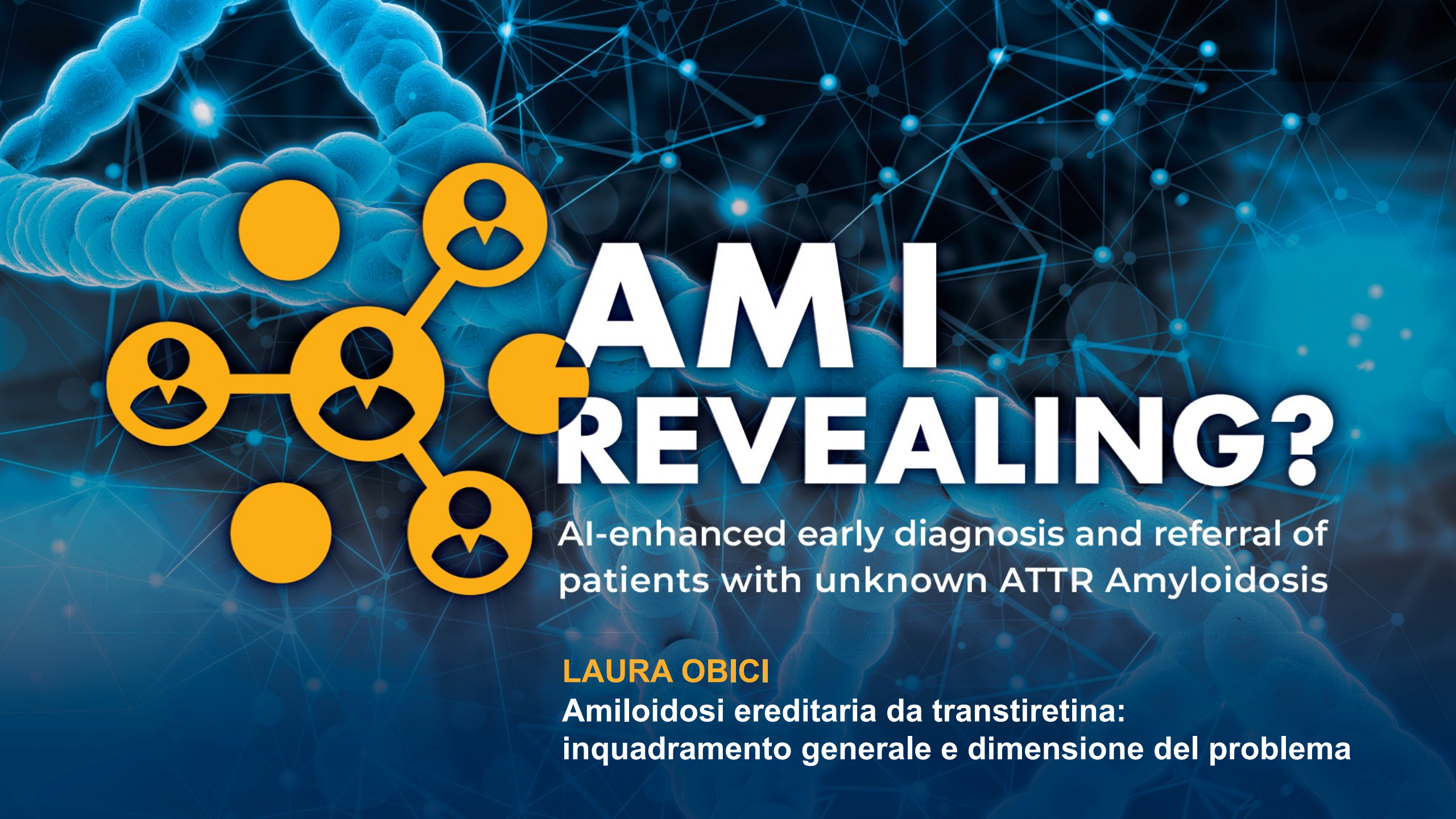
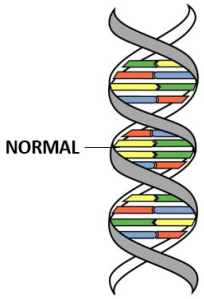


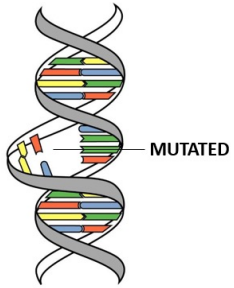
LAURA OBICI

Amiloidosi ereditaria da transtiretina: inquadramento generale e dimensione del problema



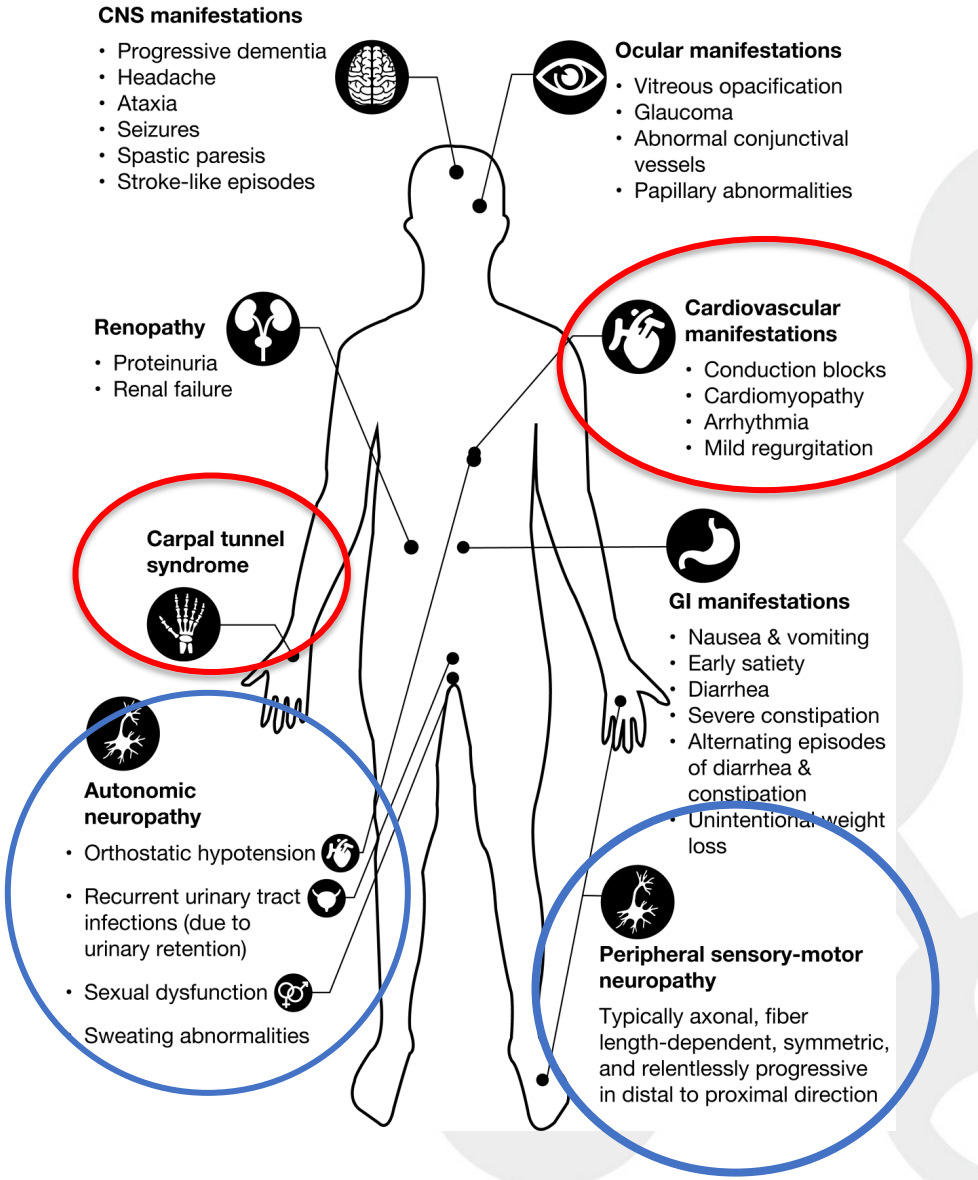
wt ATTR amyloidosis

- Non-hereditary, progressive disease
- Age-related, male prevalence
- Predominantly manifests as cardiomyopathy



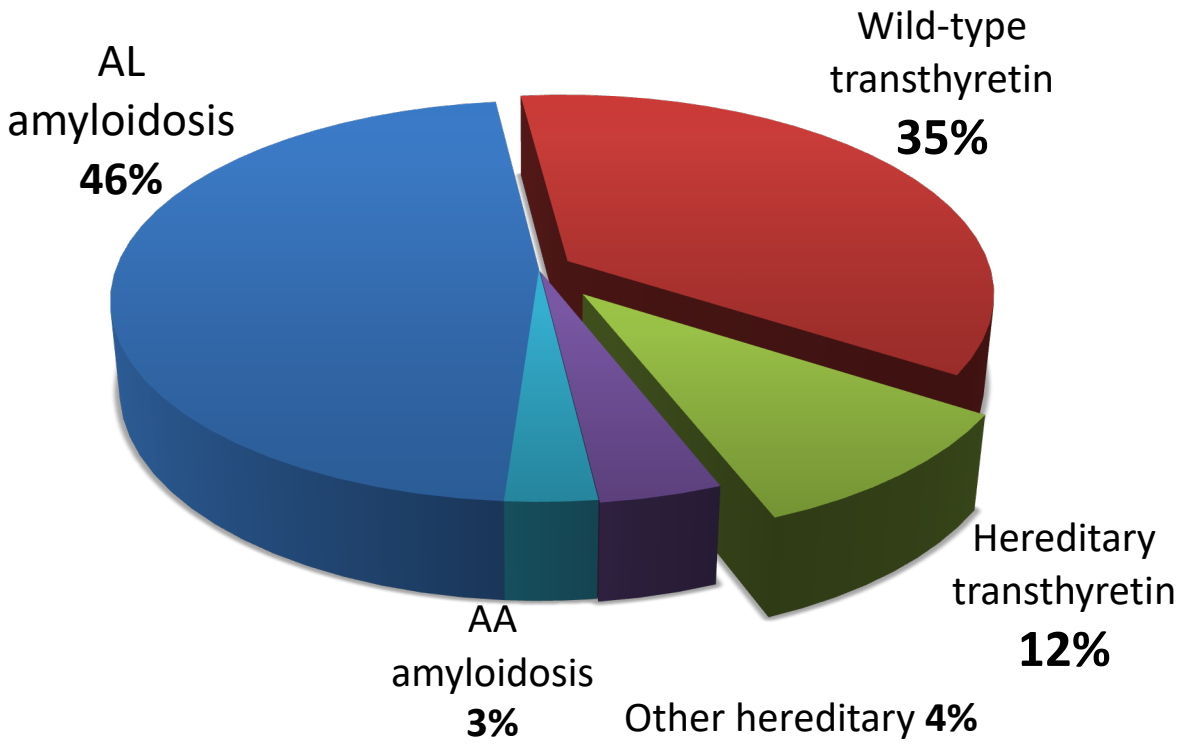
hereditary ATTR amyloidosis

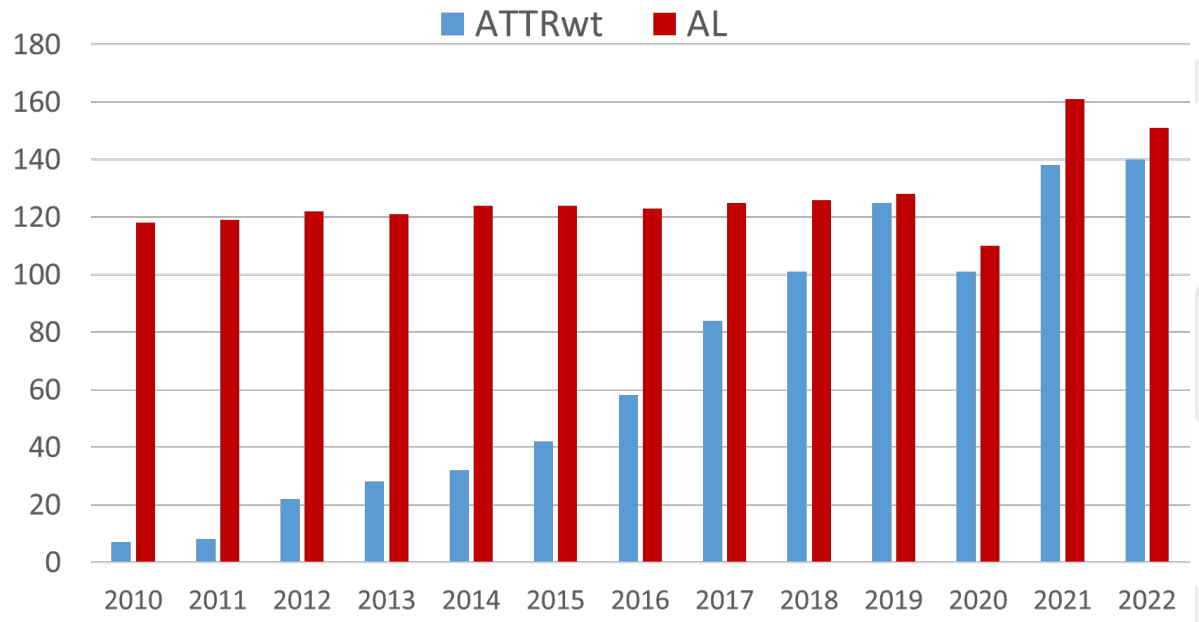
- Inherited, rapidly progressive disease caused by *TTR* gene mutation
- Multisystem disease that manifests with a combination of polyneuropathy, cardiomyopathy, GI, renal, and ocular dysfunction



Transthyretin amyloidosis (ATTR): an emerging disease

≈ 1600 patients followed-up in Pavia





Pavia Amyloidosis Centre Experience

International Journal of Cardiology 335 (2021) 123–127

Contents lists available at ScienceDirect

International Journal of Cardiology

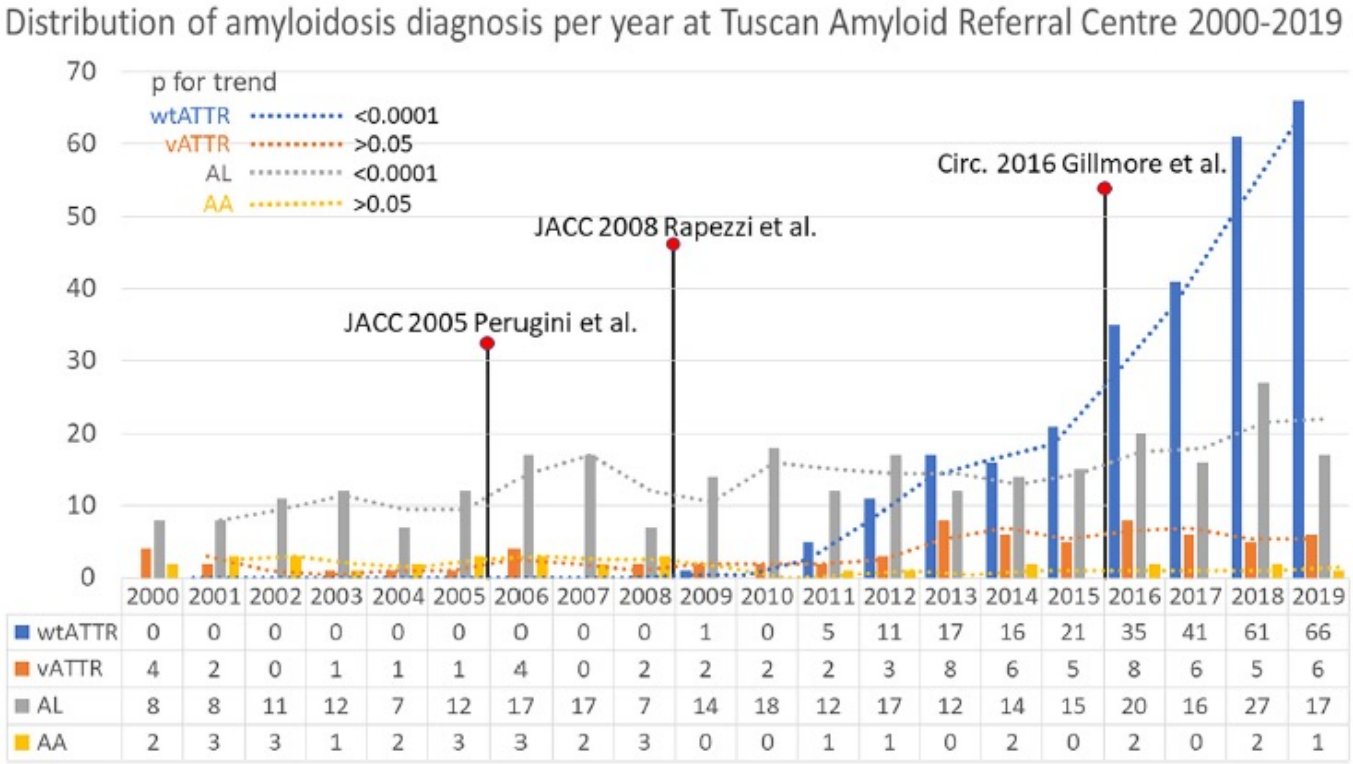
journal homepage: www.elsevier.com/locate/ijcard

Changes in the perceived epidemiology of amyloidosis: 20 year-experience from a Tertiary Referral Centre in Tuscany

Mattia Zampieri [a,b,*], Giulia Nardi [a], Guido Del Monaco [a], Marco Allinovi [a], Martina Gabriele [a], Chiara Zocchi [a,b], Silvia Casagrande [a], Carlo Fumagalli [b,c], Carlo Di Mario [d], Iacopo Olivotto [b], Federico Perfetto [a,e], Francesco Cappelli [a,d]

2000-2019
(n=654)

274 wtATTR
68 vATTR
281 AL
31 AA



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
wtATTR	0	0	0	0	0	0	0	0	0	1	0	5	11	17	16	21	35	41	61	66
vATTR	4	2	0	1	1	1	4	0	2	2	2	2	3	8	6	5	8	6	5	6
AL	8	8	11	12	7	12	17	17	7	14	18	12	17	12	14	15	20	16	27	17
AA	2	3	3	1	2	3	3	2	3	0	0	1	1	0	2	0	2	0	2	1

Fig. 1. Diagnoses of Amyloidosis over a 20-year period at Careggi University Hospital, tertiary referral centre for amyloidosis. Figure shows number of diagnosis of different subtypes of amyloidosis per year, from 2000 to 2019. Dashed lines show diagnosis moving average trend lines for each amyloidosis subtypes. Wild type transthyretin-associated amloidosis (wtATTR) and light chain amyloidosis (AL) number of diagnosis increased significantly during study period (p for trend < 0.0001). Abbreviations: AA serum amyloid A amyloidosis, AL light chain amyloidosis, vATTR genetic variant transthyretin-associated amloidosis, wtATTR wild type transthyretin-associated amloidosis.

International Journal of Cardiology 382 (2023) 87–90

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International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Short communication

Prevalence of transthyretin-related amyloidosis in Tuscany: Data from the regional population-based registry

Francesco Cappelli [a,b,1], Annamaria Del Franco [a,b,1], Giuseppe Vergaro [c,d], Carlotta Mazzoni [a,b,*], Alessia Argirò [a,b], Maurizio Pieroni [e], Elisa Giacomin [f], Serena Poli [g], Marco Allinovi [h], Iacopo Olivotto [a,b,i,j], Federica Pieroni [k], Cristina Scaletti [l,m,n], Michele Emdin [c,d], Federico Perfetto [a]

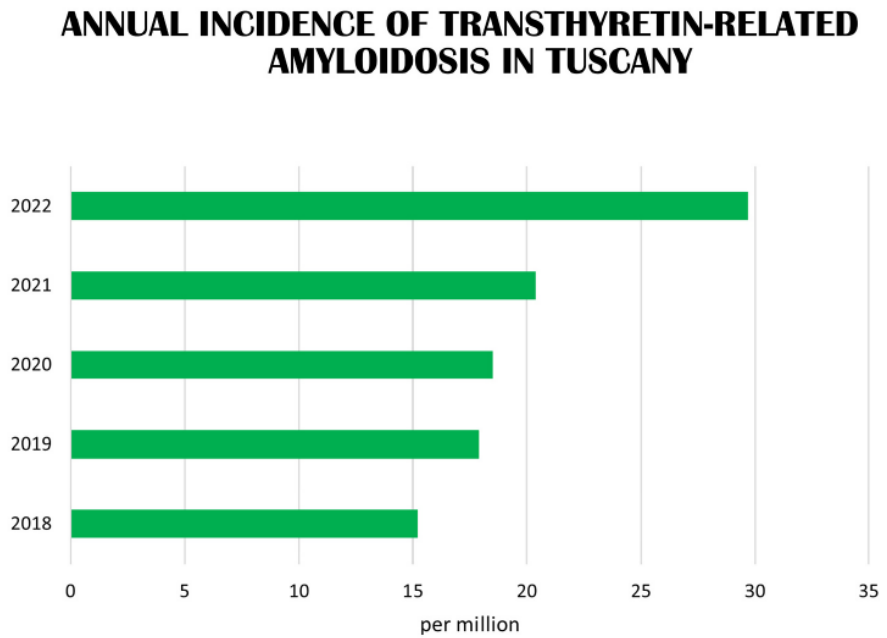


Fig. 2. Annual incidence of transthyretin-related amyloidosis in Tuscany region, for the period from 2018 to 2022.

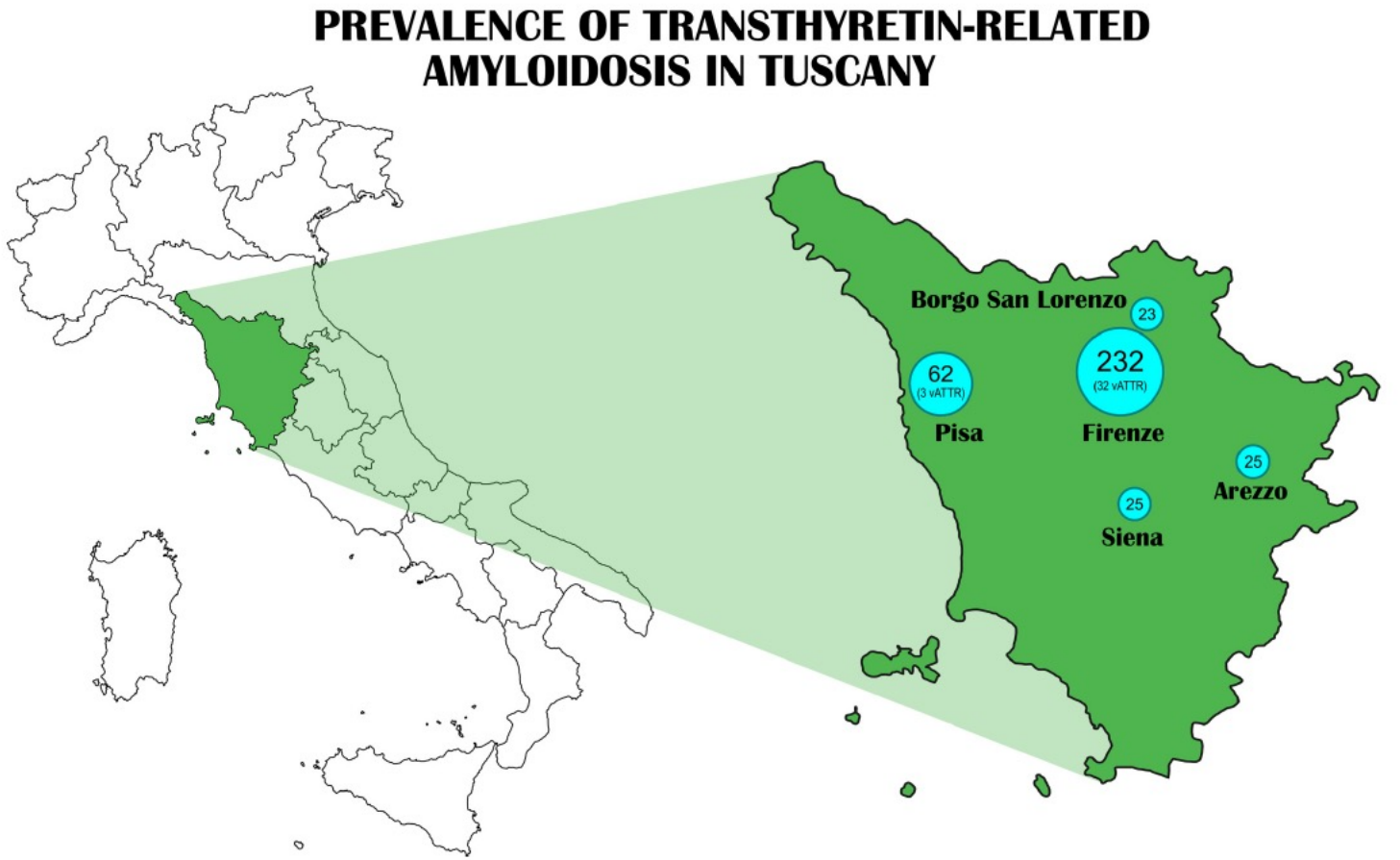
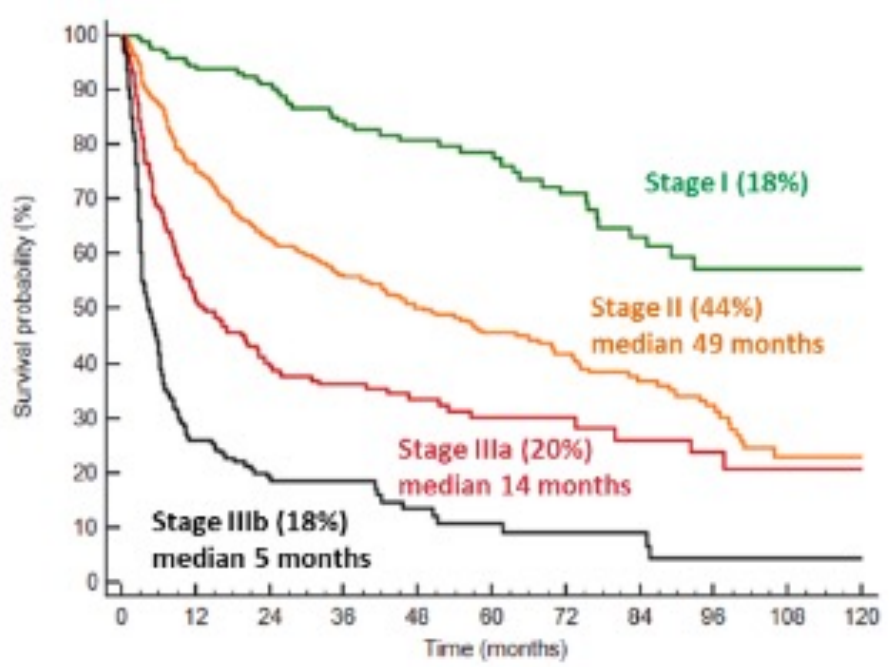


Fig. 1. Geographical distribution in Tuscany region of the centres involved in the management of patients with transthyretin-related amyloidosis and related numbers of alive patients regularly followed. Numbers in brackets indicate the subset of patients with the hereditary form.

Heart involvement is the major determinant of survival

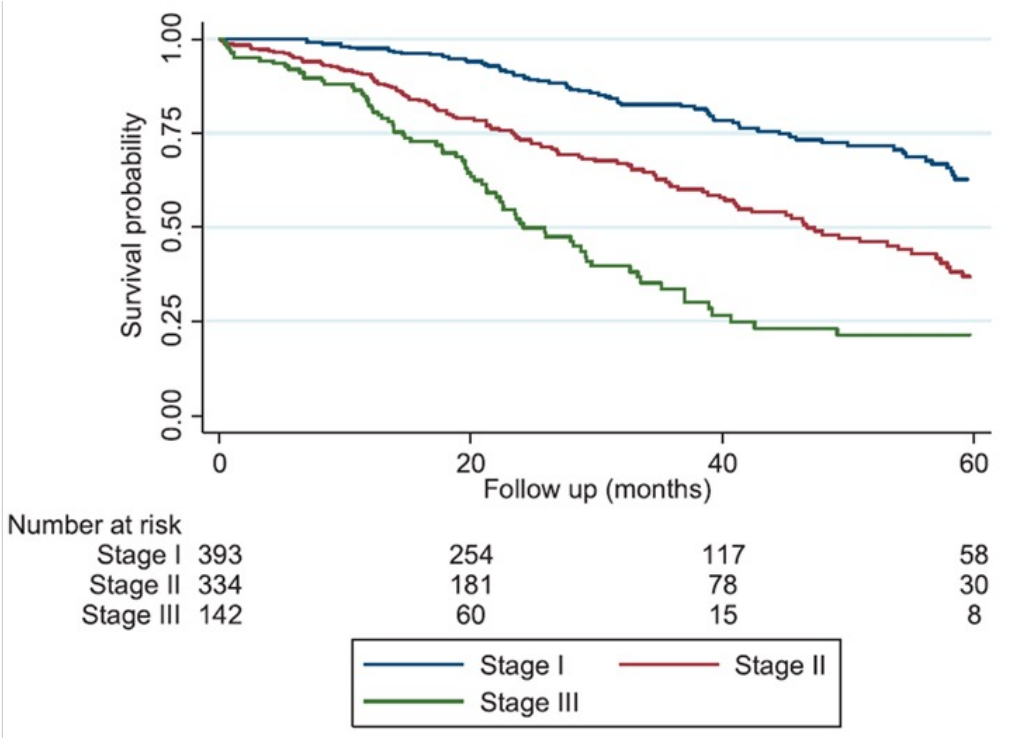
Mayo Clinic / European staging system for AL amyloidosis



Staging is based on **NT-proBNP (cutoff 332 ng/L)** and **troponin I (cutoff 0.1 ng/mL)** with stage I, II, and III patients having 0, 1, or 2 markers above the cutoffs.

Very high (>8500 ng/L) NT-proBNP identifies patients with advanced cardiac dysfunction (Stage IIIb)

European staging system for ATTR amyloidosus

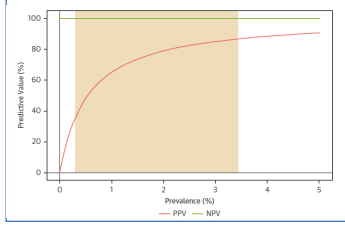


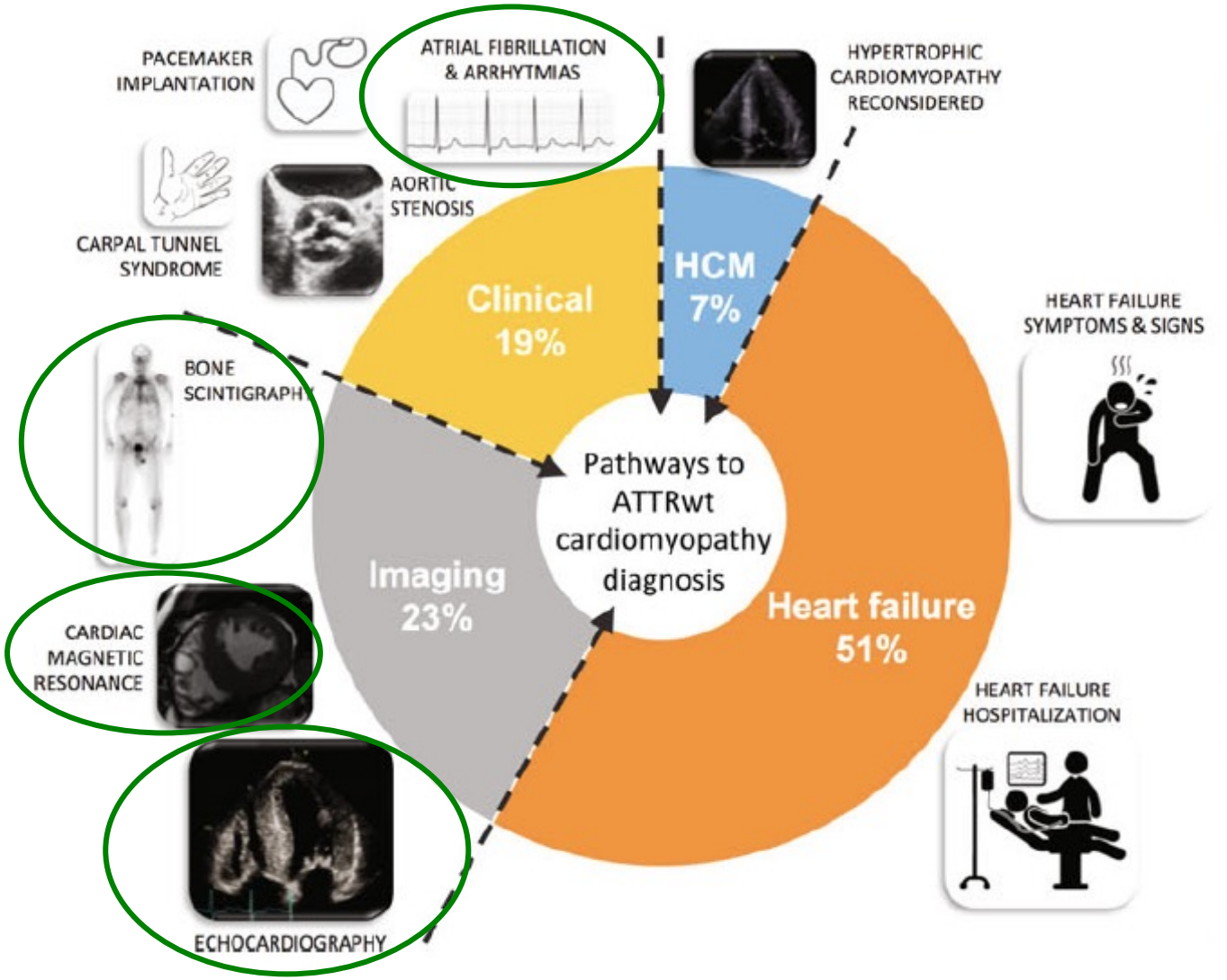
Staging is based on **NT-proBNP (cutoff 3000 ng/L)** and **eGFR (cutoff 45 mL/min)** with stage I, II, and III patients having 0, 1, or 2 markers above the cutoffs

Dispenzieri, et al. JCO 2004, Wechalekar, et al. Blood 2013, Palladini, et al. Blood 2015, Gillmore et al. Eur Heart J 2017

Diagnostic pathways to wild-type transthyretin amyloid cardiomyopathy

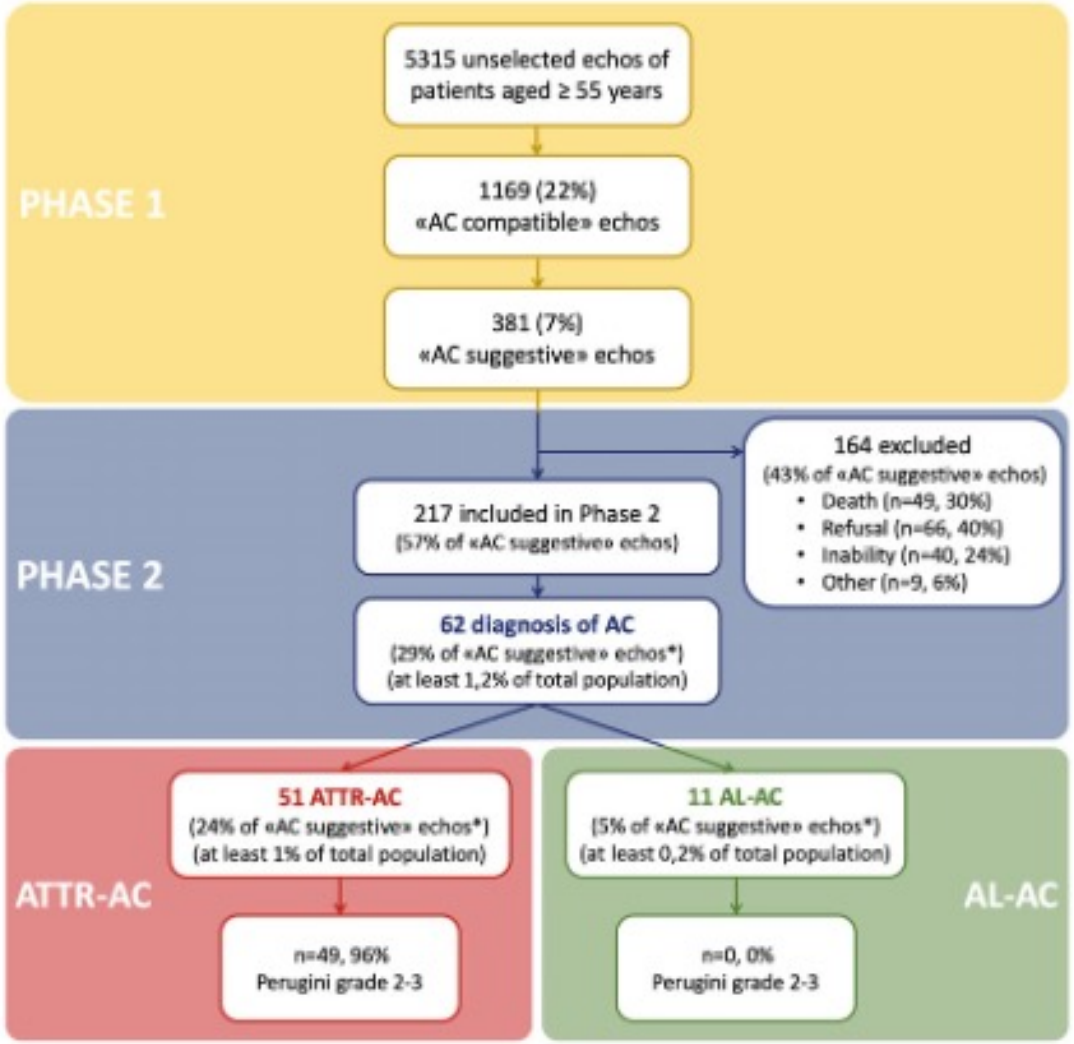
Deep learning-based models for detection of cardiac amyloidosis





- **1281 ATTRwt patients**
- **Males: 89%**
- **Mean age: 78 years**
- **NYHA III-IV: 29%**

Timi et al. Eur J Heart Fail 2023; Delbarre et al. JACC: Cardiovasc Imag 2023



ESC European Society of Cardiology

European Journal of Heart Failure (2022) 24, 1377–1386
doi:10.1002/ejhf.2504

RESEARCH ARTICLE

Unmasking the prevalence of amyloid cardiomyopathy in the real world: results from Phase 2 of the AC-TIVE study, an Italian nationwide survey

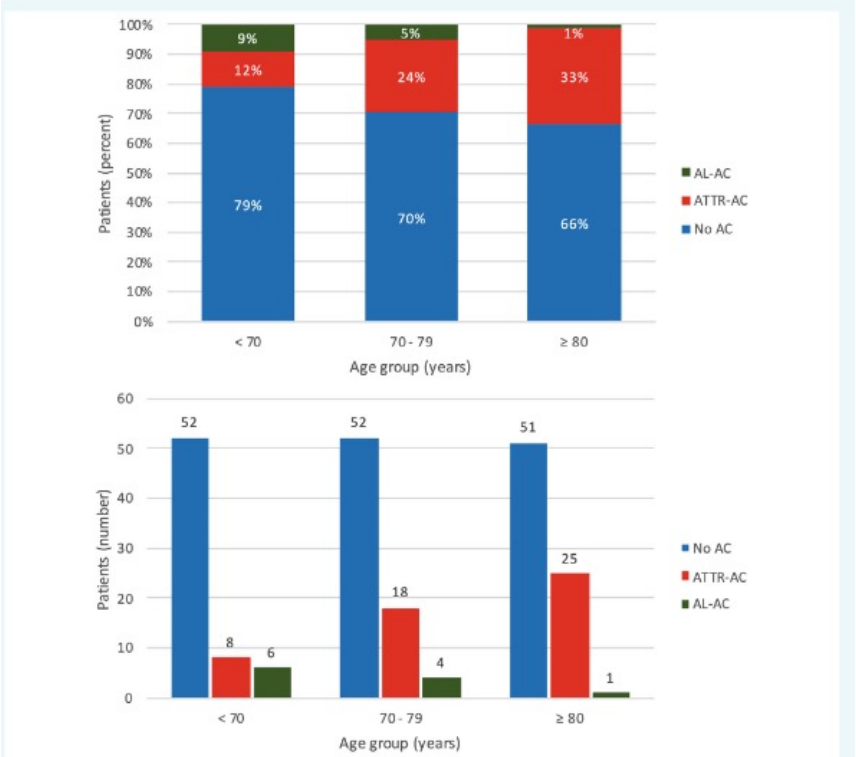
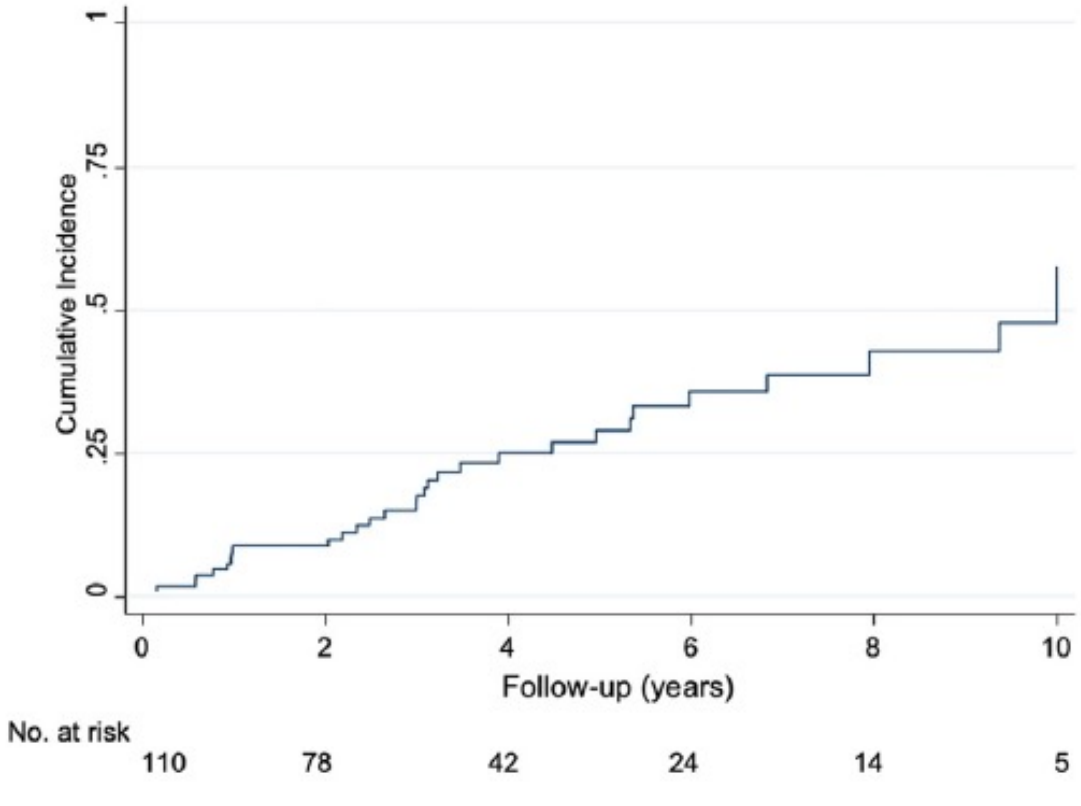
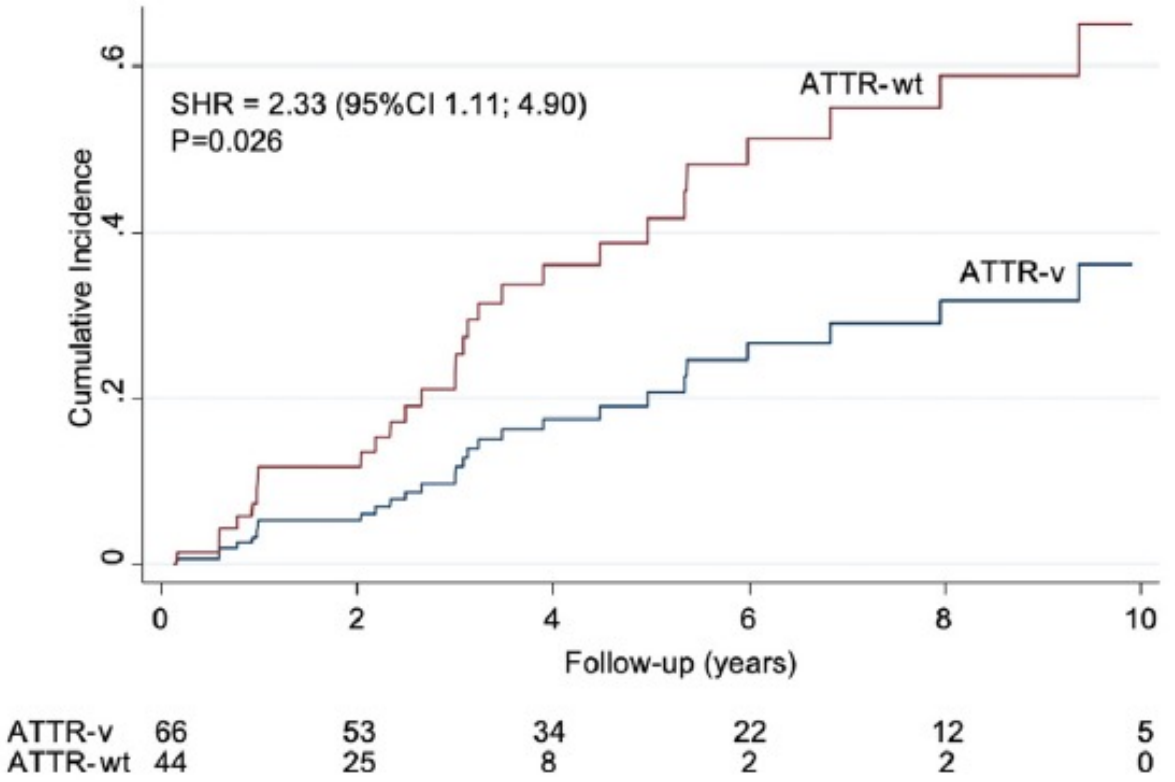


Figure 2 Amyloid cardiomyopathy (AC) prevalence, either transthyretin-related AC (ATTR) or light chain-related AC (AL), according to age (upper panel expressed in percentage, lower panel expressed in absolute number) in the study population.

Heart failure rapidly develops in ATTR-CM patients

- In a multicenter, retrospective study, **one-third of ATTR-CM patients** asymptomatic at diagnosis developed heart failure over a median follow-up period of 3.7 years and nearly 20% of patients required PM implantation.





- Gonzalez-Lopez et al. JACC: Cardiooncolgy 2022

Staging of cardiac ATTRwt amyloidosis

	Pavia cohort *(unpublished)*[3]	Pavia cohort Pre-2018[3]	Pavia cohort Post-2018[3]	P
N.	691	354 (51)	337 (49)	-
Mayo staging[1]				<0.001
I	215 (32)	**87 (25)**	**128 (39)**	
II	226 (34)	112 (32)	114 (35)	
III	225 (34)	**146 (42)**	**79 (24)**	

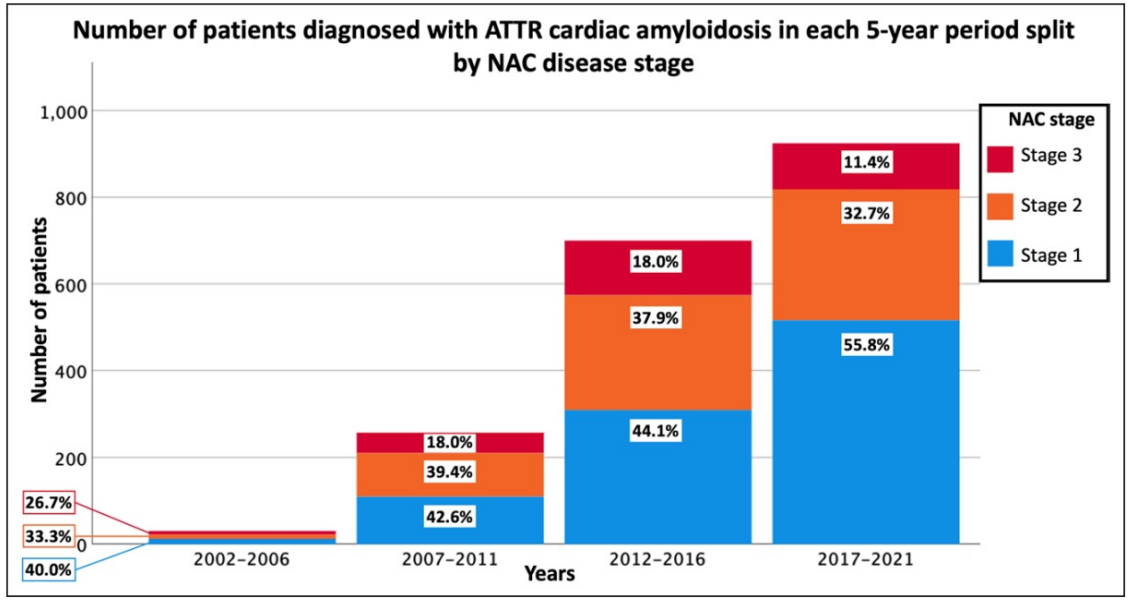
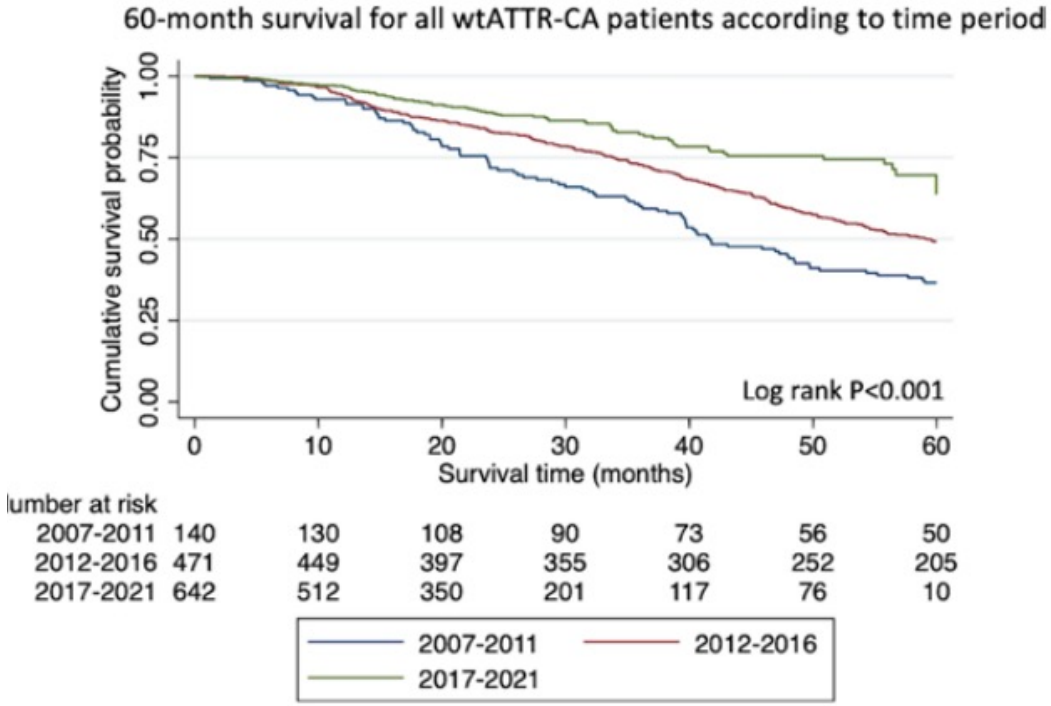
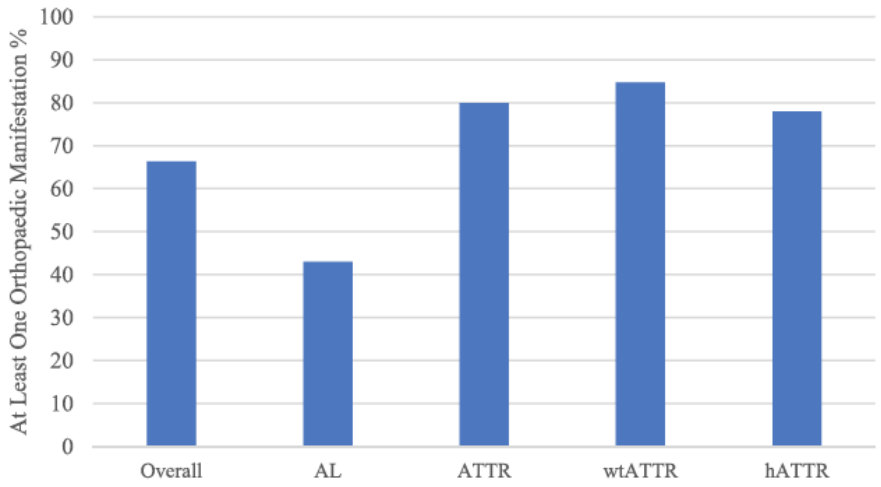


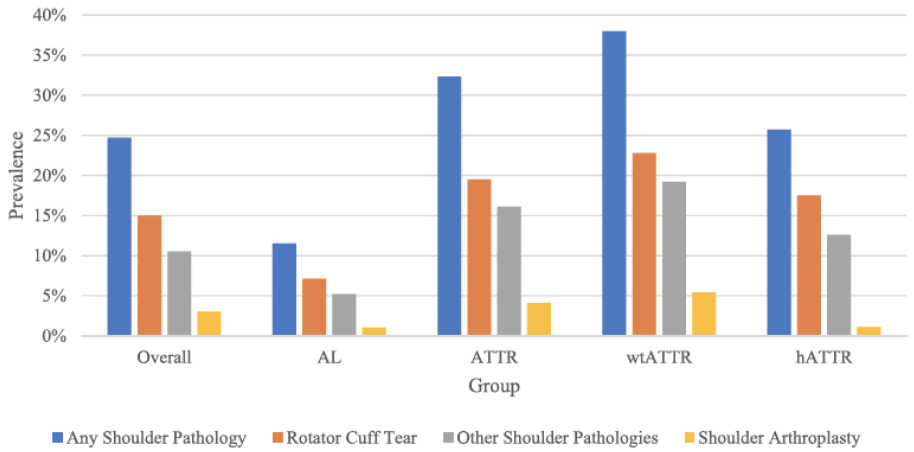
Figure 4. Number of patients diagnosed with transthyretin cardiac amyloidosis between 2002 and 2021, and the proportion of patients with each NAC disease stage for each 5-year period.
NAC indicates National Amyloidosis Centre.

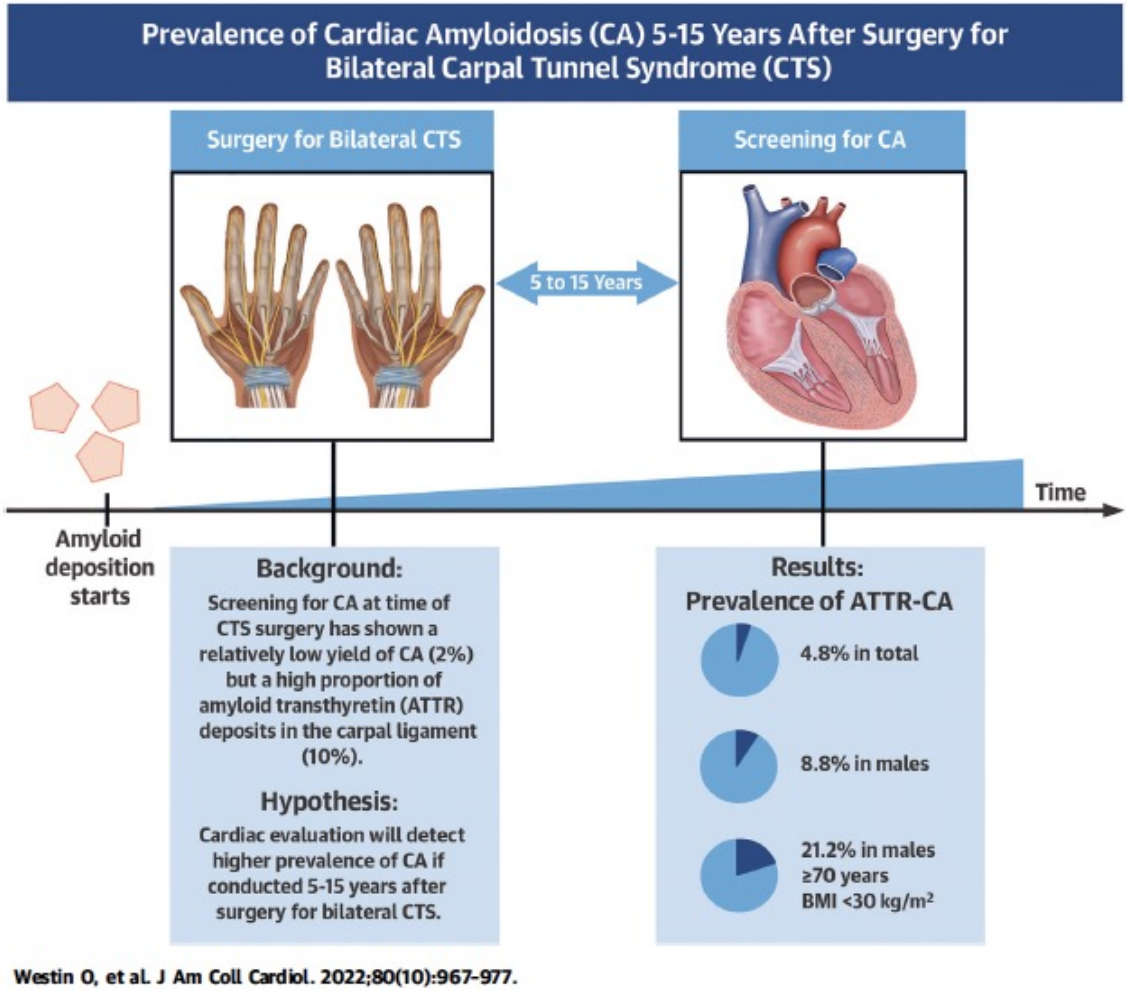


1. Grogan et al JACC 2016; 2. Personal communicatio. 3. Iannou et al. Circulation 2022

Screening for cardiac ATTR amyloidosis in several musculoskeletal conditions



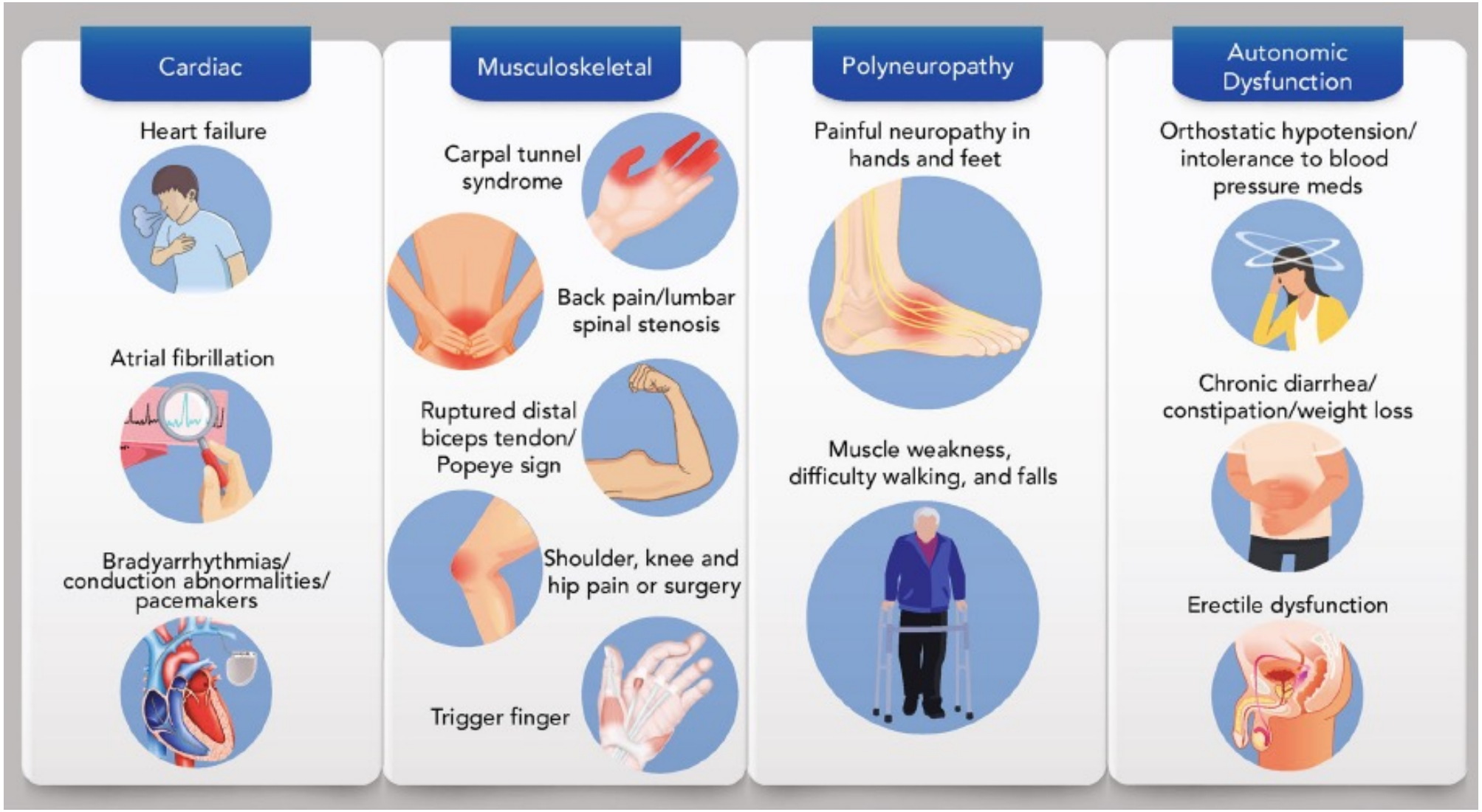




Westin O, et al. J Am Coll Cardiol. 2022;80(10):967-977.

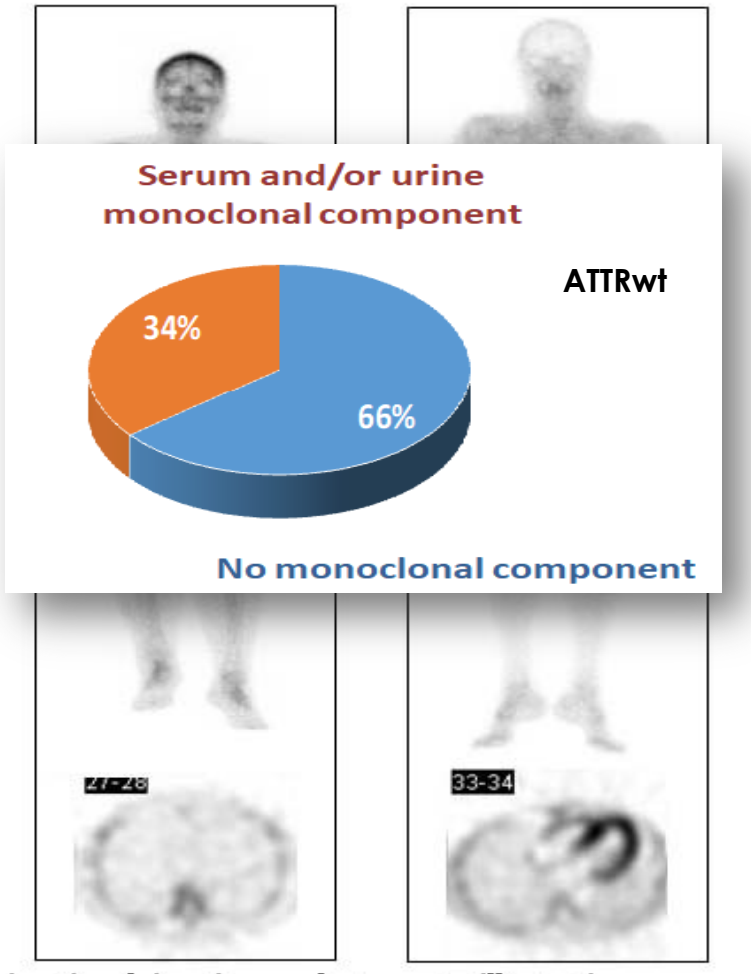
Basdavanos et al. Am J Cardiol 2023

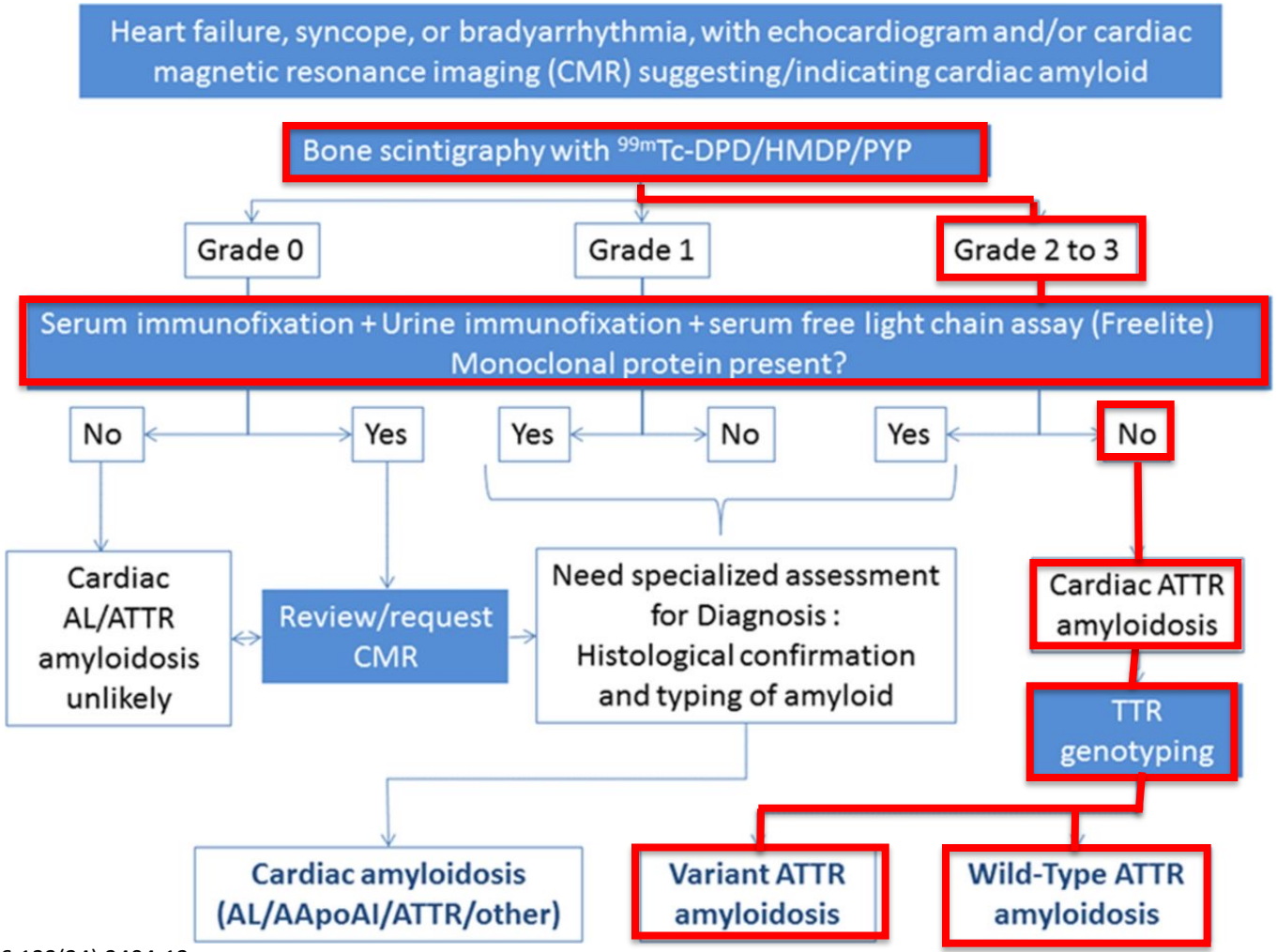
Clinical Presentation and Red Flags for ATTR Amyloidosis



Nativi-Nicolau JN, et al. Heart Failure Reviews (2022) 27:785–793

Non-invasive diagnosis of ATTR amyloidosis

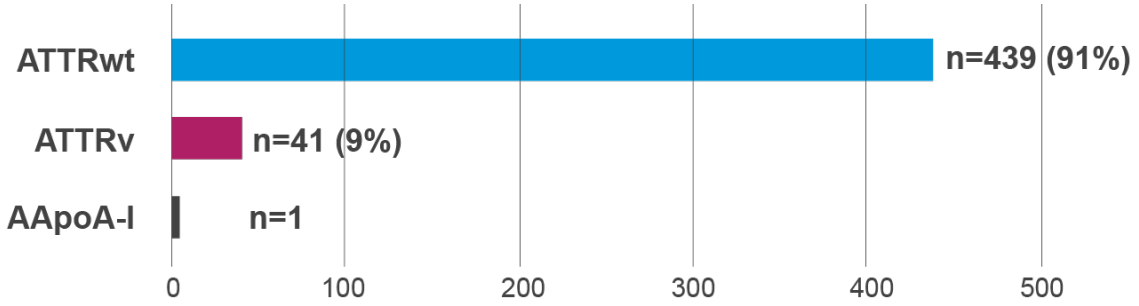


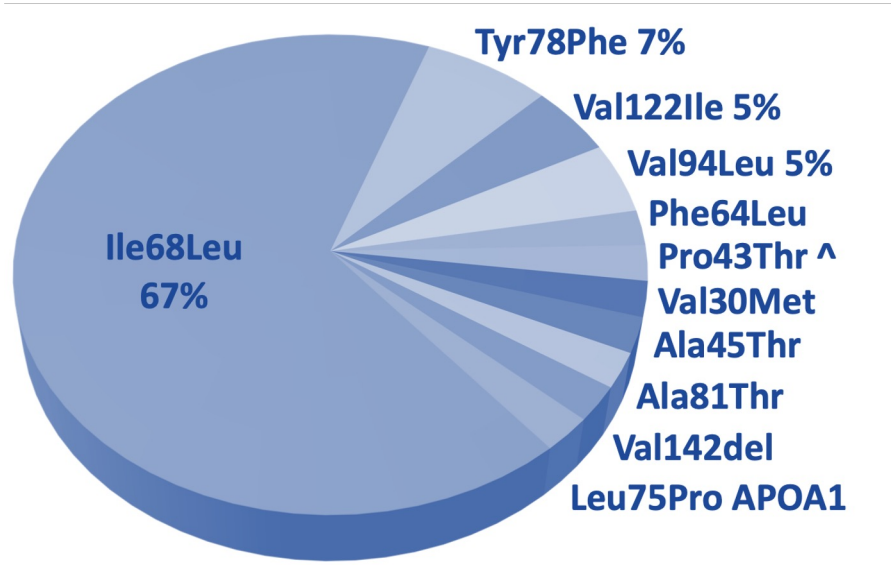


- Rapezzi C, et al. *JACC Cardiovasc Imaging* 2011;4(6):659-70; Gillmore JD, et al. *Circulation* 2016;133(24):2404-12.

Prevalence of variant genotype in patients with suspected cardiac ATTR amyloidosis

- 481 patients referred for suspected ATTR-CM wild-type amyloidosis (92% males)
- Mean age 76 years (range 50–93)

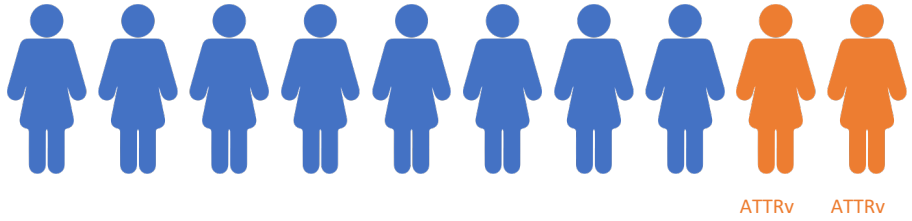




Patient' characteristics at presentation	All cohort (n=481)	ATTRwt (n=439)	ATTRv (n=41)
Age at diagnosis, years	76 (±7.7)	76.4 (±7.5)	74.1 (±8)
Male, n	441 (92%)	407 (93%)*	34 (83%)*
NYHA class (I/II/III)	21%, 63%, 16%	20%, 63%, 17%	23%, 67%, 10%
Gillmore stage (I/II/III)	40%, 46%, 14%	39%, 48%, 13%	52%, 32%, 16%
IVS (mm)	17.6 (±2.6)	17.6 (±2.7)	17.3 (±2.5)
EF (%)	50 (±10)	51 (±10)	52 (±8)

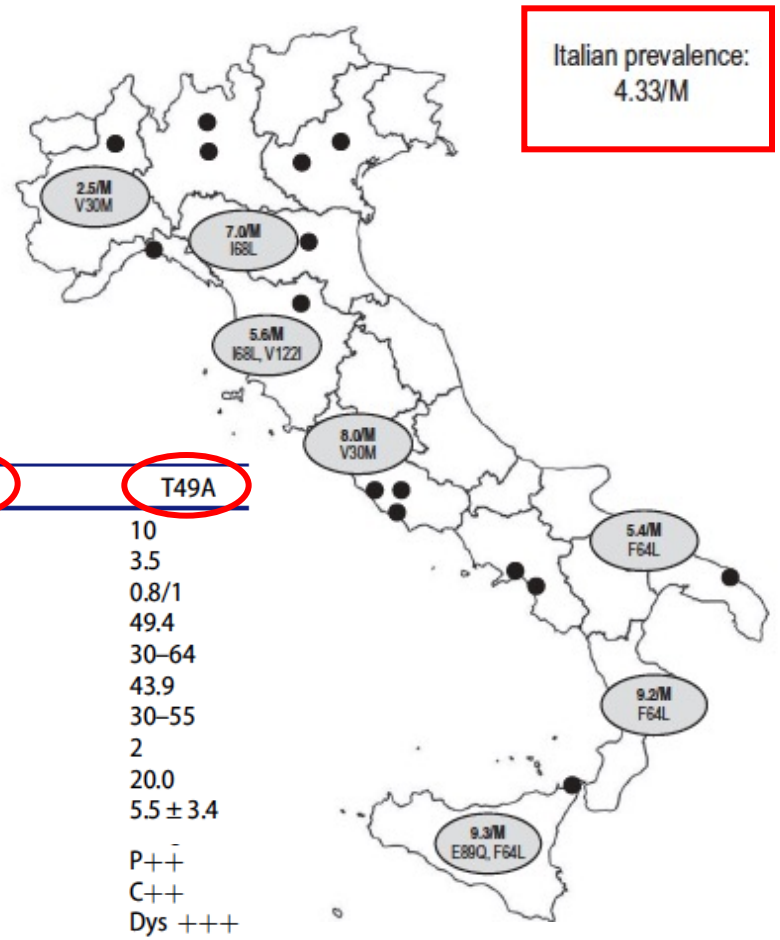
Prevalence of ATTRv among men aged <80 years

Prevalence of ATTRv among women



ATTRv amyloidosis Italian Registry: clinical and epidemiological data

Massimo Russo[a*], Laura Obici[b*], Ilaria Bartolomei[c], Francesco Cappelli[d], Marco Luigetti[e], Silvia Fenu[f], Tiziana Cavallaro[g], Maria Grazia Chiappini[h], Chiara Gemelli[i], Luca Guglielmo Pradotto[j,k], Fiore Manganelli[l], Luca Leonardi[m], Filomena My[n], Simone Sampaolo[o], Chiara Briani[p], Luca Gentile[a], Claudia Stancanelli[a], Eleonora Di Buduo[b], Paolo Pacciolla[b], Fabrizio Salvi[c], Silvia Casagrande[d], Giulia Bisogni[q], Daniela Calabrese[f], Fiammetta Vanoli[m], Giuseppe Di Iorio[o], Giovanni Antonini[m], Lucio Santoro[l], Alessandro Mauro[j,k], Marina Grandis[i], Marco Di Girolamo[h], Gian Maria Fabrizi[g], Davide Pareyson[f], Mario Sabatelli[e], Federico Perfetto[d], Claudio Rapezzi[r,s], Giampaolo Merlini[b], Anna Mazzeo[a] and Giuseppe Vita[a]



31 different mutations

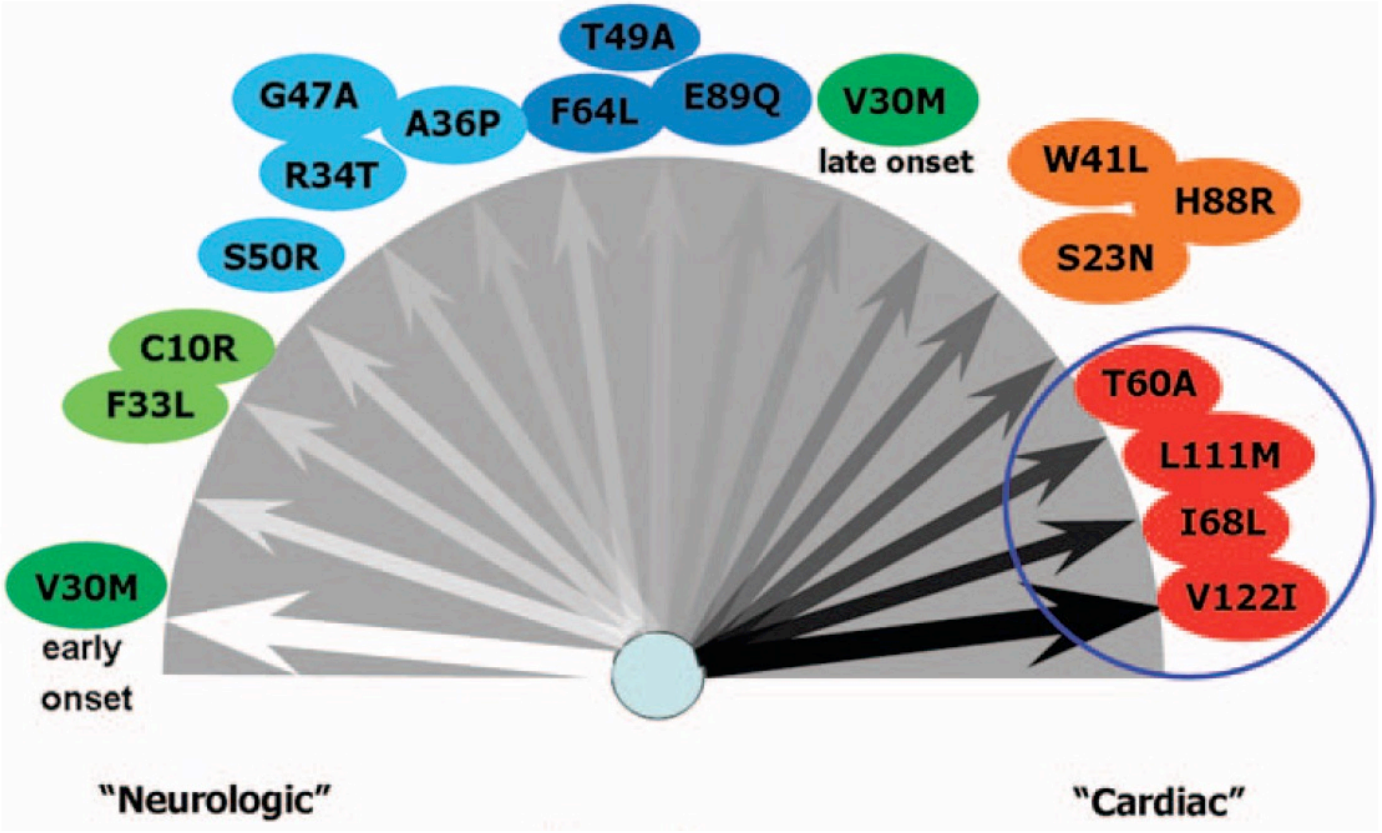
Table 1. Clinical characteristics.

	I68L	F64L	V30M	E89Q	V122I	Y78F	T49A
Number of symptomatic patients	47	58	60	33	13	13	10
%	18.1	22.3	23.1	12.7	5.0	5.0	3.5
Male/female ratio	2.6/1	3.8/1	3/1	1.3/1	3.3/1	12/1	0.8/1
Mean age (years)	72.4	70.2	66.2	58.5	73.7	72.6	49.4
Age range (yrs)	56–82	44–86	44–87	43–79	64–87	61–87	30–64
Mean age at the onset (years)	67.9	63.7	58.9	50.5	67.5	64.1	43.9
Age range at the onset (years)	47–79	42–80	31–81	37–70	56–82	55–81	30–55
Number of late onset (≥50 years)	45	56	48	18	13	13	2
%	95.7	96.6	80	54,5	100	100	20.0
Disease duration (mean ± SD; years)	4.5 ± 2.4	6.5 ± 4.4	7.2 ± 5.2	8.0 ± 4.4	6.2 ± 4.2	8.5 ± 5.0	5.5 ± 3.4
Phenotype at prevalence day	P+ C+++ Dys +	P+++ C+ Dys +	P+++ C+ Dys +	P++ C++ Dys ++	P++ C+++ Dys +	P+++ C+ Dys +	P++ C++ Dys +++

Russo M et al. Amyloid 2020

Genotype is the major phenotypic driver in ATTRv

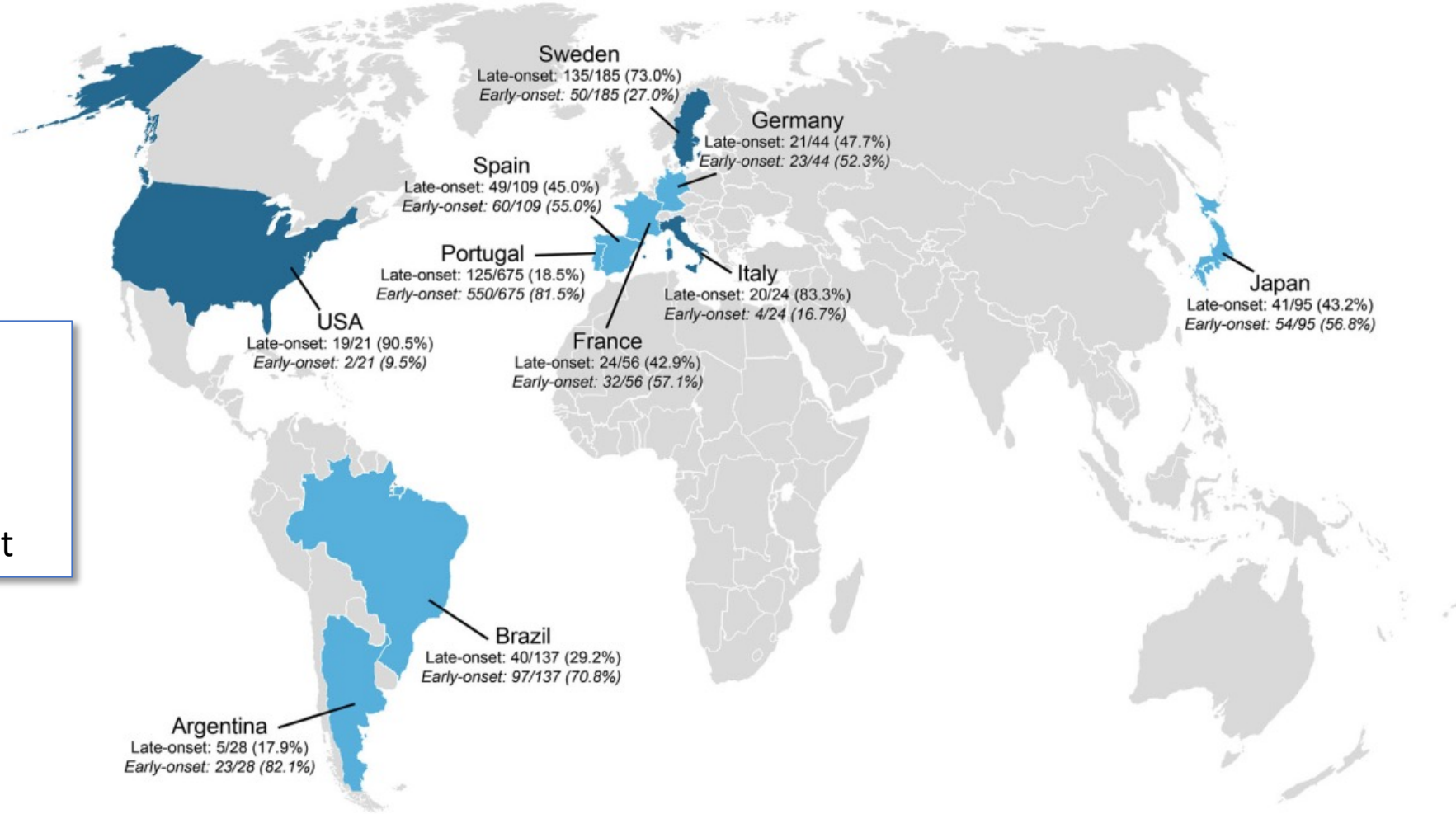
- Some variants are associated with an exclusive cardiologic phenotype indistinguishable from wild-type ATTR
- A mixed neurologic and cardiologic phenotype predominates in non-endemic areas.
- Natural history data indicate rapid disease progression and worse prognosis in patients with mixed phenotype



Rapezzi et al. *Eur Heart J 2012.*

ATTR Val30Met: one mutation, two distinct diseases

Late onset V30M
- 491/1389 (35.3%)
- Male 66.2% (vs EO 53.6%)
- Longer time to diagnosis
- More impaired at enrollment



Marcia Waddington-Cruz et al. Neurol Ther 2021

Early-onset Val30Met TTR amyloidosis

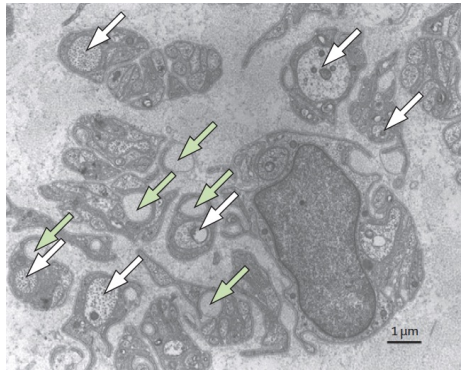
A PECULIAR FORM OF PERIPHERAL NEUROPATHY

FAMILIAR ATYPICAL GENERALIZED AMYLOIDOSIS WITH SPECIAL INVOLVEMENT OF THE PERIPHERAL NERVES

BY

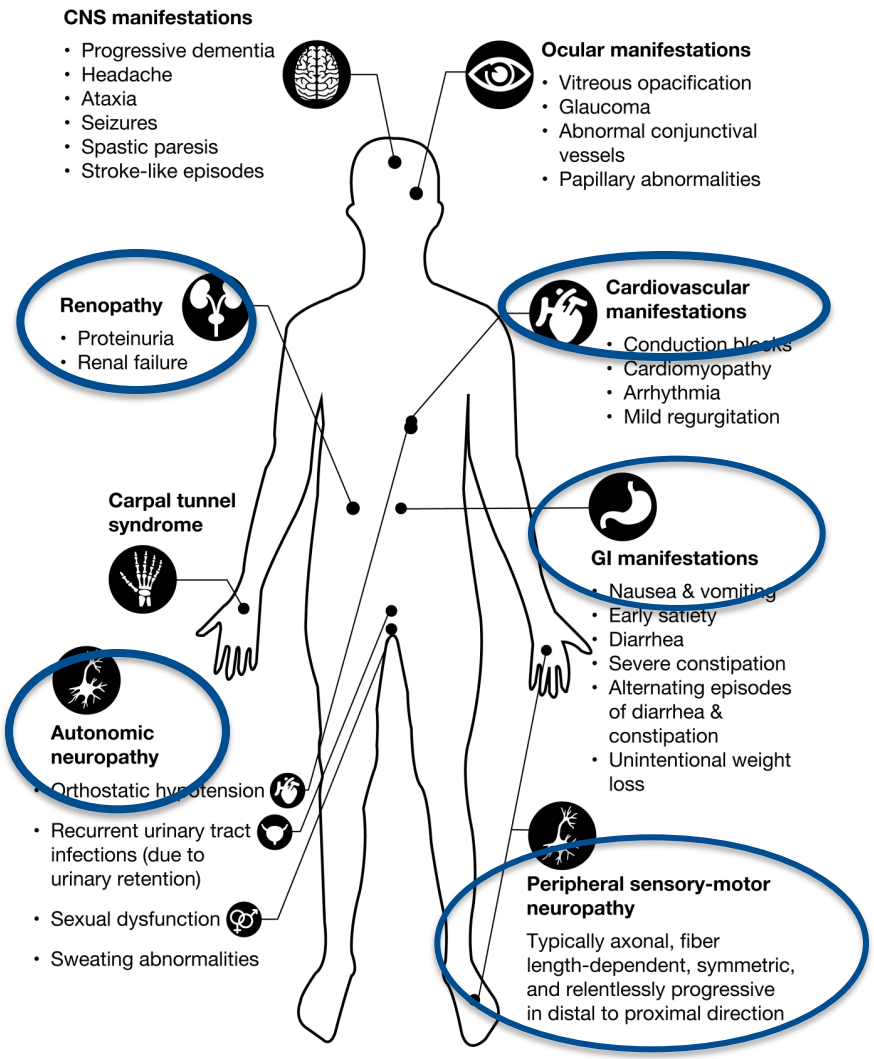
CORINO ANDRADE

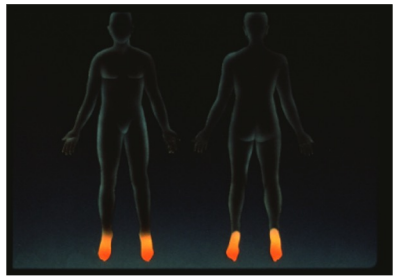
(From the Neurological Department of the Sto. António Hospital, Oporto, Portugal)

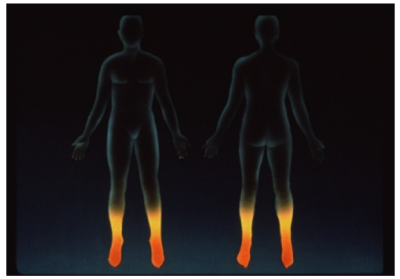


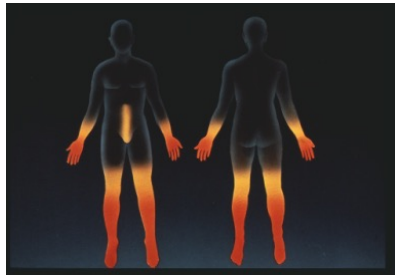
Mean age at onset 33,5 years

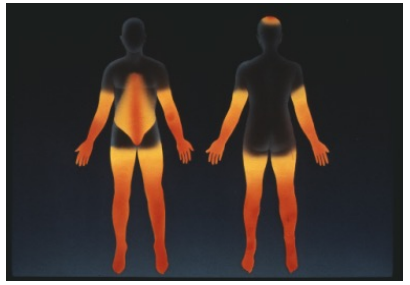
High penetrance
Genetic anticipation possible



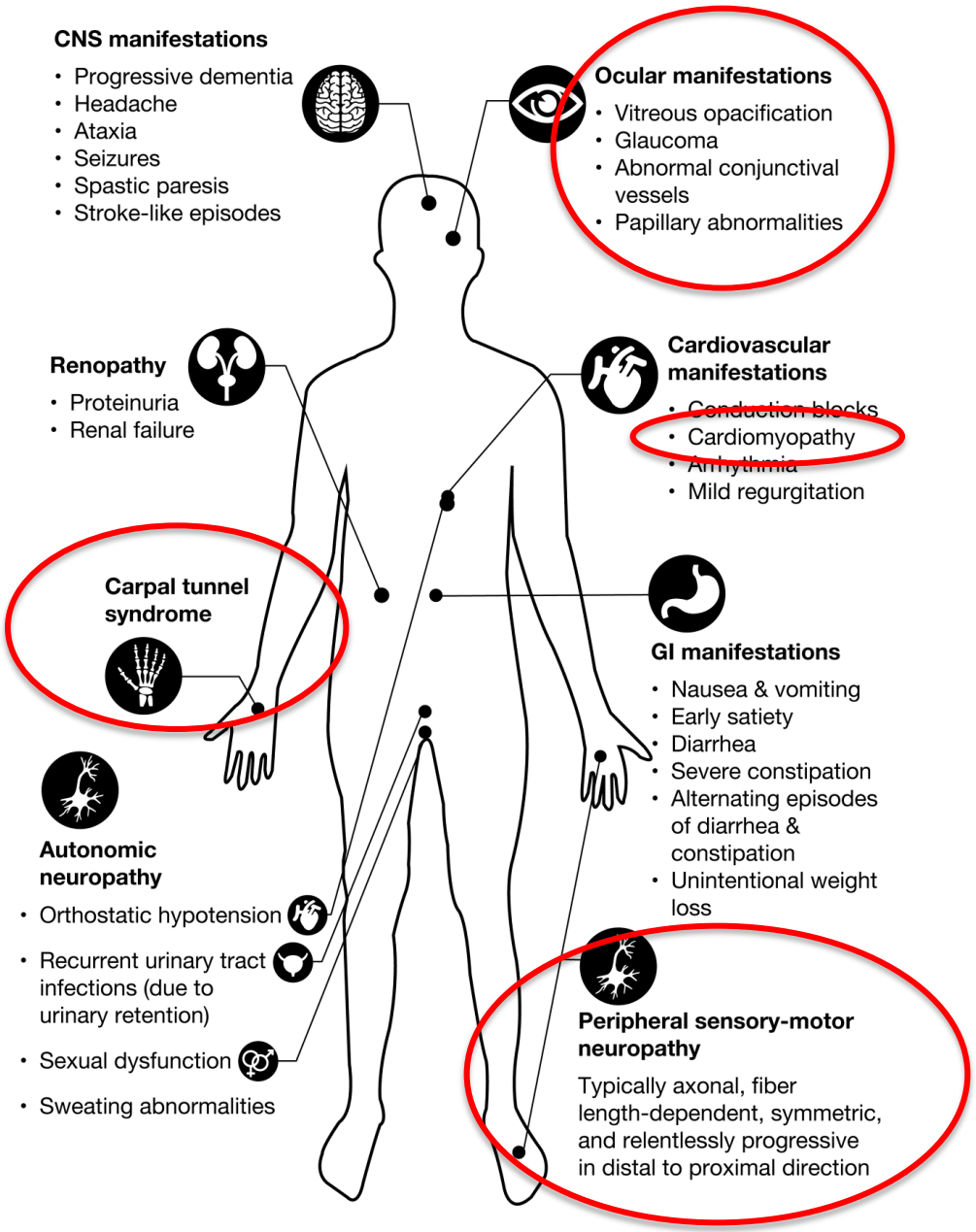






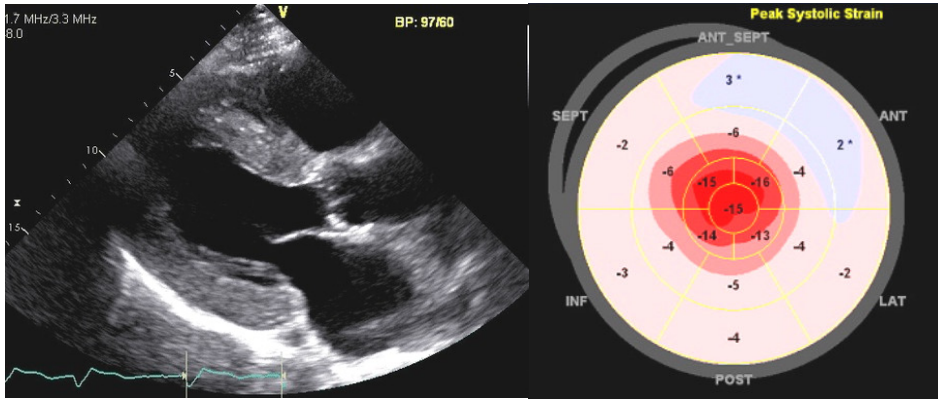


Late-onset Val30Met ATTRv

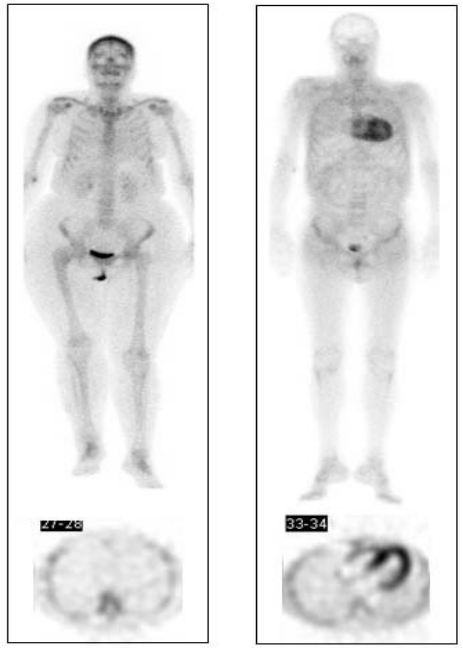


Male predominance

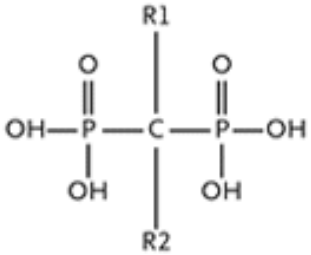
Echocardiography: wall thickness-GLS



Bone scintigraphy



Bisphosphonates

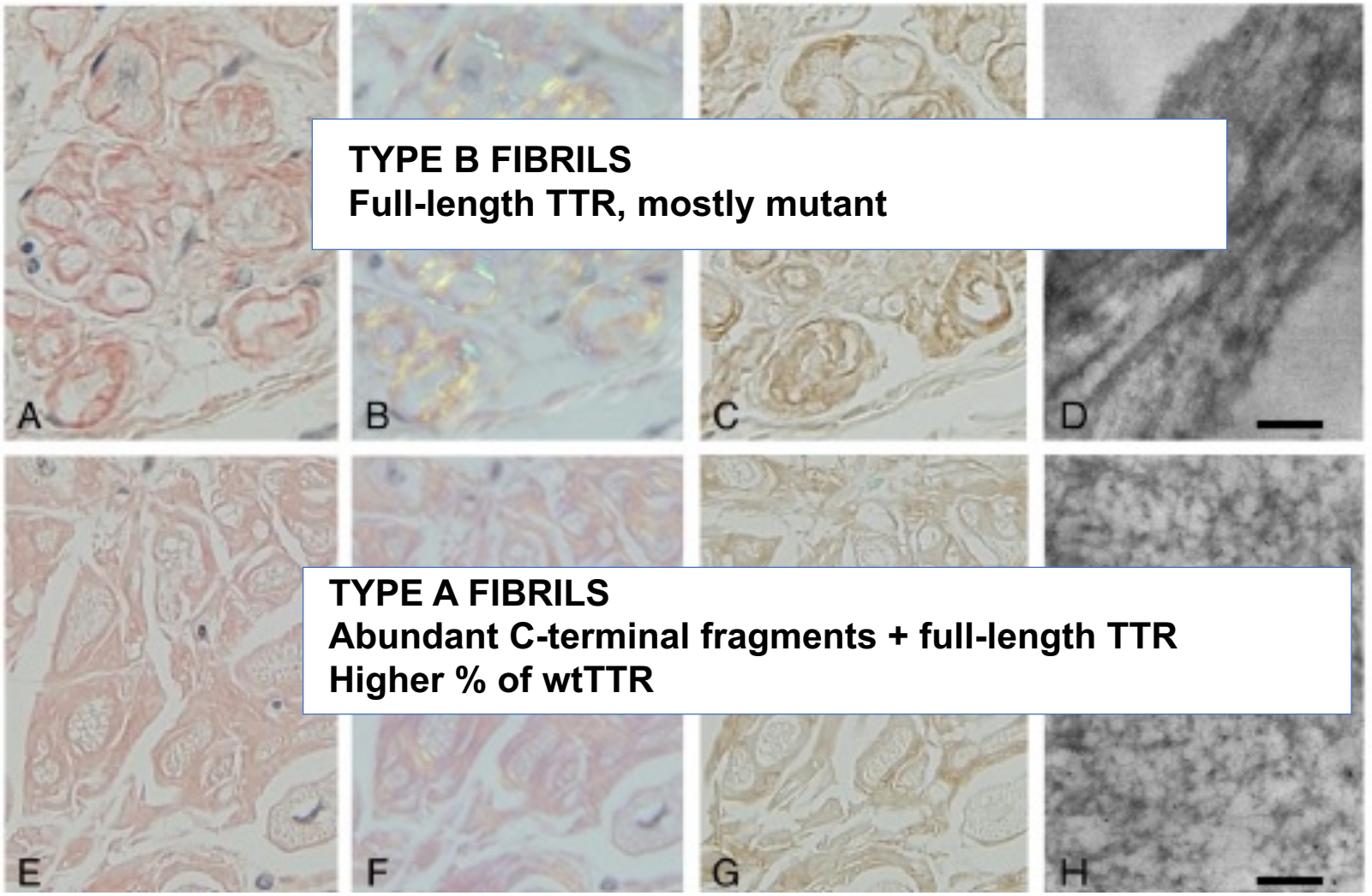


Rapezzi et al JACC Imaging 2011

Distinct characteristics of amyloid deposits in early- and late-onset transthyretin Val30Met familial amyloid polyneuropathy

Haruki Koike [a], Yukio Ando [b], Mitsuharu Ueda [b], Yuichi Kawagashira [a], Masahiro Iijima [a], Junko Fujitake [c], Michiyuki Hayashi [c], Masahiko Yamamoto [d], Eiichiro Mukai [e], Tomohiko Nakamura [a], Masahisa Katsuno [a], Naoki Hattori [a], Gen Sobue [a,*]

Patients
Early-onset cases[b]
1
2
3
Late-onset cases[c]
4
5
6
7
8



TYPE B FIBRILS
Full-length TTR, mostly mutant

TYPE A FIBRILS
Abundant C-terminal fragments + full-length TTR
Higher % of wtTTR

J Neurol Science 2009

ATTRv amyloidosis is rapidly progressive, leading to loss of mobility, autonomy and shortened life expectancy

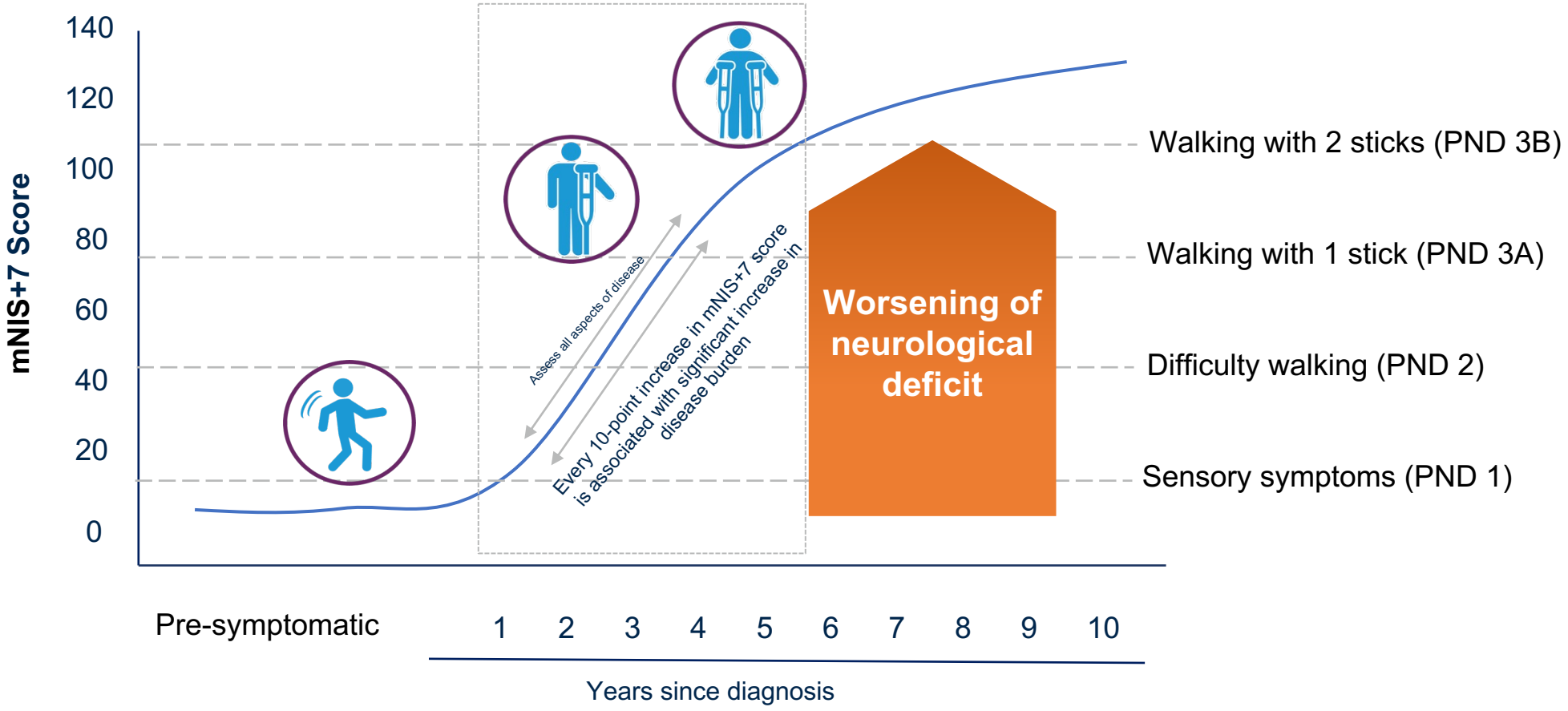
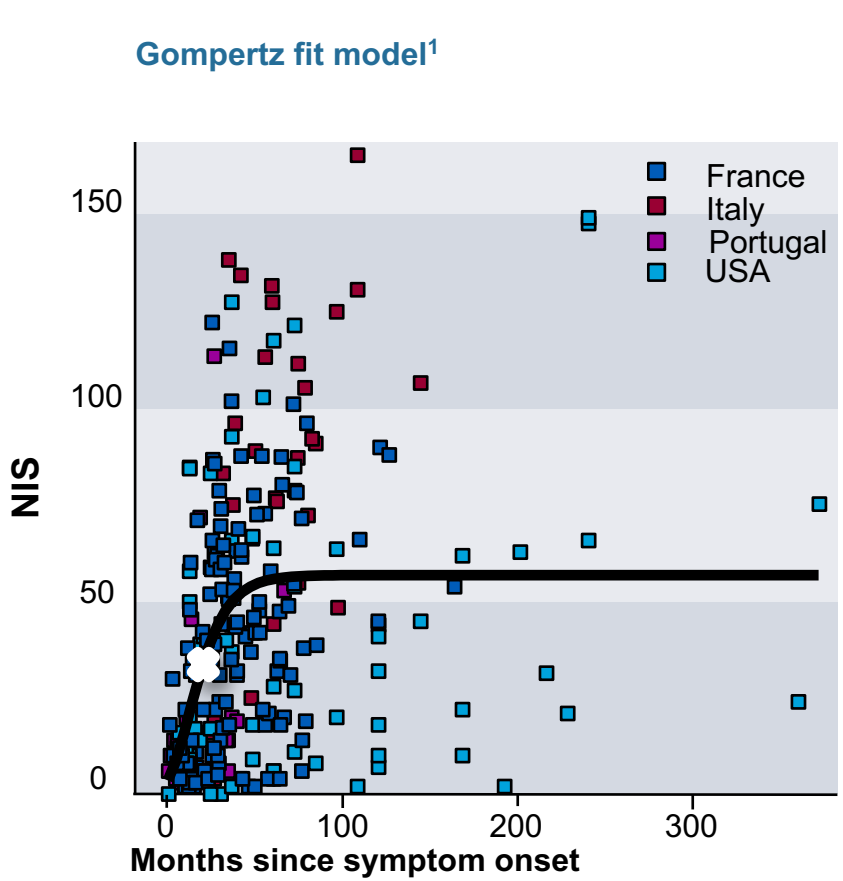


Figure modified from Adams D et al. Neurology. 2015;85:675–82.

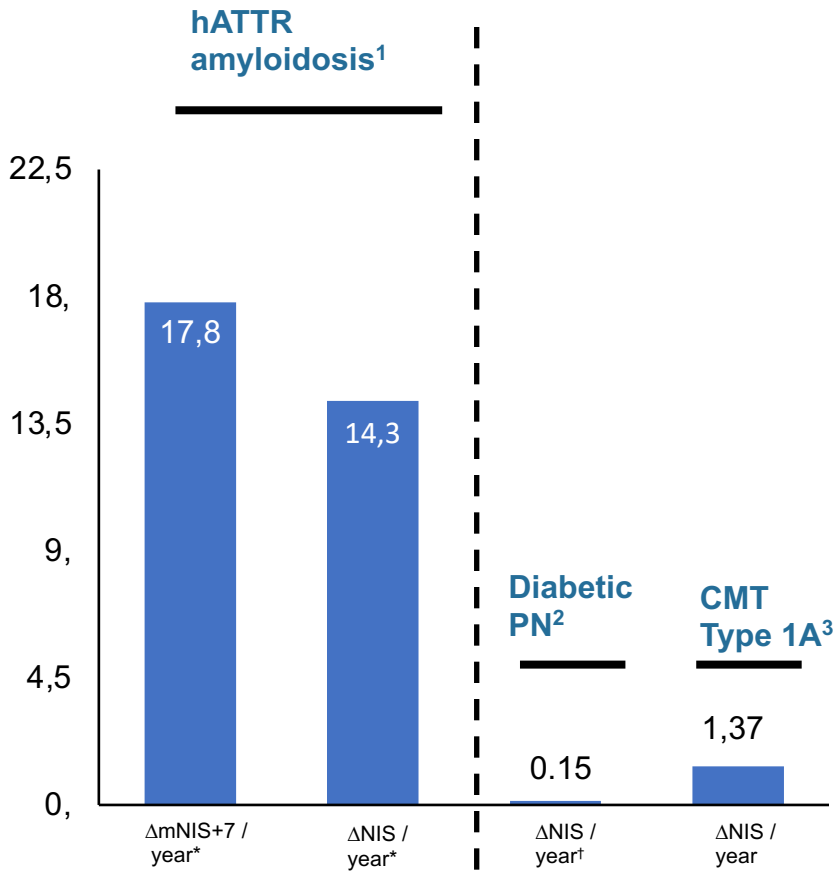
hATTR, hereditary transthyretin amyloidosis
mNIS+7, modified neuropathy impairment test

1. Adams D et al. Neurology. 2015;85:675–82 4; 2. Adams D et al. Ther Adv Neurol Disord. 2013;6:129–39;
3. Mariani L et al. Ann Neurol. 2015;78:901–16; 4. Koike J et al. J Neurol Neurosurg Psychiatry. 2012;83:152–8.

Natural history study of hATTR amyloidosis: neuropathy progresses rapidly without treatment



Based on figure from: 1. Adams et al. *Neurology* 2015;85:675–82.



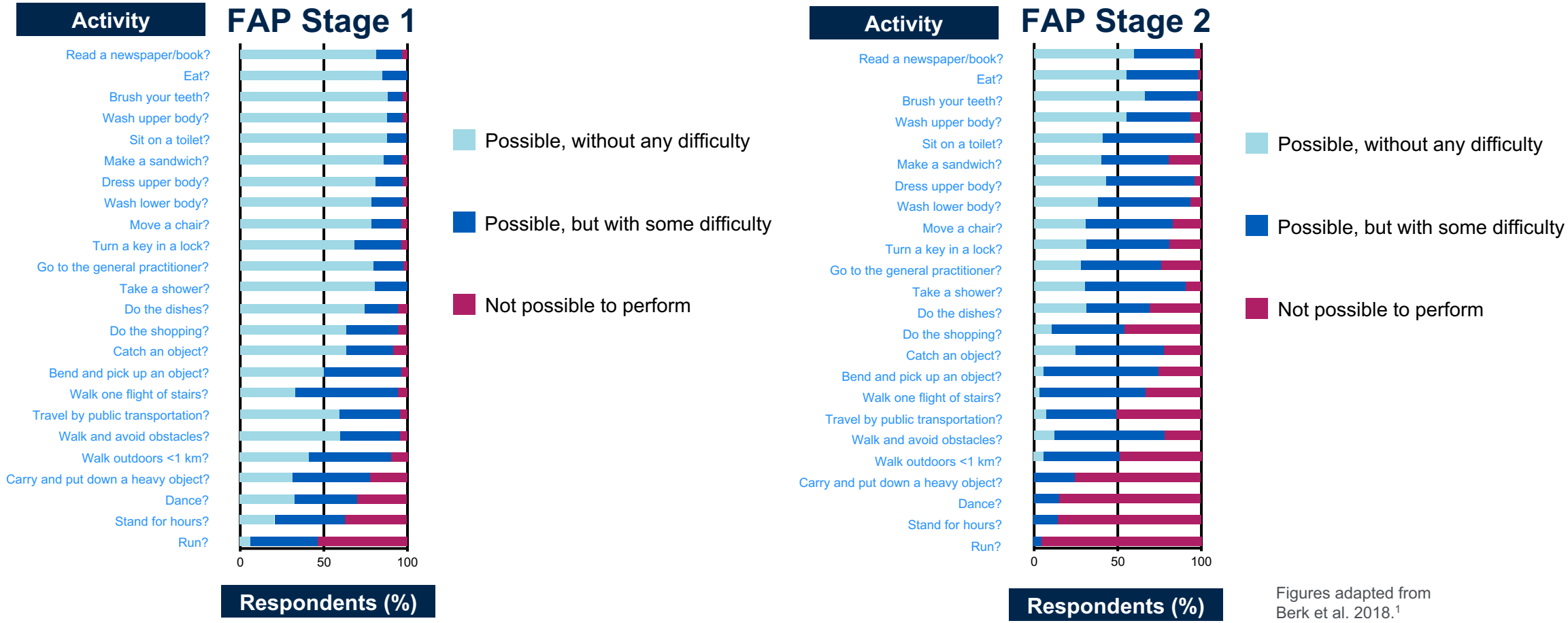
Based on data from: 1. Adams et al. *Neurology* 2015;85:675–82; 2. Ziegler et al. *Diabetes Care* 2011;34:2054–60; 3. Shy et al. *Neurology* 2008;70:378–83.
†Calculated based on change in NIS over 4 years in placebo group.

*Median baseline NIS 32.0.
hATTR amyloidosis, hereditary transthyretin amyloidosis; CMT, Charcot-Marie-Tooth; mNIS, modified NIS; NIS, Neuropathy Impairment Score; PN, polyneuropathy.

1. Adams D, et al. *Neurology* 2015;85:675–82; 2. Ziegler D, et al. *Diabetes Care* 2011;34:2054–60; 3. Shy ME, et al. *Neurology* 2008;70:378–83.

ATTRv polyneuropathy significantly limits daily activities from its earliest stages

Activity limitations based on R-ODS (n=225; APOLLO)[1]



Figures adapted from Berk et al. 2018.[1]

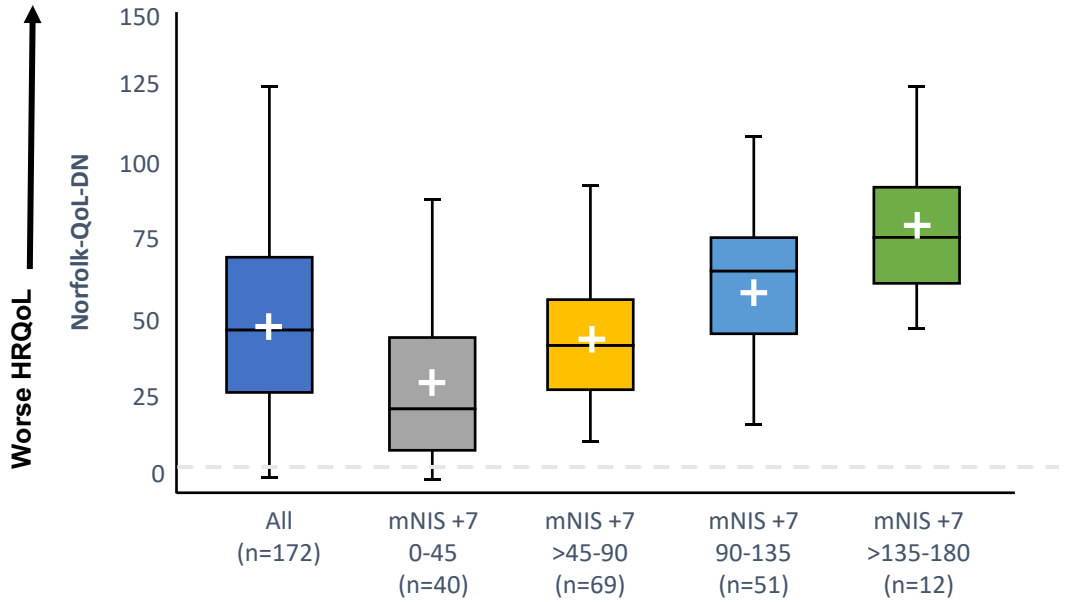
FAP, familial amyloidotic polyneuropathy; hATTR, hereditary transthyretin-mediated amyloidosis (hATTR or ATTRv; v for variant); R-ODS, Rasch-built Overall Disability Scale.

1. Berk J et al. Presented at: The XVI International Symposium on Amyloidosis, March 26–29, 2018, Kumamoto, Japan (Poster.

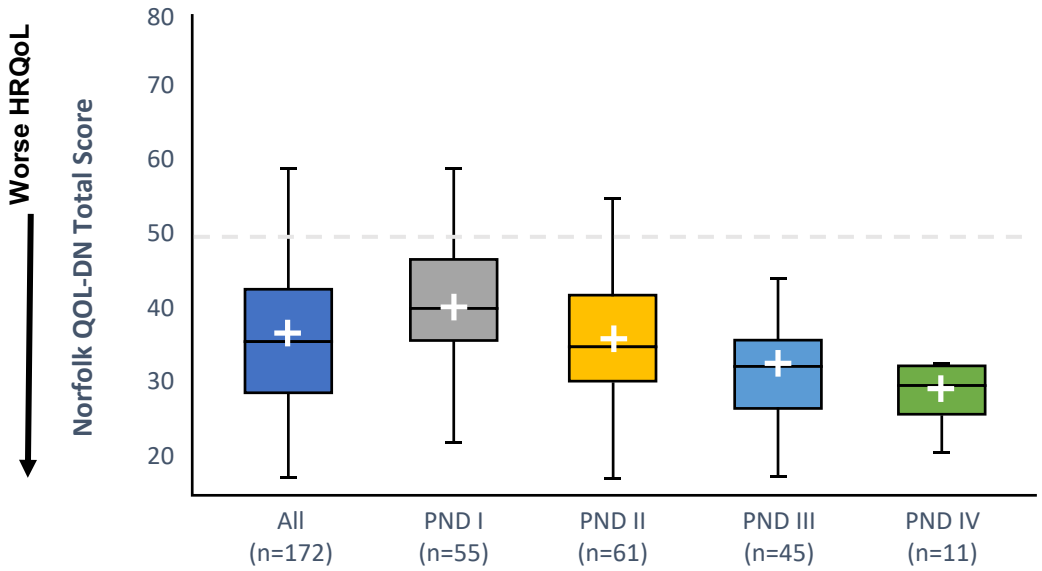
ATTRv polyneuropathy has a measurable impact on quality of life[1,2]

Analysis of the baseline study population from the NEURO-TTR hATTR polyneuropathy phase 3 study[1]

QoL measured using a diabetic neuropathy tool (Norfolk QoL-DN) validated in hATTR



General QoL measured using SF-36 (physical component score)



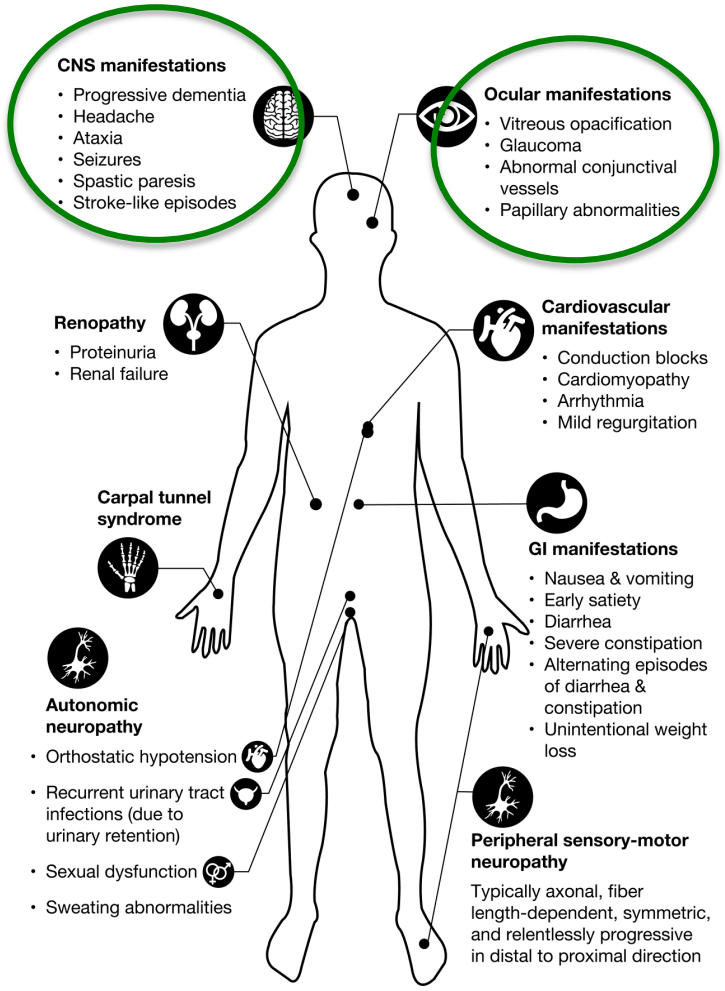
- Neuropathy-specific QoL for patients with hATTR has been reported to be comparable to QoL in type 2 diabetes, with diabetic neuropathy accompanied by history of ulceration, gangrene, or amputation[2]

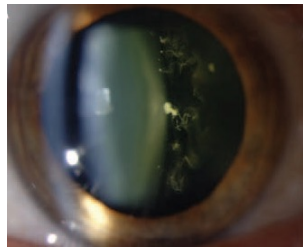
hATTR, hereditary transthyretin amyloidosis; mNIS+7, modified neuropathy impairment score +7 neurophysiologic tests; QoL, quality of life; Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy; PCS, physical component score; PND, polyneuropathy disability; SF-36, Short Form, 36-item.
PND I: Sensory disturbances in limbs without motor impairment; PND II: Difficulty walking without the need of a walking aid; PND III: One stick or one crutch required for walking; PND IV: Two sticks or two crutches needed.

1. Waddington-Cruz M et al. *Amyloid*. 2018;25(3):180-188; 2. Yarlas A et al. *Muscle Nerve*. 2019;60(2):169-175.

Eye and CNS involvement

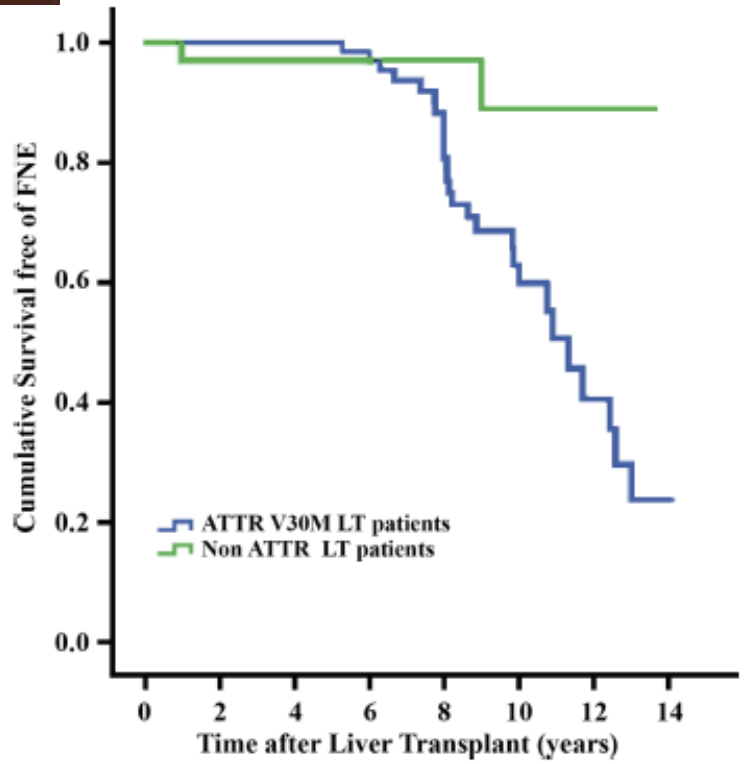
Arg34Gly

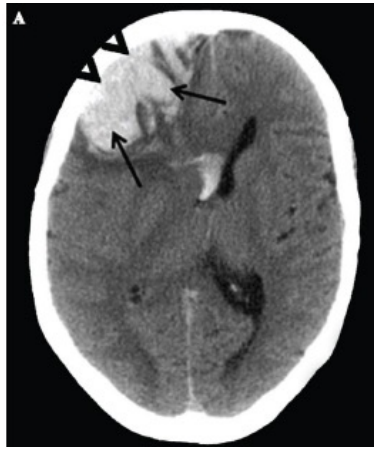


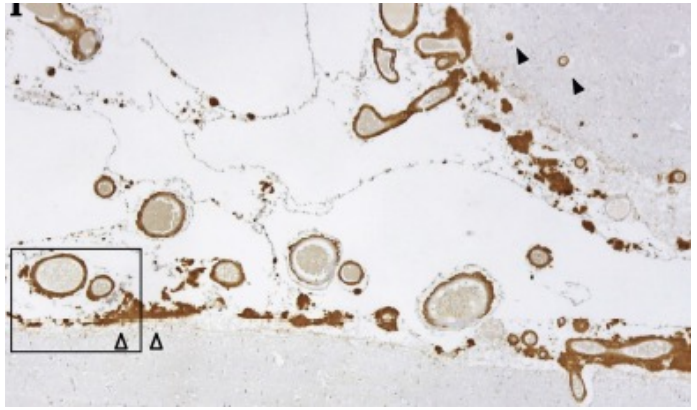


CNS involvement in V30M transthyretin amyloidosis: clinical, neuropathological and biochemical findings

Luís F Maia,[1,2,3] Rui Magalhães,[4] Joel Freitas,[2] Ricardo Taipa,[5] Manuel Melo Pires,[5] Hugo Osório,[6] Daniel Dias,[7] Helena Pessegueiro,[8] Manuel Correia,[2] Teresa Coelho[1,9]



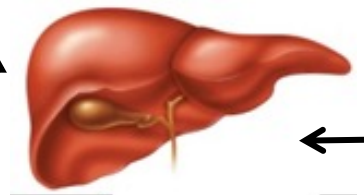




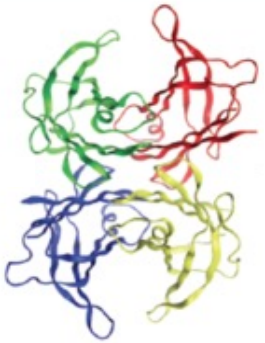
Maia et al. JNNP 2015

ATTR: disease mechanisms and treatment targets

Removal of mutant TTR by liver transplant



Knockdown of mutant and variant TTR
- Patisiran (RNAi)
- Inotersen (ASO)
- Vutrisiran (RNAi)
- Eplontersen (ASO)
- NTLA-2001 (CRISPR/Cas9)



TTR stabilizers
- Tafamidis
- Diflunisal*
- Acoramidis

Proteolysis + shear forces

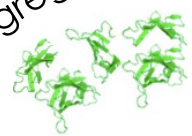
Truncated monomers (49-127)

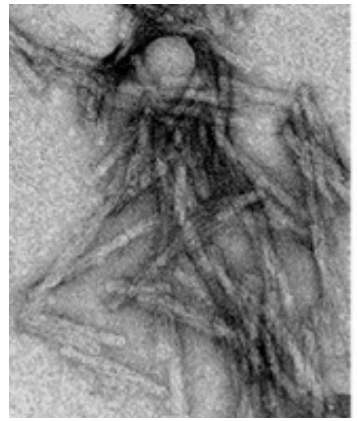
Folded full length monomer

misfolding

Misfolded monomers

Aggregation



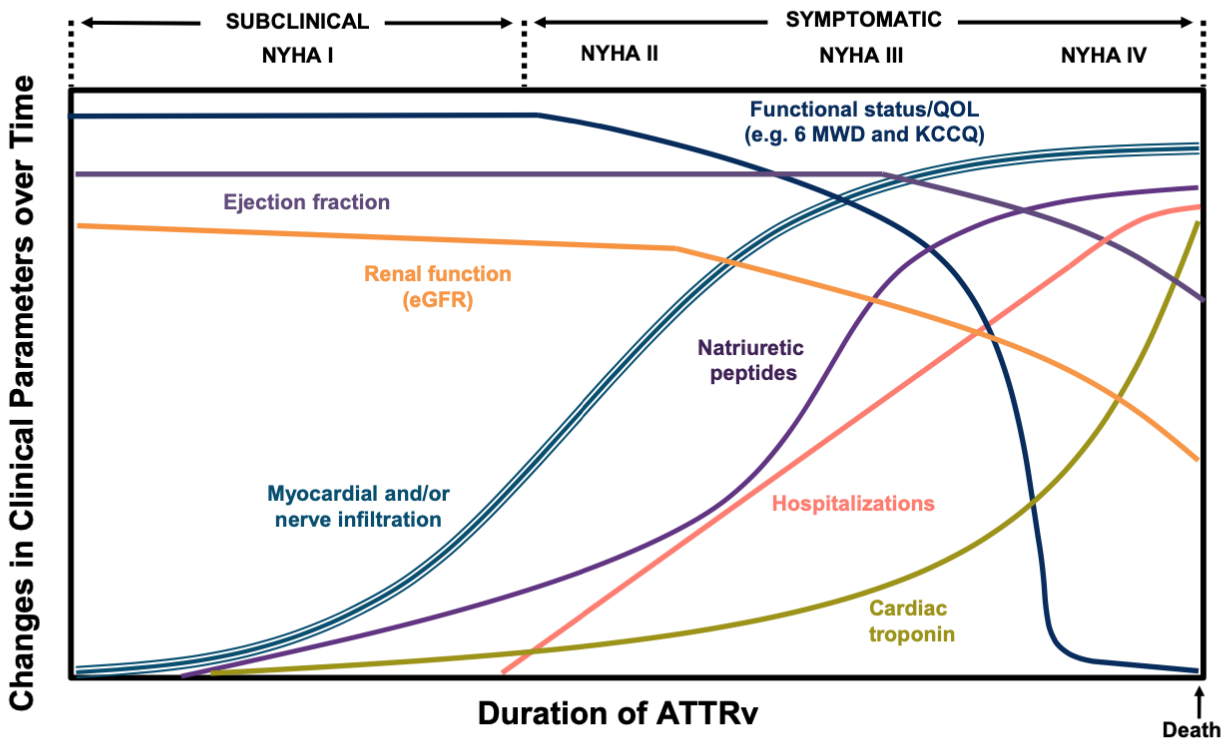


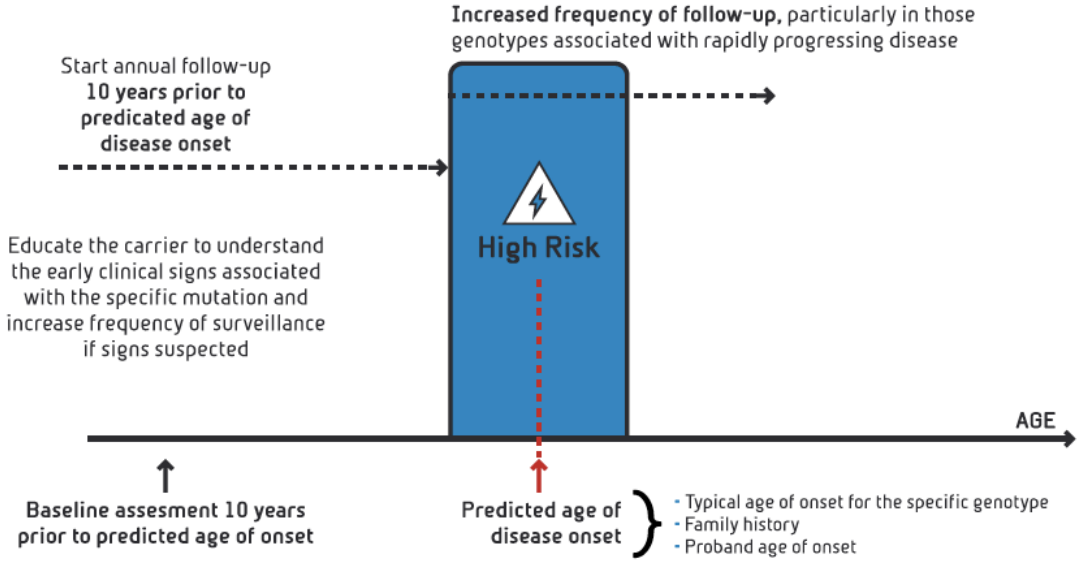
Amyloid fibril reabsorption
- NNC6019-0001 anti-TTR antibody
- NI006 (ALXN 2220) anti-TTR antibody

*not approved for ATTR amyloidosis

Adapted from Obici and Adams JPNS *2020.*

The natural history of the disease informs management of asymptomatic carriers





Increase frequency of surveillance if:

i. Signs suspected

ii. In older patients

iii. Genotypes associated with progressive disease

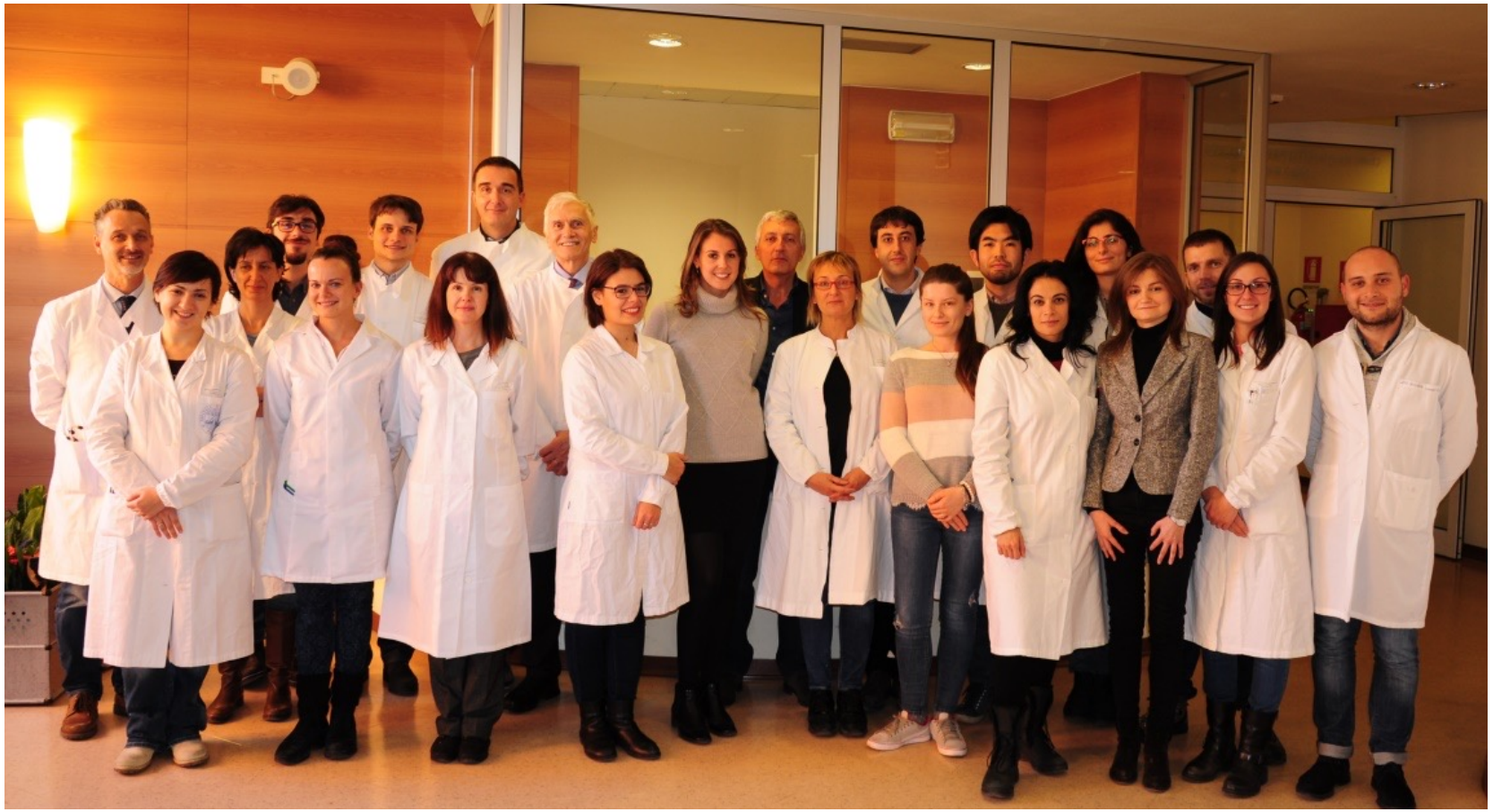
Conceicao et al. Amyloid *2019*

Tranthyretin amyloidosis is becoming an increasingly curable disease

but it remains dramatically challenging for patients diagnosed late

Thank you for your attention!

Acknowledgements



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