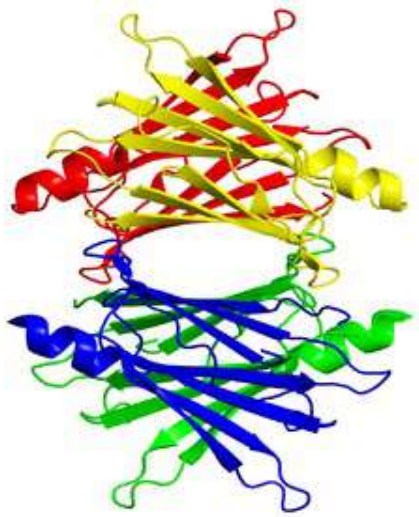

AMILOIDOSI TRANSTIRETINA relata (ATTr): un'epidemia silenziosa?

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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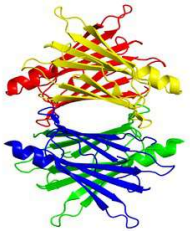


THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

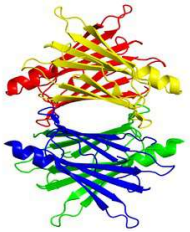
Transthyretin Amyloid Cardiomyopathy

JACC State-of-the-Art Review

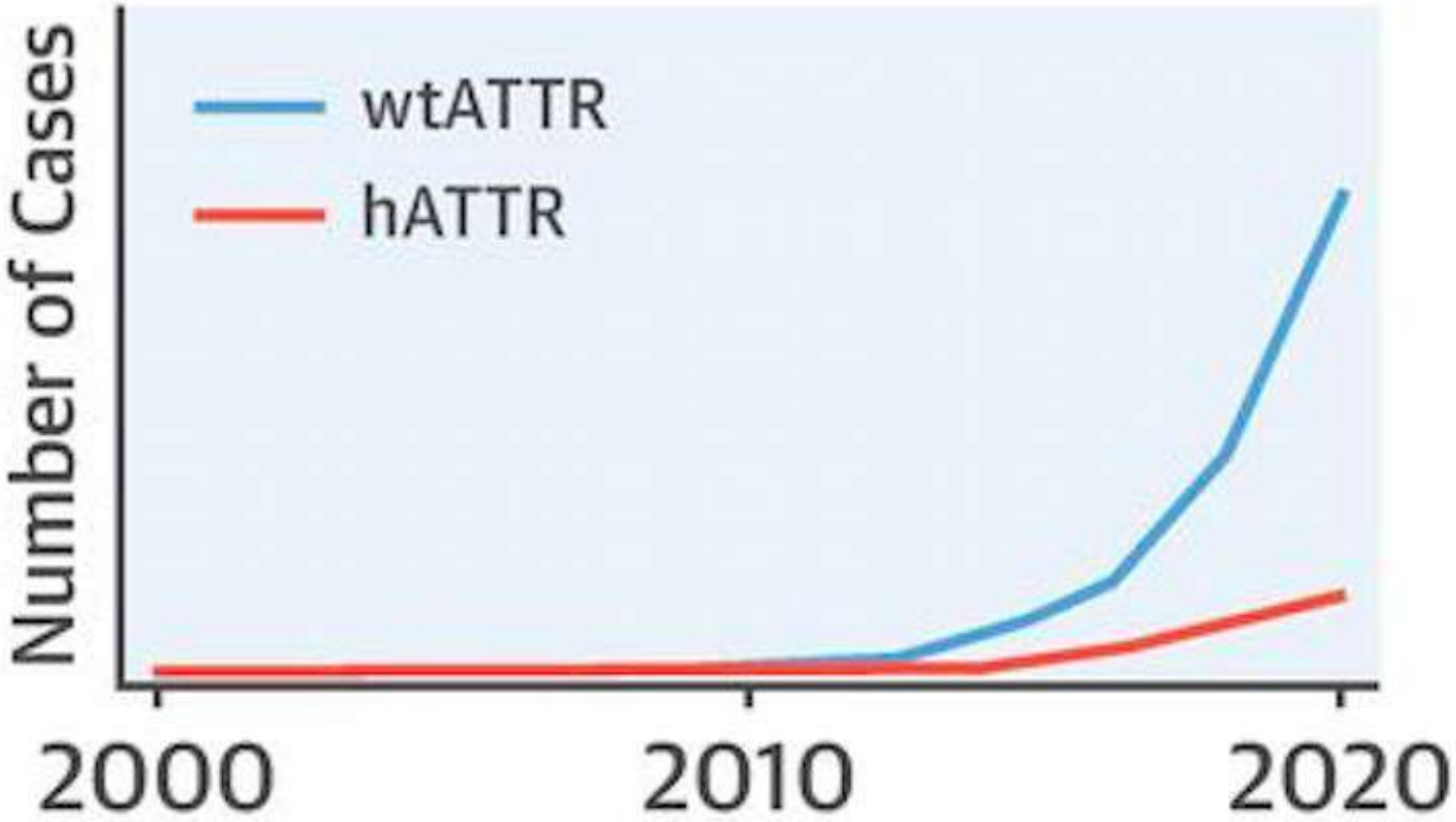
Frederick L. Ruberg, MD,[a] Martha Grogan, MD,[b] Mazen Hanna, MD,[c] Jeffery W. Kelly, PhD,[d] Mathew S. Maurer, MD[e]

ABSTRACT

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an under-recognized cause of heart failure (HF) in older adults, resulting from myocardial deposition of misfolded transthyretin (TTR) or pre-albumin. Characteristic patterns of echocardiography and cardiac magnetic resonance can strongly suggest the disease but are not diagnostic. The diagnosis can be made with noninvasive nuclear imaging when there is no evidence of a monoclonal protein. Amyloid fibril formation results from a destabilizing mutation in hereditary ATTR amyloidosis (hATTR) or from an aging-linked process in wild-type ATTR amyloidosis (wtATTR). Recent studies have suggested that up to 10% to 15% of older adults with HF may have unrecognized wtATTR. Associated features, including carpal tunnel syndrome and lumbar spinal stenosis, raise suspicion and may afford a means for early diagnosis. Previously treatable only by organ transplantation, pharmaceutical therapy that slows or halts ATTR-CM progression and favorably affects clinical outcomes is now available. Early recognition remains essential to afford the best treatment efficacy. (J Am Coll Cardiol 2019;73:2872–91)

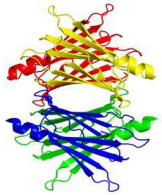


…un fenomeno in espansione…



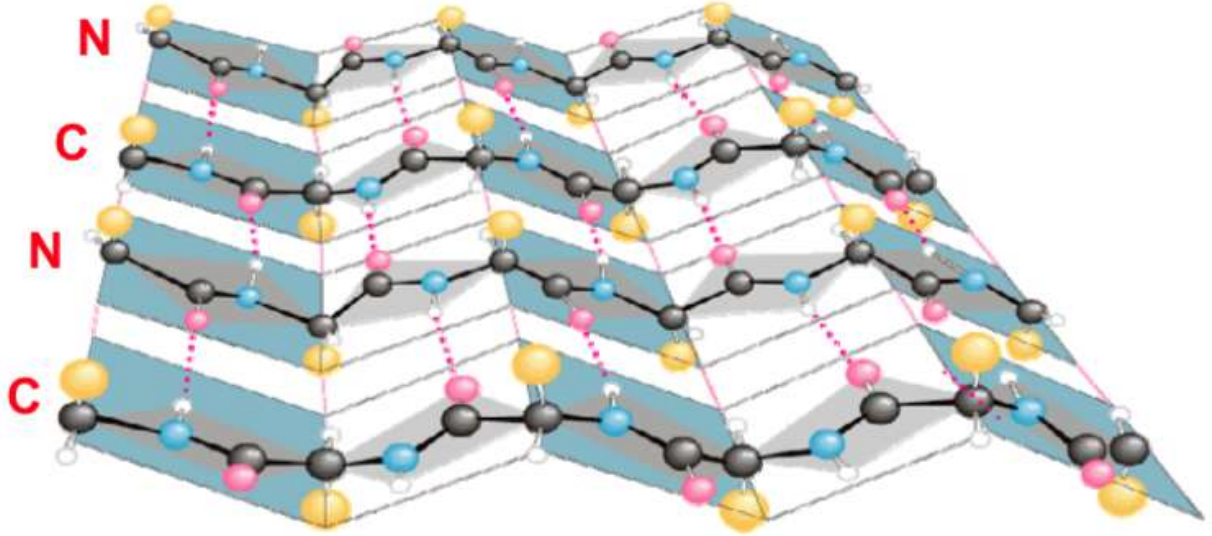
J Am Coll Cardiol 2019;73:2872-91

AMILOIDE e AMILOIDOSI

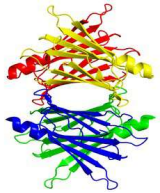


- L'amiloide è una sostanza proteica patologica, depositata tra le cellule in vari organi e tessuti del corpo sotto forma di fibrille di foglietti β-pieghettati in un'ampia varietà di malattie.

β- sheet basics



AMILOIDE e AMILOIDOSI



- L'amiloidosi è un disordine acquisito o ereditario che riguarda il folding delle proteine
- frammenti o intere proteine normalmente solubili sono depositate nello spazio extracellulare come fibrille insolubili che si accumulano e distruggono la struttura e la funzione di organi e tessuti e causano malattia.
- Nell'amiloidosi sistemica i depositi possono essere presenti nel parenchima di tutti i tessuti (eccetto il cervello) così come nella parete dei vasi sanguigni.
- Forme localizzate di amiloidosi nelle quali i depositi sono confinati a particolari organi o tessuti.

Le proteine che formano amiloidosi si raggruppano in due gruppi

1. Proteine normali che hanno intrinseca tendenza ad assemblarsi impropriamente, ad aggregarsi e formare fibrille, e a farlo quando sono prodotte in eccesso.

2. Proteine mutate che sono strutturalmente instabili e inclini a un folding difettoso con successiva aggregazione

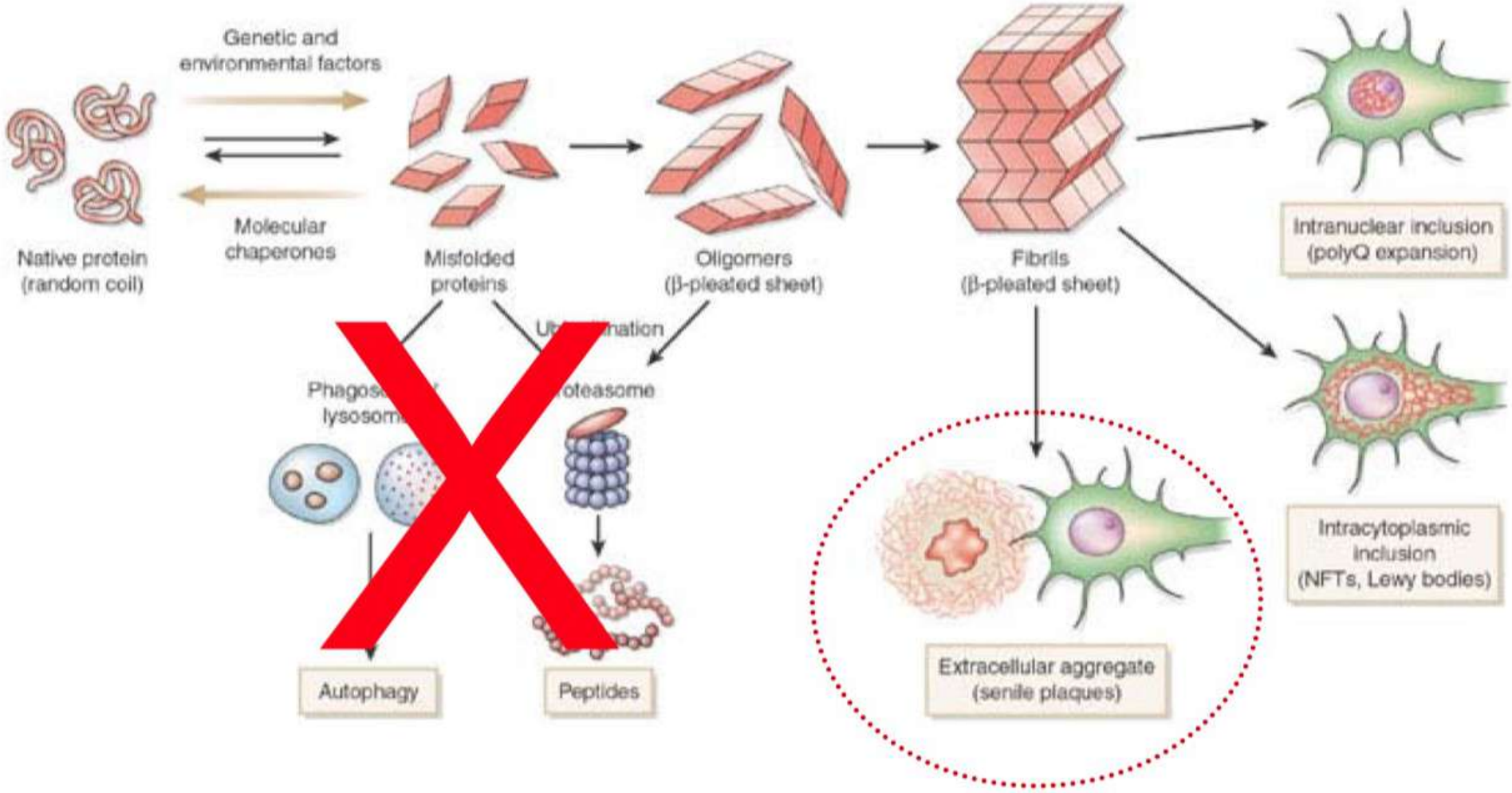
AMILOIDE e AMILOIDOSI

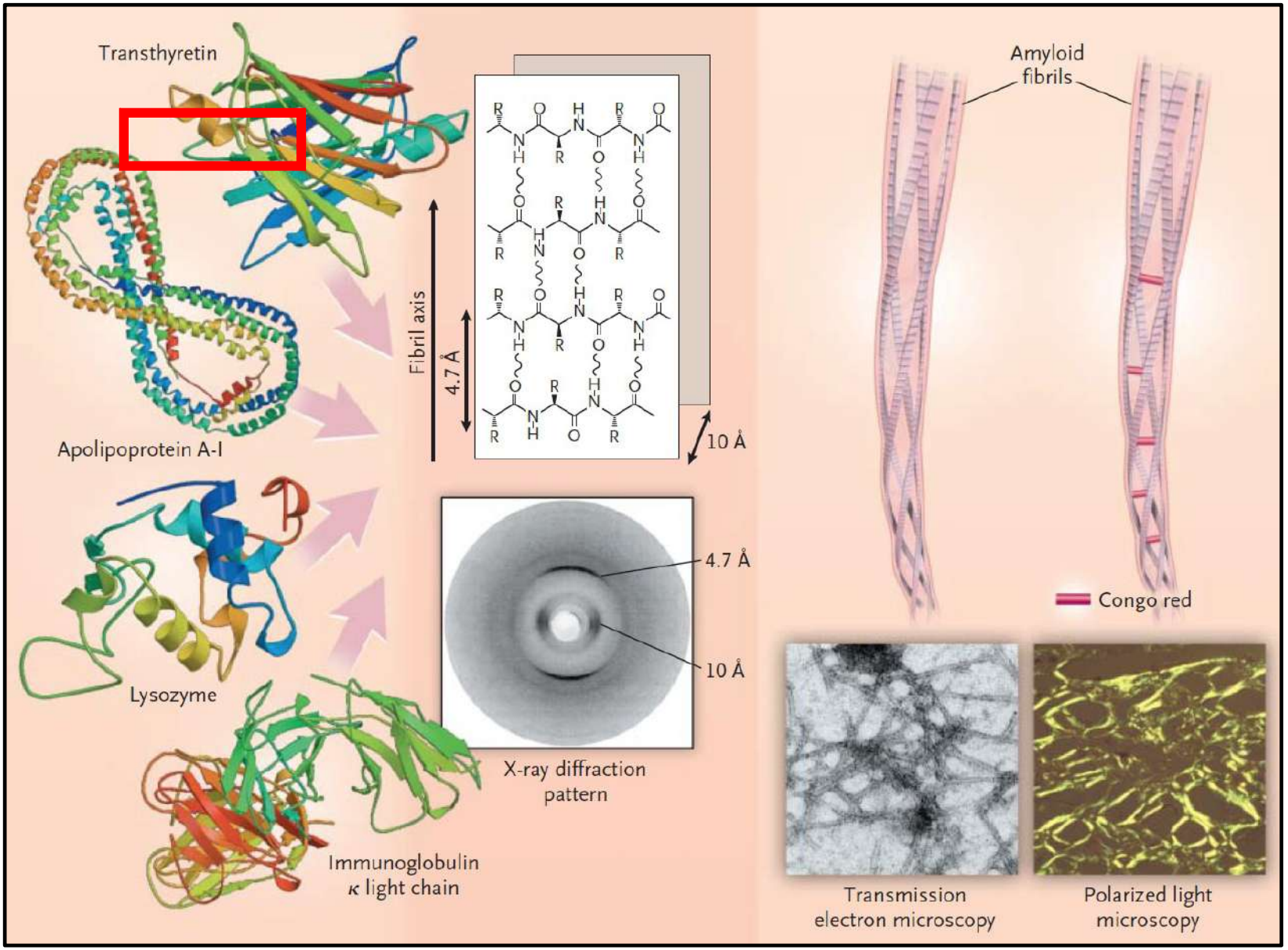
- Amiloide è un disordine del folding delle proteine nel quale normalmente proteine solubili sono depositate come fibrille anormali insolubili che distruggono la struttura del tessuto e causano malattia.
- Sebbene circa 20 differenti proteine non correlate tra loro possano formare fibrille amiloidi *in vivo*, tali fibrille mostrano una struttura con un core di tipo beta in comune.
- Alcune proteine naturali "wild type" sono inherently amiloidogeniche, formano fibrille e causano amiloidosi in età avanzata o se presenti per lungo tempo a concentrazioni elevate in maniera anomala.
- Altre proteine amiloidi sono varianti acquisite o ereditate che contengono sostituzioni aminoacidiche che le rendono instabili così, in condizioni fisiologiche popolano parzialmente uno stato unfolded e tali intermedi poi aggregano in amiloide stabile.

Cosa succede alle proteine male assemblate

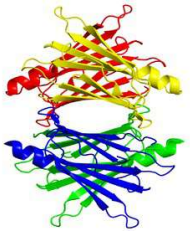
- Le proteine male assemblate sono *normalmente* degradate dentro le cellule nei proteosomi, o all'esterno della cellula dai macrofagi
- Nell'amiloidosi questo meccanismo fallisce e si verifica accumulo delle proteine male assemblate all'esterno delle cellule.

Accumulo di proteine male assemblate





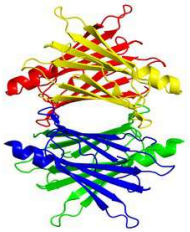
Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003;349:583–596. doi: 10.1056/NEJMra023144



TRANSTIRETINA (TT)

- **PROTEINA SERICA**
- **DEPUTATA AL TRASPORTO DELLA TIROXINA E DELLA PROTEINA LEGANTE IL RETINOLO**
- **PRODOTTA PRINCIPALMENTE DAL FEGATO ED IN PICCOLA PARTE DAL PLESSO CORIOIDEO E DALLA RETINA**
- **TETRAMERO SOLUBILE**

Coinvolgimento cardiaco nell'AMILOIDOSI: tre eziologie distinte



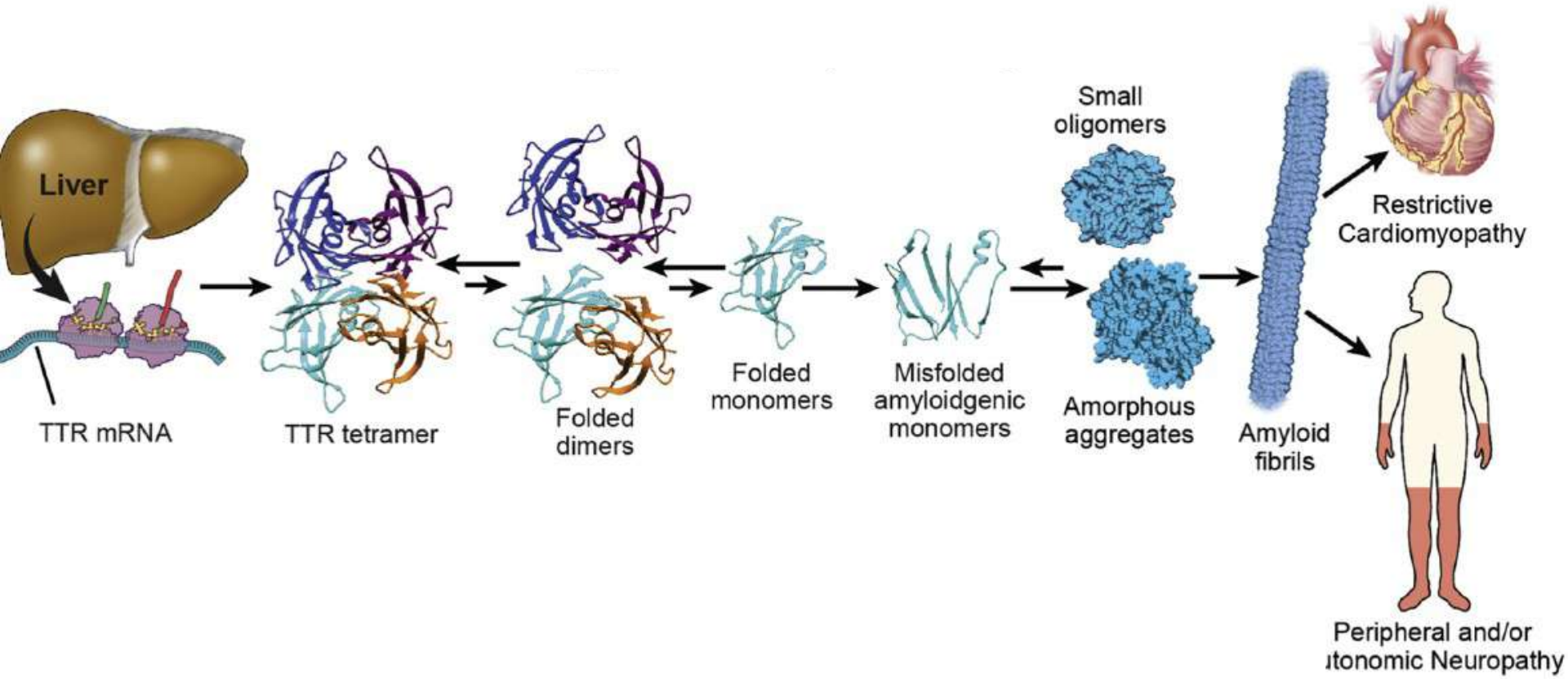
1. AL -> catene leggere Ig

2. ATTr wild type (senile o SSA)

3. ATTr mutata

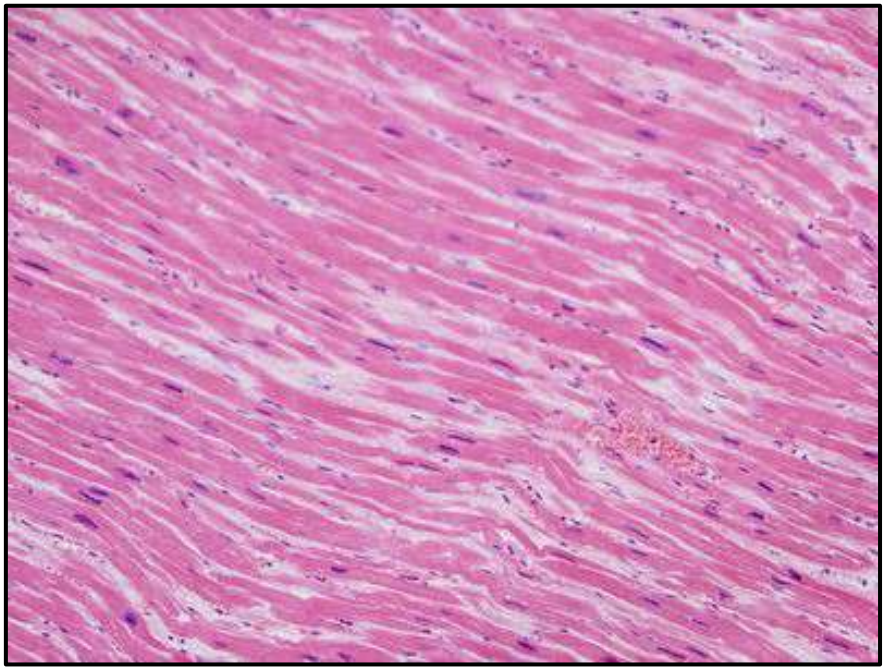
- **→ le fibrille di amiloide sono composte da TRANSTIRETINA**

BIOPATOLOGIA dell' ATTr

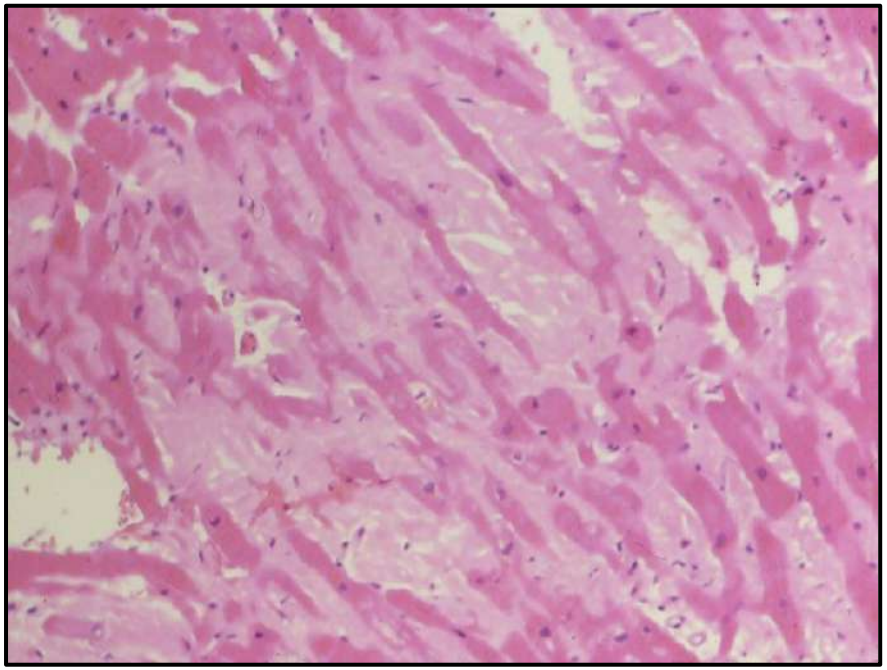


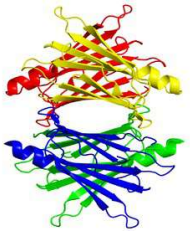
ATTr-CM: istologia cardiaca

Miocardio normale



Miocardio amiloidotico



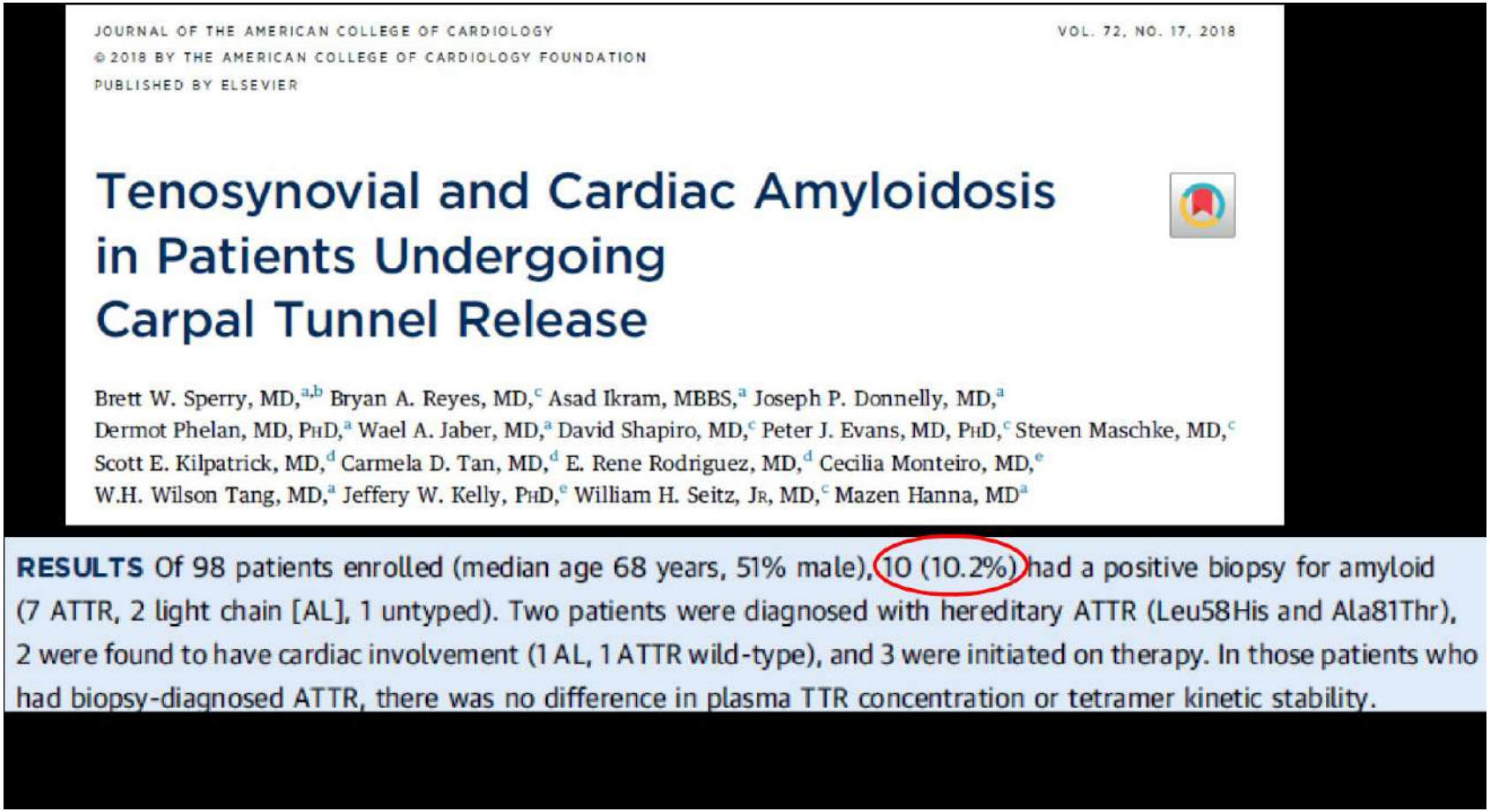


ATTr wild type (senile o SSA)

- **FENOTIPO GENERALMENTE CARDIOLOGICO**

- **MANIFESTAZIONI NEUROLOGICHE : SINDROME DEL TUNNEL CARPALE**

ATTr: epidemiological considerations



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VOL. 72, NO. 17, 2018

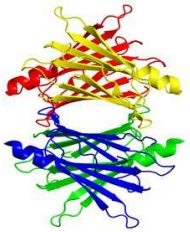
Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release

Brett W. Sperry, MD,[a,b] Bryan A. Reyes, MD,[c] Asad Ikram, MBBS,[a] Joseph P. Donnelly, MD,[a] Dermot Phelan, MD, PhD,[a] Wael A. Jaber, MD,[a] David Shapiro, MD,[c] Peter J. Evans, MD, PhD,[c] Steven Maschke, MD,[c] Scott E. Kilpatrick, MD,[d] Carmela D. Tan, MD,[d] E. Rene Rodriguez, MD,[d] Cecilia Monteiro, MD,[e] W.H. Wilson Tang, MD,[a] Jeffery W. Kelly, PhD,[e] William H. Seitz, Jr, MD,[c] Mazen Hanna, MD[a]

RESULTS Of 98 patients enrolled (median age 68 years, 51% male), 10 (10.2%) had a positive biopsy for amyloid (7 ATTR, 2 light chain [AL], 1 untyped). Two patients were diagnosed with hereditary ATTR (Leu58His and Ala81Thr), 2 were found to have cardiac involvement (1 AL, 1 ATTR wild-type), and 3 were initiated on therapy. In those patients who had biopsy-diagnosed ATTR, there was no difference in plasma TTR concentration or tetramer kinetic stability.

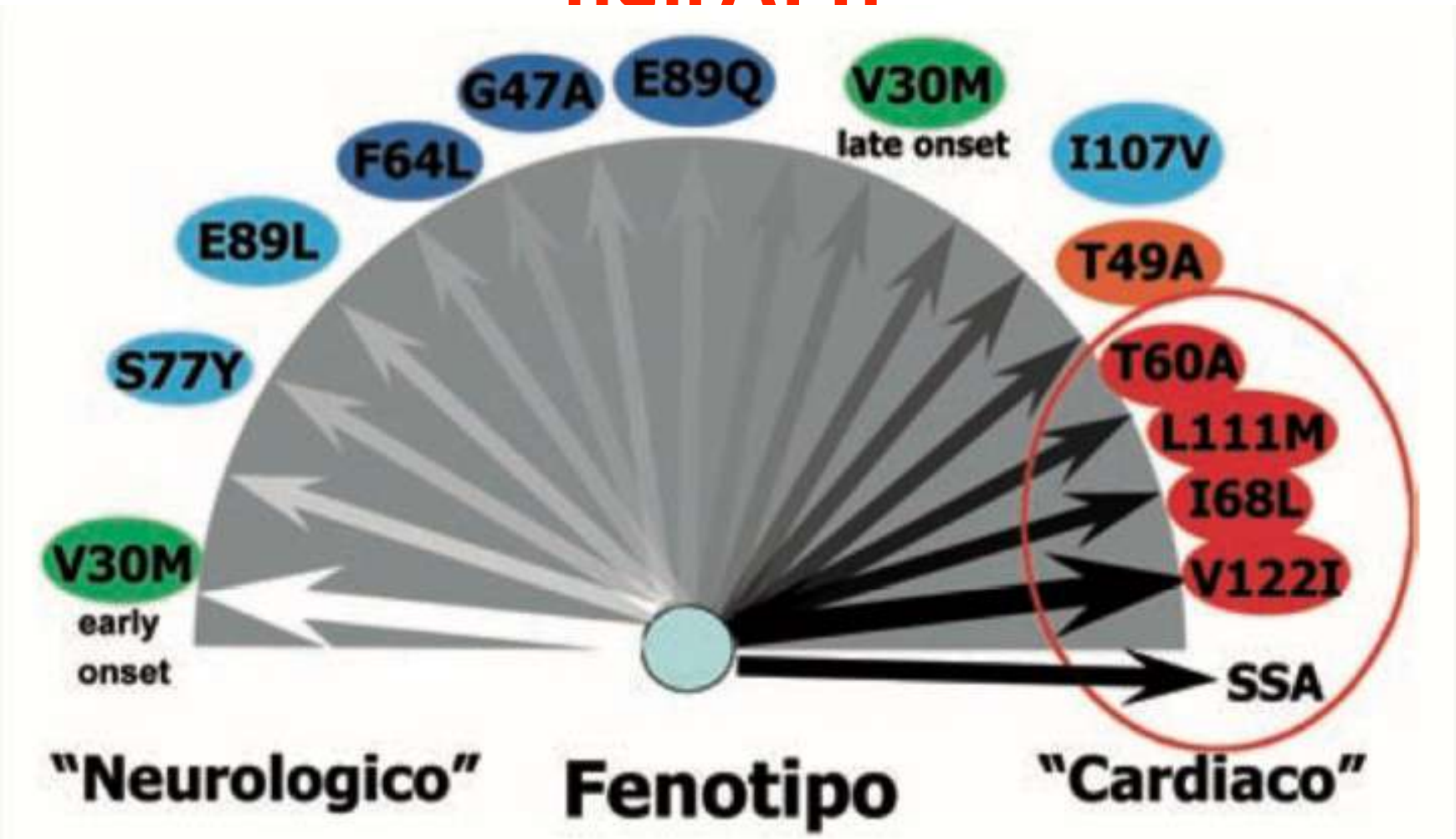
Bilateral tunnel carpal syndrome in 50% of patients 5-7 years prior to cardiac involvement

ATTr m (mutata)



- MALATTIA AUTOSOMICA DOMINANTE
- MUTAZIONI GENETICHE DELLA TT
- TROPISMO PARTICOLARE PER TESSUTO NERVOSO E CARDIACO
- CASI CON FENOTIPO PREVALENTEMENTE NEUROLOGICO
- CASI CON FENOTIPO PREVALENTEMENTE CARDIACO
- CASI MISTI

Correlazioni genotipo-fenotipo nell'ATTr



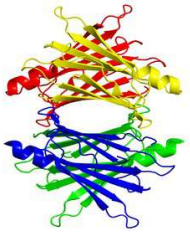
THAOS database
Rapezzi EHJ 2013

ATTR: clinical features at presentation

	AL[39,47]	ATTRwt[34,37,39]	Val122Ile[34]	Ile 68Leu[31]	Thr60Ala[33]
Median age at diagnosis, y	62	76	70	70	62
Males, %	66	95	75	75	70
Common ethnicity	Variable	White	African American Caribbean	White (Italy)	White (United States, Ireland)
Cardiac referral route, %	65	>80	>80	>80	30
IVS/PW (median values)	15/14	18/17	17/17	17/16	17/17
LVEF, %	56	50	50	50	53
Low QRS voltages, %	45	33	45	30	16
Peripheral sensory-motor neuropath, %	10–20	<10	15	25	54
History of carpal tunnel syndrome, %	<10	30–45	30	37	Unknown
Autonomic symptoms, %	24	12–20	10	<10	75
Median survival, y	Depends on stage	3.5	2–3	4–5	3.5
NT-pro-BNP, pg/L (median)	↑↑↑	↑↑	↑	↑	↑|

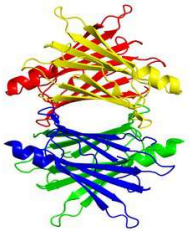
AL, immunoglobulin light chain; ATTR, amyloid transthyretin; ATTRwt, wild-type ATTR; CA, cardiac amyloidosis; IVS, interventricular septum; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro brain natriuretic peptide; and PW, posterior wall.

Circulation 2017



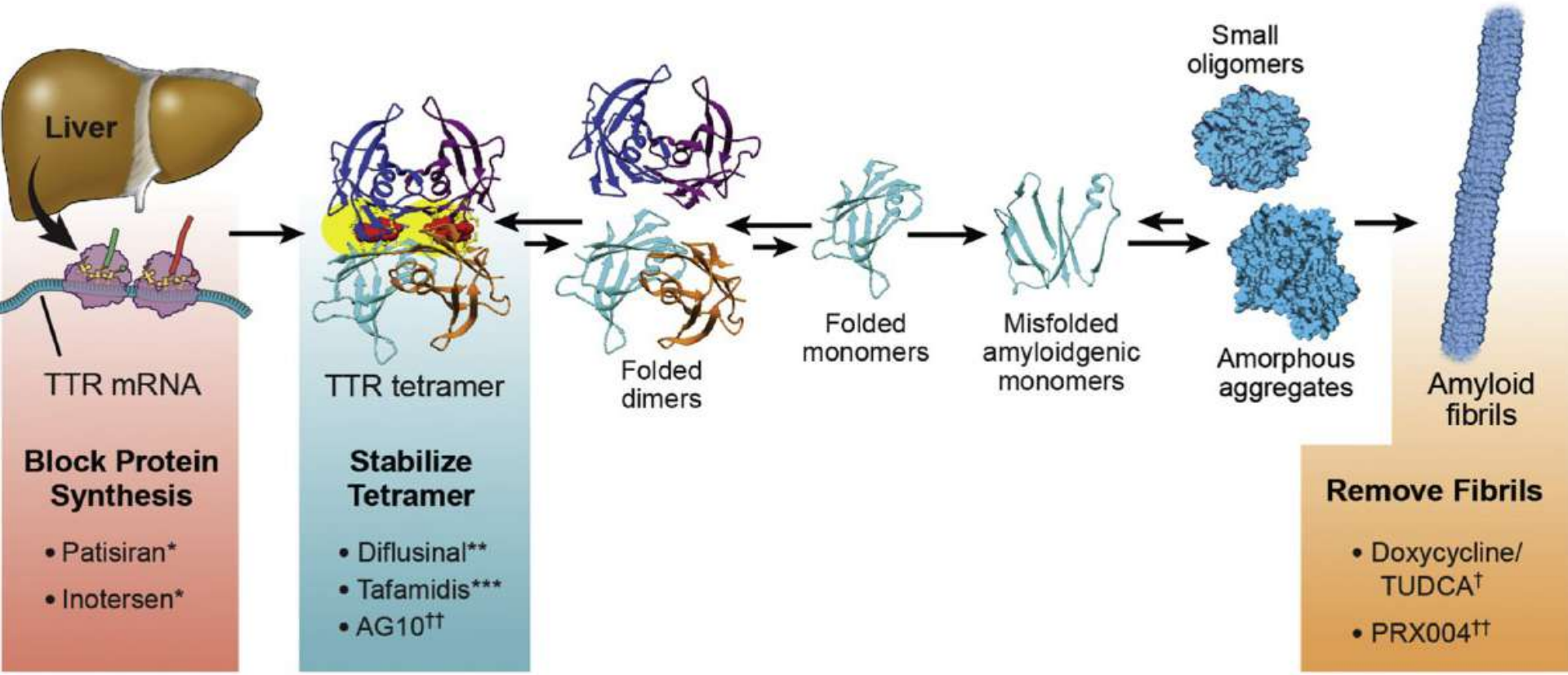
Quando il cardiologo dovrebbe sospettare una CardioMiopatia da Amiloidosi TransTiretino-relata (ATTr-CM)?

ETEROGENEITÀ CLINICA: UNA SFIDA!

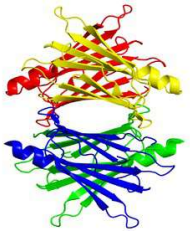


- L'AMILOIDE PUÒ INFILTRARE QUALSIASI STRUTTURA CARDIOVASCOLARE:
- SISTEMA DI CONDUZIONE: BLOCCHI (BB, BAV, BSA)
- PARETI VENTRICOLARI E SETTI (SIA) -> FENOTIPO "IPERTROFICO"
- APPARATI VALVOLARI
- PERICARDIO

TRATTAMENTO dell'ATTr



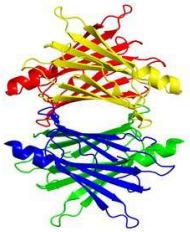
ATTr - CM?



cercare i SEGNI di amiloidosi cardiaca:

te malattia neurologica (o compromissione neu

ATTr - CM?



- **SEGNI e SINTOMI di INSUFFICIENZA CARDIACA SINISTRA**
- **INSUFFICIENZA CARDIACA DESTRA in CARDIOPATIA IPERTENSIVA**
- **ASTENIA**
- **SINCOPE**
- **IPOTENSIONE ORTOSTATICA**
- **STENOSI AORTICA SEVERA LF/LG con EF lievemente ridotta**

OXFORD JOURNALS European Heart Journal

Eur Heart J. 2017 Oct 7; 38(38): 2879–2887.
Published online 2017 Aug 1. doi: 10.1093/eurheartj/ehx350

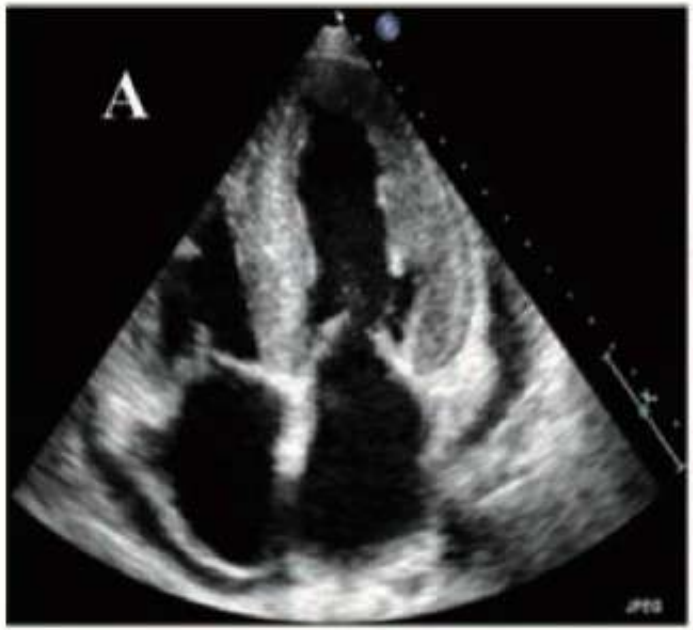
Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement

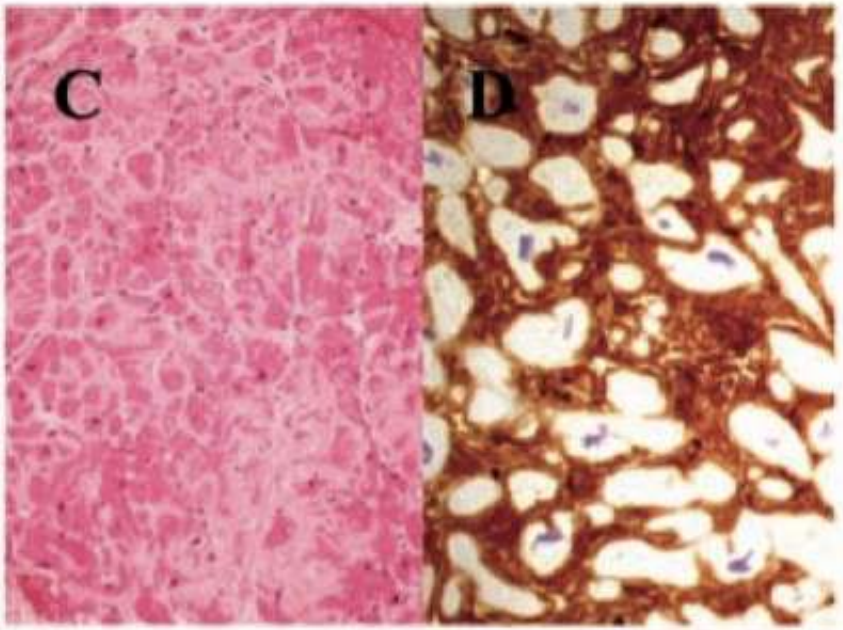
Adam Castaño,[1,2] David L Narotsky,[1] Nadira Hamid,[3] Omar K Khalique,[3] Rachelle Morgenstern,[2] Albert DeLuca,[2] Jonah Rubin,[1] Codruta Chiuzan,[4] Tamim Nazif,[3] Torsten Vahl,[3] Isaac George,[3] Susheel Kodali,[3] Martin B Leon,[3] Rebecca Hahn,[3] Sabahat Bokhari,[2] and Mathew S Maurer[1]

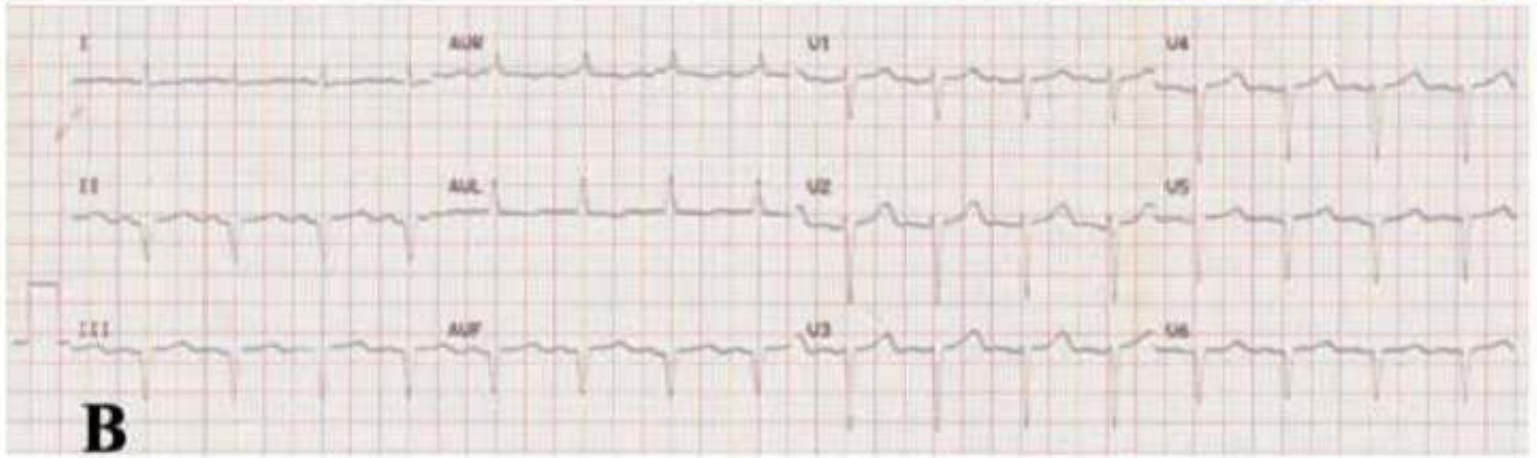
Conclusions

Transthyretin cardiac amyloidosis is prevalent in 16% of patients with severe calcific AS undergoing TAVR and is associated with a severe AS phenotype of low-flow low-gradient with mildly reduced ejection fraction. Average tissue Doppler mitral annular S' of < 6 cm/s may be a sensitive measure that should prompt a confirmatory ^{99m}Tc-PYP scan and subsequent testing for ATTR-CA. Prospective assessment of outcomes after TAVR is needed in patients with and without ATTR-CA.

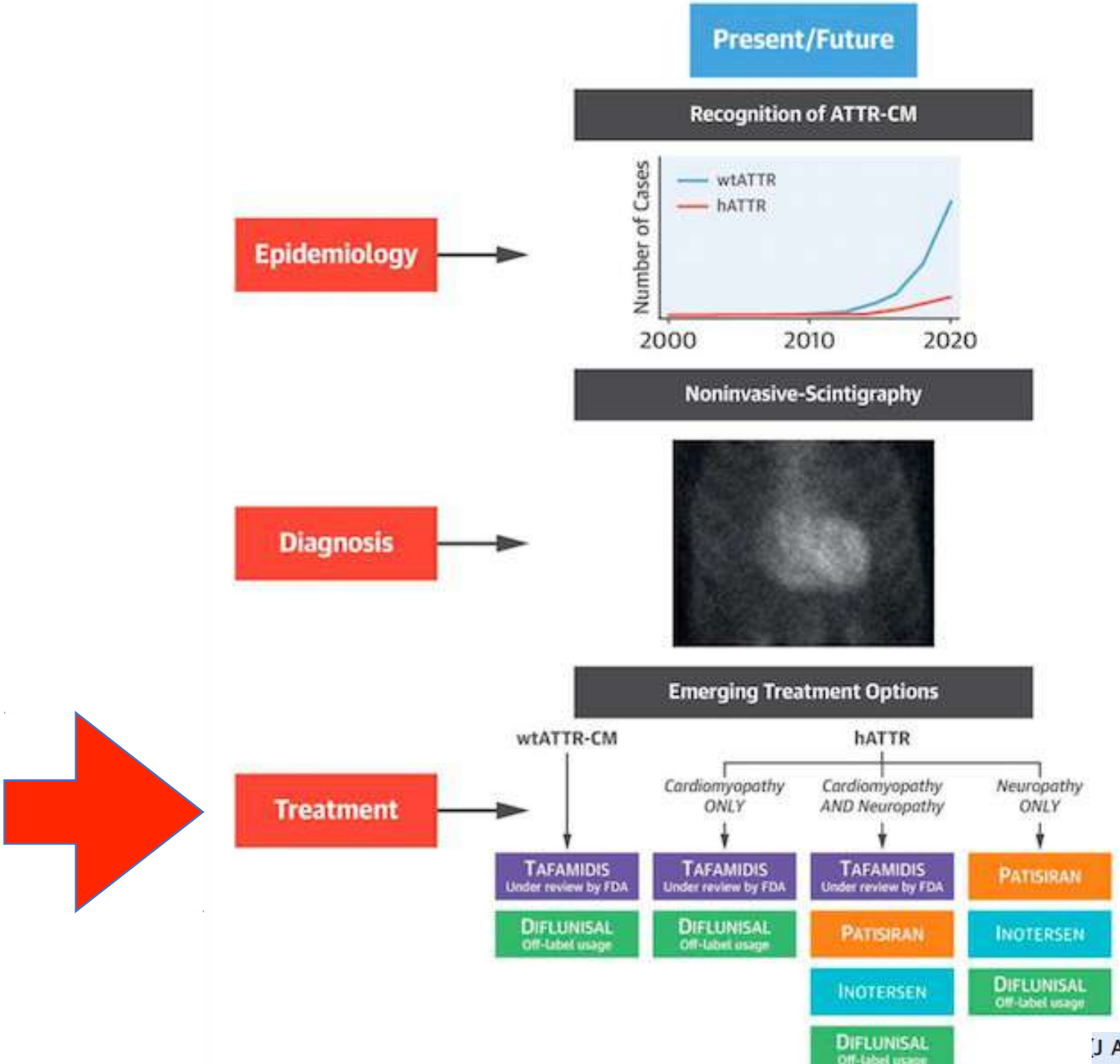
PRINCIPALI ESAMI DIAGNOSTICI



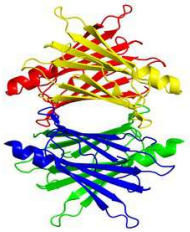




Perchè è importante che il cardiologo sospetti una cardiomiopatia da Amiloidosi TransTiretino-relata (ATTr-CM)?

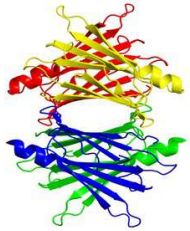


J Am Coll Cardiol 2019;73:2872-91

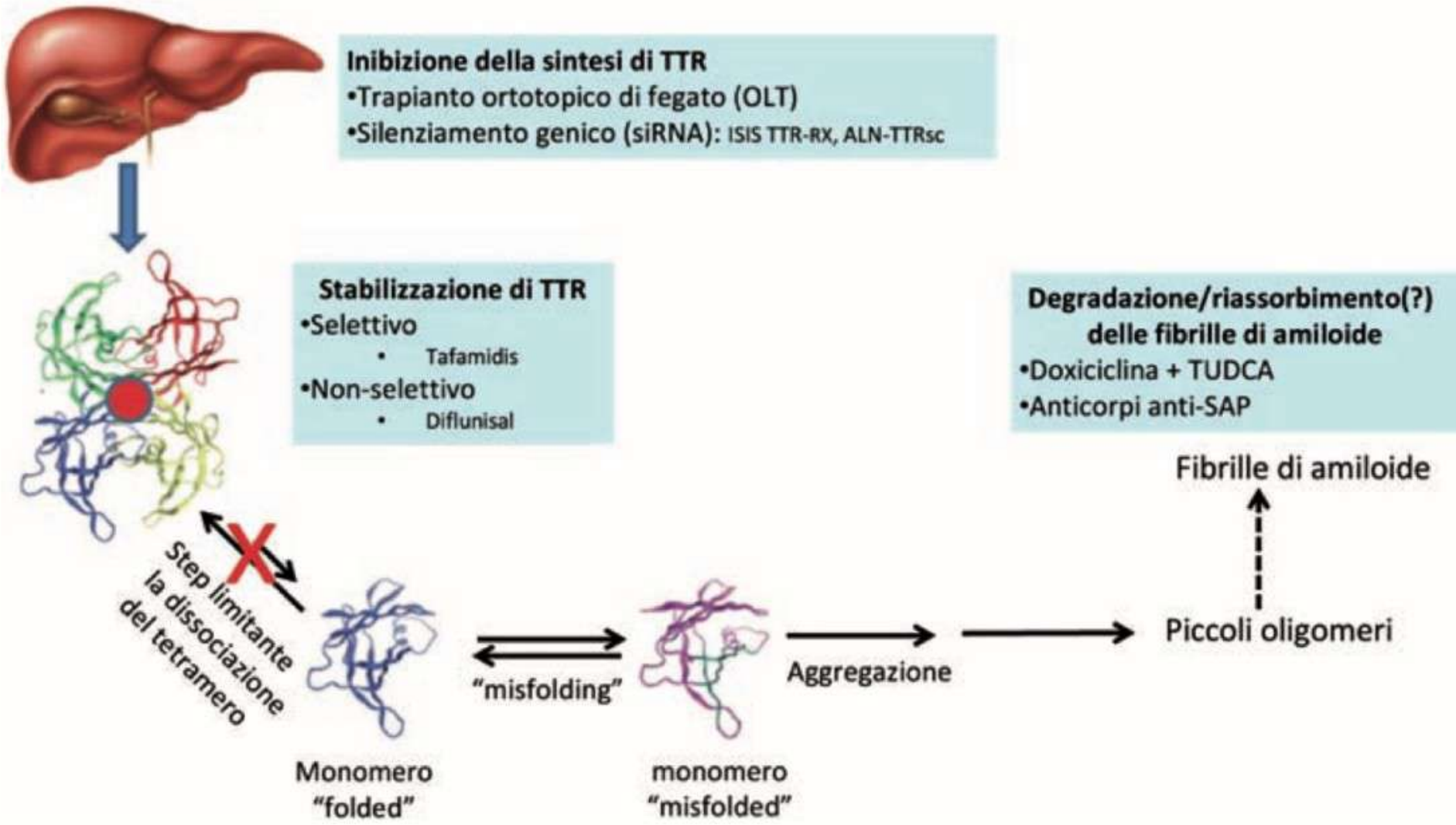


ATTr-CM: the great pretender

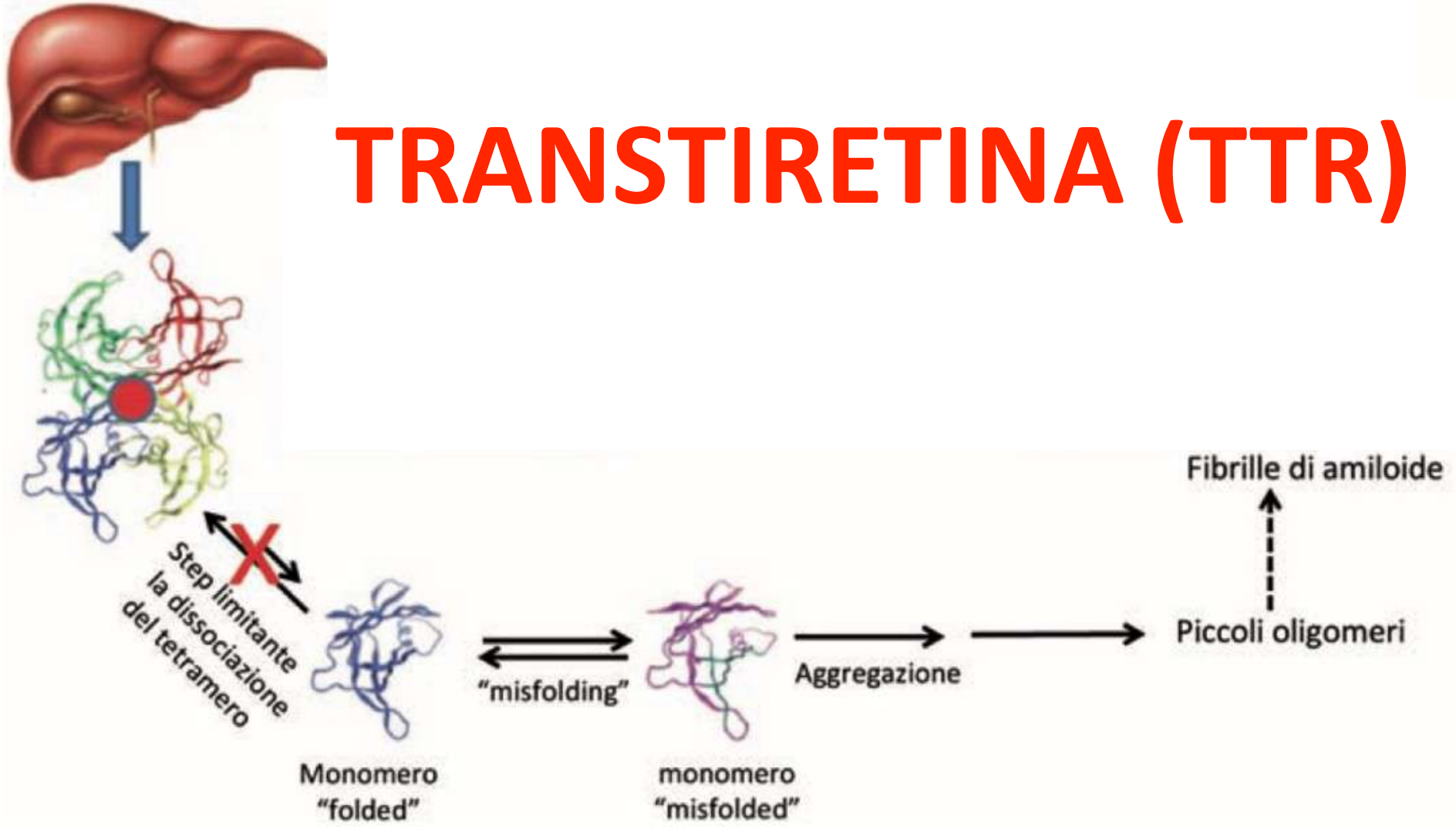
- Challenging
- Fascinating
- Mysterious
- Not as rare as supposed
- Relative easy to detect (when suspected!)
- Treatable !!



TRATTAMENTO DELL'ATTr



TRANSTIRETINA (TTR)



CARATTERISTICHE DELLE TRE FORME DI AMILOIDOSI SISTEMICA AD INTERESSAMENTO CARDIACO E DELLA CARDIOMIOPATIA IPETROFICA

	ATTRm	AL	SSA	CMPI
Spessore parietale VS	Moderatamente aumentato (1.5-2.0 cm)	Lievemente aumentato (1.2-1.5 cm)	Severamente aumentato (1.8-12.2 cm)	Estremamente variabile (1.2-3.5 cm)
Ipertrofia VS	Tendenzialmente simmetrica	Tendenzialmente simmetrica	Tendenzialmente simmetrica	Variabile (asimmetrica, apicale, raramente simmetrica)
Frazione di eiezione VS	Lievemente ridotta	Normale/lievemente ridotta	Moderatamente ridotta	Normale o aumentata
Ipertrofia VD	Frequente	Frequente	Frequente	Possibile
Ispessimento del setto interatriale	Frequente	Frequente	Frequente	Assente
Disfunzione diastolica	Frequente	Frequente	Frequente	Frequente
Ispessimento delle valvole atrioventricolari	Frequente	Possibile	Frequente	Assente
Versamento pericardico	Frequente	Frequente	Frequente	Estremamente raro
Bassi voltaggi del QRS	<25% dei casi	Frequente	<25% dei casi	Estremamente raro
Captazione miocardica di 99mTc-DPD	Forte	Assente o debole	Forte	Assente
Valori di NT-proBNP e troponina cardiaca	Moderatamente aumentati	Severamente aumentati	Moderatamente aumentati	Moderatamente aumentati

up to 5% of the
population >65 years of age have a monoclonal gammopathy
of undetermined significance.

- up to 5% of the population >65 years of age have a monoclonal gammopathy of undetermined significance

Avoiding misdiagbosis with AL amyloidosis

misdiagnosis of AL-CA in elderly patients who actually
have TTR-related CA and monoclonal gammopathy
of undetermined significance (up to 10% of misdiagnosis
even in referral centers).49

misdiagnosis of AL-CA in elderly patients who actually have TTR-related CA and monoclonal gammopathy of undetermined significance (up to 10% of misdiagnosis even in referral centers).49

AL, serum and urine
immunofixation and quantification of serum free light
chains in combination have a 99% sensitivity for identifying
the underlying substrate for AL-CA. It is important to
note that an abnormal free light chain ratio alone is not
specific for AL amyloidosis, -> always PTP SPECT

AL, serum and urine
immunofixation and quantification of serum free light
chains in combination have a 99% sensitivity for identifying
the underlying substrate for AL-CA. It is important to
note that an abnormal free light chain ratio alone is not
specific for AL amyloidosis, -> always PTP SPECT

Natriuretic peptides tend to be
particularly high in CA, often out of proportion from the
hemodynamic burden.53 Circulating light chains exert a
direct toxic effect by modulating p38 mitogen-activated
protein kinase, which can directly promote NT-pro-BNP
expression.54–56 Thus, for the same range of hemodynamic
abnormalities, plasma levels of NT-pro-BNP are
higher in AL than in ATTRwt and ATTRm.

ATTR-CA: physiopathology

Physiopathology

Progressive left ventricular dysfunction in ATTR-CA is mediated by physiological derangements that include reduction in chamber capacitance, declines in chamber contractility, and increases in arterial elastance. (cit 43)

blood pressure falls because of a reduction in cardiac output and heart rate increases to compensate for a reduced stroke volume.

Cardiac cachexia is particularly common with ATTR-CA, potentially mediated, in part, by right heart failure, liver congestion, and possibly alterations in bowel flora.

Amyloidosis is the archetype for diastolic LV dysfunction, with findings dependent on the stage of disease.65 Early cardiac involvement is often associated with impairment of relaxation that progresses to typical restrictive LV pathophysiology in advanced symptomatic disease.

Analogous changes in right ventricular diastolic function occur in the right ventricular inflow, superior vena cava, and hepatic vein flow velocities.66 CA is often listed as a cause of heart failure with preserved ejection fraction, but this underplays its impact on ventricular systolic performance.7,39,67–70 Although LV ejection fraction may be normal until the advanced stage of disease, reduction in peak systolic wall motion velocities, especially in the longitudinal axis, are present even in early disease.71 In general, CA alters strain parameters to a much greater degree than other causes of LV hypertrophy and is characterized

Circulation. 2017;13

A) QUANTO FREQUENTEMENTE LA DIAGNOSI E PERSA O RITARDATA?

B) perché QUESTO AVVIENE?

1. n addition, the absence of disease-modifying therapies for A late presentation of AL-CA patients have contributed to a nihilistic attitude about the condition.

2. The main disease-related factor that hinders a correct and timely diagnosis is heterogeneity with respect to the cardiac phenotype, and systemic involvement, as well.

3. The need for a histological demonstration of target organ amyloid infiltration has also delayed the diagnosis as the technique is restricted to referral centers with expertise in the performance of endomyocardial biopsy and requires skilled pathological analysis of obtained samples.

When to suspect cardiac amyloidosis?

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.

INCREASED AWARENESS OF CARDIAC AMYLOIDOSIS IS ESSENTIAL TO REDUCE UNDERDIAGNOSIS AND MISDIAGNOSIS

Multimodality evaluation of ATTR-CA

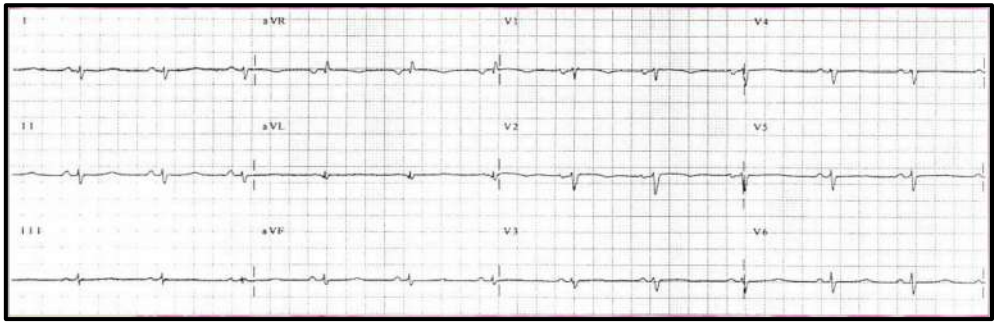
Phase of Workup	Imaging and Biomarkers of Cardiac Amyloidosis			
	ECHO	MRI*	"Bone Tracers" Scintigraphy	BNP
Suspicion	+++	++	+/– (TTR)	++
Early diagnosis	+/–	++	++ (TTR)	+/–
Definite diagnosis	+/–	+/–	+++	+/–
Etiologic diagnosis	+/–	+/–	+++ (TTR)	–
Functional evaluation	+++	++	+ (MIBG)	+/–
Prognostic stratification	++	+	+	+++
Amyloid burden	–	++	+/–	–
Response to therapy	+/	+/–	+/–	+++ (AL)

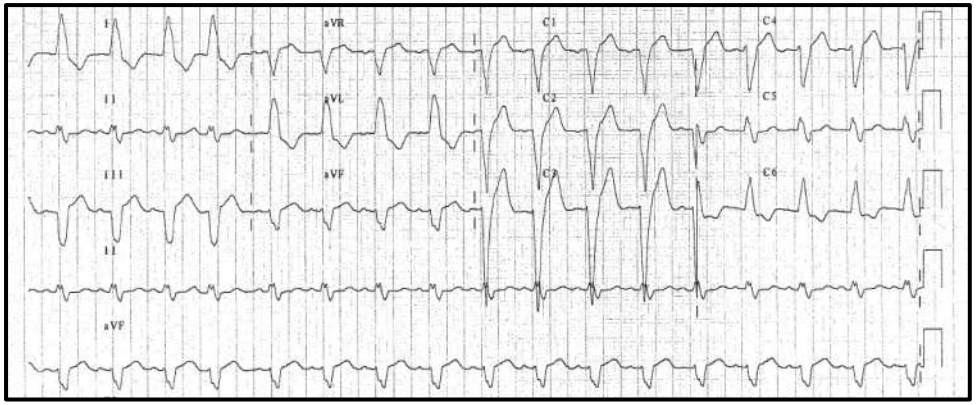
THERE IS NO «BEST EXAMINATION» IN ATTR-CA
each examination best suit specific questions relative to different steps of the diagnostic and therapeutic pathway

ECG in ATTR-CA

	ATTRwt
ECG	
n	15
Atrial fibrillation, n (%)	4 (27)
Pacemaker, n (%)	2 (13)
First-degree atrioventricular block, n/N (%)	5 (33)
Total QRS score, mV (n)	19.7±37.3 (15)
Low QRS voltage, n/N (%)	6 (40)
Right bundle-branch block, n/N (%)	2 (13)
Left bundle-branch block, n/N (%)	6 (40)
Left anterior hemiblock, n/N (%)	3 (20)
LV hypertrophy (Sokolow >35 mm), n/N (%)	1 (6)
Presence of any infarct pattern, n/N (%)	10 (66)
"Ischemic pattern" (negative T waves), n/N (%)	6 (40)
QTc, ms (n)	465±37 (15)
Normal ECG, n (%)	0 (0)

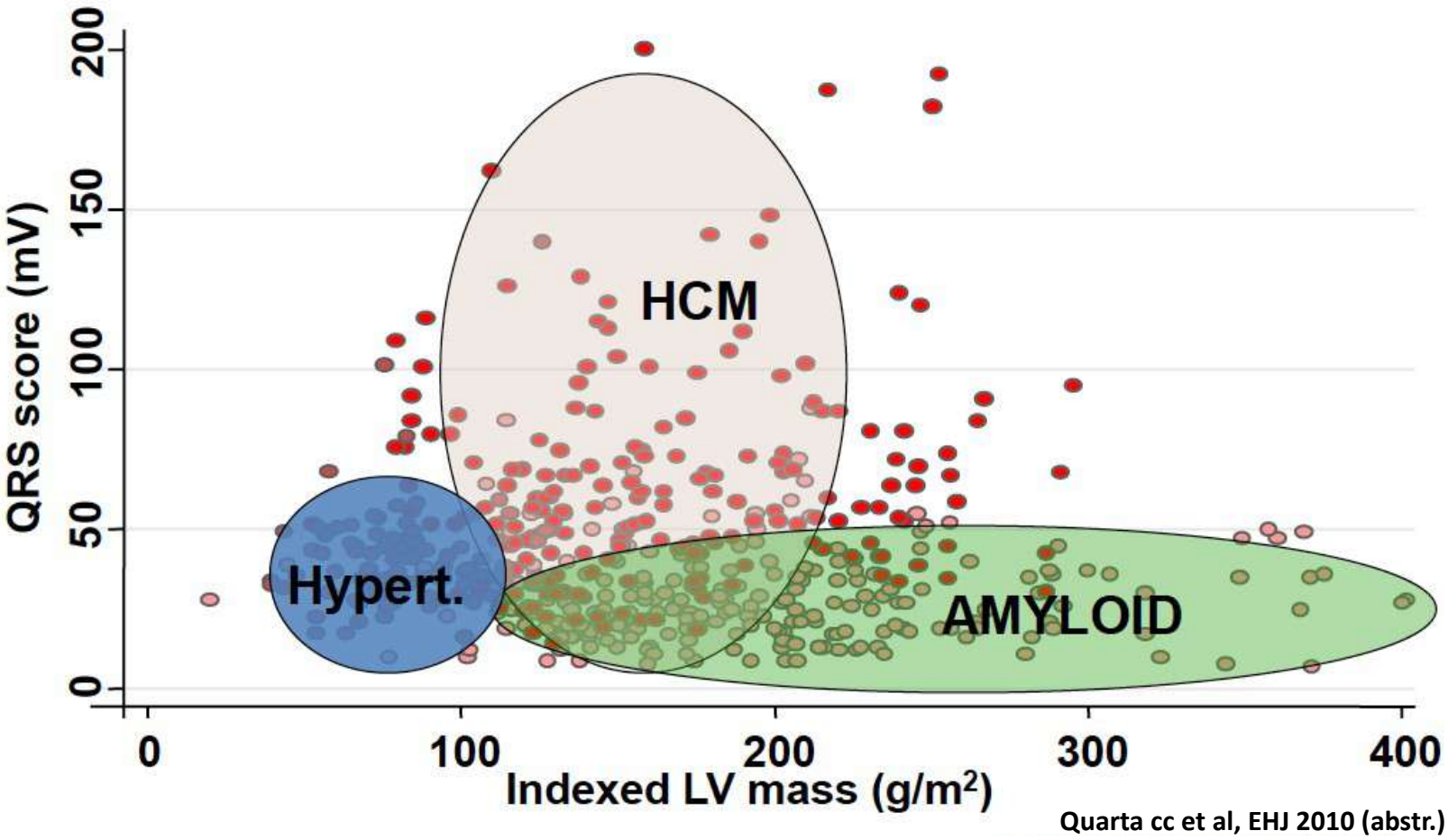
Rapezzi C et al, Circulation 2009:120:1203-1212





- **Absence of low QRS voltage does not rule-out ATTR-CA**
- **Common pseudoinfarct-like pattern**
- **Always suspect ATTR-CA in elderly patients with hypertrophy and AV block, especially if normotensive**

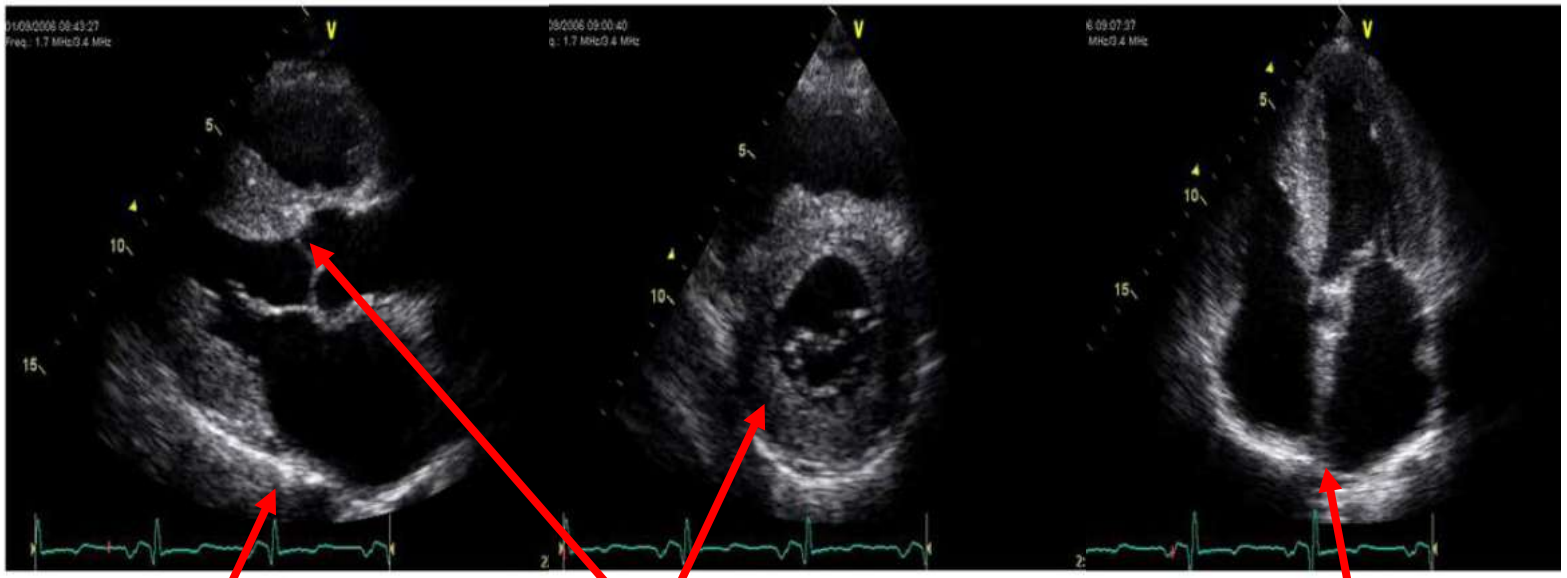
VOLTAGE/MASS INDEX in patients with increased LV wall thickness



Quarta cc et al, EHJ 2010 (abstr.)

The hallmark of CA is the disproportion between LV wall thickness and QRS voltages

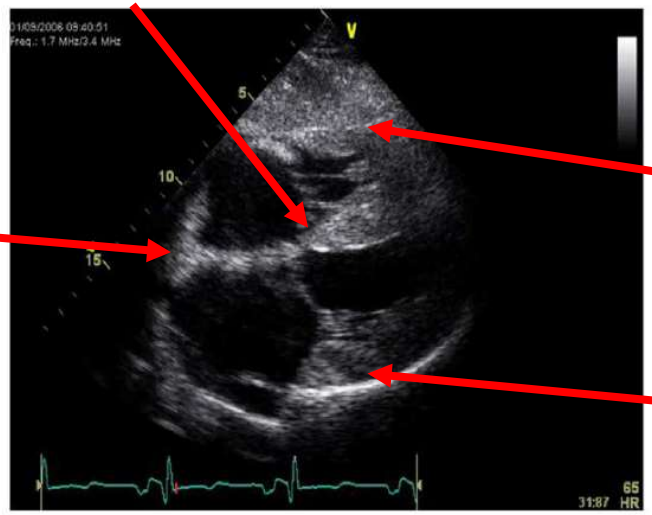
Echocardiogram in ATTR-CA (1)



Left atrial dilatation

Bright myocardium and concentric symmetrical LVH

Biatrial dilatation



Thickened interatrial septum

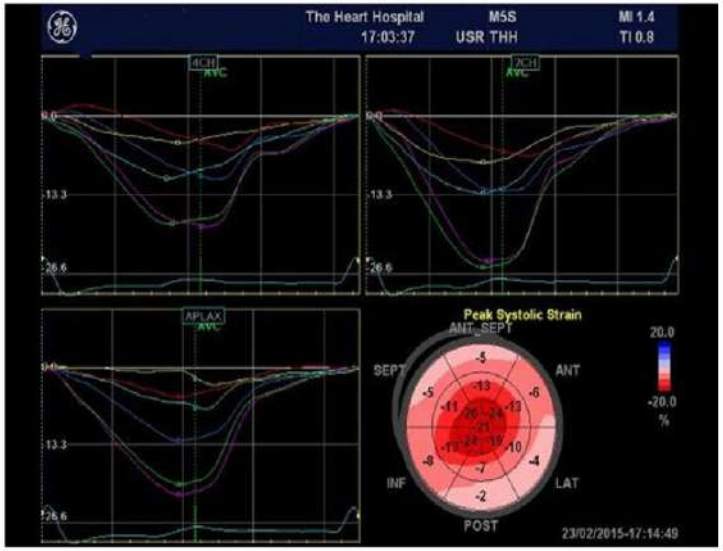
Thickening of RV free wall

Thickened valves

Circulation. 2017;135:1357–1377. DOI: 10.1161/CIRCULATIONAHA.116.024438

Echocardiogram in ATTR-CA (2)

STRAIN ECHO

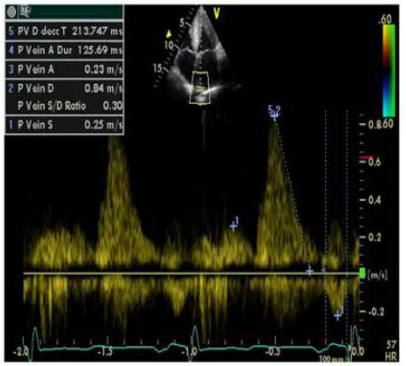


Impaired sistolic longitudinal shortening, with a base-apex gradient

DOPPLER WAVES

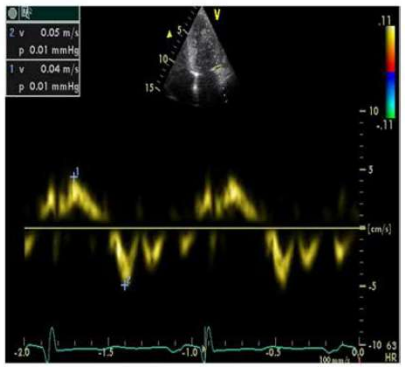
Mitral inflow PW Doppler

- Increased E/A ratio
- Normal E wave decT time
- Marked reduction in transmitral A-wave velocity



Pulm. vein inflow PW Doppler

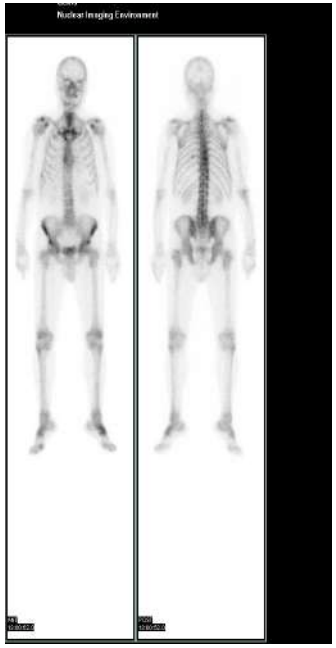
- Diastolic atrial reversal with increased duration and peak velocity as compared to transmitral signal



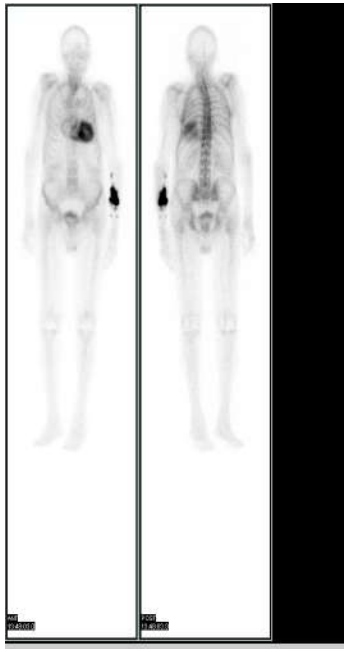
Mitral annulus tissue Doppler

- Marked reduction in apical systolic and diastolic velocities

Bone tracer scintigraphy in ATTR-CA



Healthy control



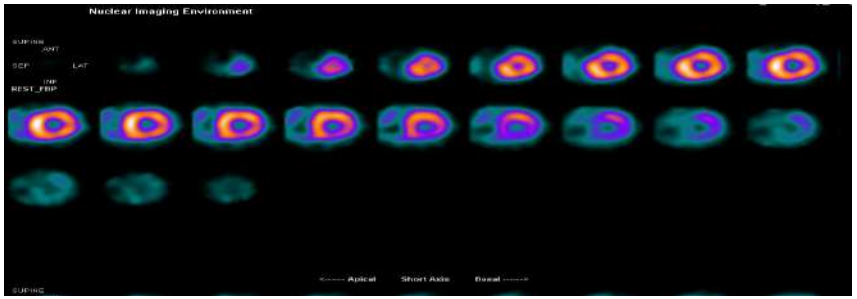
ATTR-CA

Perugini Score

Visual Cardiac Score

0 Absent Myocardial Uptake
1 Myocardial Uptake < Bone
2 Myocardial Uptake = Bone
3 Myocardial Uptake > Bone

Quantitative and regional assessment



Courtesy of Dr.ssa Casoni

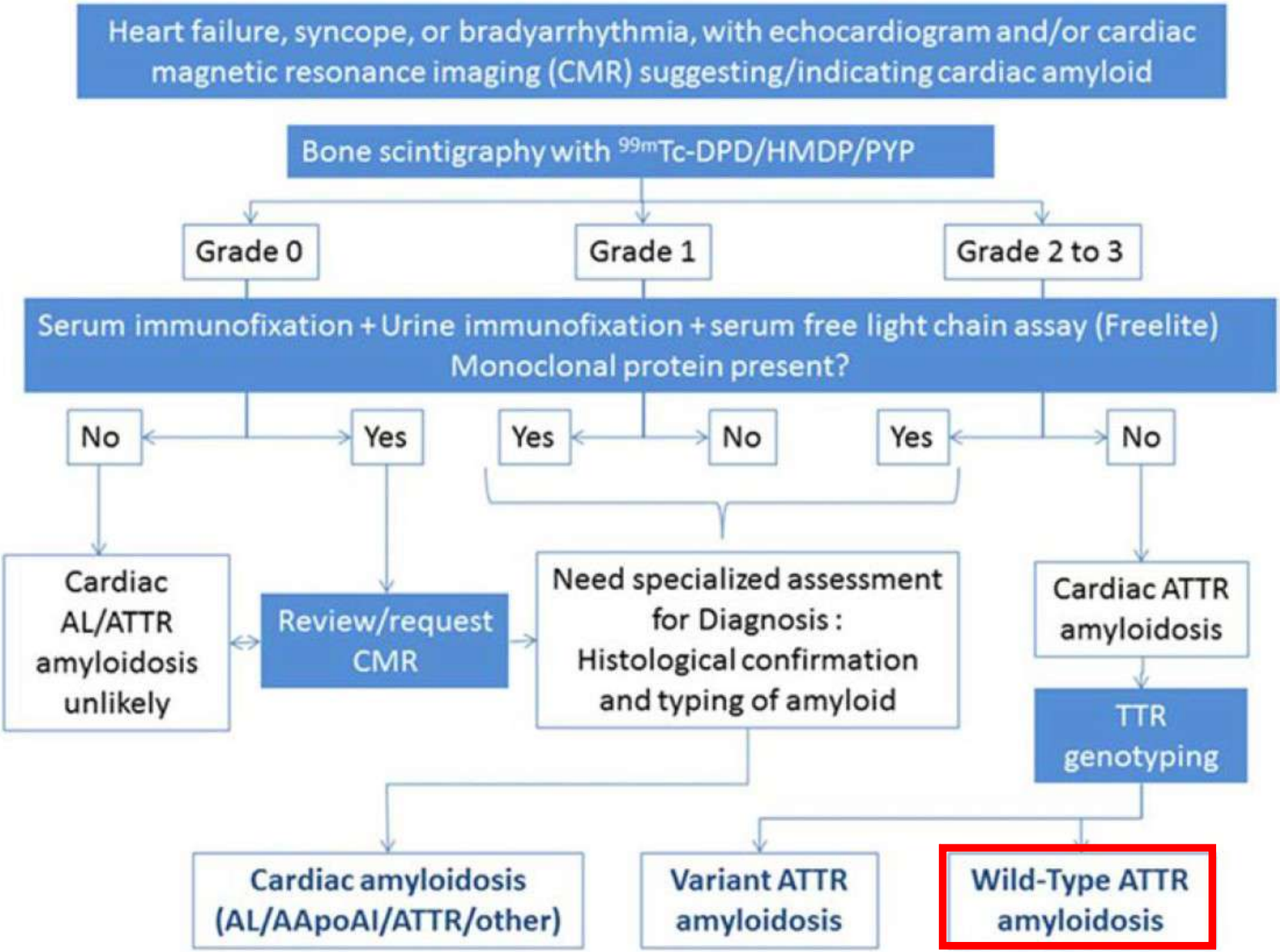
Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

Julian D. Gillmore, MD, PhD; Mathew S. Maurer, MD; Rodney H. Falk, MD; Giampaolo Merlini, MD; Thibaud Damy, MD; Angela Dispenzieri, MD; Ashutosh D. Wechalekar, MD, DM; John L. Berk, MD; Candida C. Quarta, MD, PhD; Martha Grogan, MD; Helen J. Lachmann, MD; Sabahat Bokhari, MD; Adam Castano, MD; Sharmila Dorbala, MD, MPH; Geoff B. Johnson, MD, PhD; Andor W.J.M. Glaudemans, MD, PhD; Tamer Rezk, BSc; Marianna Fontana, MD; Giovanni Palladini, MD, PhD; Paolo Milani, MD; Pierluigi L. Guidalotti, MD; Katarina Flatman; Thirusha Lane, MSc; Frederick W. Vonberg, MBBS; Carol J. Whelan, MD; James C. Moon, MD; Frederick L. Ruberg, MD; Edward J. Miller, MD, PhD; David F. Hutt, BApSc; Bouke P. Hazenberg, MD, PhD; Claudio Rapezzi, MD; Philip N. Hawkins, PhD, FMedSci

Circulation. 2016;133:2404–2412.
doi: 10.1161/ CIRCULATIONAHA.116.021612.

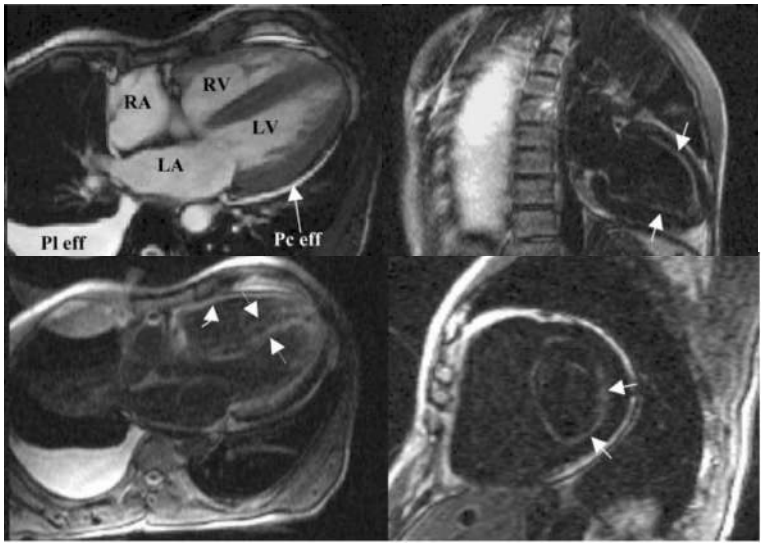
- **>99% sensitive and 86% specific for ATTR-CA**
- **false positives almost exclusively from uptake in patients with cardiac AL amyloidosis**
- **Grade 2-3 Perugini score + the absence of a monoclonal protein: 100% Sp and PPV**

Nonbiopsy diagnosis of ATTR-CA (2)



Cardiac MRI in ATTR-CA (2)

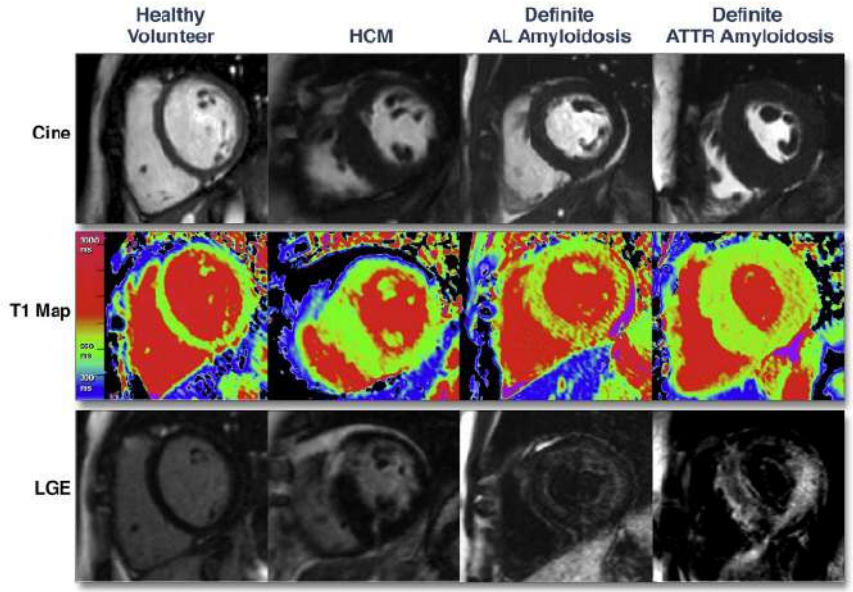
Contrast-based CMR



https://doi.org/10.1161/01.CIR.0000152819.97857.9D
Circulation. 2005;111:186–193

- Diffuse subendocardial enhancement
- «Zebra appearence» (septal biventricular subendocardial enhancement)
- Dark blood pool (abnormal gadolinium handling in CA patients)

Parametric non-Contrast-based CMR (T1-mapping)

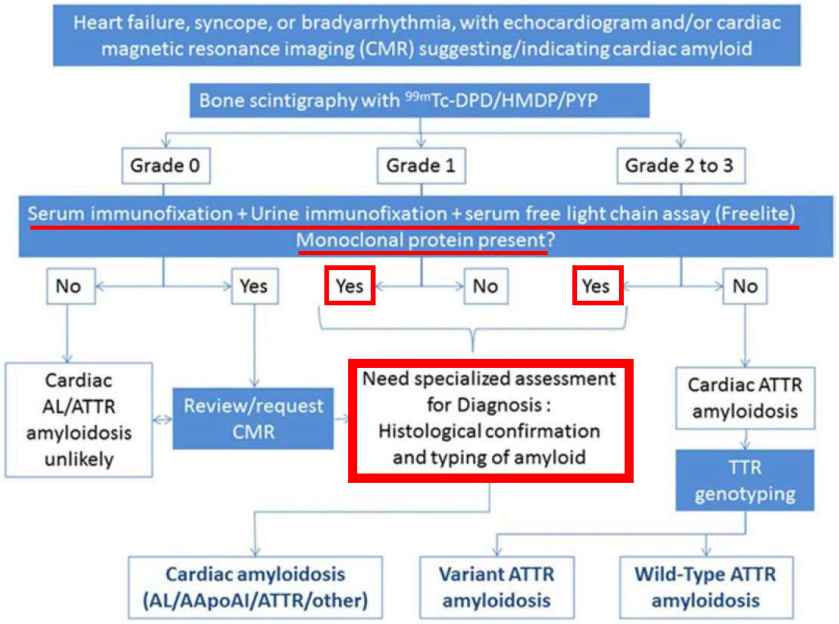


M. Fontana et al. Native T1 Mapping in Transthyretin Amyloidosis. JACC Cardiovasc Imaging. 2014

- Increased T1 signal in MOLLY sequences
- Differential diagnosis of AL/ATTR-CA /HCM

False pos/neg 15-20% -> Does not substitute bone scintigraphy for diagnosis, but useful for (a) therapy response, (b) prognostic stratification

When and How Should Tissue Biopsy BeUndertaken?



- Positive 99mTc-phosphate scan without evidence for plasma clone on blood and urine testing -> **diagnosis of ATTR-CA without a biopsy**

- Positive 99mTc-phosphate scan without evidence for plasma clone on blood and urine testing -> **histological diagnosis is still required because the uptake on a 99mTc-phosphate scan is not 100% specific for ATTR-CA**.

EXTRACARDIAC BIOPSY *(abdominal fat pad, gingiva, skin, salivary gland, or gastrointestinal tract*

Diagnostic accuracy:

- 70% for AL-CA / 67% for ATTRm / 14% for ATTRwt

Fine NM et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. Am J Cardiol. 2014;113:1723–1727. doi: 10.1016/j.amjcard.2014.02.030.

although a fat pad biopsy is a preferred initial site, a negative result is insufficient to exclude the diagnosis

CARDIAC BIOPSY

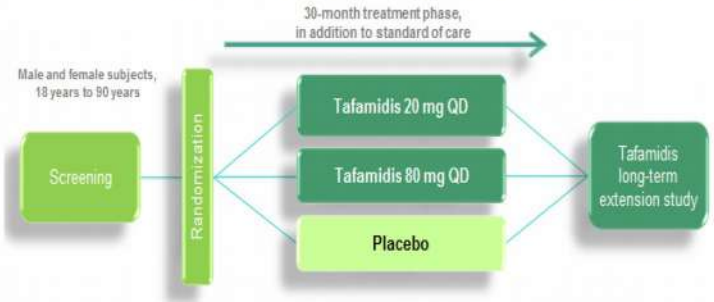
Tissue diagnosis is required for AL amyloid and endomyocardial biopsy should be pursued if the index of suspicion is high despite a negative fat pad.

ATTR-CA treatment

ORIGINAL ARTICLE

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

ATTR-ACT Study Design



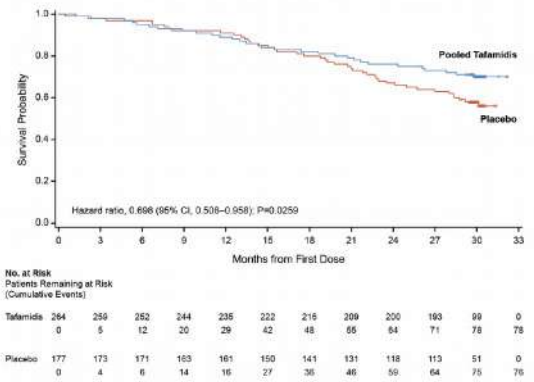
- Patients randomized 2:1:2 to tafamidis 80 mg, tafamidis 20 mg, and placebo
- Stratification for genotype (wild-type or variant) and disease severity (NYHA class)
- A sample size of 400 pts was estimated to give 90% power to detect either a 30% reduction in mortality, or a reduction in the frequency of CV-related hospitalizations from 2.5 to 1.5, or both

ESC Congress
Munich 2018

All-cause Mortality-Cox Proportional Hazard Model

30% reduction in the risk of all-cause mortality with tafamidis compared with placebo

Heart transplant and implantation of a cardiac mechanical assist device were treated as death for this analysis



Key Secondary Endpoints: 6-minute Walk Test and KCCQ-OS