SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA
68° CONGRESSO NAZIONALE SIGG
Ritorno al futuro
FIRENZE, 13-16 DICEMBRE 2023
PALAZZO DEI CONGRESSI

Epidemiologia e storia naturale dell'amiloidosi da transtiretina

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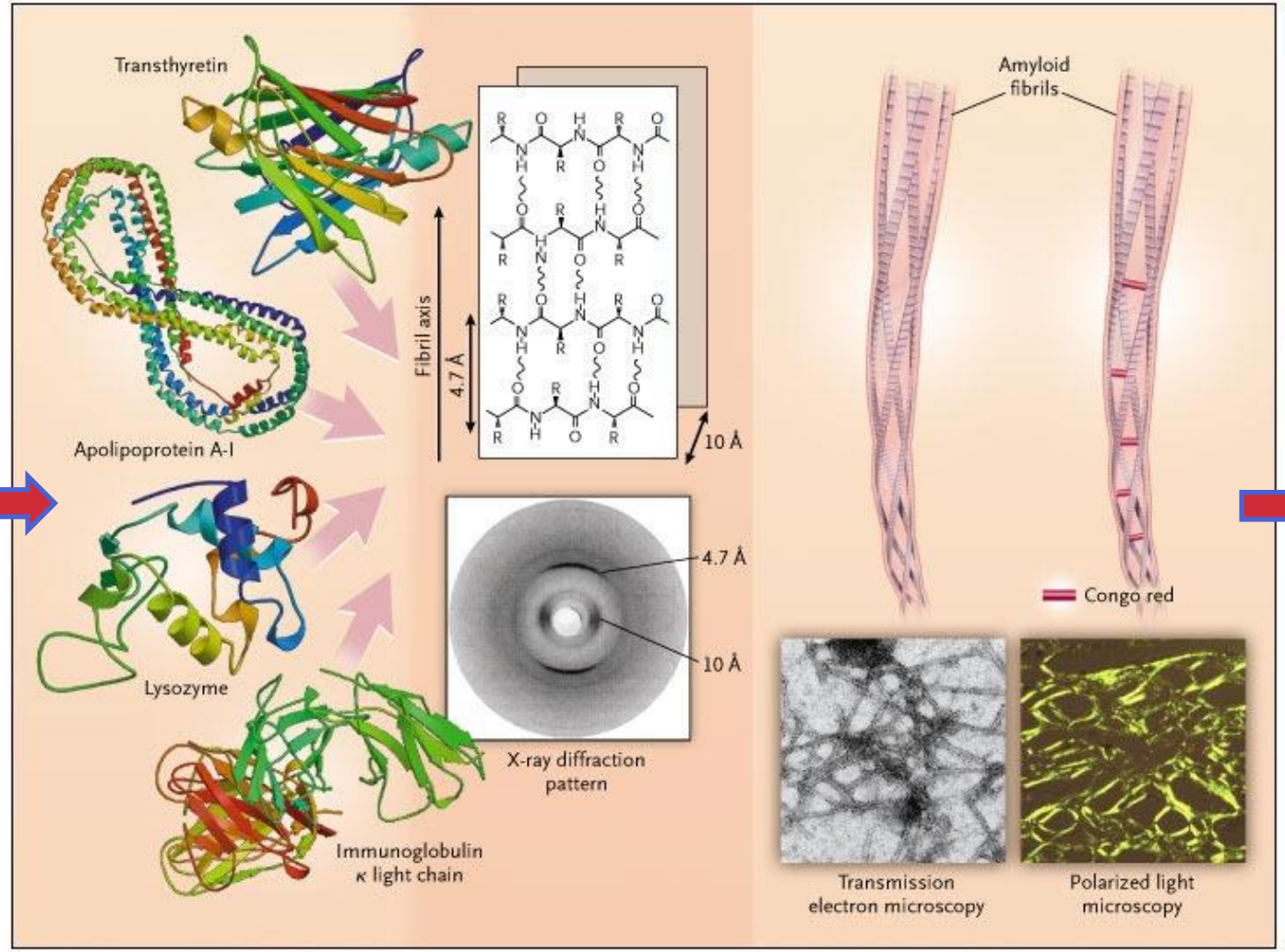
Systemic amyloidoses: protein misfolding diseases

- Intrinsic propensity
- Increased propensity (mutations)
- Increased concentration (increased synthesis reduced clearance)



- Cell death
- Tissue damage
- Organ dysfunction

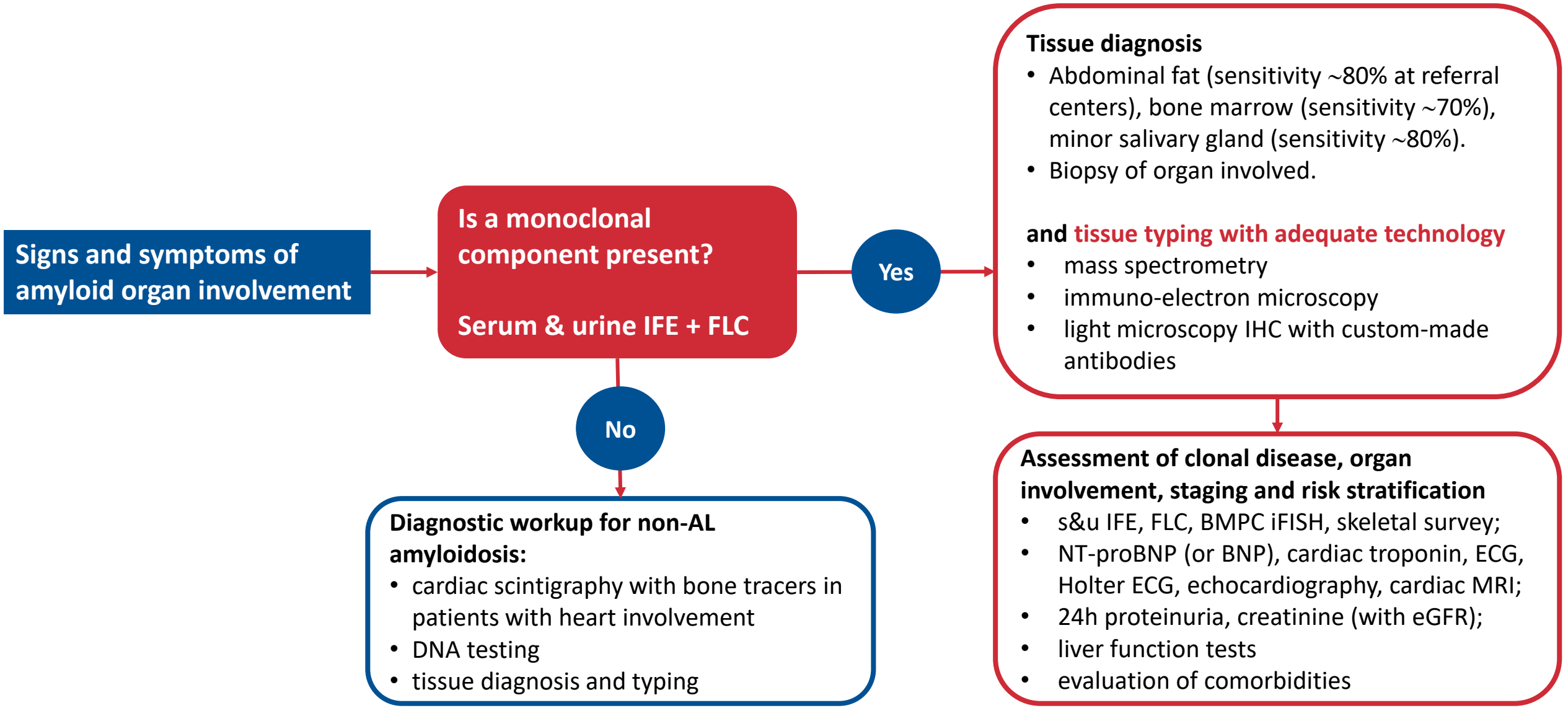
Merlini & Bellotti NEJM 2003

The main types of systemic amyloidosis have overlapping clinical presentations

Amyloid Type	Precursor protein	Major organ involvement					
		Heart (bone tracers uptake)	**Kidney**	**Liver**	**PNS**	**ANS**	**ST**
AL amyloidosis (acquired)	Immunoglobulin light chain	+++ (usually absent, can be intense)	+++	++	+	+	++
ATTRv amyloidosis (hereditary)	Mutated transthyretin	+++ (usually intense, can be absent in some variants)	-	-	+++	+++	-
ATTRwt amyloidosis (acquired)	Wild type transthyretin	+++ (usually intense)	-	-	-	-	+
ApoAI amyloidosis (hereditary)	Mutated apolipoprotein AI	+ (present)	+	+++	-	-	-
AA amyloidosis (acquired)	Serum amyloid A protein	+	+++	+	-	+	-
ALECT2 (acquired)	Leukocyte chemotactic factor 2	-	+++	+	-	-	-

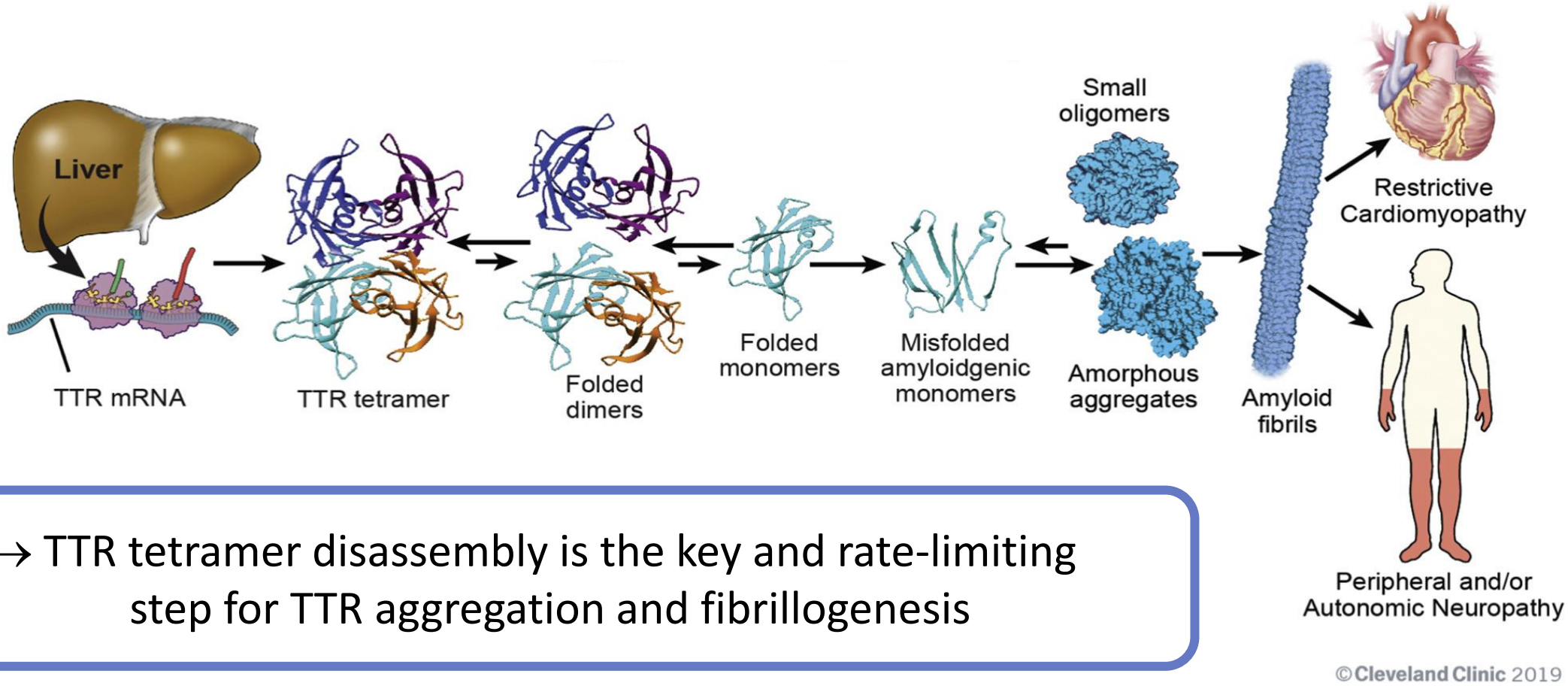
Palladini, et al. Blood 2020

Diagnosis of systemic amyloidosis



Palladini, et al. Blood 2020

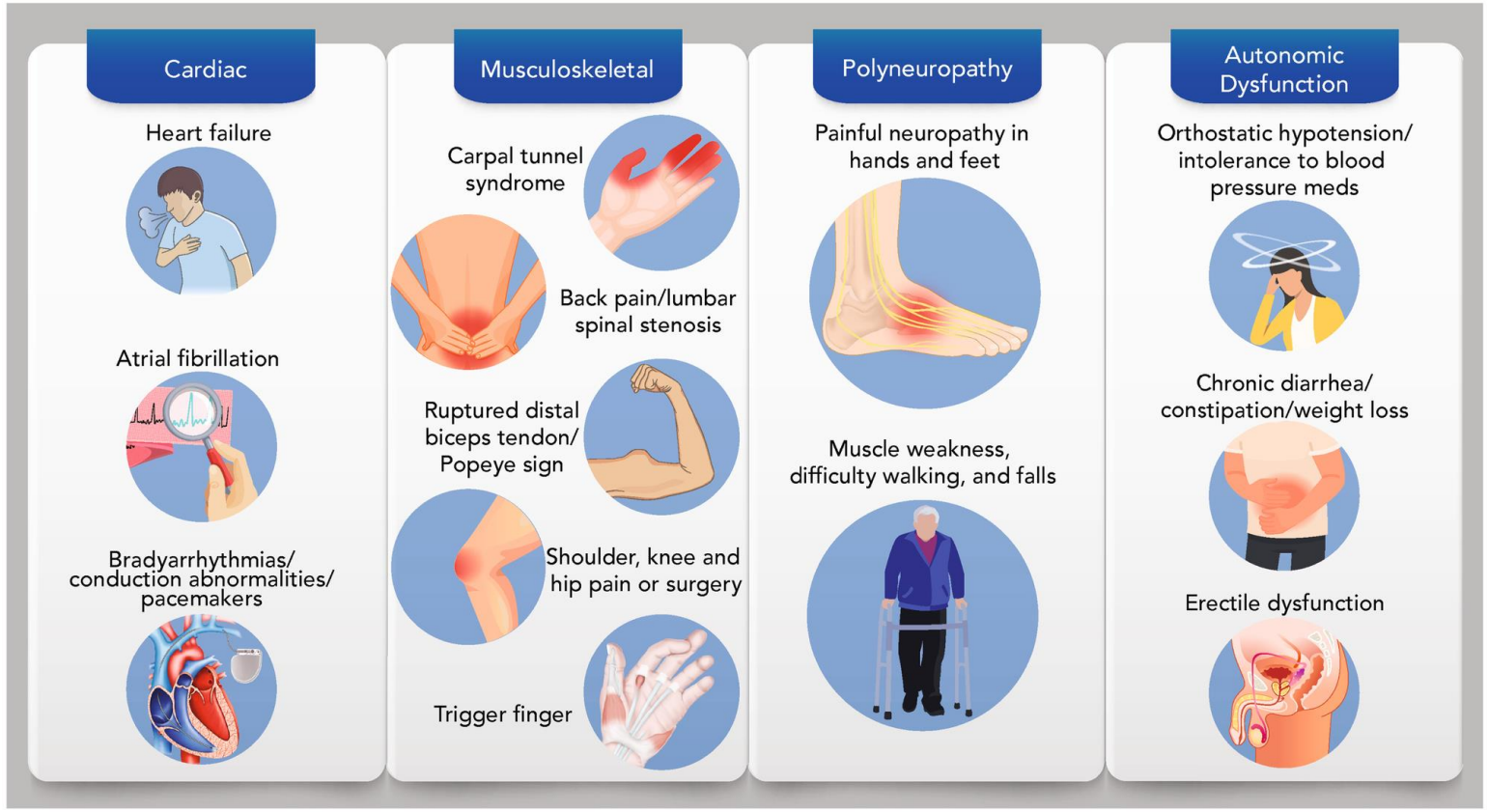
Pathobiology of ATTR amyloidosis: tetramer dissociation



→ TTR tetramer disassembly is the key and rate-limiting step for TTR aggregation and fibrillogenesis

Ruberg, et al. J Am Coll Cardiol 2019

ATTR amyloidosis: clinical manifestations and disease burden

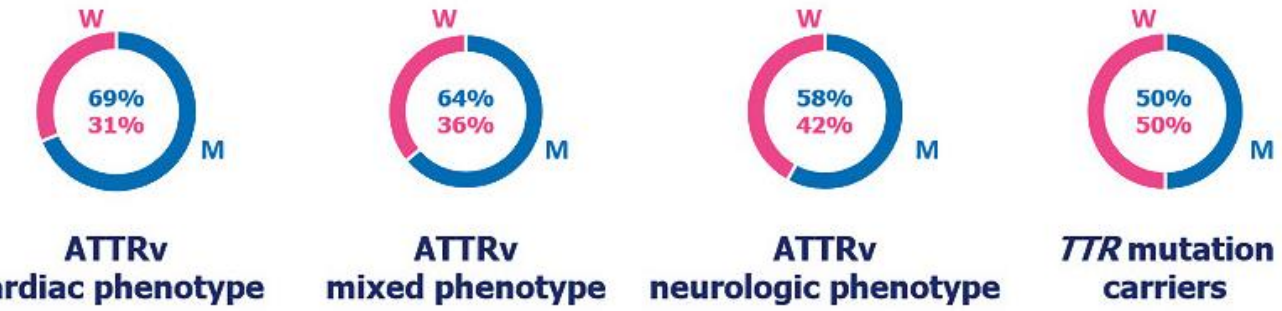


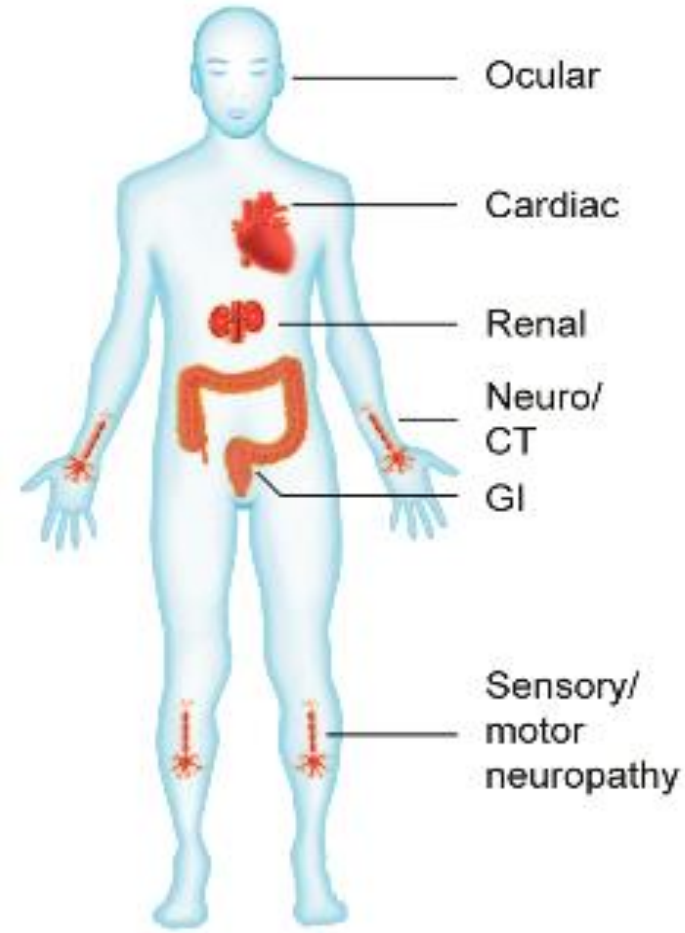
Nativi-Nicolau & Maurer, Curr Opin Cardiol 2018
Muchtar, et al. J Intern Med 2021

ATTRv amyloidosis

ATTRv amyloidosis[1]

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

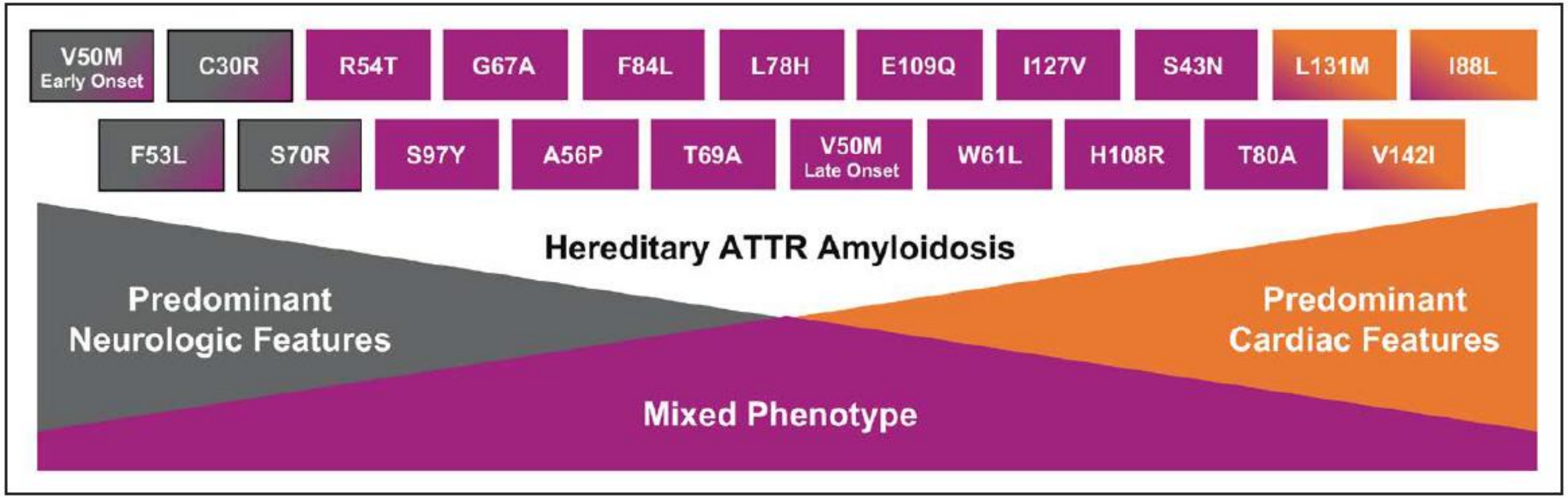




Nativi-Nicolau & Maurer Curr Op Cardiol 2018
Rapezzi, et al. Eur J Heart Fail 2022

ATTRv amyloidosis: genotype/phenotype correlations

- Some variants associated with an exclusive cardiac phenotype are **indistinguishable from ATTRwt amyloidosis**[1,2]
- A mixed neurologic and cardiac phenotype predominates in non-endemic areas
- Rapid disease progression and worse prognosis in patients with mixed phenotype



Maurer MS, et al. Circ Heart Fail 2019
Scirpa R, et al. Front Cardiovasc Med 2023

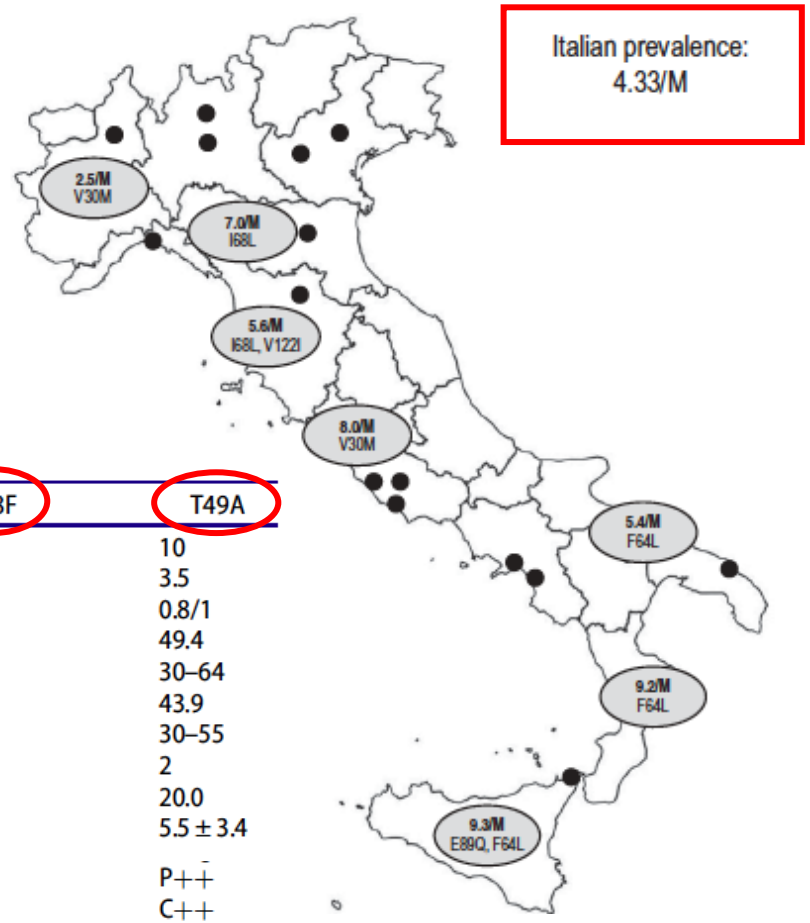
Genetics of ATTRv amyloidosis

Obi, et al. Methodist Debakey Cardiovasc J 2022

Genetics of ATTRv amyloidosis

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.

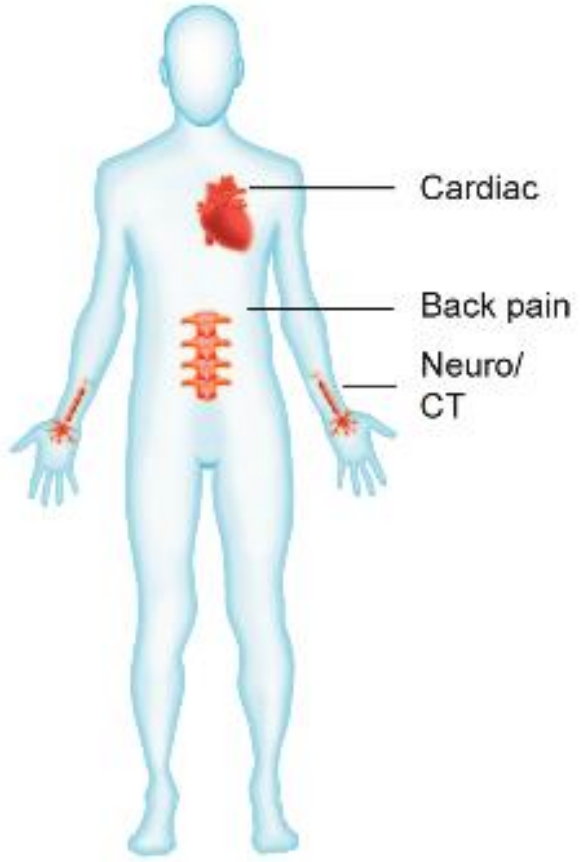
	I68L	F64L	V30M	E89Q	V122I	Y78F	T49A
Number of symptomatic patients	47	58	60	33	13	13	10
%	18.1	22.3	23.1	12.7	5.0	5.0	3.5
Male/female ratio	2.6/1	3.8/1	3/1	1.3/1	3.3/1	12/1	0.8/1
Mean age (years)	72.4	70.2	66.2	58.5	73.7	72.6	49.4
Age range (yrs)	56–82	44–86	44–87	43–79	64–87	61–87	30–64
Mean age at 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, et al. Amyloid 2020

ATTRwt amyloidosis

ATTRwt amyloidosis[2]

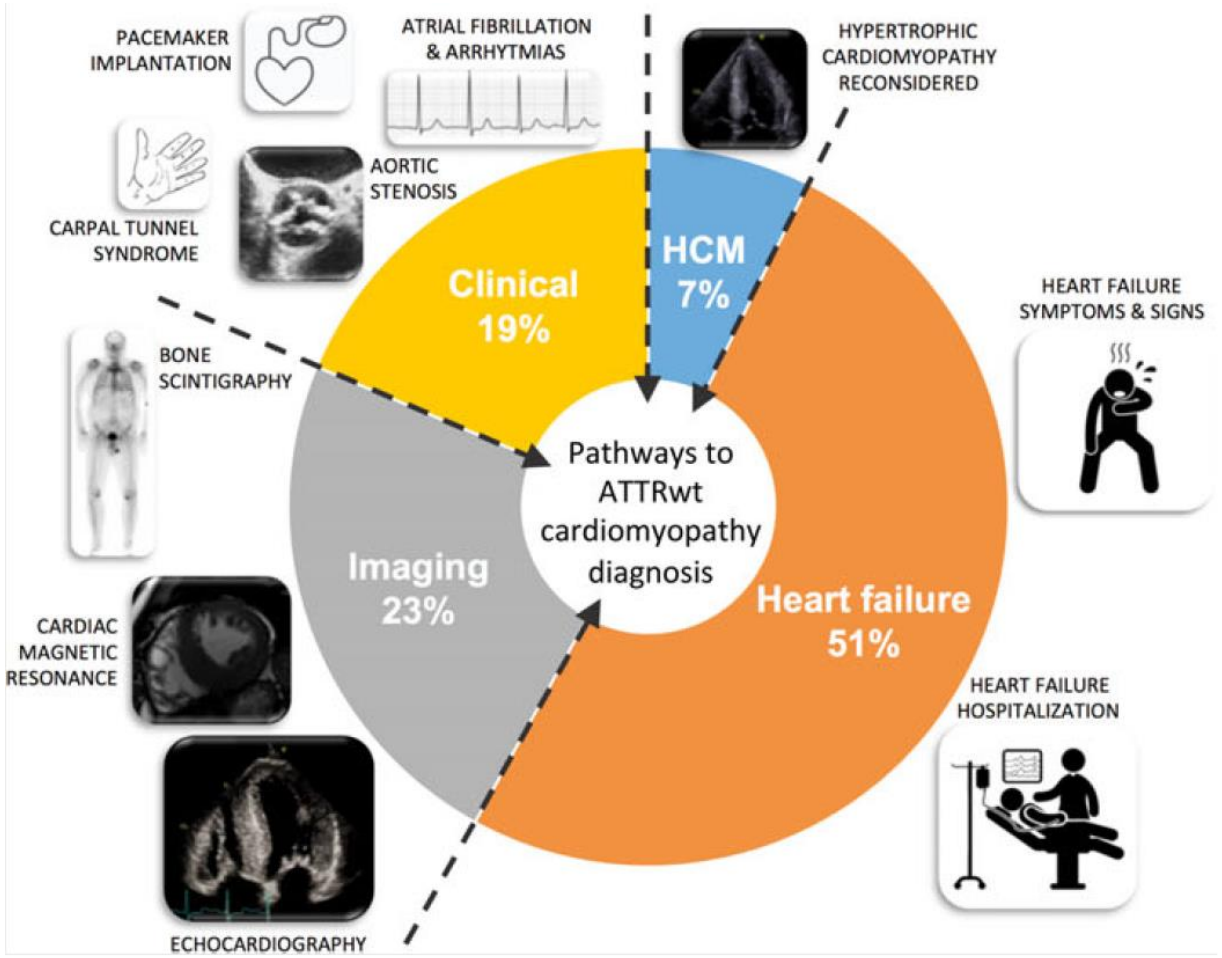
- Non-hereditary, progressive disease
- Predominantly manifests as cardiomyopathy

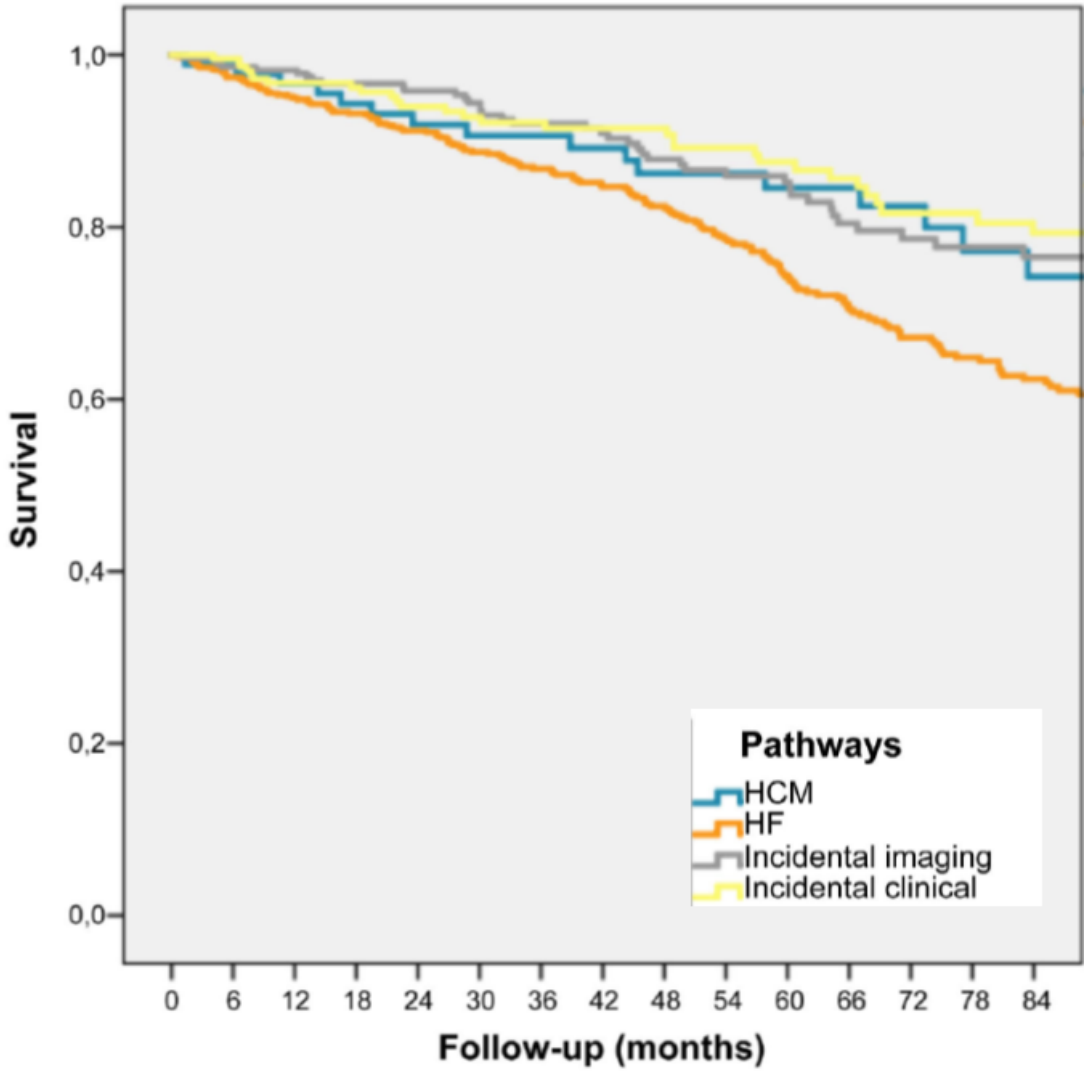


Images adapted from Rapezzi C, et al. *Eur J Heart Fail* 2022;24(12):2364–6 and Nativi-Nicolau J, Maurer MS. *Curr Opin Cardiol* 2018;33(5):571–79.

Nativi-Nicolau & Maurer, Curr Opin Cardiol 2018
Muchtar, et al. J Intern Med 2021
Rapezzi, et al. Eur J Heart Fail 2022

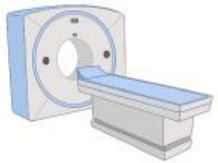
ATTRwt amyloidosis: pathways to diagnosis





- *Tini, et al. Eur J Heart Failure 2023*

Prevalence of cardiac amyloidosis in screening studies

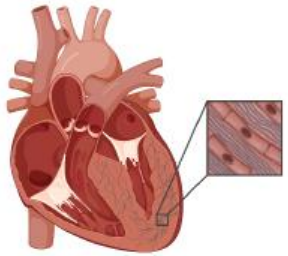


Bone scintigraphy
for non-cardiac reasons:
≥81 years: ~1.3% M, ~0.4% W

Autopsy in unselected
elderly individuals: 21%
(95% CI 7-39%)

HFpEF: 12%
(95% CI 6-20%)
M 73% (39-100%)
77 years (66-86)
AL-CA 10% (0-40%)

Aortic stenosis: 8%
(95% CI 5-13%)
M 67% (50-89%)
84 years (75-88)
AL-CA 2% (0-6%)



HFrEF/HFmrEF: 10%
(95% CI 6-15%)
M 100%
81 years (76-85)
AL-CA 0%

Prevalence of cardiac amyloidosis in screening studies

HCM: 7%
(95% CI 5-9%)
M 80% (73-87%)
74 years
AL-CA 0-9%

Surgery for carpal tunnel
syndrome: 7%
(95% CI 5-10%)
M 64% (33-100%)
76 years (73-79)
AL-CA 18% (0-33%)

Conduction disorders: 2%
(95% CI 0-4%)
M 50%
90 years
AL-CA 0%

Aimo, et al. Eur J Heart Fail 2022;24(12):2342–51.

ATTRwt amyloidosis and orthopedic surgery

Amyloid. 2017 Dec;24(4):226-230. doi: 10.1080/13506129.2017.1375908. Epub 2017 Sep 14.

Hip and knee arthroplasty are common among patients with transthyretin cardiac amyloidosis, occurring years before cardiac amyloid diagnosis: can we identify affected patients earlier?

Rubin J[1], Alvarez J[1], Teruya S[1], Castano A[1], Lehman RA[2], Weidenbaum M[2], Geller JA[2], Helmke S[1], Maurer MS[1].

- 23.3% of patients with ATTR cardiac amyloidosis underwent lower extremity arthroplasty[1]
- On an average, arthroplasty occurred 7.2 years before ATTR cardiac amyloidosis diagnosis[1]

Clin Res Cardiol. 2019 Apr 5. doi: 10.1007/s00392-019-01467-1. [Epub ahead of print]

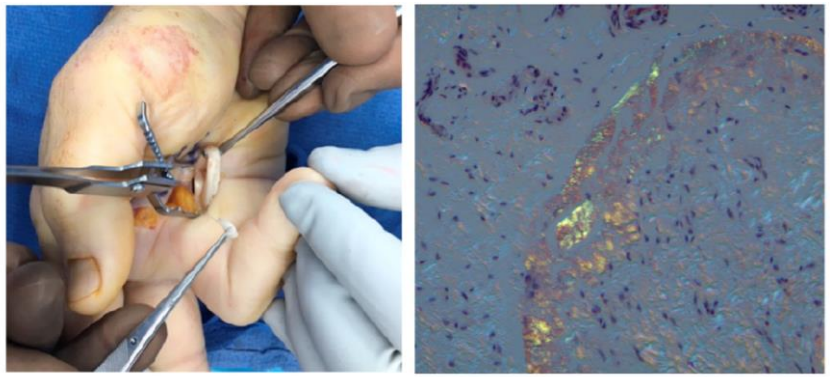
Carpal tunnel syndrome and spinal canal stenosis: harbingers of transthyretin amyloid cardiomyopathy?

Aus dem Siepen F[1], Hein S[2], Prestel S[2], Baumgärtner C[2], Schönland S[3], Hegenbart U[3], Röcken C[4], Katus HA[2,5], Kristen AV[2].

- History of CTS in 60% of patients with ATTRwt amyloidosis
- History of clinically significant spinal canal stenosis in 14% of patients with ATTRwt amyloidosis

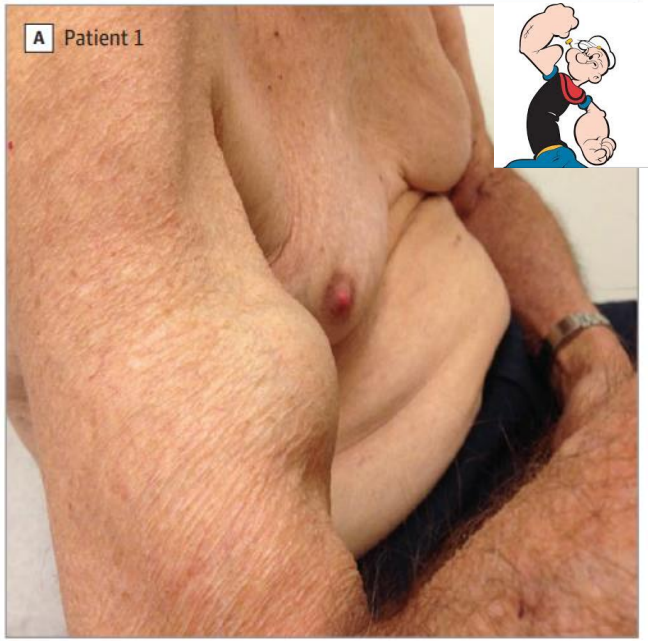
Other musculoskeletal manifestations of ATTR amyloidosis

Trigger finger



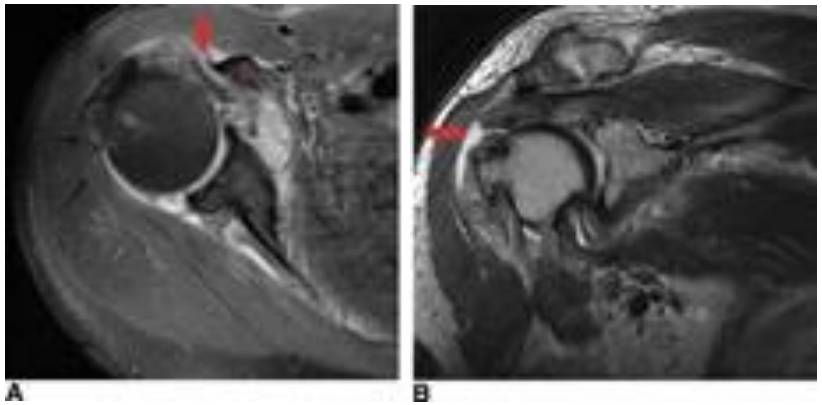
- Common orthopedic manifestation of amyloidosis
- Biopsy of tenosynovium can detect amyloid[1,3]

Distal biceps tendon rupture



- In 33.3% of patients with ATTRwt amyloidosis vs 2.5% of patients with other causes of HF[2,3]

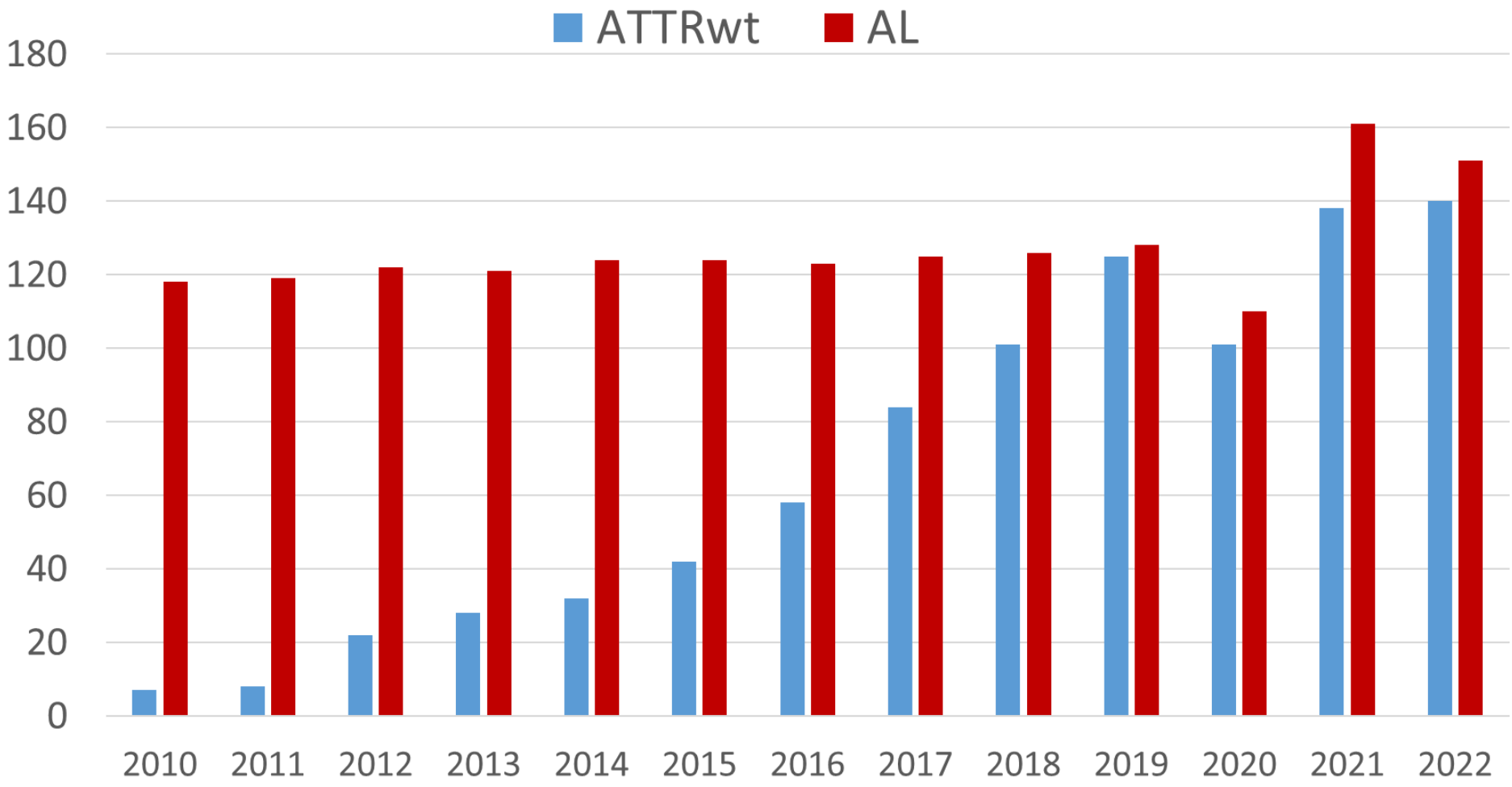
Rotator cuff disease



- Common in patients with ATTRwt amyloidosis
- Can cause spontaneous or minimally traumatic rotator cuff rupture[3]

Sperry, et al. Am J Cardiol 2021
Geller, et al. JAMA 2017
Zhang, et al. J Am Acad Orthop Surg 2021

Cardiac amyloidosis in Pavia



International Journal of Cardiology 382 (2023) 87–90

Contents lists available at ScienceDirect

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]

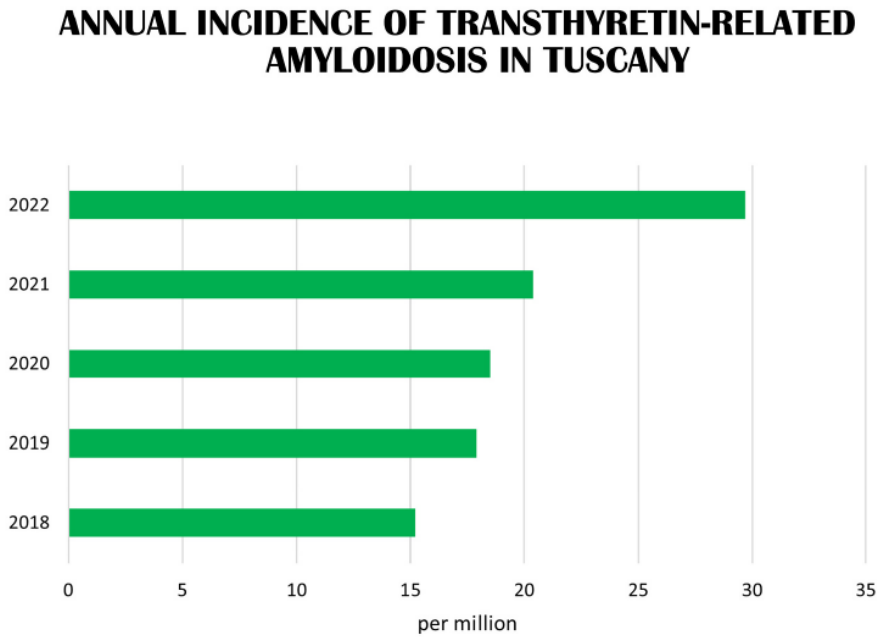


Fig. 2. Annual incidence of transthyretin-related amyloidosis in Tuscany region, for the period from 2018 to 2022.

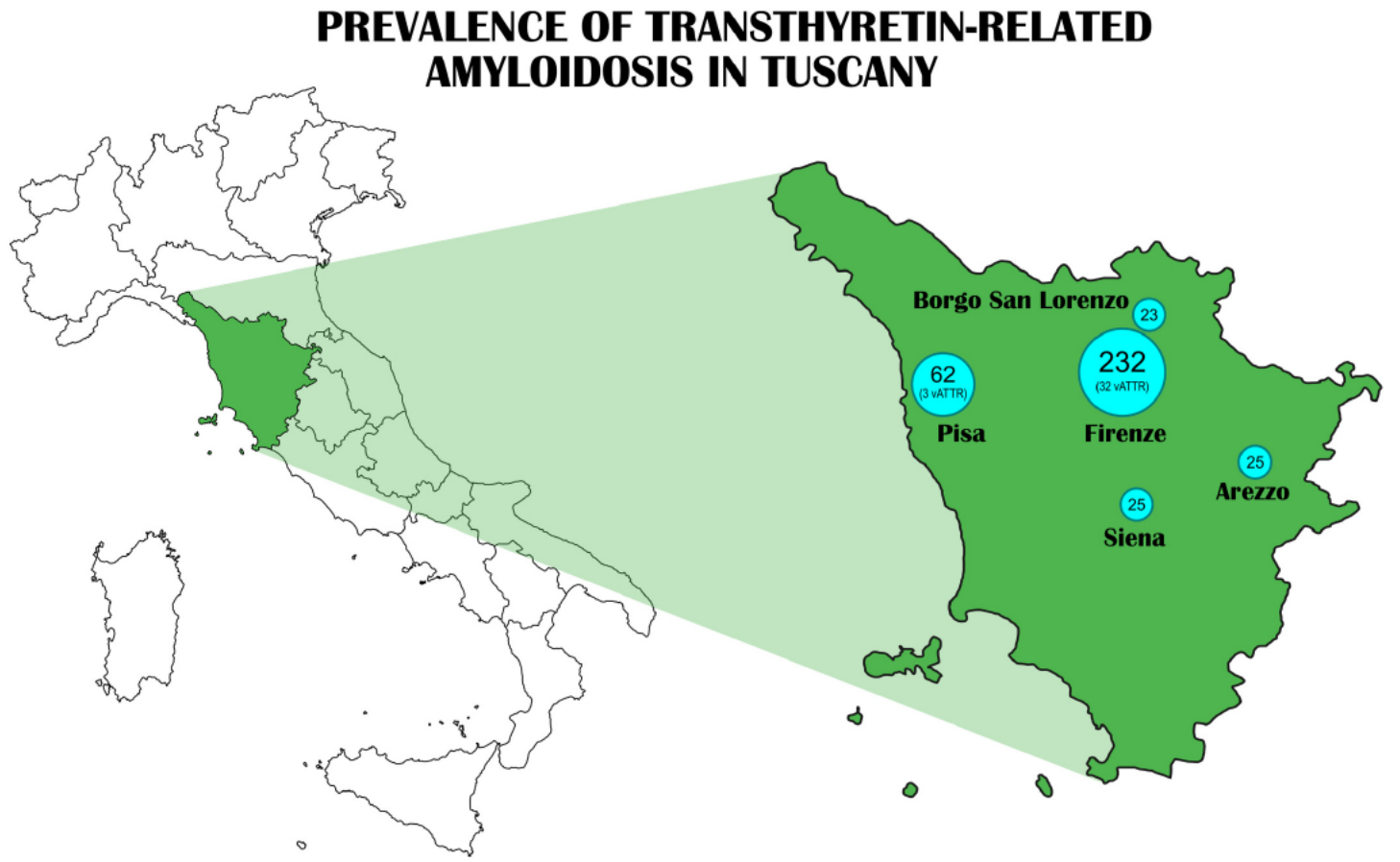
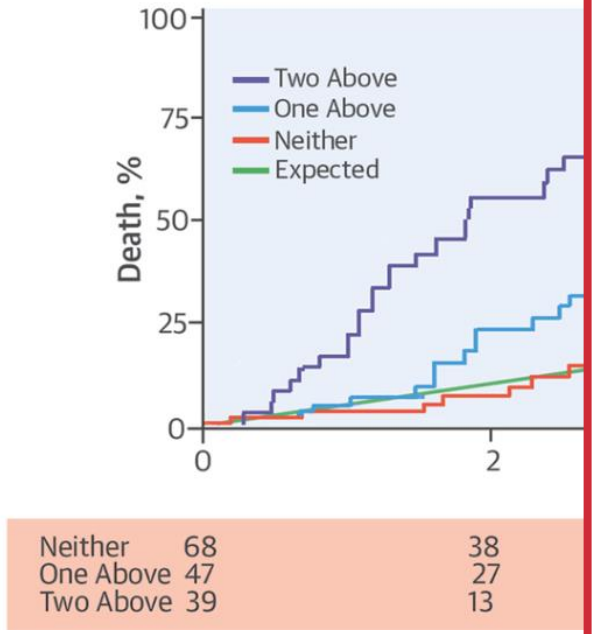


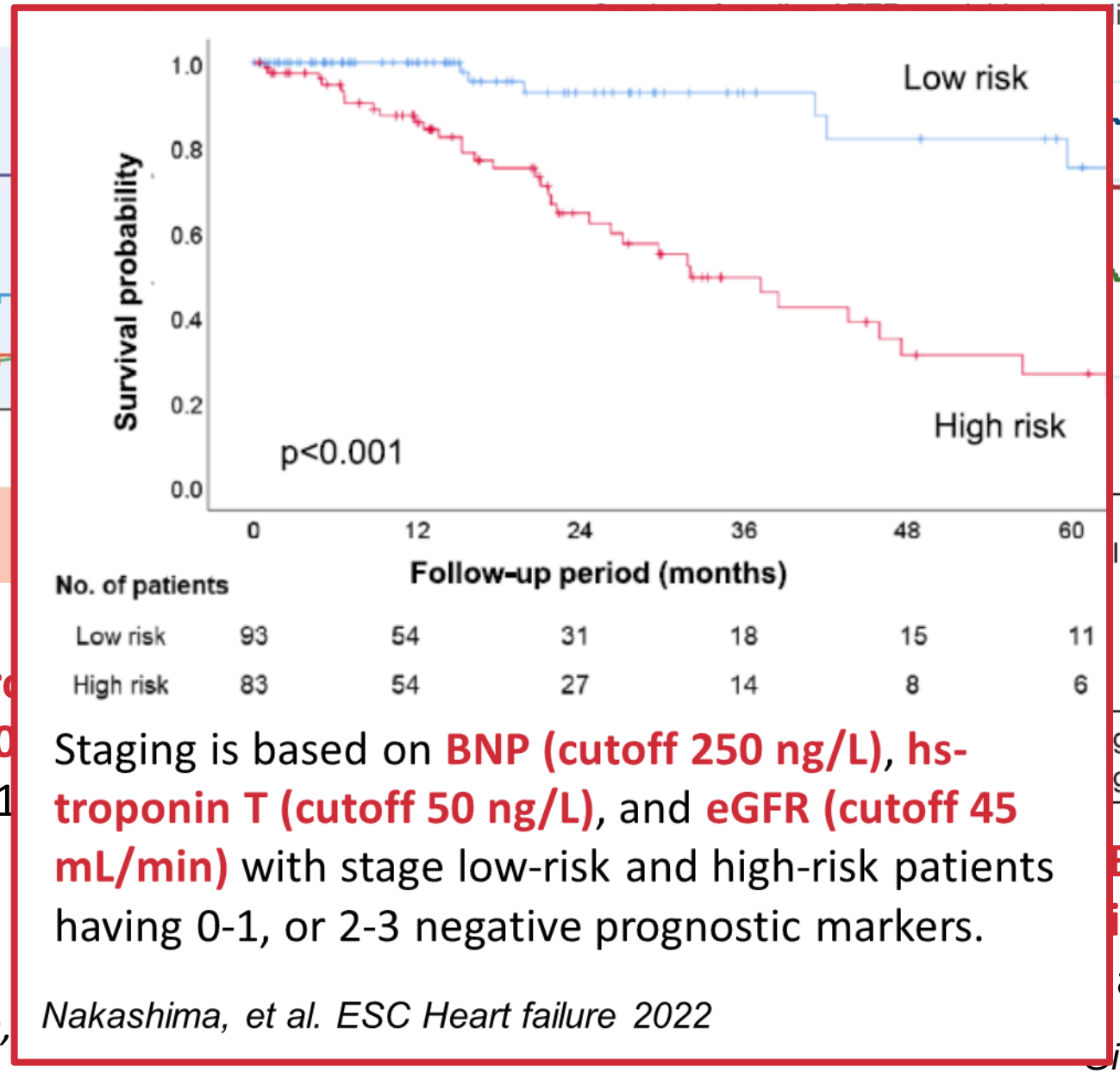
Fig. 1. Geographical distribution in Tuscany region of the centres involved in the management of patients with transthyretin-related amyloidosis and related numbers of alive patients regularly followed. Numbers in brackets indicate the subset of patients with the hereditary form.

Biomarker-based staging in ATTR amyloidosis



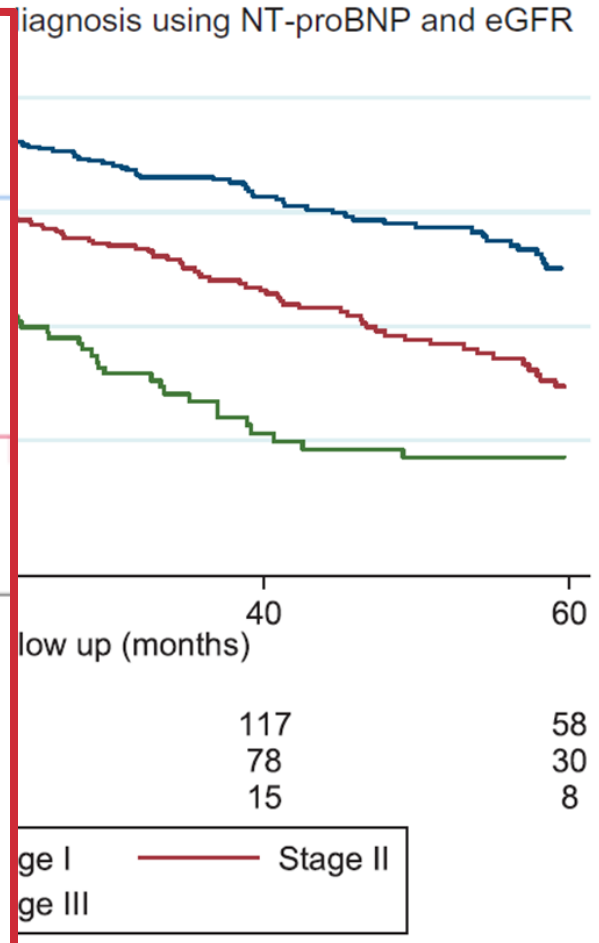
Staging is based on **NT-pro**
and **troponin T (cutoff 0.0**
and III patients having 0, 1
cutoffs.

Grogan,



Staging is based on **BNP (cutoff 250 ng/L)**, **hs-troponin T (cutoff 50 ng/L)**, and **eGFR (cutoff 45 mL/min)** with stage low-risk and high-risk patients having 0-1, or 2-3 negative prognostic markers.

Nakashima, et al. ESC Heart failure 2022



BNP (cutoff 3000 ng/L)
in) with stage I, II, and III
arkers above the cutoffs

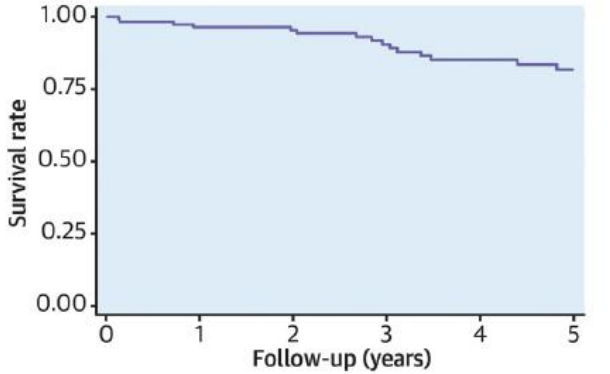
illmore, et al. Eur Heart J 2017

ATTR-CM without heart failure symptoms: natural history

118 Transthyretin amyloid cardiomyopathy patients without HF at 6 international amyloid centers
57.6% Variant transthyretin amyloidosis, 42.4% Wild-type transthyretin amyloidosis
Median age: 66 yrs Median follow-up: 3.7 years (IQR 1-6 years)

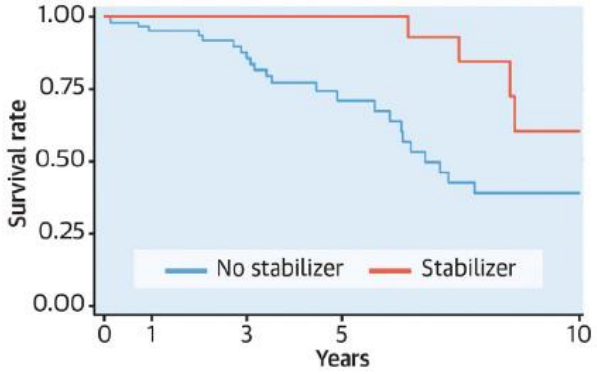
Cumulative incidence of HF onset
- 1 year: 8% (95% CI: 4%-14%)
- 3 years: 15% (95% CI: 9%-23%)
- 5 years: 27% (95% CI: 18%-37%)
- 20 patients required permanent pacemakers and 13 developed AF

Overall survival



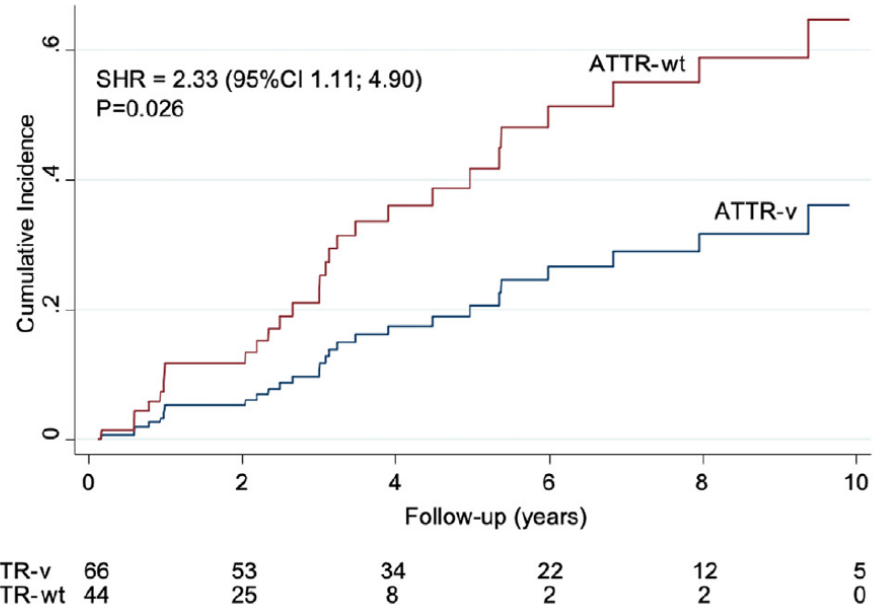
- 1 year: 96.5% (95% CI: 91%-99%)
- 3 years: 90.4% (95% CI: 82%-95%)
- 5 years: 82% (95% CI: 71%-89%)

Improved survival with stabilizers



HR: 0.31; 95% CI: 0.12-0.082; *P*=0.019

Heart failure development during follow-up



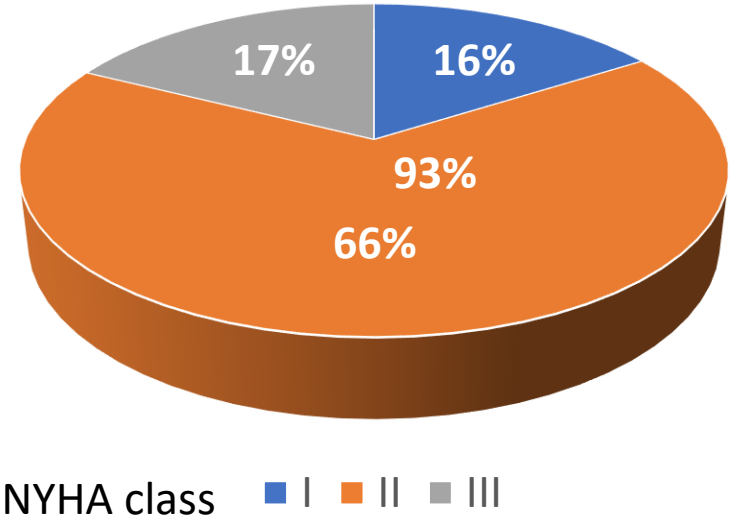
ATTR-v	66	53	34	22	12	5
ATTR-wt	44	25	8	2	2	0

Images adapted from Gonzalez-Lopez E, et al. *JACC CardioOncol* 2022;4(4):442–54..

Gonzalez-Lopez, et al. JACC CardioOncol 2022

ATTRwt - Pavia cohort (N=691 patients from 2006 to 2021)

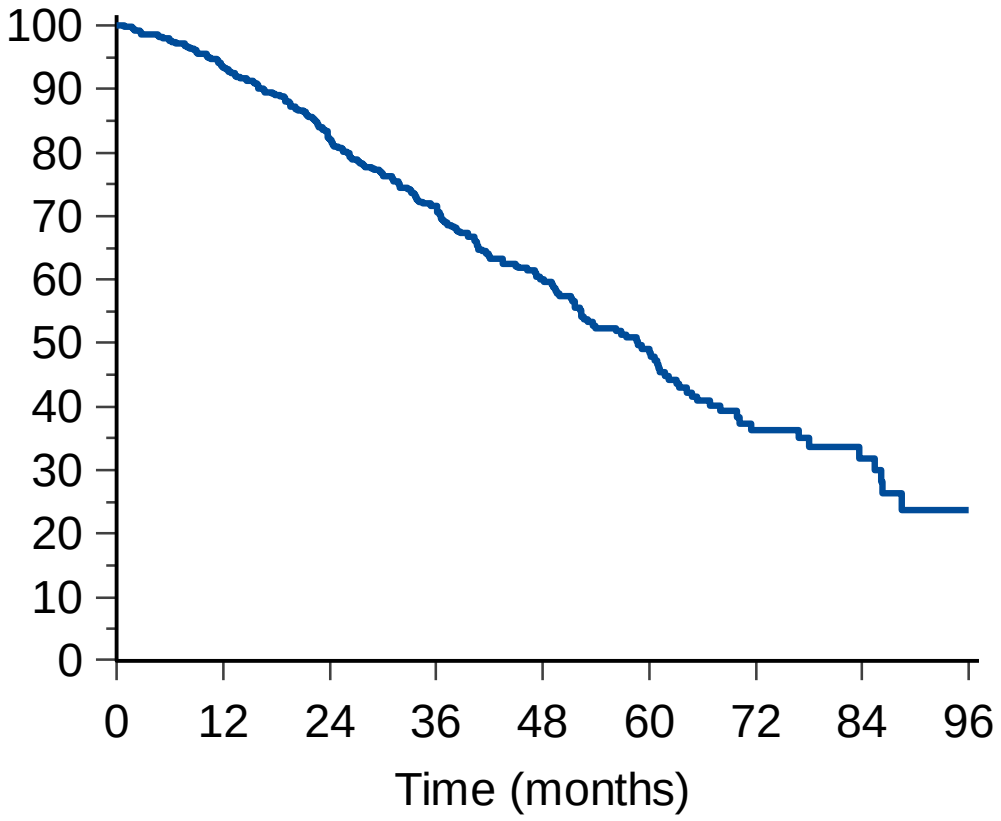
Variables	N (%) – median (IQR)
Male sex	648 (93)
Age, years	77 (72-80)
NT-proBNP, ng/L	3150 (1726-5609)
Troponin I, ng/mL	0.078 (0.046-0.132)
Creatinine, mg/dL	1.13 (0.94-1.37)
eGFR, mL/min	62 (48-77)
Alkaline phosphatase, U/L	84 (67-116)
IVS, mm	17.5 (15.5-19.3)
mLVW, mm	16.2 (14.5-18.0)
Perugini score 2 / 3 (evaluable in 526 pts.)	103 (19) / 423 (80)
Fat aspirate positive	28 (4)
Positive IFE serum and/or urine and/or abnormal FLC ratio	229 (33)



Comorbidities	N (%)
Atrial fibrillation/flutter	368 (53)
History of ischemic cardiopathy	108 (16)
Pacemaker/ICD implantation	133 (19)
Carpal tunnel syndrome	394 (57)
Hip/knee arthroplasty	167 (24)
Lower limb paresthesia	149 (21)
Lumbar spinal stenosis	28 (4)

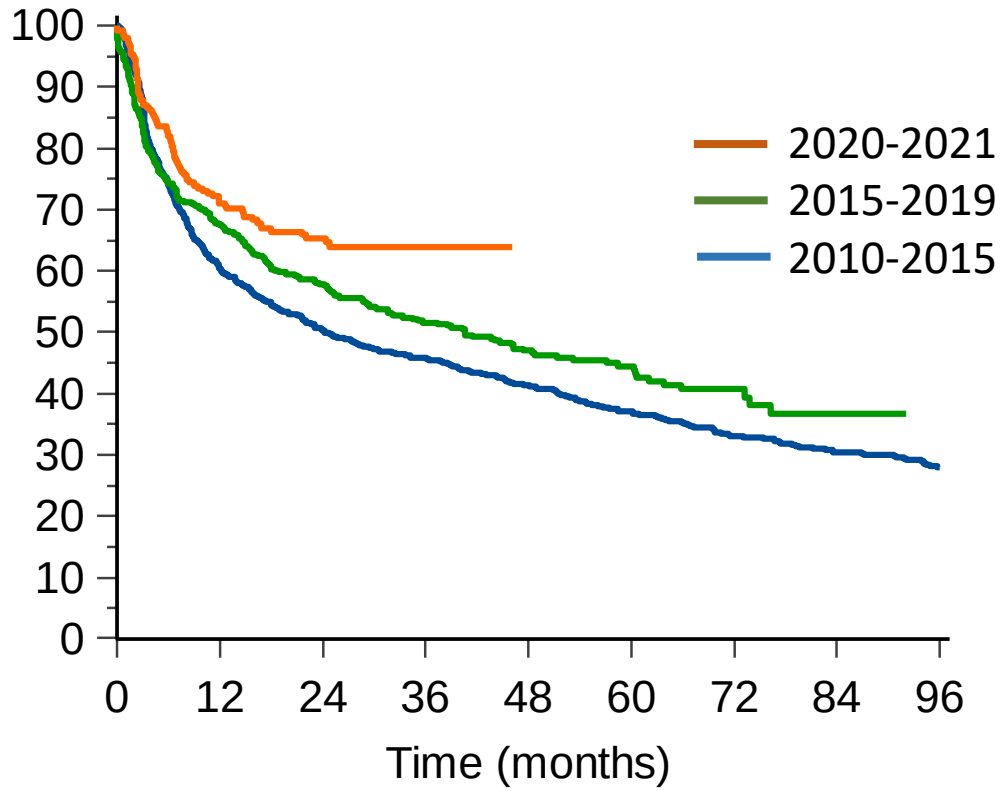
Overall survival in systemic amyloidoses

ATTRwt – N. 691



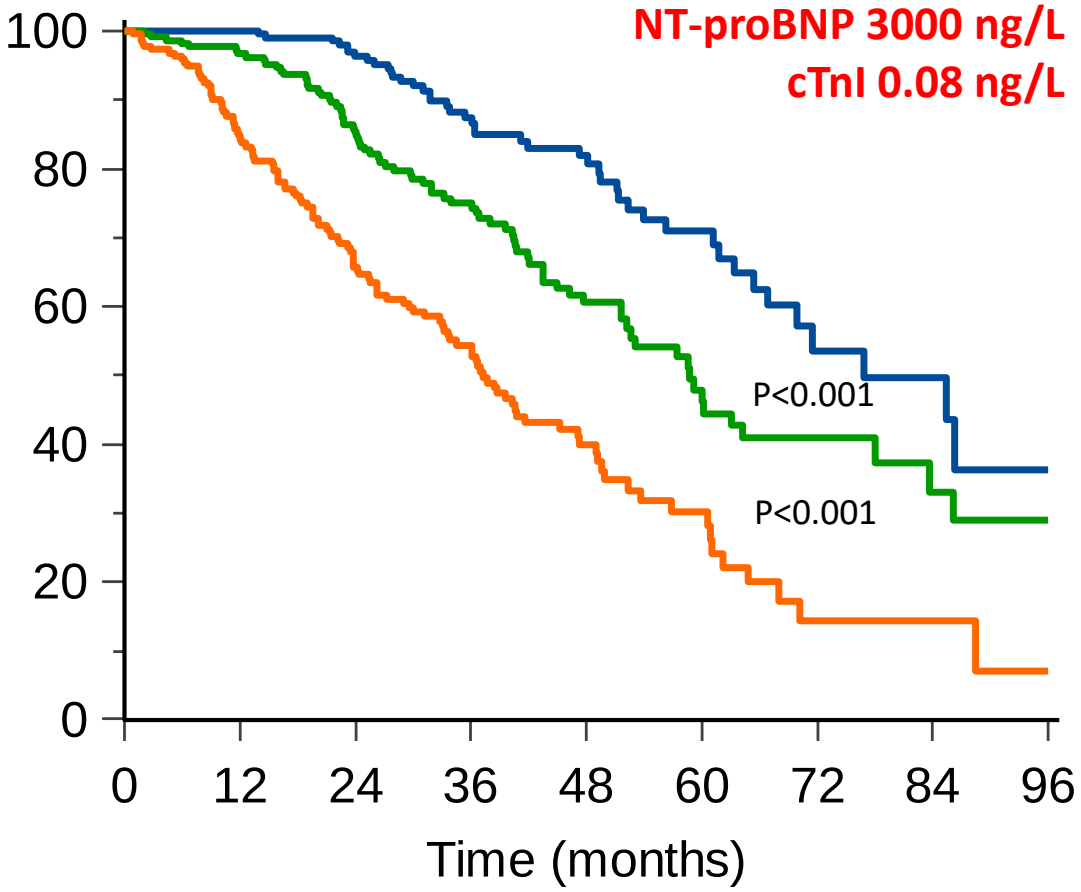
Overall median survival 58.7 months

AL amyloidosis – N. 1275



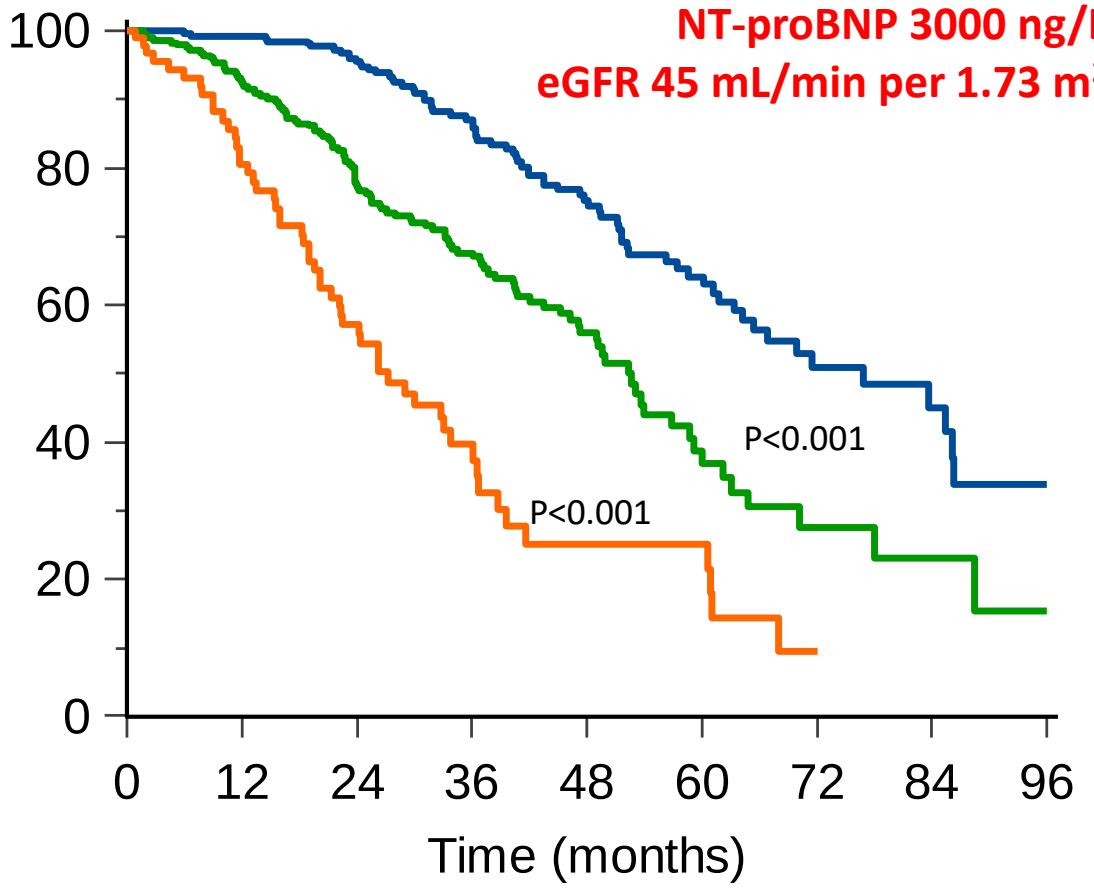
Overall survial according to the years of diagnosis

ATTRwt - Mayo Clinic staging



Stage I, N=215: median survival 77 months
Stage II, N=226: median survival 58 months
Stage III, N=225: median survival 37 months

ATTRwt - UK/French staging



Stage I, N=278: median survival 77 months
Stage II, N=294: median survival 52 months
Stage III, N=91: median survival 27 months

Conclusion

- The prevalence of ATTR amyloidosis is increasing mainly because of more frequent diagnosis of ATTRwt-CA
- Diagnosis remains complex and, in some cases, requires referral to specialized centers
- The clinical manifestations are heterogeneous but can be recognized early
- Compared to AL amyloidosis the disease progresses more slowly also in patients with heart failure
- New disease-modifying therapies give hope for future improvements.

Acknowledgments

Amyloidosis Research and Treatment Center

Giovanni Palladini
Giampaolo Merlini
Marco Basset
Claudia Bellofiore
Pietro Benvenuti
Serena Caminito
Chiara Corpina
Andrea Foli
Gianluigi Guida
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Funding/support

Amyloidosis Foundation
Societá Italiana per I'Amiloidosi
Fondazione Cariplo
European Reference Network in Rare Hematological Diseases (EuroBloodNet)
E-Rare
The Italian Foundation for Cancer Research (AIRC)
FC AECC and AIRC under the Accelerator Award Program
Cancer Research UK
Agenxia Italiana del Farmaco

EM-GLB-RDT-0091; November 2023
PP-UNP-ITA-3033; November 2023