LV wall thickness, mild LV dilation, normal EF	Increased QRS complex, nonspecific ST-T-wave changes	No pattern, predominantly subendocardial	Enlarged myocytes with enlarged or replicated nuclei

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL

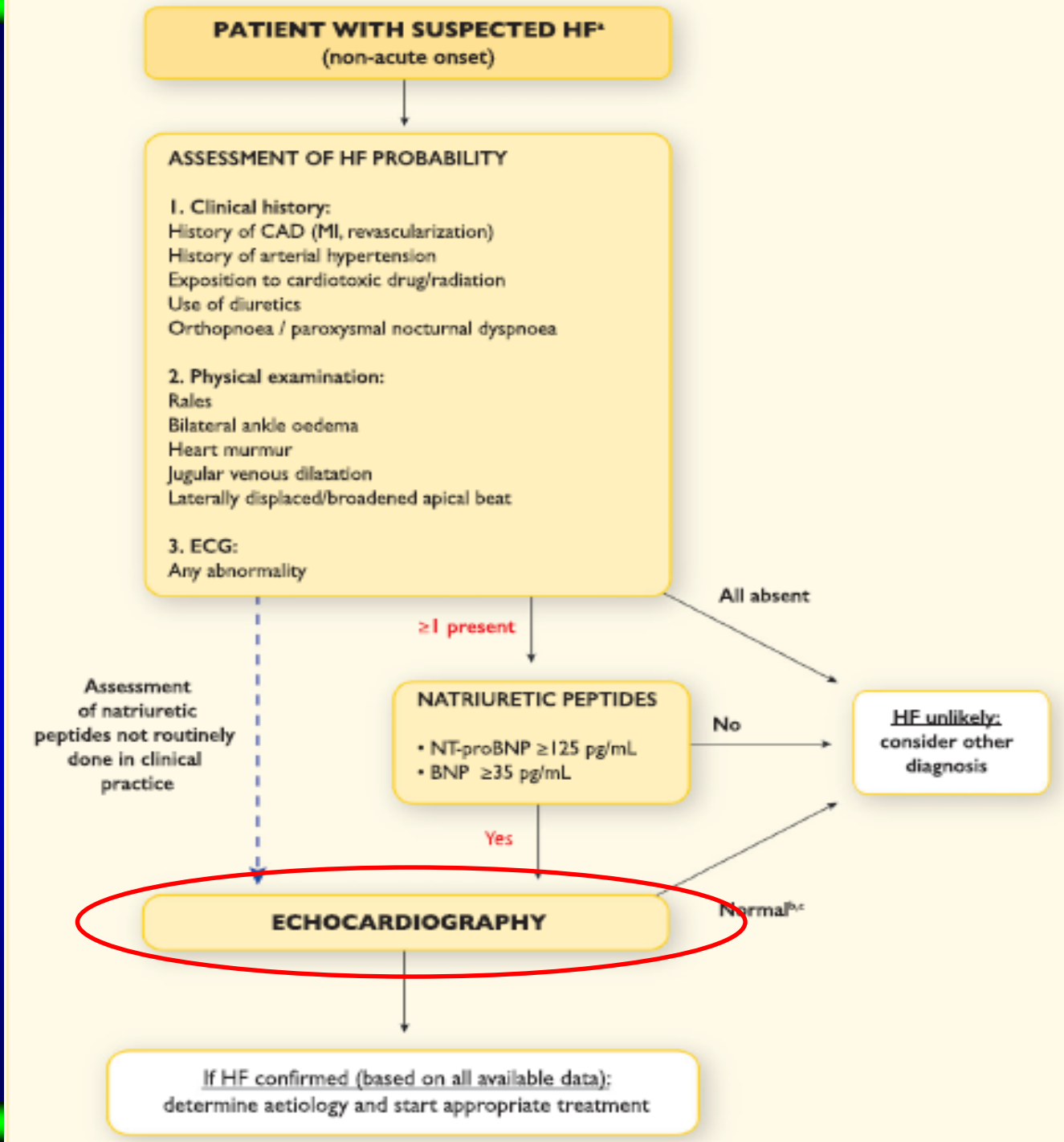
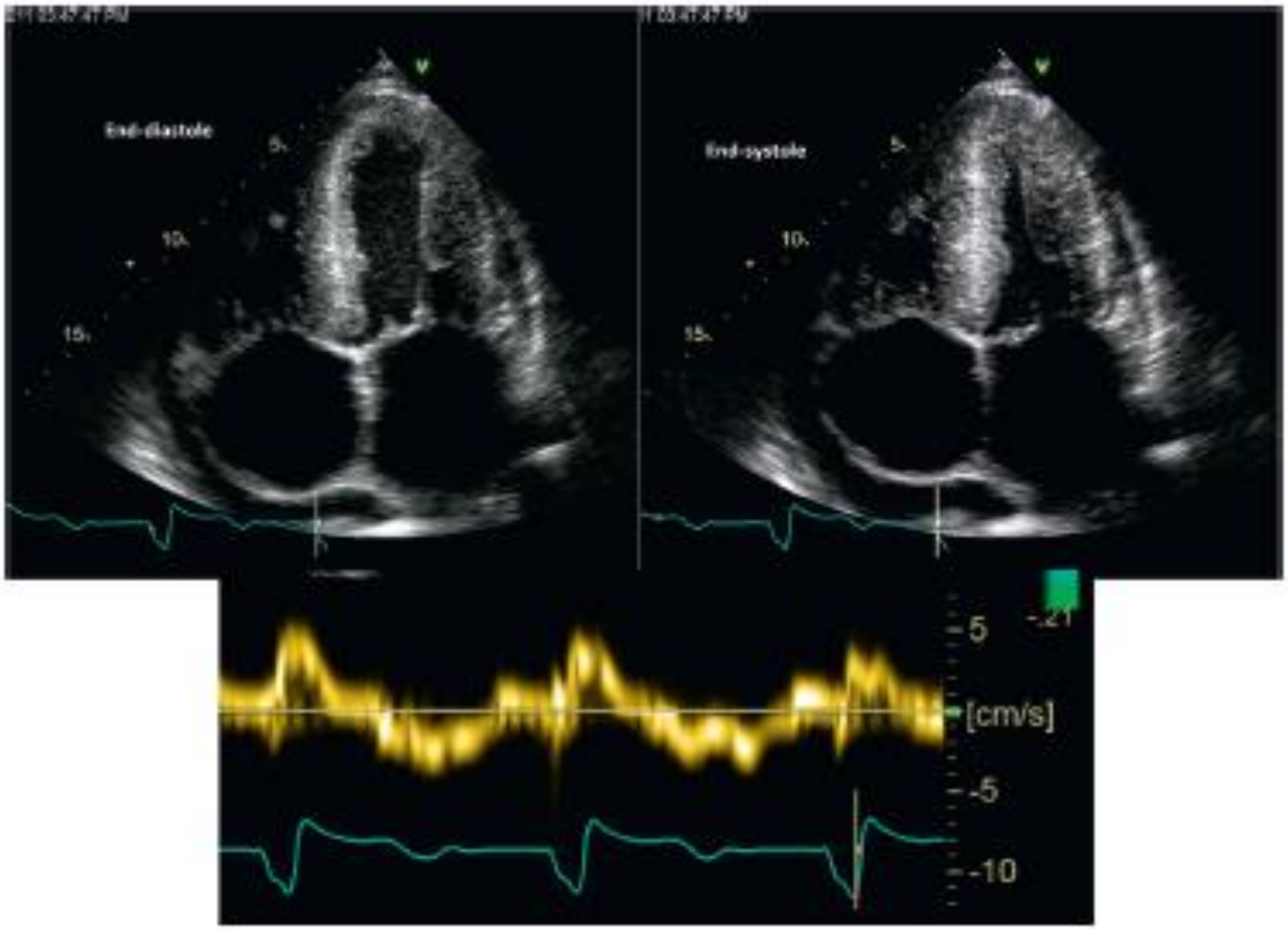
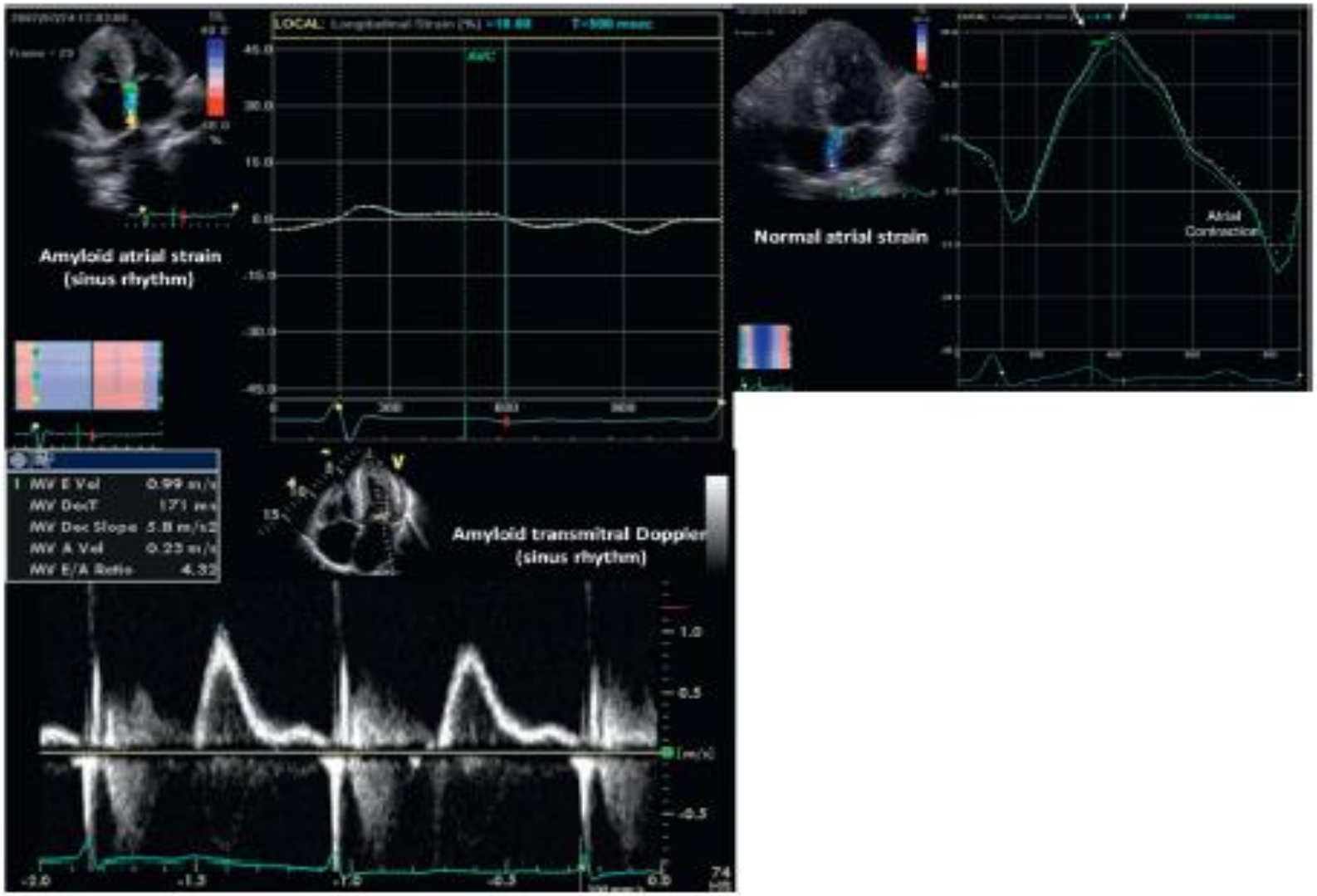

PATIENT WITH SUSPECTED HF[a]
(non-acute onset)
ASSESSMENT OF HF PROBABILITY
1. Clinical history:
History of CAD (MI, revascularization)
History of arterial hypertension
Exposition to cardiotoxic drug/radiation
Use of diuretics
Orthopnoea / paroxysmal nocturnal dyspnoea
2. Physical examination:
Rales
Bilateral ankle oedema
Heart murmur
Jugular venous dilatation
Laterally displaced/broadened apical beat
3. ECG:
Any abnormality
All absent
≥1 present
Assessment of natriuretic peptides not routinely done in clinical practice
NATRIURETIC PEPTIDES
• NT-proBNP ≥125 pg/mL
• BNP ≥35 pg/mL
No
HF unlikely: consider other diagnosis
Yes
ECHOCARDIOGRAPHY
Normal[b,c]
If HF confirmed (based on all available data):
determine aetiology and start appropriate treatment

FIGURE 6 Typical Echocardiogram in AL Amyloidosis



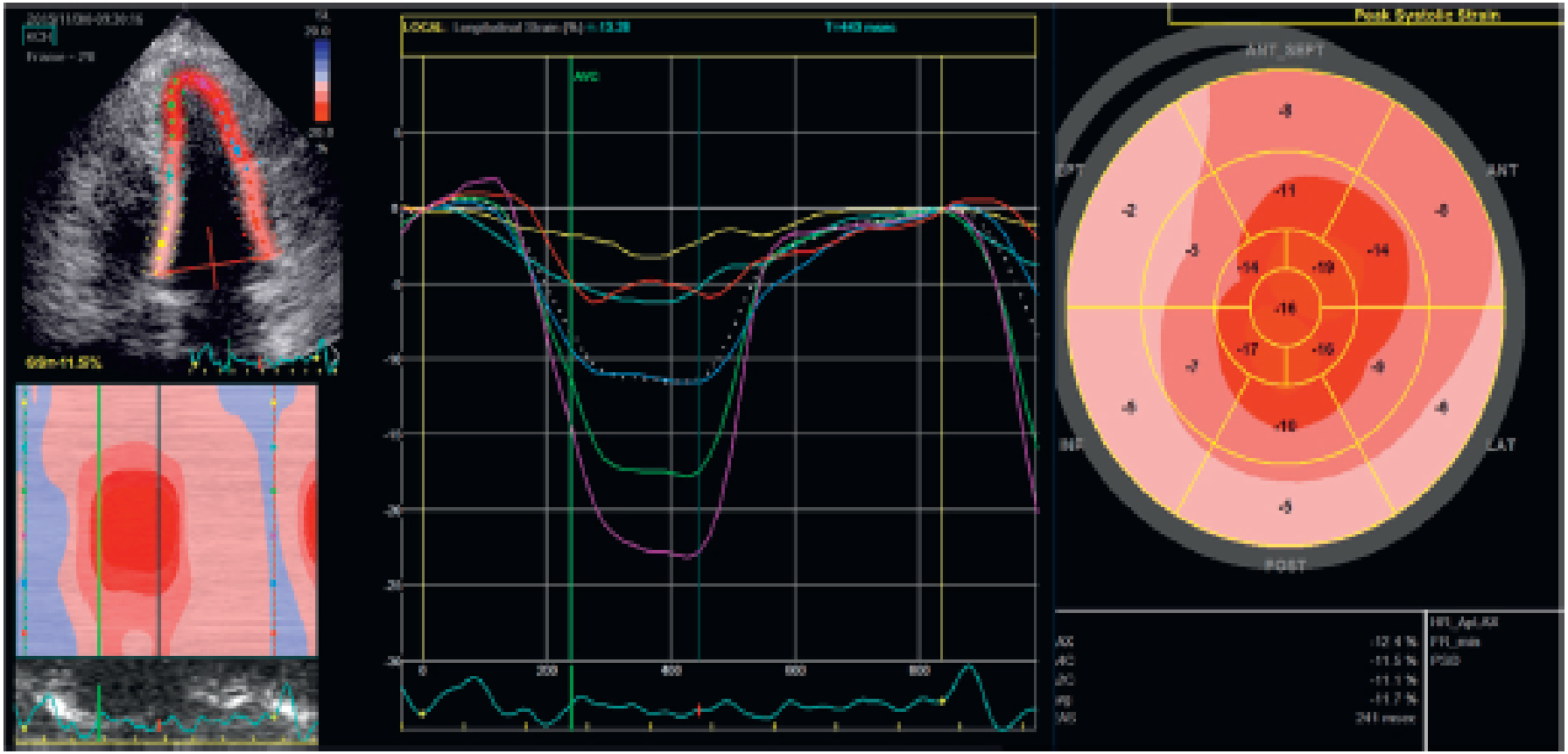
(Top left and right) End-systolic and end-diastolic frames, respectively, demonstrating normal ejection fraction. Note moderately thick left ventricular walls with biatrial enlargement. The atrial size changes minimally throughout the cardiac cycle, representing failure of atrial function, despite sinus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

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



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

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



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

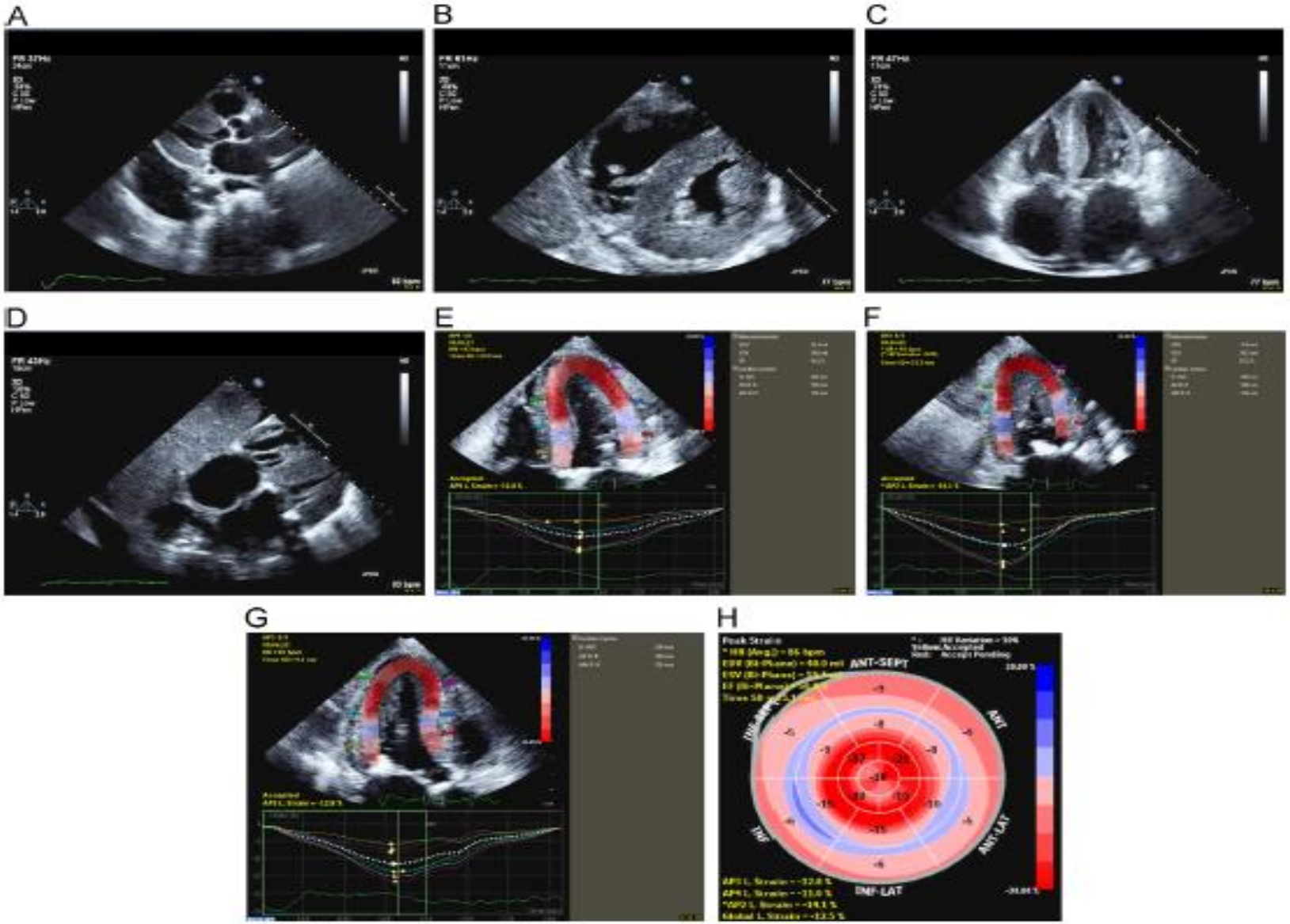
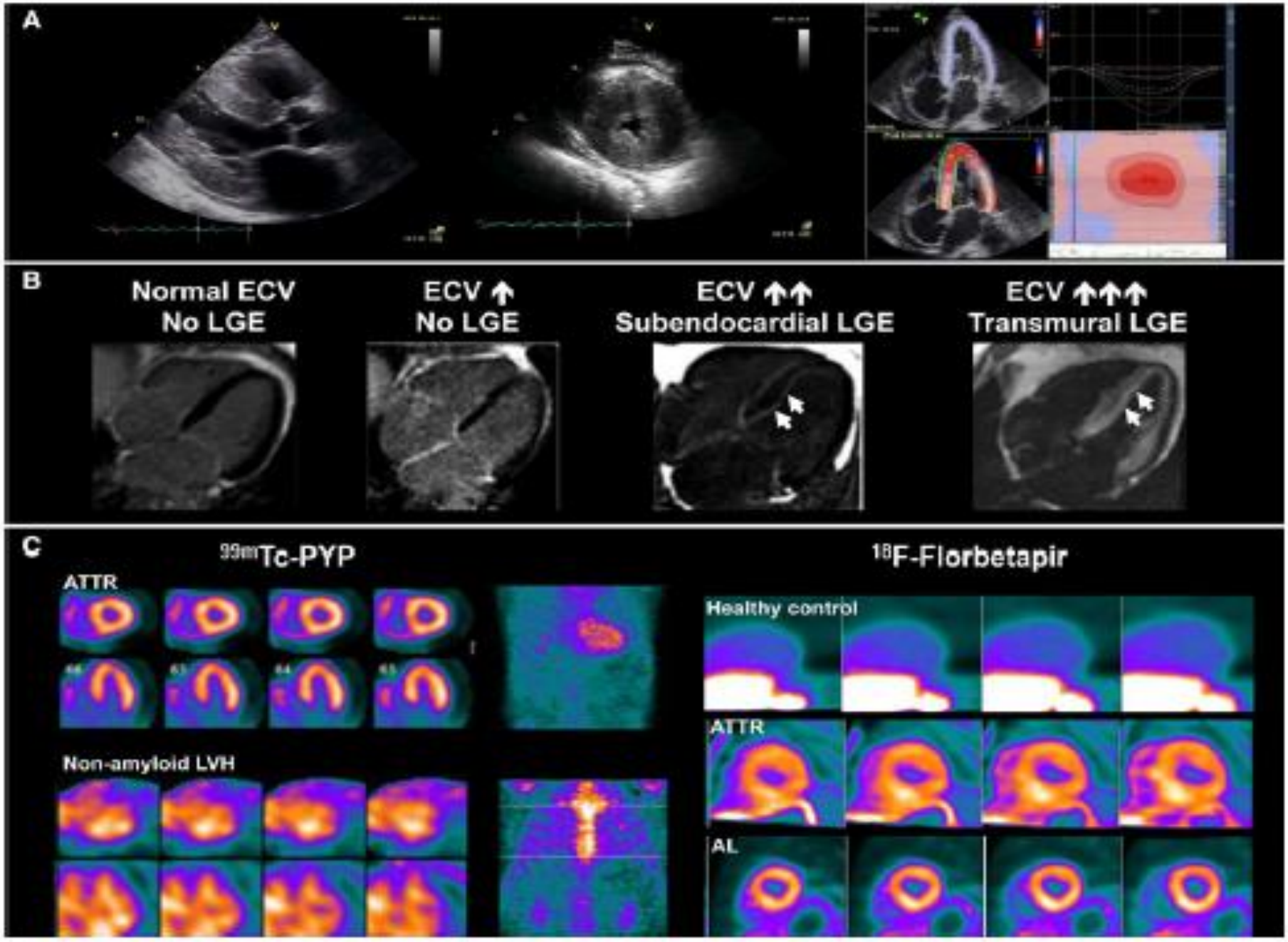
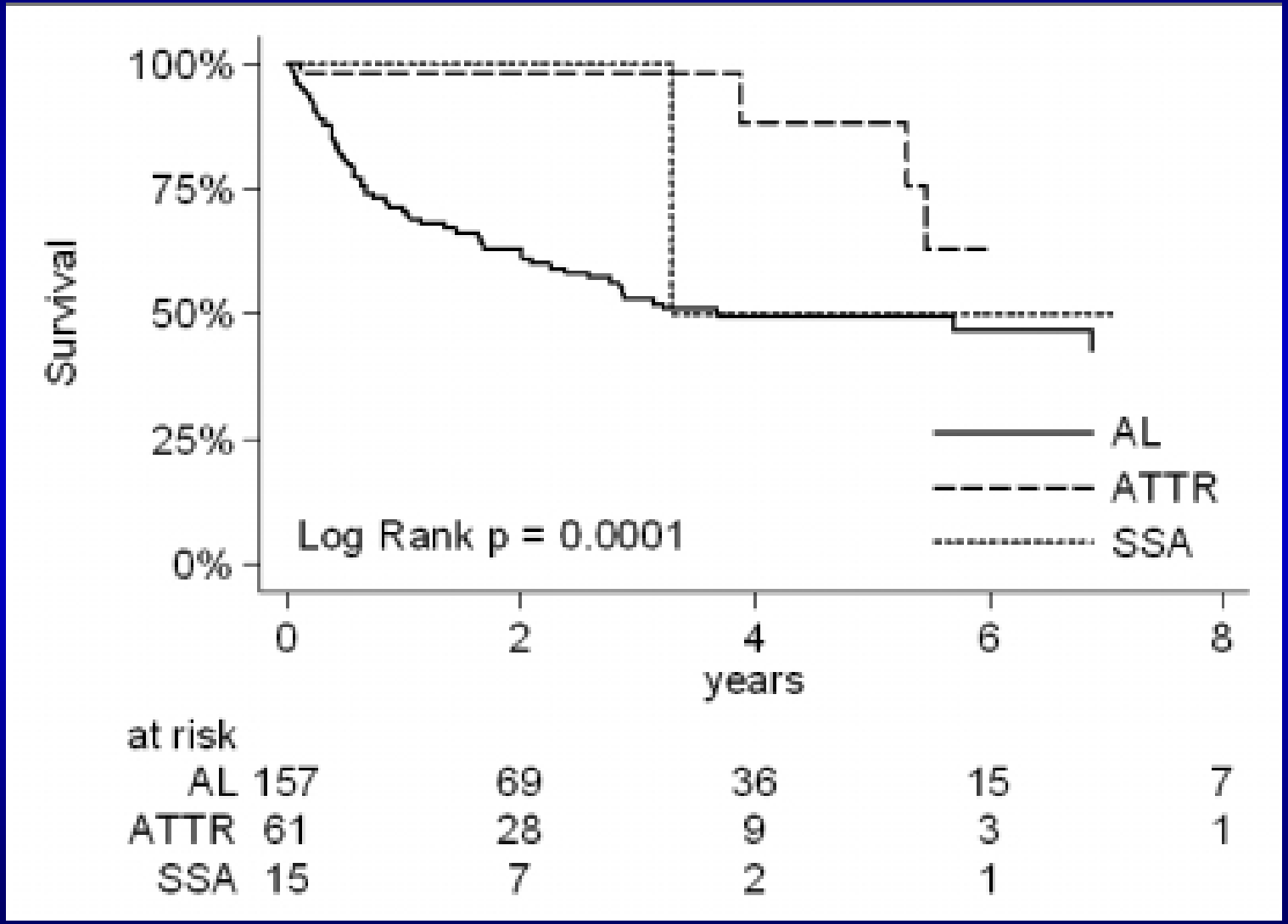


Fig. 1 – Echocardiography characteristics of cardiac amyloidosis. Parasternal long- and short-axis views demonstrating severely increased LV wall thickness, with granular sparkling, which may be seen in cardiac amyloidosis. Pericardial effusions are common (A and B). Atrial dilation reflects elevated filling pressures, as well as atrial infiltration of amyloid protein (C). Elevated RV wall thickness (>5 mm) is often seen as well (D). Longitudinal strain in apical 4-, 2-, and 3-chamber views showing severely reduced global longitudinal strain (GLS) of −12.5% with an apical to basal strain ratio of 2.7 (E–H).


A
B
Normal ECV
No LGE
ECV ↑
No LGE
ECV ↑↑
Subendocardial LGE
ECV ↑↑↑
Transmural LGE
C
99mTc-PYP
ATTR
Non-amyloid LVH
18F-Florbetapir
Healthy control
ATTR
AL

Overall survival of patients with the **three** main types of systemic amyloidosis **(233 pts)**



Circulation 2009:120:1203-1212

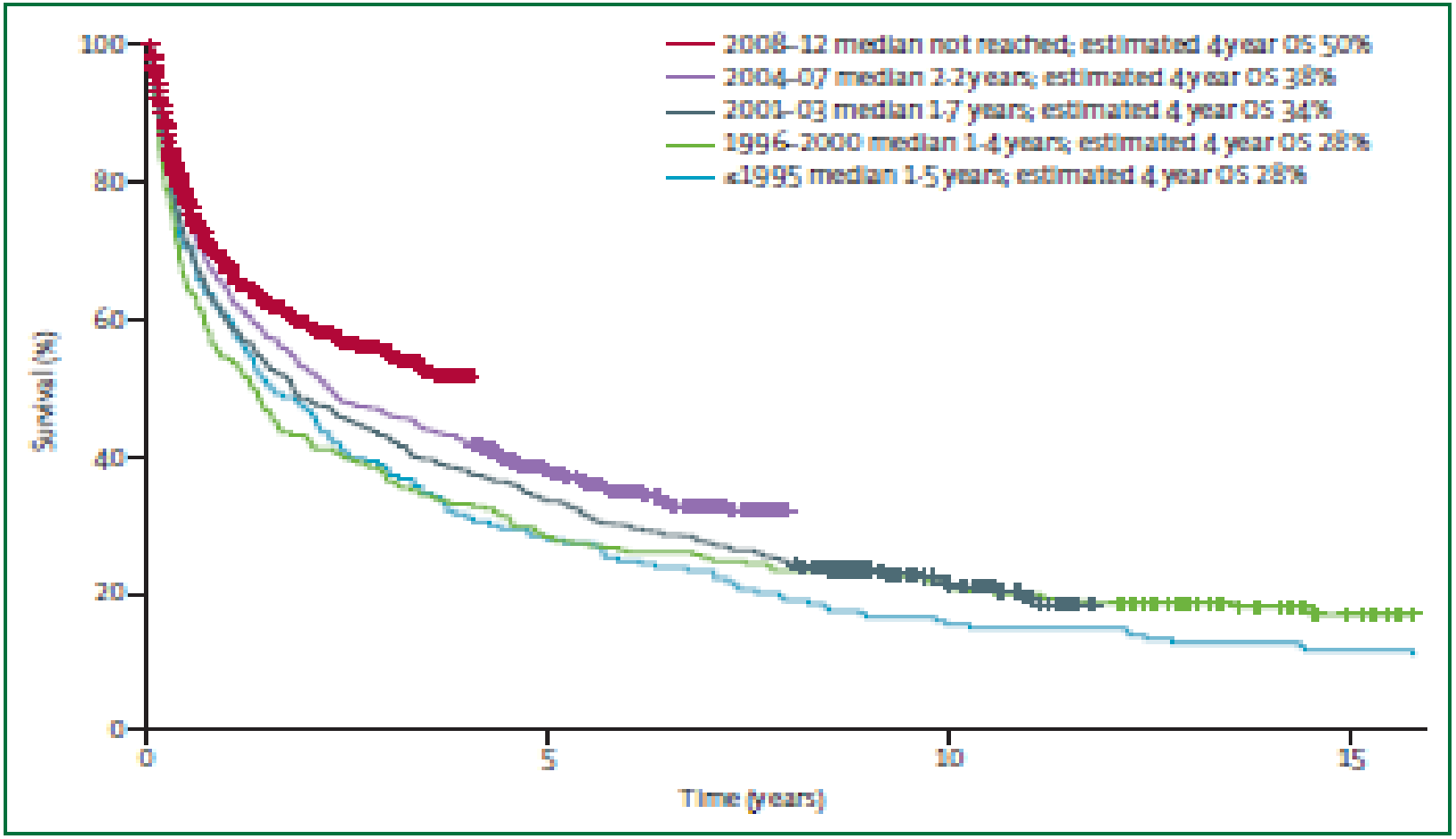


Figure 5: Kaplan–Meier survival curve showing improvement over time in overall survival of patients with systemic AL amyloidosis seen at the National Amyloidosis Centre in the UK (n=3486)

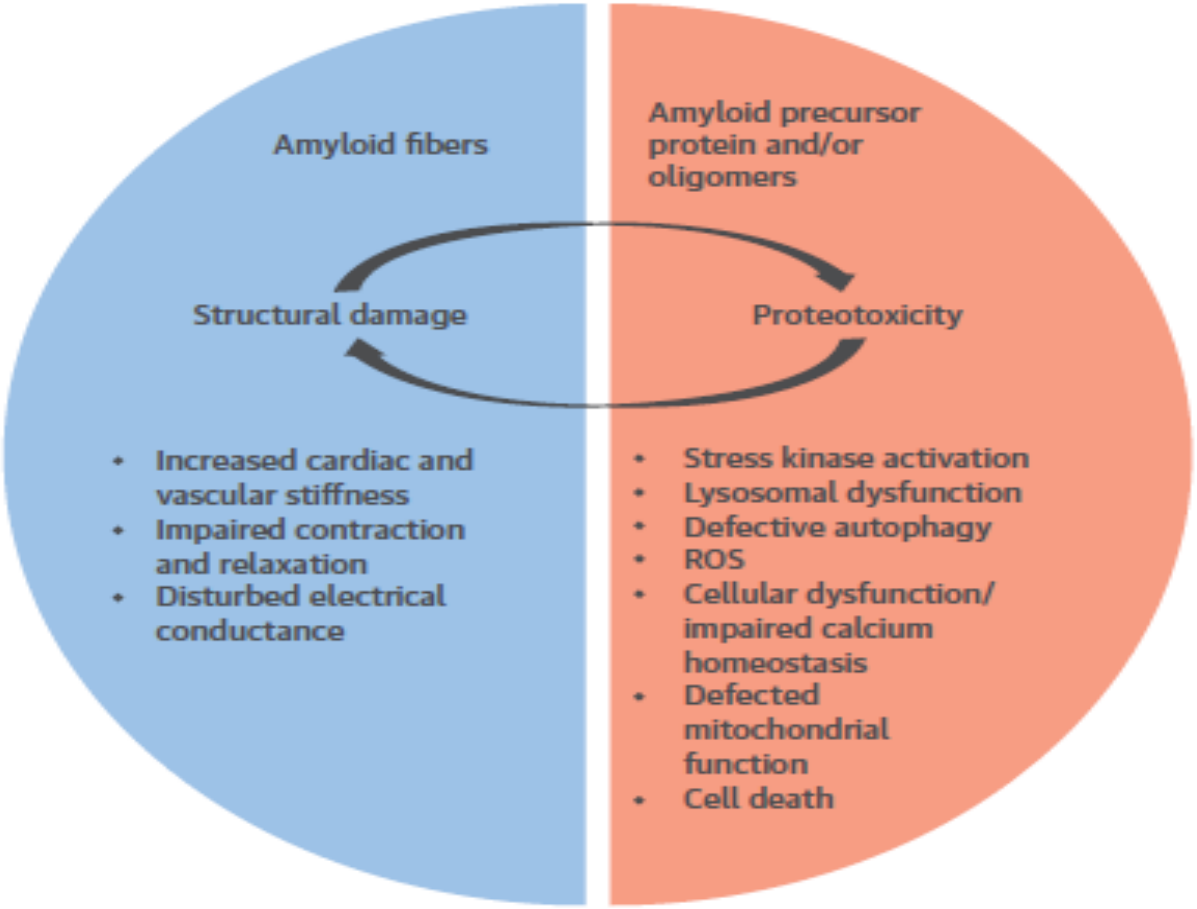
Estimated 4-year survival has improved from 28% for patients diagnosed in the early part of the past decade to nearly 50% for patients diagnosed in the past four years (log rank p values: p=0·008 for 2008–12 *vs* 2004–07; p=0·03 for 2004–07 *vs* 2001–03; p=0·29 for 2001–03 *vs* 1996–2000; p=0·64 for 1996–2000 *vs* up to 1995). This improvement in survival coincides with the availability of novel agents such as thalidomide and bortezomib for the treatment of AL amyloidosis. However, over the past two decades, no improvement has been seen in early mortality in the first few months after diagnosis of AL amyloidosis. AL=amyloid light chain. OS=overall survival.

Principali forme di Amiloidosi cardiaca

Amyloidosis Type	Protein	Cardiac Involvement	Median Survival, mo	Extracardiac Manifestations	Diagnostic Testing
Primary (AL)	Light chain	22%-34%	13 (4 mo if heart failure present at diagnosis)	Renal failure, proteinuria, hepatomegaly, autonomic dysfunction, macroglossia, purpura, neuropathy, carpal tunnel syndrome	SPEP, UPEP, bone marrow biopsy tissue analysis revealing plasma cell dyscrasia, κ and λ light-chain antiserum staining
Hereditary (ATTR)	Mutant TTR	Variable	70	Severe neuropathy, autonomic dysfunction, renal failure, blindness	ATTR antiserum staining, serum TTR isoelectric focusing, restriction fragment length polymorphism analysis
Senile systemic (ATTR)	TTR	Common	75	Diffuse organ involvement	ATTR antiserum staining
Isolated atrial (AANF)	Atrial natriuretic factor	Limited to heart	. . .	None	Atrial natriuretic factor antiserum staining
Reactive (AA)	Amyloid A	<10%	24½	Renal failure, proteinuria, hepatomegaly associated with chronic inflammatory conditions	Target organ biopsy specimen analysis, AA antiserum staining
Dialysis-related (β_2-microglobulin)	β_2-Microglobulin	Unknown, asymptomatic	. . .	Arthralgias, carpal tunnel syndrome, arthropathies, bone cysts, pathologic fractures	Synovial and bone biopsy specimen analysis, β_2-microglobulin antiserum, serum β_2-microglobulin concentration

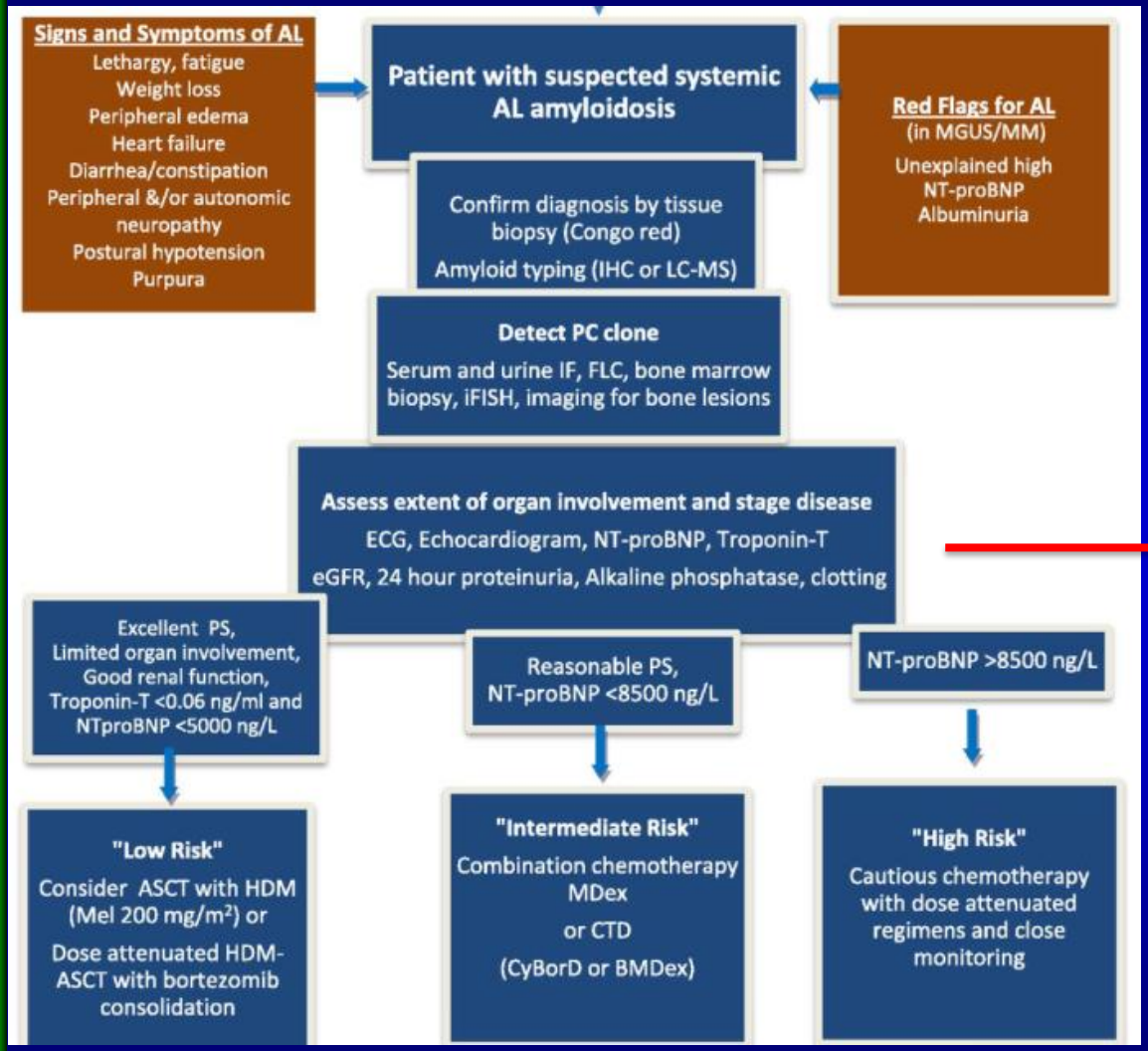
Shah, Arch Intern Med. 2006;166:1805-1813

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



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

Diagnosi e Valutazione del Coinvolgimento d'Organo



MRI indicata se ipertrofia/aumento della massa inspiegabili → Late-enhancement subendocardico diffuso

Cardiac
NT-proBNP (or BNP), cTnT (or hs-cTnT, or cTnI)
Echocardiography (plus strain imaging)
ECG (plus Holter ECG)
Cardiac MRI (if indicated)
^{99}mTc-DPD scan (if indicated)

Renal
24 h urinary protein
Serum creatinine (and eGFR)

Liver
Liver function tests
Liver US / CT scan

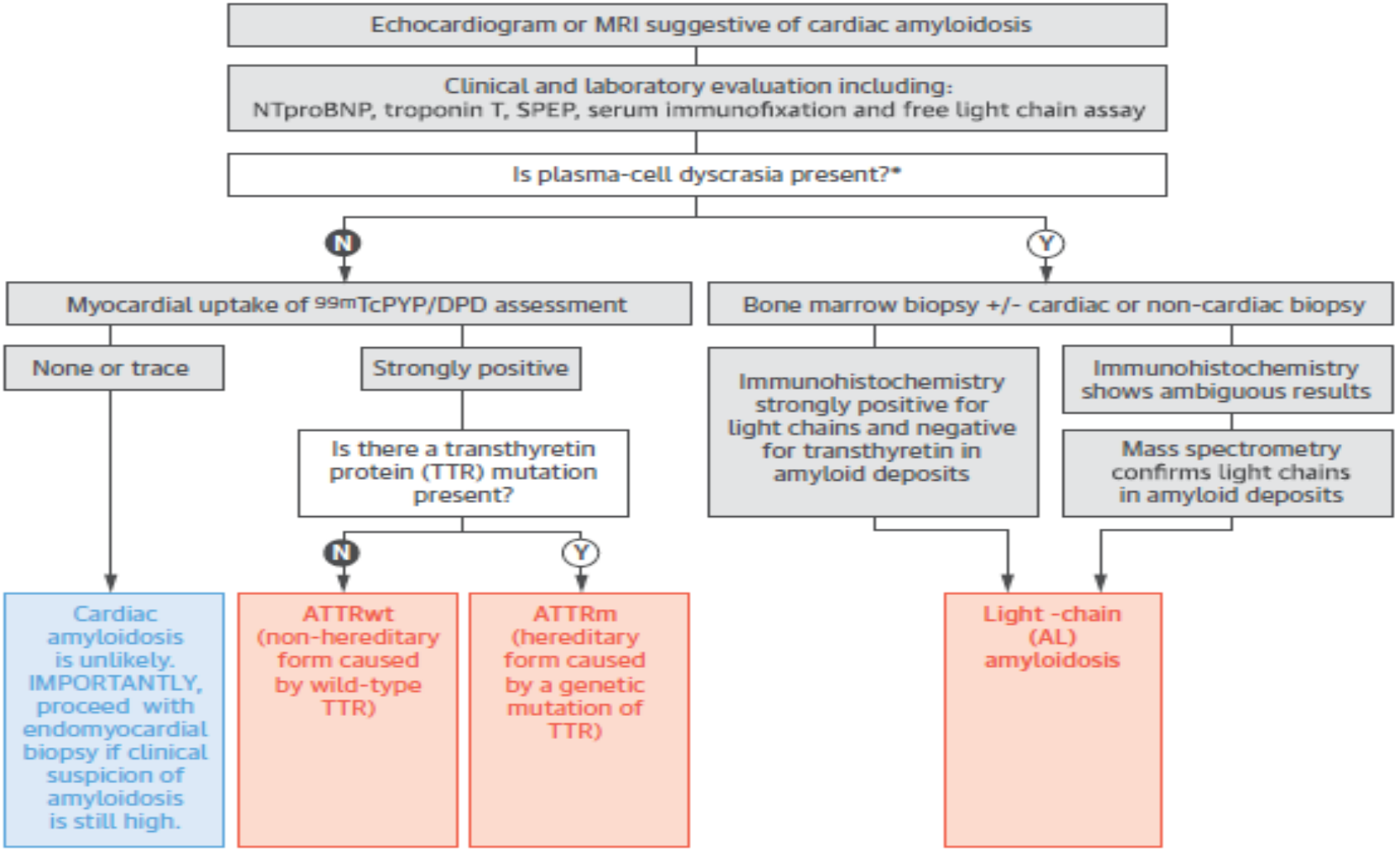
Nerves
Nerve conduction studies (if indicated)
Autonomic testing

Whole body amyloid load
^{123}I labeled SAP scintigraphy (if available)

Merlini, Blood 2013; 121:5124-5130

Mahmood. Haematologica 2014 (99)2

CENTRAL ILLUSTRATION **Diagnosing and Typing Cardiac Amyloidosis in a Patient With Unexplained Heart Failure**



Falk, R.H. et al. J Am Coll Cardiol. 2016;68(12):1323–41.

*The finding of evidence of a plasma cell dyscrasia does not necessarily confirm light-chain (AL) amyloidosis because monoclonal gammopathy of unknown significance (MGUS) might coexist with transthyretin (TTR) amyloidosis. Thus, if the clinical picture suggests TTR amyloidosis (e.g., isolated cardiac amyloidosis in an elderly man with a history of carpal tunnel syndrome and no proteinuria or neuropathy), further workup is required to exclude transthyretin amyloidosis (ATTR). A classical appearance on imaging for amyloidosis, with a strong ^{99m}technetium pyrophosphate (Tc^{99m}PYP) (or 2,3-dicarboxypropane-1, 1-diphosphonate [DPD] in Europe) cardiac uptake, and no evidence of a plasma cell dyscrasia appears to be diagnostic of TTR amyloidosis, without the need for a biopsy (42). ATTRm = mutant transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SPEP = serum protein electrophoresis.

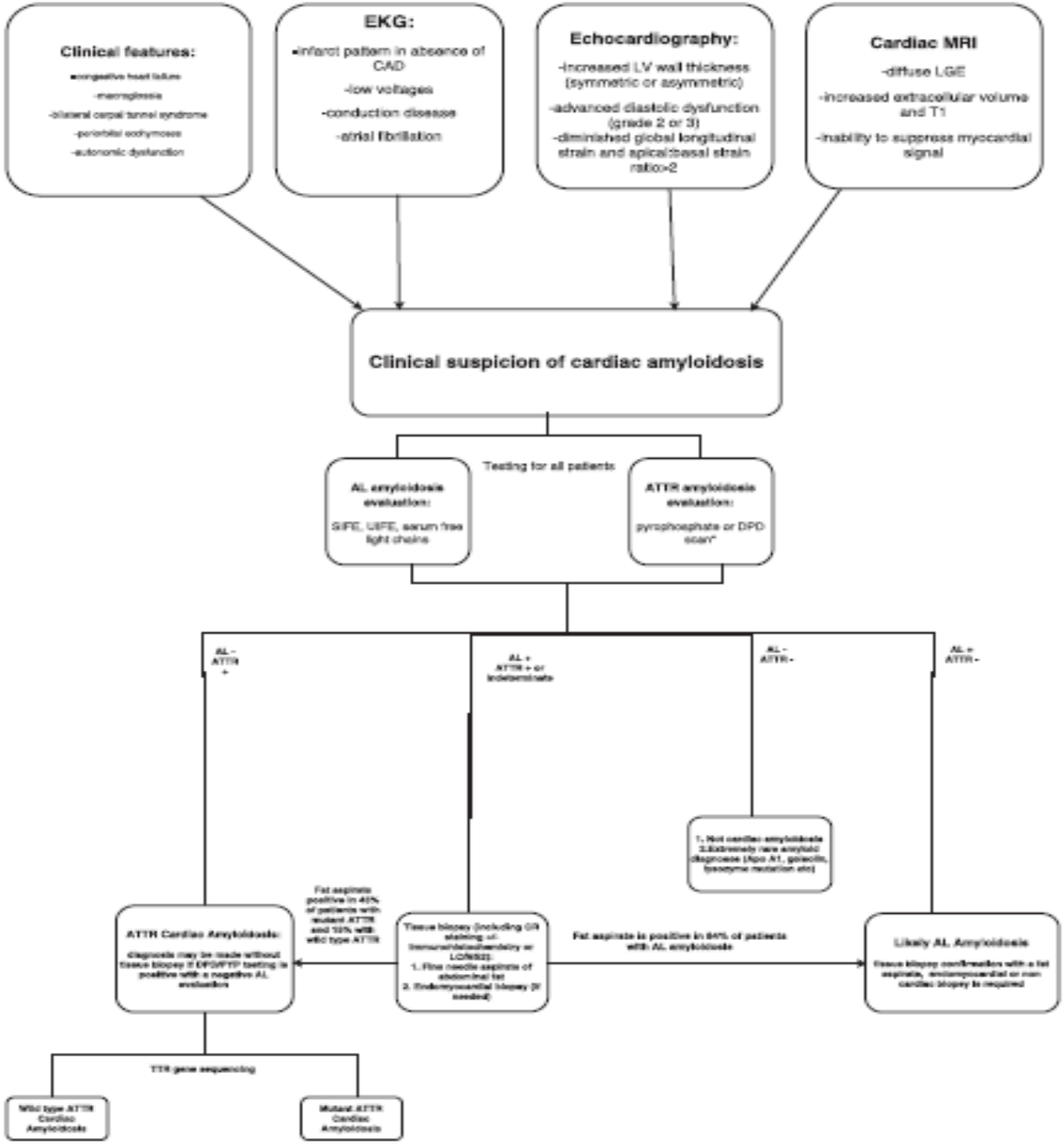


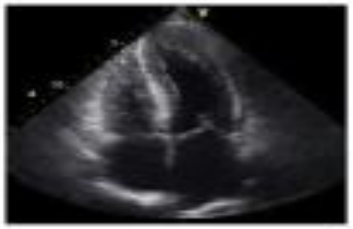
Fig. 4 – Suggested algorithm for the diagnosis of cardiac amyloidosis, and for differentiating between ATTRwt, ATTRm, and AL cardiac amyloidosis. (Adapted with permission from Siddiqi and Ruberg [64].)

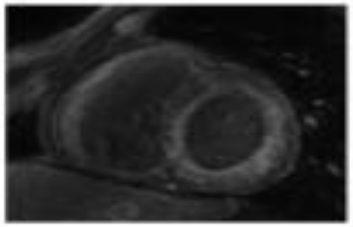
Table 2
Comparison of cardiac phenotype between AL amyloidosis-CM and ATTR-CM.

Subtype	AL amyloidosis-CM	ATTR-CM	
		Wild type	Hereditary type (Val30Met)
Mean age	Depending on underlying hematologic diseases	Late 60s	50s
Sex	Male > Female	Male ⋙ Female	Male = Female
Carpal tunnel syndrome	±	++	+
Autonomic symptoms	++	+	+++
NT-pro BNP and hs-TnT	↑↑↑	↑↑	↑ or →
ECG			
Low voltage	++	+	+
Pseud-infarction pattern	++	+	+
Conduction disturbance	+	++	++
Atrial arrhythmia	+	++	++
UCG			
Wall thickness	+	++	+
CMR			
Wall thickness	+	++	+
Bone scintigraphy	±	++	++

Abbreviations: AL, amyloid-light chain; ATTR, transthyretin amyloidosis; CM, cardiomyopathy; NT-pro BNP, N-terminal pro-brain natriuretic peptide; hs-TnT, high sensitive troponin T; ECG, electrocardiogram; UCG, ultrasound cardiography; CMR, cardiac magnetic resonance imaging.

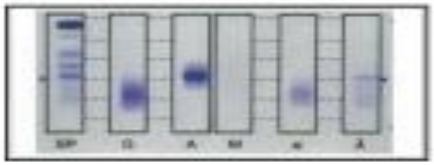
A patient shows rapidly progress heart failure with left ventricular hypertrophy in echocardiography and cardiac magnetic resonance imaging.



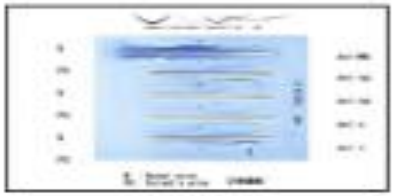


Suspect AL amyloidosis-related CA

Perform biochemical analysis



Serum monoclonal protein



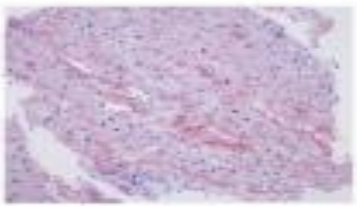
Urinary Bence Jones protein

Serum free light chain analysis

Histological confirmation of amyloid deposition

Subcutaneous tissue

Gastrointestinal tract



heart

REVIEW

Rationale, application and clinical qualification for NT-proBNP as a surrogate end point in pivotal clinical trials in patients with AL amyloidosis

G Merlini[1,9], I Lousada[2], Y Ando[3], A Dispenzieri[4], MA Gertz[4], M Grogan[4], MS Maurer[5], V Sanchorawala[6], A Wechalekar[7], G Palladini[1] and RL Comenzo[8,9]

Amyloid light-chain (LC) amyloidosis (AL amyloidosis) is a rare and fatal disease for which there are no approved therapies. In patients with AL amyloidosis, LC aggregates progressively accumulate in organs, resulting in organ failure that is particularly lethal when the heart is involved. A significant obstacle in the development of treatments for patients with AL amyloidosis, as well as for those with any disease that is rare, severe and heterogeneous, has been satisfying traditional clinical trial end points (for example, overall survival or progression-free survival). It is for this reason that many organizations, including the United States Food and Drug Administration through its Safety and Innovation Act Accelerated Approval pathway, have recognized the need for biomarkers as surrogate end points. The international AL amyloidosis expert community is in agreement that the N-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP) is analytically validated and clinically qualified as a biomarker for use as a surrogate end point for survival in patients with AL amyloidosis. Underlying this consensus is the demonstration that NT-proBNP is an indicator of cardiac response in all interventional studies in which it has been assessed, despite differences in patient population, treatment type and treatment schedule. Furthermore, NT-proBNP expression is directly modulated by amyloidogenic LC-elicited signal transduction pathways in cardiomyocytes. The use of NT-proBNP will greatly facilitate the development of targeted therapies for AL amyloidosis. Here, we review the data supporting the use of NT-proBNP, a biomarker that is analytically validated, clinically qualified, directly modulated by LC and universally accepted by AL amyloidosis specialists, as a surrogate end point for survival.

Leukemia (2016) **30,** 1979–1986; doi:10.1038/leu.2016.191

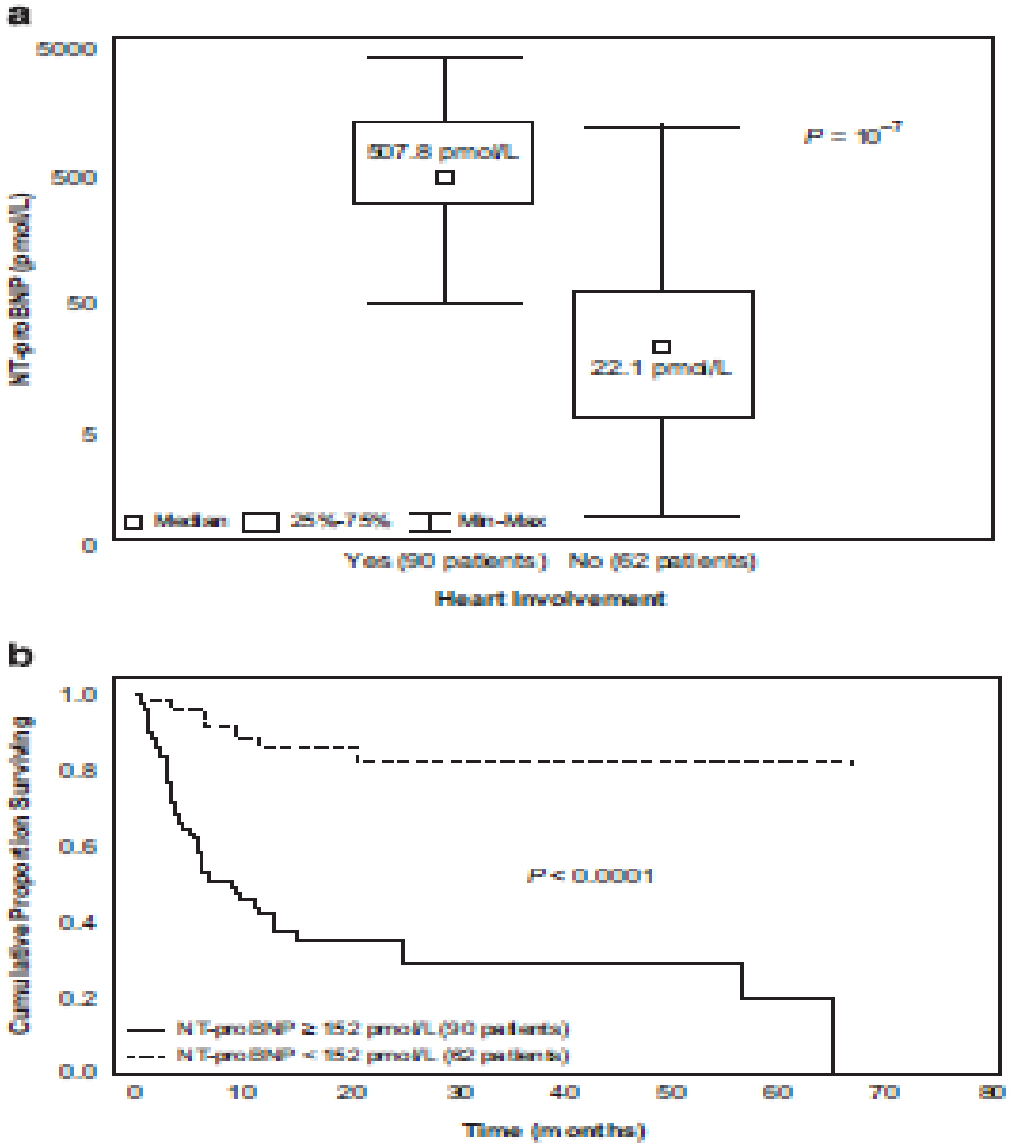


Figure 1. NT-proBNP levels indicate cardiac involvement (**a**) and predict overall survival (**b**) in Palladini *et al.*[42] Adapted with permission from Palladini *et al.*[42] Max, maximum; Min, minimum.

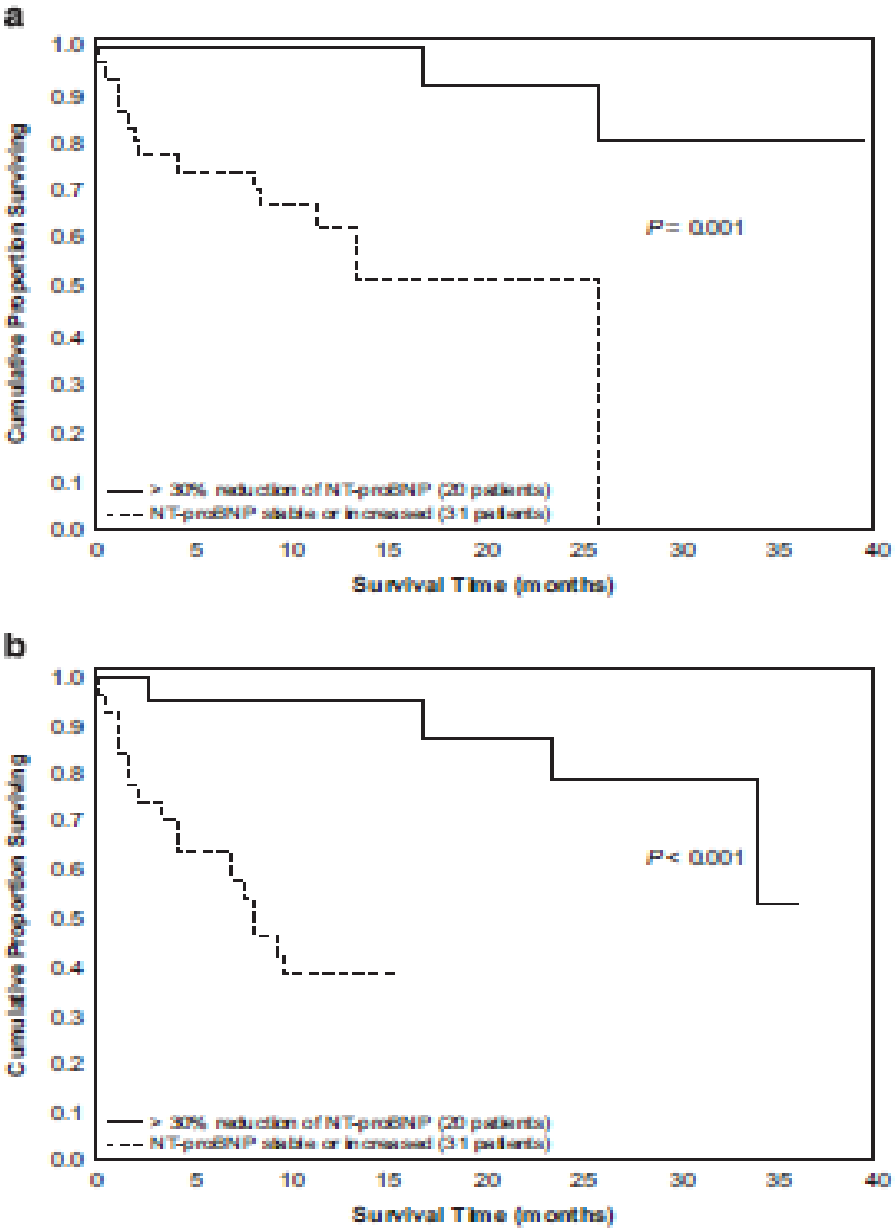


Figure 2. Overall (**a**) and progression-free (**b**) survival with respect to NT-proBNP response in Palladini *et al.*[54] Adapted with permission from Palladini *et al.*[54]

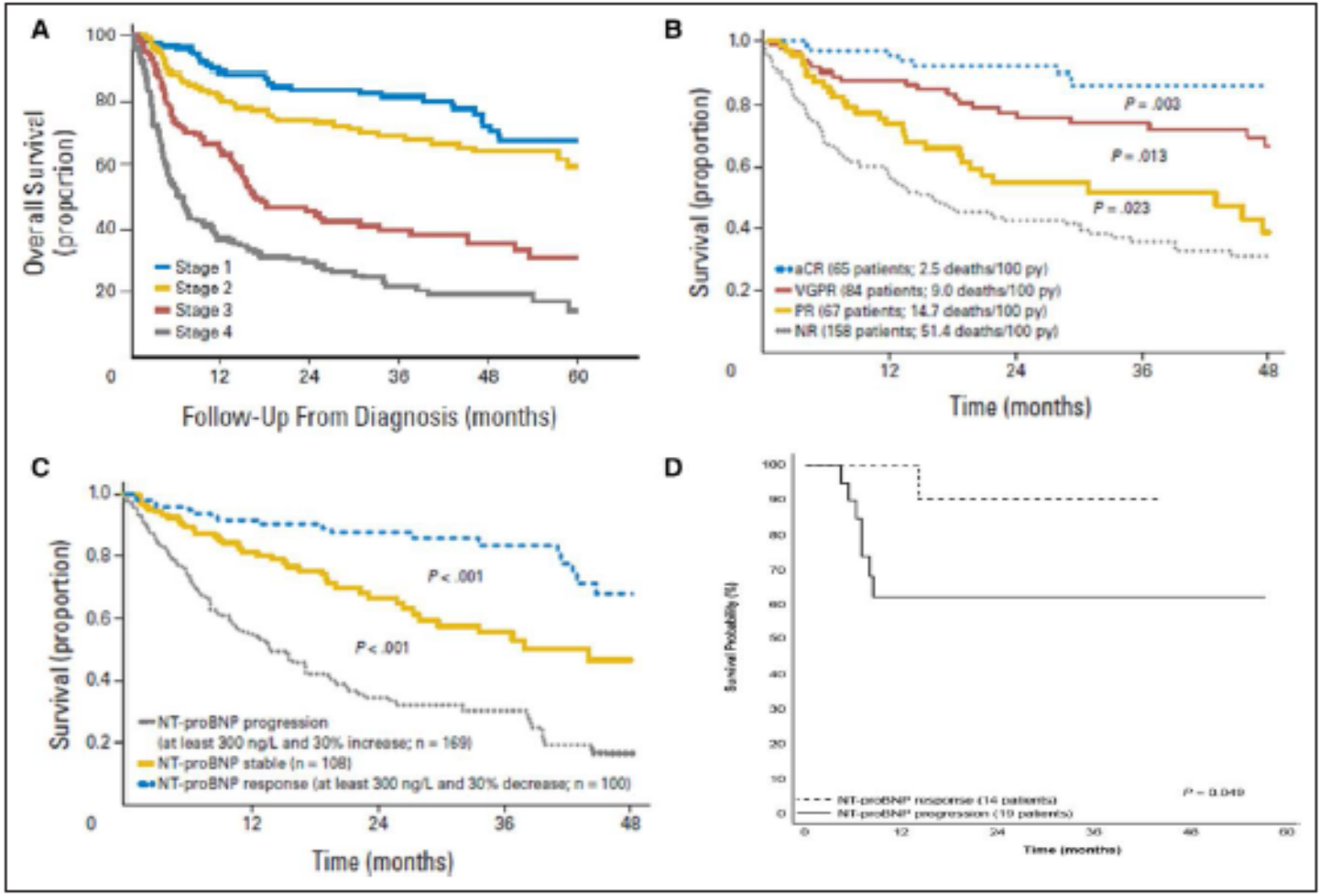


Figure 1. Biomarker staging system for AL cardiac amyloidosis and response criteria.
A, Mayo staging system for risk stratifying subjects with AL-CA in which 1 point is assigned for each of the following: NT-proBNP ≥1800 pg/mL, troponin T ≥0.025 ng/mL, and difference in serum-free light chains ≥18 mg/dL. Those with highest score have the worst prognosis.[57] **B**, Survival from the 3-month landmark of 300 patients with AL amyloidosis based on hematologic response. The proportion of stage III patients was not significantly different among the 4 hematologic response groups. CR indicates complete response; NR, no response; PR, partial response; VGPR, very good partial response; and py, person-year.[60] **C**, Prognostic relevance of cardiac response and progression criteria showing survival from the 6-month landmark of 377 patients with immunoglobulin light chain (AL) amyloidosis and baseline N-terminal natriuretic peptide type B (NT-proBNP) >650 ng/L according to NT-proBNP response and progression.[60] **D**, Survival according to NT-proBNP response in an ongoing phase 3 trial comparing melphalan-dexamethasone with melphalan-bortezomib-dexamethasone (NCT01277016).[61]

Table 1. Red Flags and Caveats in Cardiac Amyloidosis

A high index of suspicion is mandatory for the recognition of CA (ie, if you don't think of it, you won't diagnose it).
Cardiac amyloid should be suspected in any patient with heart failure, unexplained increased LV wall thickness, and a nondilated LV.
In a patient with a suspicion for HCM, look for the infiltrative features that suggest amyloid such as pericardial effusion, AV block, interatrial septal and valvular thickening, and apical sparring.
A distinctive sign of CA is the abnormal ratio between LV thickness and QRS voltages rather than low QRS voltages alone. The absence of low QRS voltages does not rule out a CA and up to 20% of subjects with CA can have electrocardiographic evidence of LV hypertrophy.
In an elderly man with unexplained symmetrical LV hypertrophy, especially in the absence of hypertension, always consider the possibility of ATTRwt-CA.
CA in an elderly patient with a monoclonal gammopathy is not necessarily attributable to AL: consider the possibility of ATTRwt and MGUS.
Longitudinal LV function can be severely depressed despite a normal LVEF, and the myocardial contraction fraction is often low, suggesting reduced global myocardial shortening.
Myocardial deformation is reduced in cardiac amyloidosis, but the apex is generally spared.
On cardiac MRI, both T1 signal abnormalities and marked extracellular volume expansion in patients with LV hypertrophy are strongly suggestive of CA. LGE distribution is heterogeneous, and subendocardial enhancement is not the only pattern.
A history of bilateral carpal tunnel syndrome in a man with HCM-like phenotype on echocardiography is highly suggestive of ATTRwt-CA.

AL indicates immunoglobulin light chain; ATTR, amyloid transthyretin; ATTRwt, wild-type amyloid transthyretin; AV, atrioventricular; CA, cardiac amyloidosis; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; and MGUS, monoclonal gammopathy of undetermined significance.

THANK YOU
for your
ATTENTION!