66° CONGRESSO NAZIONALE

SNC

Palermo
18-21 Maggio 2022
Hotel San Paolo Palace

Inquadramento clinico, neurofisiologico e terapie nelle amiloidosi

Filippo Brighina

PANORMITANÆ STVDIORVM VNIVERSITATIS SIGILLVM

BIOMEDICINA NEUROSCIENZE DIAGNOSTICA AVANZATA

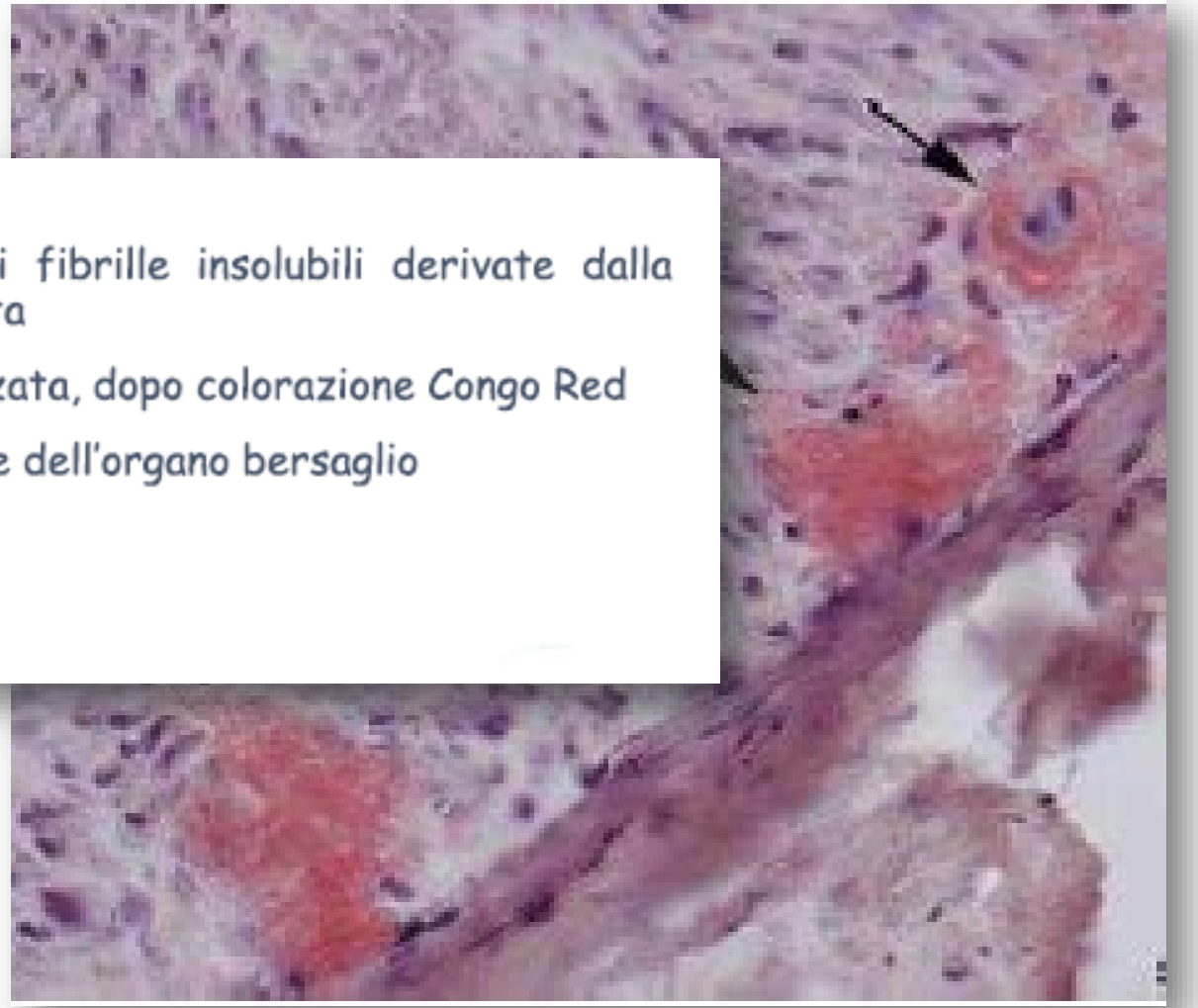
Outline

- Info generali
- Meccanismi
- Genetica, epidemiologia
- Clinica
- Terapia
- Strategie diagnostiche, attività del Centro di Palermo

AMILOIDOSI: COS'E'?

- Malattie causate dalla deposizione extracellulare di fibrille insolubili derivate dalla polimerizzazione di proteine con conformazione alterata
- Fibrilla di amiloide: birigrangenza verde in luce polarizzata, dopo colorazione Congo Red
- Decorso progressivo con danno strutturale e funzionale dell'organo bersaglio
- Espressione clinica differente; malattie rare

➢ diagnosi spesso tardiva, vera sfida per il clinico



AMILOIDOSI CLASSIFICAZIONE

Oltre 30 proteine possono formare fibrille di amiloide *in vivo*, in un singolo organo o sistemiche, con manifestazioni cliniche differenti

Amiloidosi AL (sistemica primaria)

da catene leggere immunoglobuliniche monoclonali

Amiloidosi AA (secondaria)

da proteine in corso di flogosi croniche (infettive e non) o neoplasie

Amiloidosi ereditarie

- transtiretina (hATTR)
- apoliproteina A-1
- gelsolina

AMILOIDOSI EREDITARIE

- Malattie a trasmissione AD, ad esordio adulto, causate da mutazioni di geni di proteine quali
  - Transtiretina (TTR)
  - Apoliproteina A-1
  - Gelsolina
- L' amiloidosi familiare TTR-correlata (hATTR) e' la piu' frequente
- La penetranza di queste mutazioni è elevata
- La disponibilità di test diagnostici molecolari ha favorito il riconoscimento, conducendo all'identificazione di un numero crescente di famiglie
- La prevalenza di queste forme e' ancora probabilmente sottostimata

AMILOIDOSI TTR

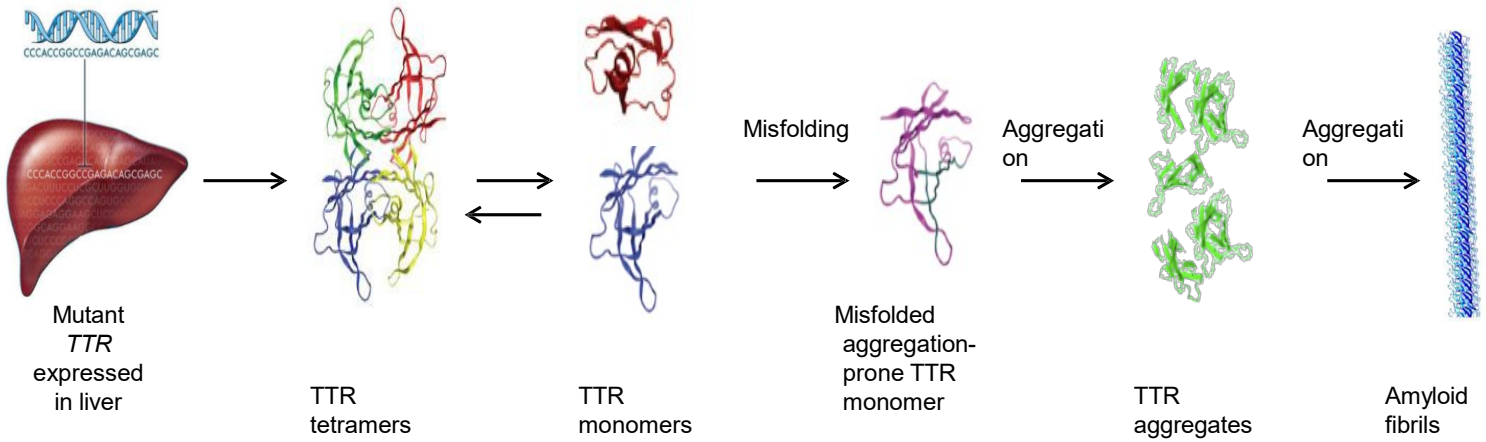
TRANSTIRETINA

- 95% of TTR is produced by the **liver** and <5% is synthesised in the **choroid plexus** of the brain and the **retinal pigment** epithelium of the eyes
- The transthyretin tetramer transports retinol through the RBP, vitamin A complex and thyroxine
- The bulk of thyroxine is carried by thyroxine-binding globulin and albumin
- <1% of TTR bound to T4

AMILOIDOSI TTR: MECCANISMI

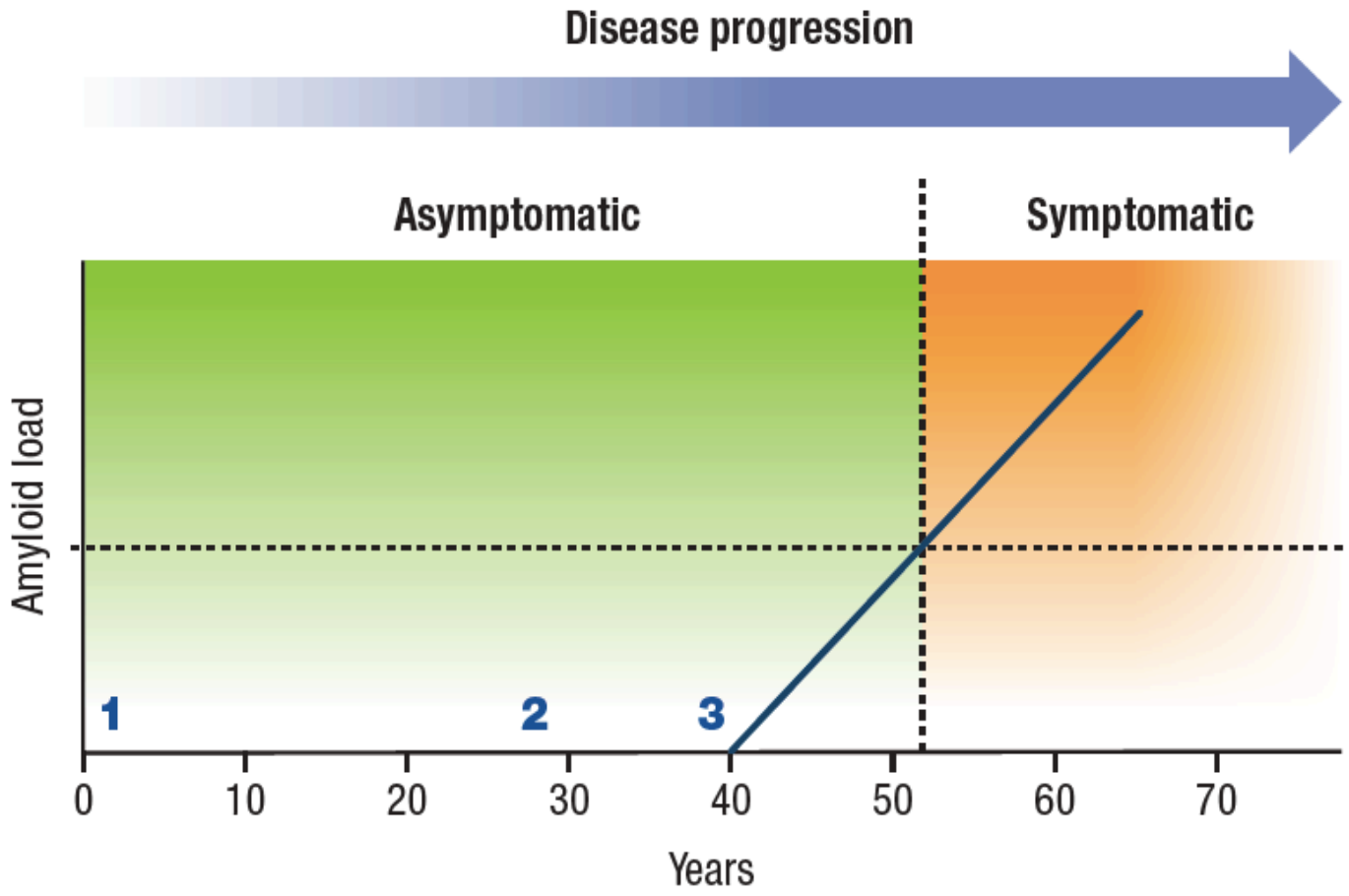
- Disordine dell' assemblaggio (*folding*) di proteine «amiloidogeniche»
- Differenti proteine possono formare fibrille amiloidi in vivo :

- proteine "wild type" : formano fibrille causando amiloidosi in età avanzata o se presenti a concentrazioni elevate
- proteine (varianti ereditarie) mutate



GI, gastrointestinal

AMILOIDOSI TTR: MECCANISMI

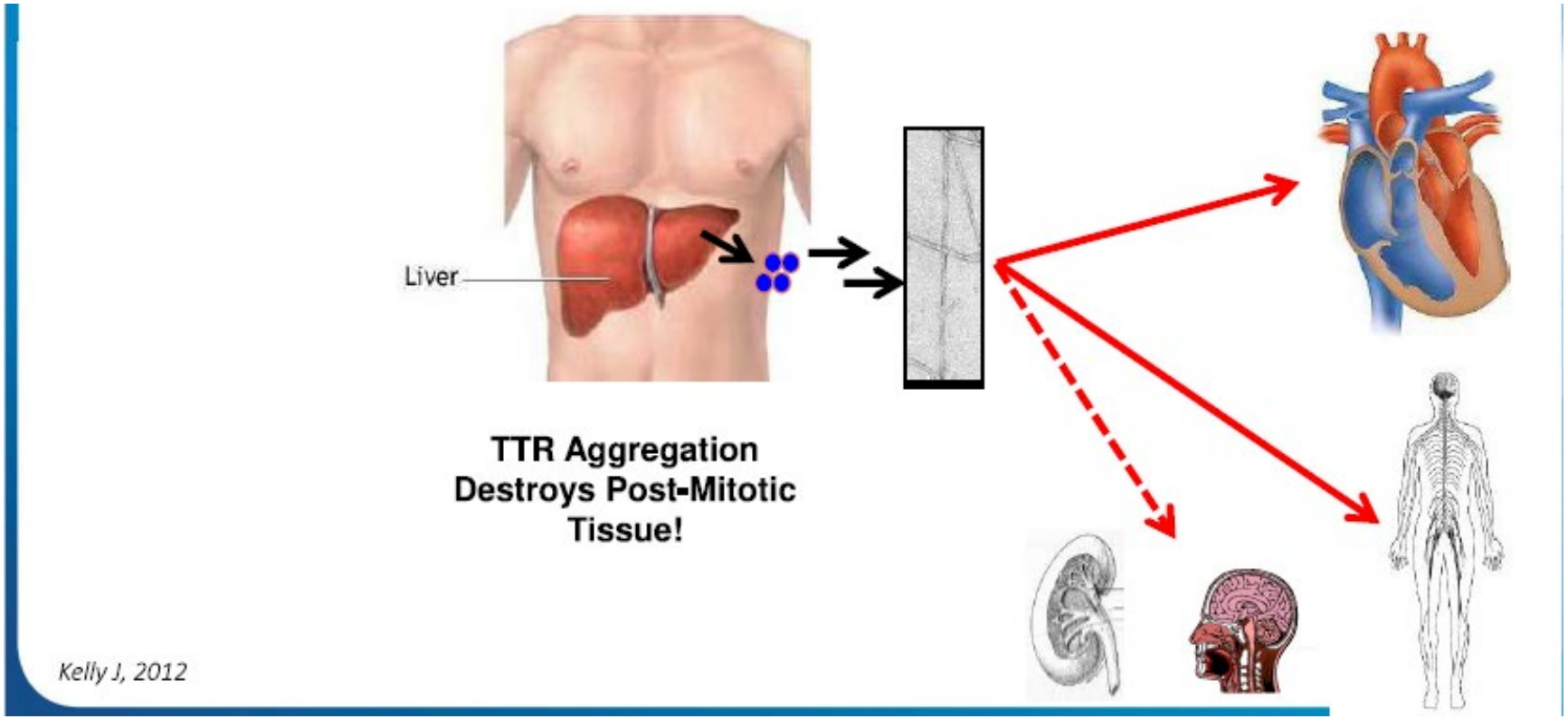


1 Production of mutant TTR

2 Initiation of non-fibrillar TTR deposition

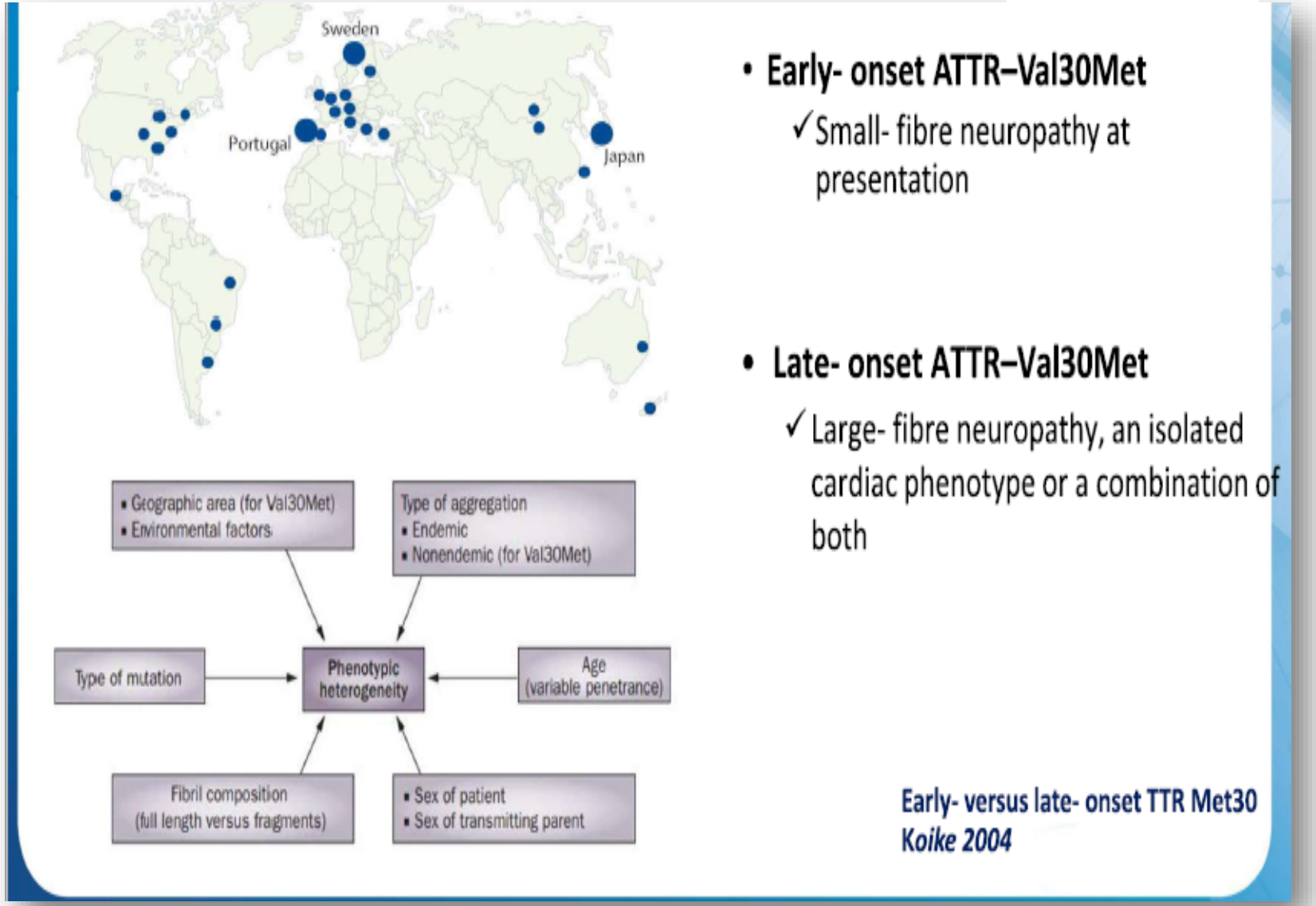
3 Initiation of amyloid deposition

Il processo patologico inizia molto prima delle comparsa dei sintomi



TTR amyloidoses are in Trans Gain-of-proteotoxicity diseases

AMILOIDOSI TTR: EPIDEMIOLOGIA, GENETICA



- **Early- onset ATTR–Val30Met**
  - ✓Small- fibre neuropathy at presentation
- **Late- onset ATTR–Val30Met**
  - ✓Large- fibre neuropathy, an isolated cardiac phenotype or a combination of both

Early- versus late- onset TTR Met30
Koike 2004

EO Val30Met

- Endemic areas :
  - Portugal, Japan, Sweden, Majorca, Brasil, Cyprus
- Major manifestations :
  - Autonomic (early satiety, alternating diarrhea, erectile dyfunction)
  - Painful , sensory loss in feet, lower limbs
  - Weight loss
- Early and easy diagnosis, positive family story
- Slowly progressive course
- Role of Mutant TTR

Late Onset Val30Met

Other variants

- Worldwide disease
- Major manifestations
  - Sensorymotor polyneuropathy 4 limbs
  - Early gait disability
  - Balance disorders
  - Few autonomic dysfunction
  - Weight loss
- Late and difficult diagnosis, TTR gene testing +++
- Uncommon positive family « sporadic »
- Rapid course
- Role of mutant TTR AND wtTTR

- **Early- onset ATTR–Val30Met**

Disturbi sensitivi

- **Late- onset ATTR–Val30Met**

and other variants

Neuropatia sensitive, sensori-motoria, CTS

Neuropatia autonomica

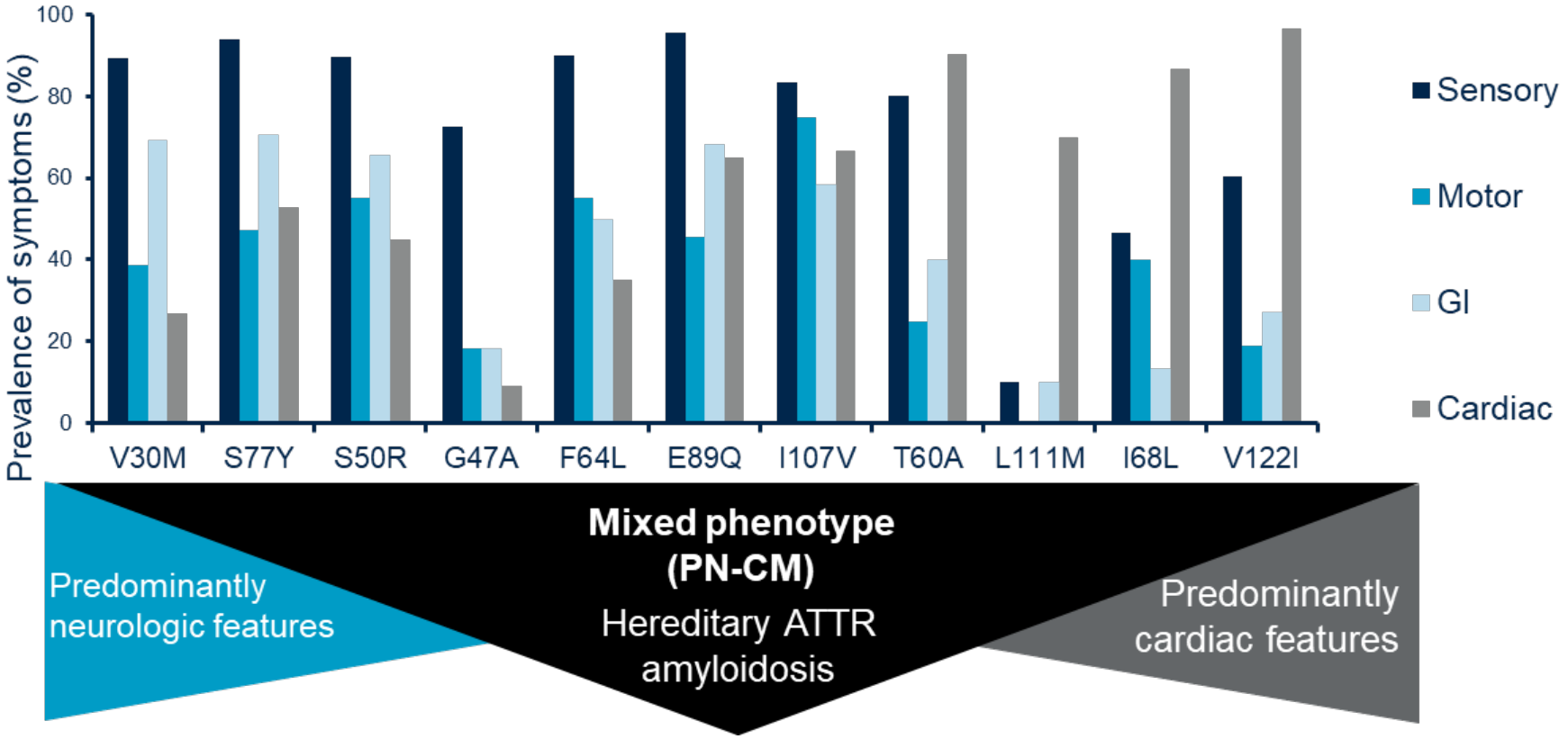
+

- **Amiloidosi cardiaca**
  - ✓Latente a lungo, sottostimata
  - ✓Manifestazioni subcliniche
  - ✓Sintomi con esordio tardivo

Sintomi

- ✓Insufficienza cardiaca con frazione eiezione conservata
- ✓Cardiomiopatia ipertrofica, sincopi cardiogene
- ✓Edemi periferici

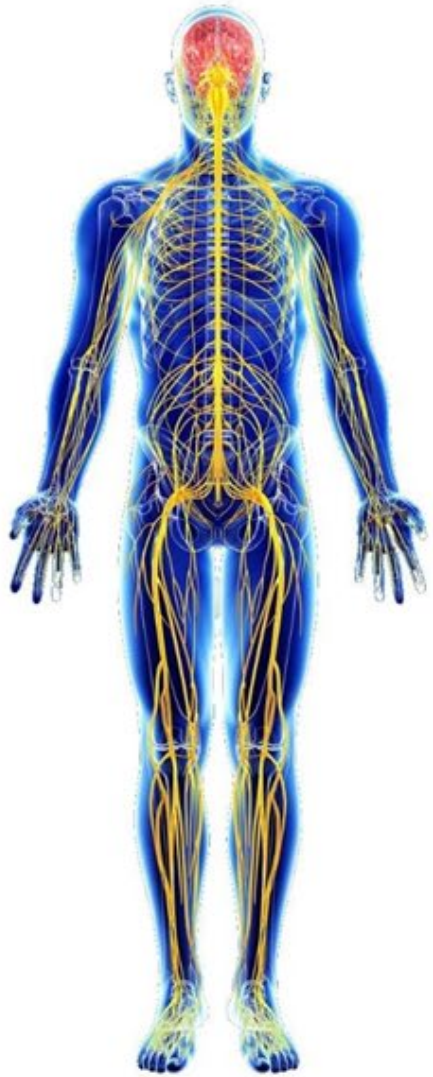
ATTRv amyloidosis is predominantly a multi-system disease that varies in symptoms according to mutation status



Adapted from Wixner J et al. 2014[1]

CM, cardiomyopathy; GI, gastrointestinal; ATTRv, hereditary transthyretin amyloidosis; PN, polyneuropathy

1. Wixner J et al. Orphanet J Rare Dis 2014;9:61.



SENSORY NEUROPATHY[1–4]

Distal at lower limbs progressing proximally to upper limbs

- Pain
- Numbness
- Impaired thermal sensitivity
- Carpal Tunnel Syndrome (CTS)

AUTONOMIC NEUROPATHY[2]

Early manifestation typically accompanying sensory deficit

- Light-headedness/dizziness
- GI disturbances
- CV disturbances
- Sexual impotence
- Impaired vasoregulation

MOTOR NEUROPATHY[1–4]

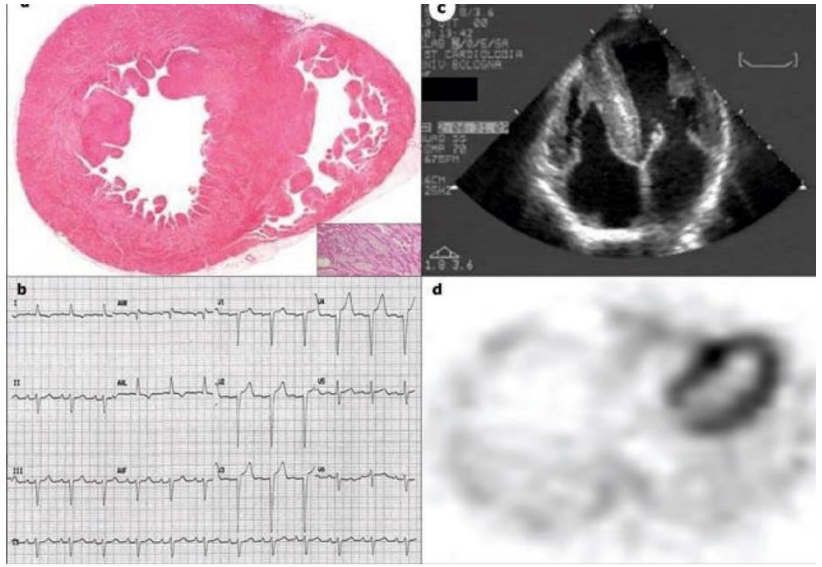
Typically occurs after sensory symptoms[2]
Involvement in distal lower limbs

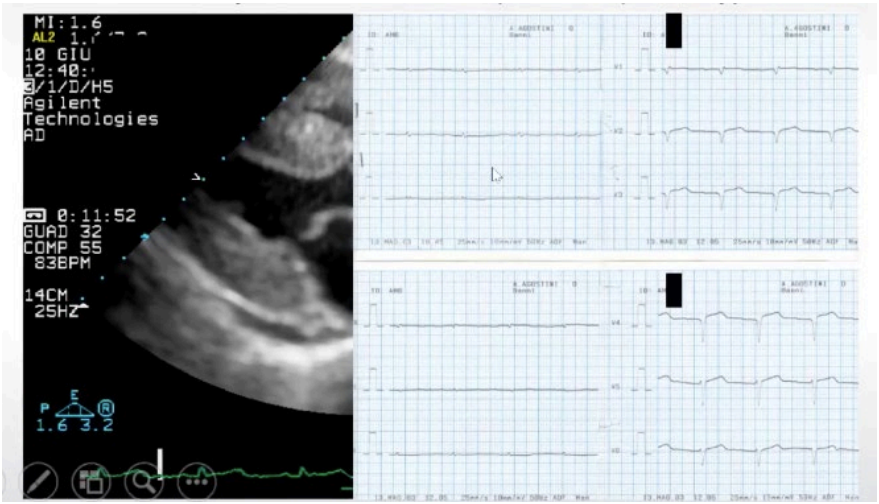
- Muscle weakness
- Increased walking difficulty
- Loss of balance
- Impaired gait

FAP, familial amyloid polyneuropathy; PND, polyneuropathy disability

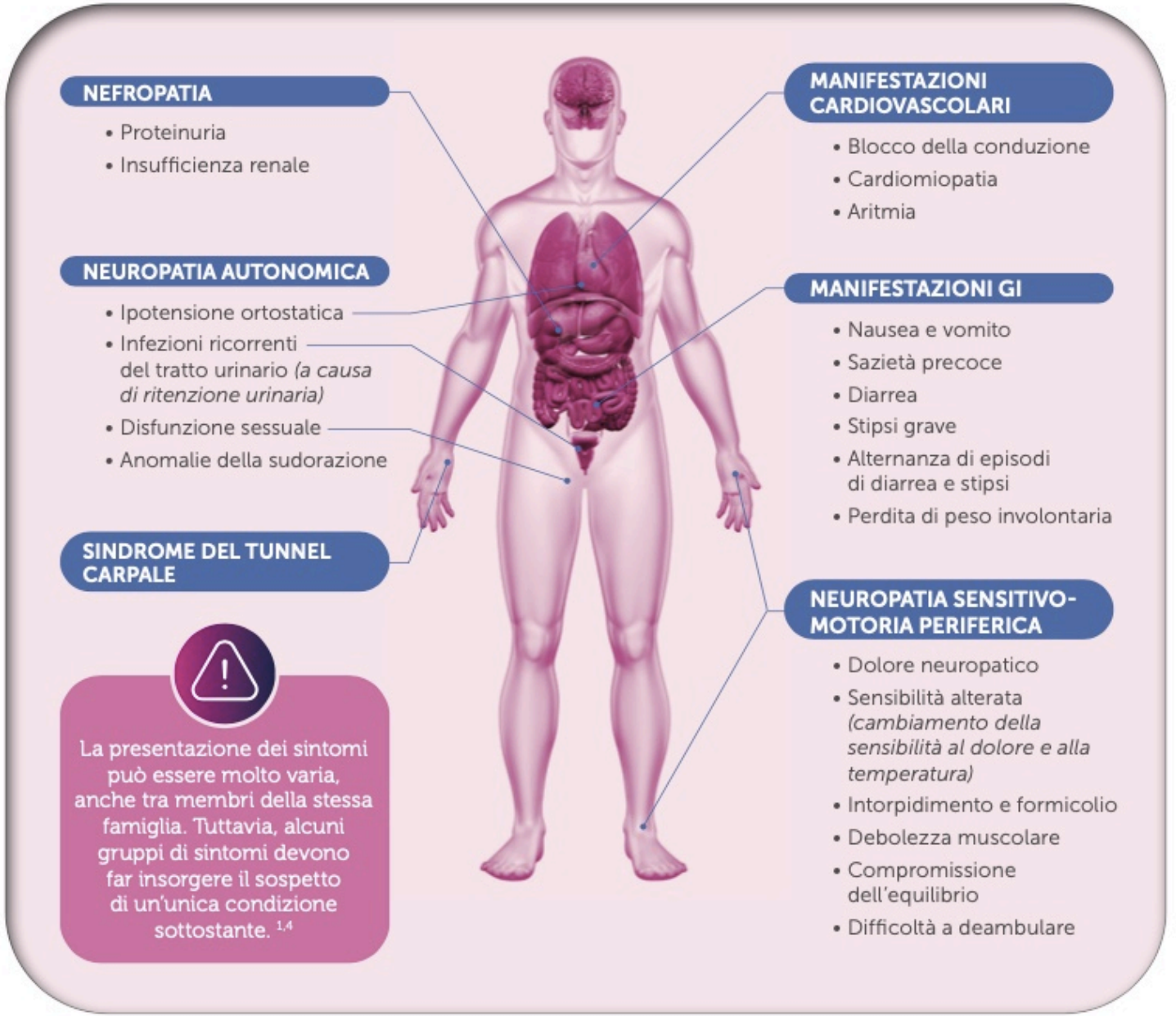
CARDIOMIOPATIA

- **Discordanza tra ECG e ecocardiografia!** Aumento degli spessore di parete con voltaggi bassi (<5mm) e onde di pseudonecrosi all'ECG che non hanno correlato all'ecocardiografia.
- **Pressione arteriosa normalizzata in un paziente precedentemente iperteso**
- **Paziente francamente ipoteso con tachicardia compensatoria**
- **Scarsa tolleranza al beta-bloccante**
- **Incremento troponina e proNTBNP in assenza di correlato clinico**

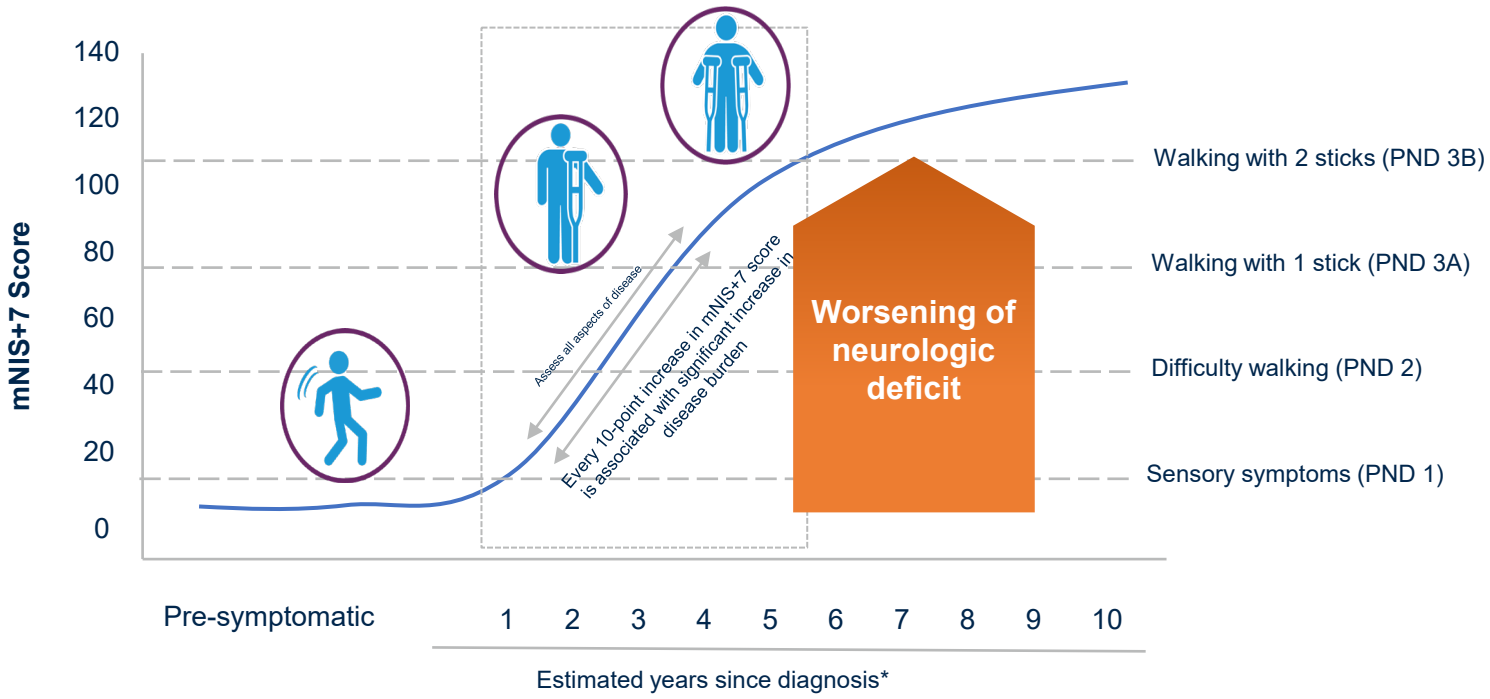




AMILOIDOSI TTR: MALATTIA MULTISISTEMICA



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



Natural history studies suggest[1–4]

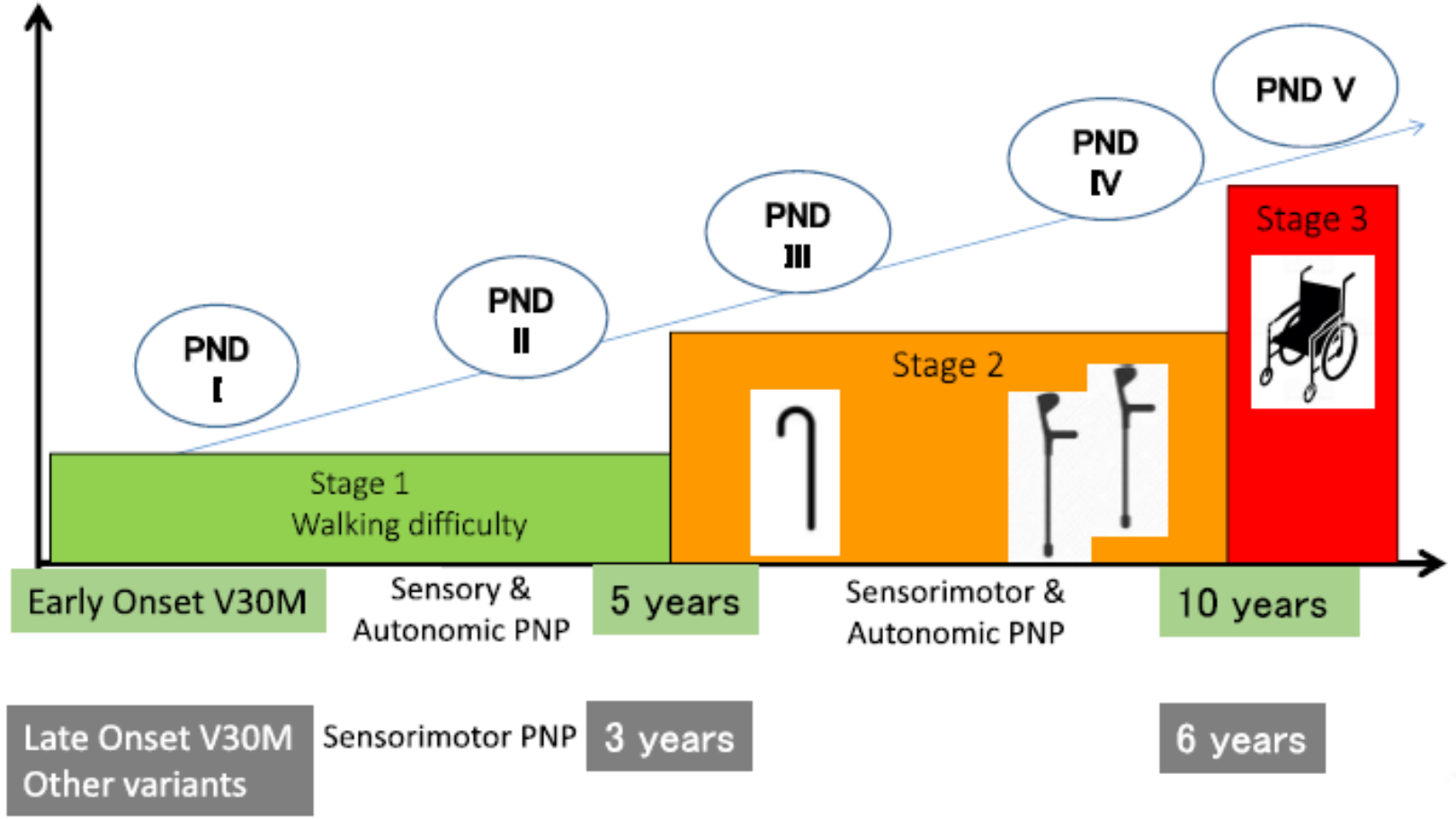
- Predicted neurologic progression: 14.3 points (NIS) and 17.8 points (mNIS +7) per year for subjects with a NIS score of 32 (typically at 19 months since symptom onset)[1]
- Without treatment, survival ranges between 6 and 12 years from symptom onset (depending on the genotype)[5]

hATTR, hereditary transthyretin amyloidosis; mNIS+7, modified Neuropathy Impairment Score; PND, polyneuropathy disability

1. Adams D et al. Neurology 2015;85:675–82; 2. Adams D. Ther Adv Neurol Disord 2013;6:129–39; 3. Mariani L-L et al. Ann Neurol 2015;78:901–16; 4. Koike H et al. J Neurol Neurosurg Psychiatry 2012;83:152–8; 5. González-Duarte A et al. Neurol Ther 2020;9:135–49.

hATTR–Polyneuropathy: progress of gait disability

(Coutinho P et al, 1980; Koike H et al, 2012; Mariani LL et al, 2015)



SCINTIGRAFIA OSSEA E TTR

Low Sensitivity of Bone Scintigraphy in Detecting Phe64Leu Mutation-Related Transthyretin Cardiac Amyloidosis

JACC Cardiovasc Imaging. 2020 Jun;13(6):1314-1321.

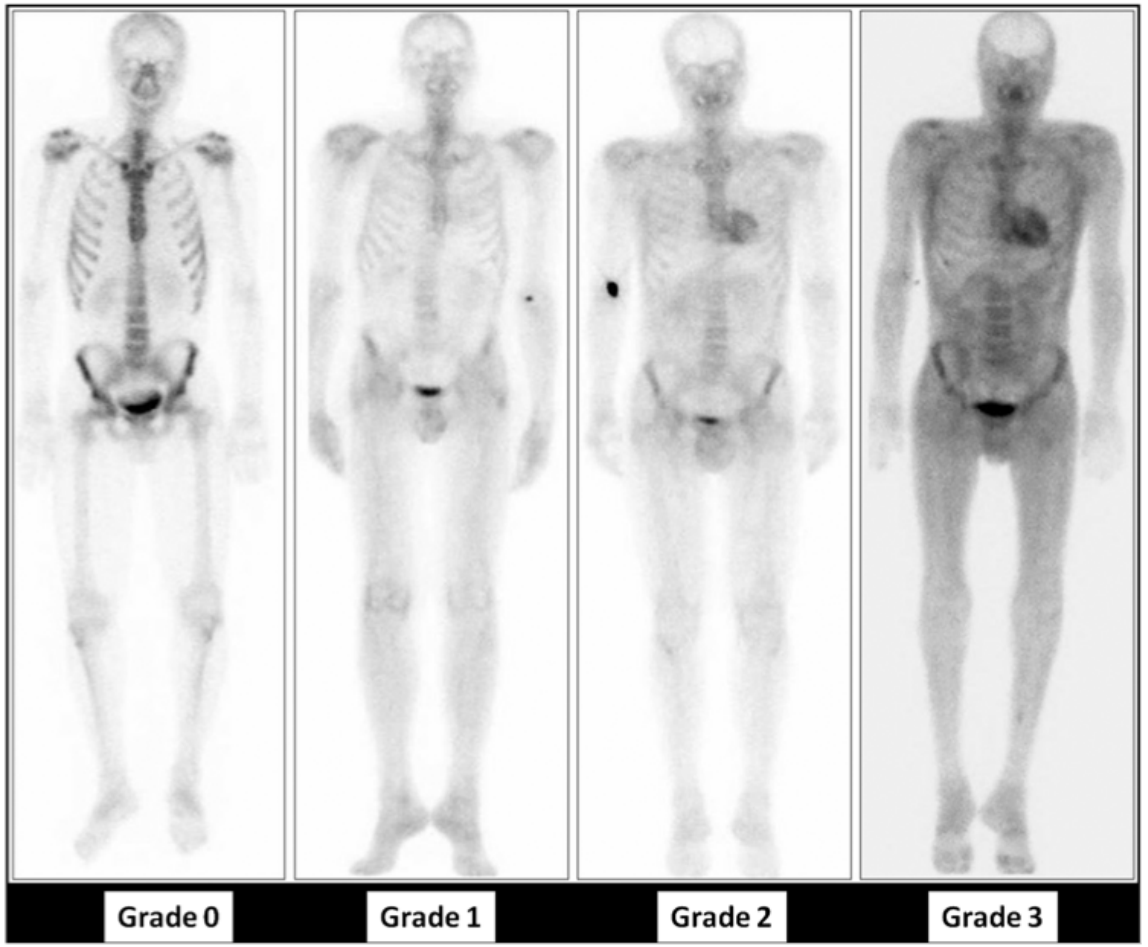
Maria Beatrice Musumeci [1], Francesco Cappelli [2], Domitilla Russo [1], Giacomo Tini [3], Marco Canepa [3], Agnese Milandri [4], Rachele Bonfiglioli [5], Gianluca Di Bella [6], Filomena My [7], Marco Luigetti [8], Marina Grandis [9], Camillo Autore [1], Stefano Perlini [10], Federico Perfetto [11], Claudio Rapezzi [4]

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-018-4013-4

ORIGINAL ARTICLE

Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis

Giorgio Treglia [1,2,3,4] · Andor W. J. M. Glaudemans [5] · Francesco Bertagna [6] · Bouke P. C. Hazenberg [7] · Paola A. Erba [8] · Raffaele Giubbini [6] · Luca Ceriani [1] · John O. Prior [4] · Luca Giovanella [1] · Riemer H. J. A. Slart [5,9]



I dati del registro Italiano confermano la presenza di cluster genetici e la natura multisistemica della amiloidosi hATTR, anche nei pazienti con manifestazioni predominanti di tipo cardiaco neurologico[1]

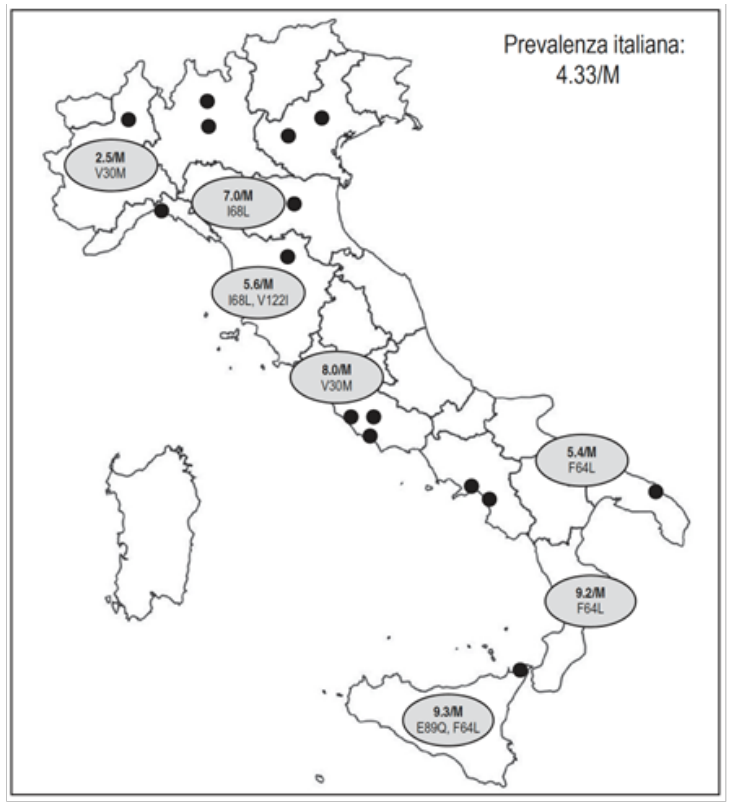


Figura 1. Prevalenza (n. pazienti/milione) e mutazioni più comuni nelle regioni Italiane con almeno 10 pazienti ciascuna. I pallini neri indicano i centri di riferimento.[1]

- Nel complesso, sintomi di polineuropatia erano presenti all'esordio della malattia in circa la metà dei pazienti e sintomi di cardiomiopatia in un quarto dei pazienti, mentre il resto dei casi presentava una sindrome del tunnel carpale, sintomi disautonomici o una stenosi spinale lombare.[1]
- Il 52,6% dei pazienti era nello stadio 1 FAP, il 20,4% nello stadio 2 e il 13,5% nello stadio 3, mentre il 13,5% dei pazienti non aveva alcuna neuropatia, avendo solo sintomi cardiologici.[1]

Tabella 1. Caratteristiche cliniche

	Totale	I68L	F64L	V30M	E89Q	V122I	Y78F	T49A
Numero di pazienti sintomatici	260	47	58	60	33	13	13	10
%	100	18.1	22.3	23.1	12.7	5.0	5.0	3.5
Rapporto maschi/femmine	2.3/1	2.6/1	3.8/1	3/1	1.3/1	3.3/1	12/1	0.8/1
Età media (anni)	67.1	72.4	70.2	66.2	58.5	73.7	72.6	49.4
Range di età (anni)	30-87	56-82	44-86	44-87	43-79	64-87	61-87	30-64
Età media all'esordio (anni)	60.3	67.9	63.7	58.9	50.5	67.5	64.1	43.9
Range di età all'esordio (anni)	29-82	47-79	42-80	31-81	37-70	56-82	55-81	30-55
Numero casi ad esordio tardivo (≥ 50 anni)	216	45	56	48	18	13	13	2
%	83.1	95.7	96.6	80	54,5	100	100	20.0
Durata della malatia (media ± DS; anni)	6.8 ± 4.7	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
Probandi	163	31	42	42	11	12	10	0
Età media alla diagnosi nei probandi (anni)	66.4	69.8	65.7	62.6	55.0	71.5	70.0	NA
Durata media dei sintomi alla diagnosi nei probandi (anni)	3.4	3.3	3.8	3.2	2.3	3	3.9	N.A.
Età media alla diagnosi nei non-probandi (anni)	56.3	67.4	58.7	59.2	50.7	63	63.3	43.9
Durata media dei sintomi alla diagnosi nei non-probandi (anni)	1.2	0.6	1.3	1.4	1.3	0.5	6.0	0
Fenotipo prevalente all'esordio	P	C	P	P	P	C	P	DYS
Sintomo d'esordio più frequente		Dispnea	Parestesia in LL	Parestesia in LL	CTS	Dispnea	Parestesia in LL	Perdita di peso
Fenotipo al giorno di prevalenza		P+	P+++	P+++	P++	P++	P+++	P++
		C+++	C+	C+	C++	C+++	C+	C++
		Dys+	Dys+	Dys+	Dys++	Dys+	Dys+	Dys+++
Solo coinvolgimento cardiaco	35 (13.5%)							
Stadio 1 FAP	137 (52.6%)							
Stadio 2 FAP	53 (20.4%)							
Stadio 3 FAP	35 (13.5%)							
Regione italiana di nascita con la maggiore prevalenza	Sicilia	Emilia Romagna	Puglia	Lazio	Sicilia	Toscana	Lombardia	Sicilia
Numero di portatori asintomatici	187	53	33	30	19	21	3	3
%	100	28.3	17.6	16.0	10.1	11.2	1.6	1.6
Rapporto maschi/femmine	0.7/1	1.1/1	0.7/1	0.7/1	0.7/1	0.4/1	0/1	0.5/1
Età media (anni)	52.3	54.8	56.8	48.3	46.2	55.7	53.3	40.0
Range di età (anni)	24-89	24-89	37-85	26-69	27-64	37-83	50-59	35-47

P, polineuropatia sensitivo-motoria; C, cardiomiopatia; DYS, disautonomia; LL, arti inferiori;
+: lieve (non clinicamente significativo); ++: moderato (clinicamente significativo); +++: grave (clinicamente predominante); NA, non applicabile

1. Russo M et al. Amyloid 2020; 27 (4): 259-265

AMILOIDOSI TTR : DIAGNOSI COMPLESSA

Ritardo diagnostico, intorno a i 4 anni

Eterogeneità genetico-clinica

Complessità clinica

Mis-diagnosi

DIAGNOSI COMPLESSA: MIS-DIAGNOSI

Diagnostic challenges in hereditary transthyretin amyloidosis with polyneuropathy: avoiding misdiagnosis of a treatable hereditary neuropathy

J Neurol Neurosurg Psychiatry May 2017 Vol 88 No 5

49 of 150 hATTR amyloid patients misdiagnosed

Table 1 Alternative diagnosis for patients with hereditary ATTR amyloidosis and variables associated with misdiagnosis of hereditary ATTR amyloidosis

Misdiagnoses	n=49 (%)
Chronic inflammatory demyelinating polyneuropathy	30 (61)
Lumbar and sacral radiculopathy and lumbar canal stenosis	11 (22)
Paraproteinaemic peripheral neuropathy	3 (6)
AL amyloidosis	3 (6)
Wild-type ATTR amyloidosis	1 (2)
Toxic peripheral neuropathy	4 (8)
Vasculitic peripheral neuropathy	1 (2)
Motor neuron disease	1 (2)
Fibromyalgia	2 (4)
Other diagnosis	2 (4)
Multiple misdiagnosis	9 (18)

Cortese A et al. J Neurol Neurosurg Psychiatry. 2017;88:457–8.

DIAGNOSI COMPLESSA: MIS-DIAGNOSI

Journal of Neurology (2021) 268:2109–2122
https://doi.org/10.1007/s00415-019-09688-0

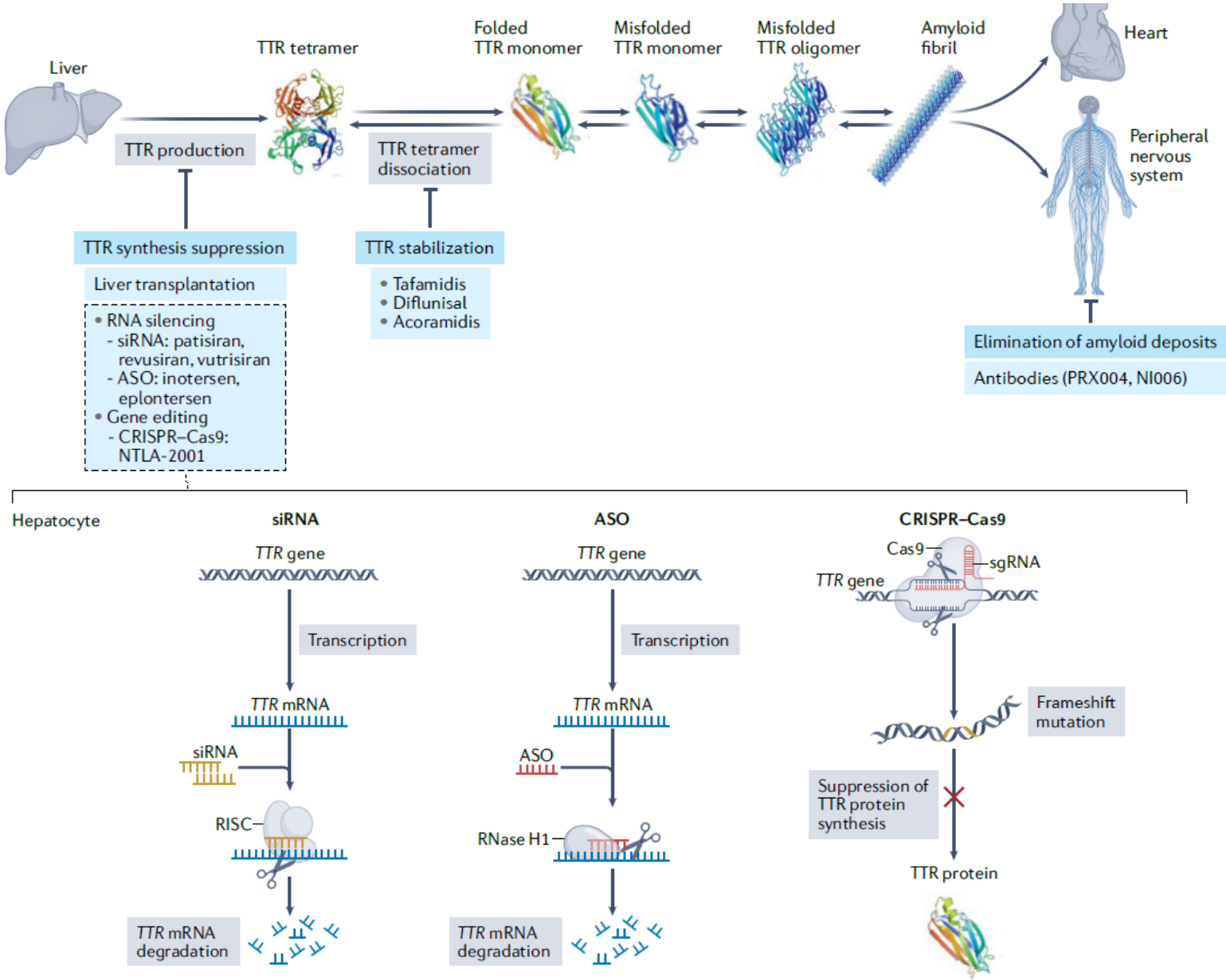
REVIEW

Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy

David Adams[1] · Yukio Ando[2] · João Melo Beirão[3] · Teresa Coelho[4] · Morie A. Gertz[5] · Julian D. Gillmore[6] · Philip N. Hawkins[6] · Isabelle Lousada[7] · Ole B. Suhr[8] · Giampaolo Merlini[9,10]

Misdiagnosis	Incidence, %	Misleading features	Red flags
CIDP	13–15	SM 4 limbs Diffuse areflexia Albuminocytologic dissociation Demyelination on biopsy Demyelinating NCS	Pain Sensory loss (wrists) Autonomic dysfunction Upper limb weakness NCS
Chronic axonal idiopathic PN	24–33	Axonal neuropathy in the elderly, seemingly idiopathic	Severity, disability, rapid Difficulties in walking
CTS	11	Paresthesia in the hands	No relief after surgery
Lumbar spinal stenosis	7.3	Progressive difficulty walking in the elderly Spinal stenosis on lumbar CT or MRI	Abnormal NCS Worsening in spite of surgery
Motor neuron disease Motor neuropathy, ALS	< 1	Upper limb and tongue amyotrophy Dysarthria Hand weakness	Abnormal sensory SNAP (NCS) No symptoms of upper motor neuron involvement
Miscellaneous			
Alcoholic PNP		Small-fiber length-dependent PN	Alcoholism
Diabetic PNP		Small-fiber length-dependent PN Autonomic dysfunction	Rapid severity/duration of diabetes Difficulties in walking
Paraneoplastic neuropathy		Non-length-dependent sensory loss + ataxia Weight loss	No anti-onconeuronal antibody Negative findings on whole-body PET

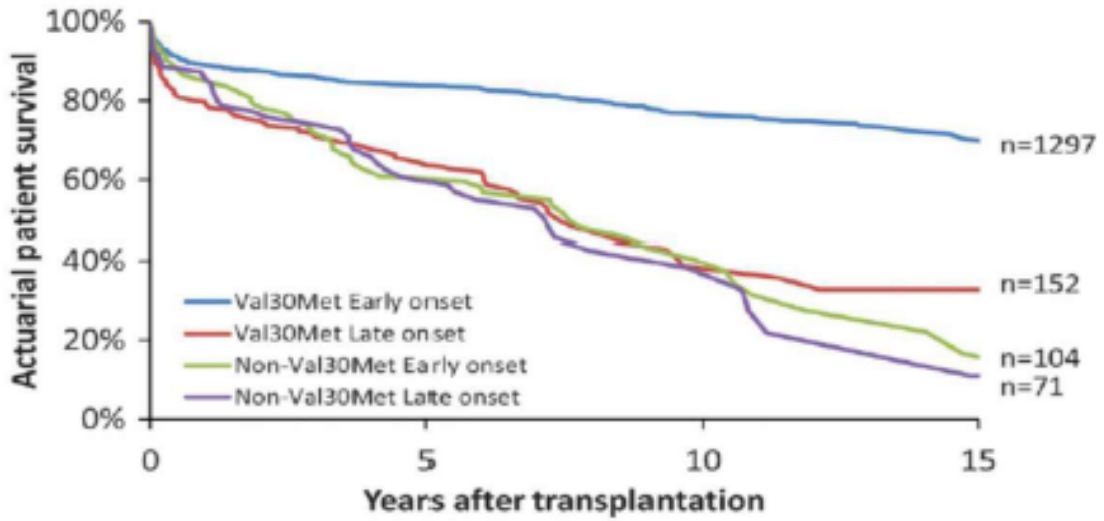
Meccanismi molecolari e terapie bersaglio



Aimo et al, 2022

Liver transplantation: long-term survival benefit

20-year survival rate 55,3% in 1940 patients from 19 countries (www.fapwtr.org)



Combined liver-heart or liver-kidney transplantation

Careful patient selection

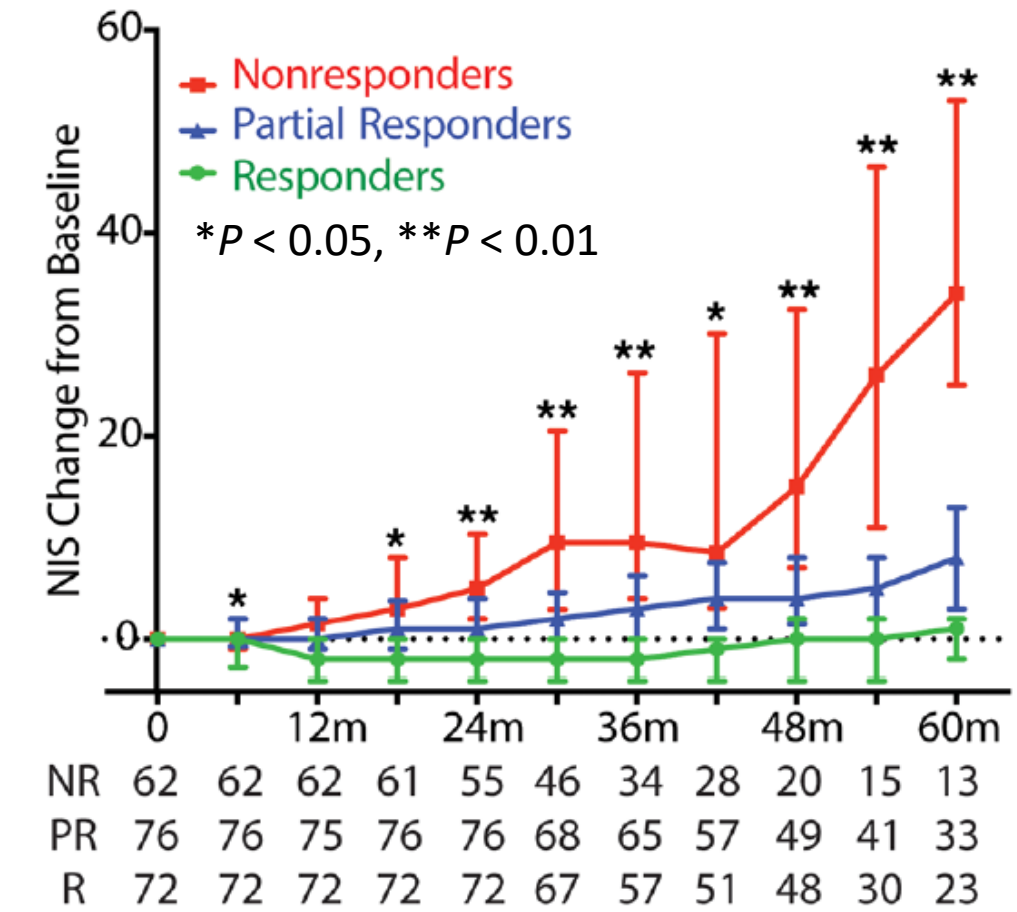
- Val30Met
- Early-onset of disease
- Short disease duration
- High mBMI

Ericzon BG et al, *Transplantation* 2015
Yamashita et al, *Neurology* 2012
Calvalho et al, *Liver Transplantation* 2015

Treatment response to tafamidis in mild-to-moderate disease (median NIS 8)

- Approximately two-thirds of patients were non- or partial responders, with an annual increase in NIS of at least 1.8 points

NIS change from baseline



Response classification based on expert opinion

29.5%
Non-responders

36.2%
Partial responders

66% progressed on tafamidis

34.3%
Responders

34.3% stabilized on tafamidis

Response: No discernible progression of sensory, autonomic, and/or motor neuropathic symptoms (**NIS change=0 points/year**)
Partial response: Continued (slower than expected) progression of sensory and/or motor neuropathy plus stability or improvement of autonomic neuropathy (**NIS increase: 1.8 points/year**)
Non-response: Continuous and rapid worsening of sensory, motor, and/or autonomic neuropathy (**NIS increase: 5.9 per year**)

- NIS, Neuropathy Impairment Score; NR, nonresponders; PR, partial responders; R, responders
- Monteiro C et al. JCI Insight 2019;4:e126526.

Predictors of outcomes

Predictors of outcome included disease severity, gender, and tetrameric TTR concentration.[1] Plasma tafamidis concentration after 12 months of therapy was also a predictor of response for male patients[1]

Women were significantly more likely to be responders than men (68.1% of responders were women)[1]

Patients with mild to moderate impairment were significantly more likely to be responders (responders had a median NIS of 6)[1]

- Moderate disease was linked with partial response, and advanced disease with non-response
- **Patients with an NIS of 10 or above** were more likely to be partial or non-responders

Patients reporting worse quality of life (Norfolk QOL-DN) were more likely to become non-responders[1]

Baseline age at disease onset and disease duration were NOT predictors of response[1]

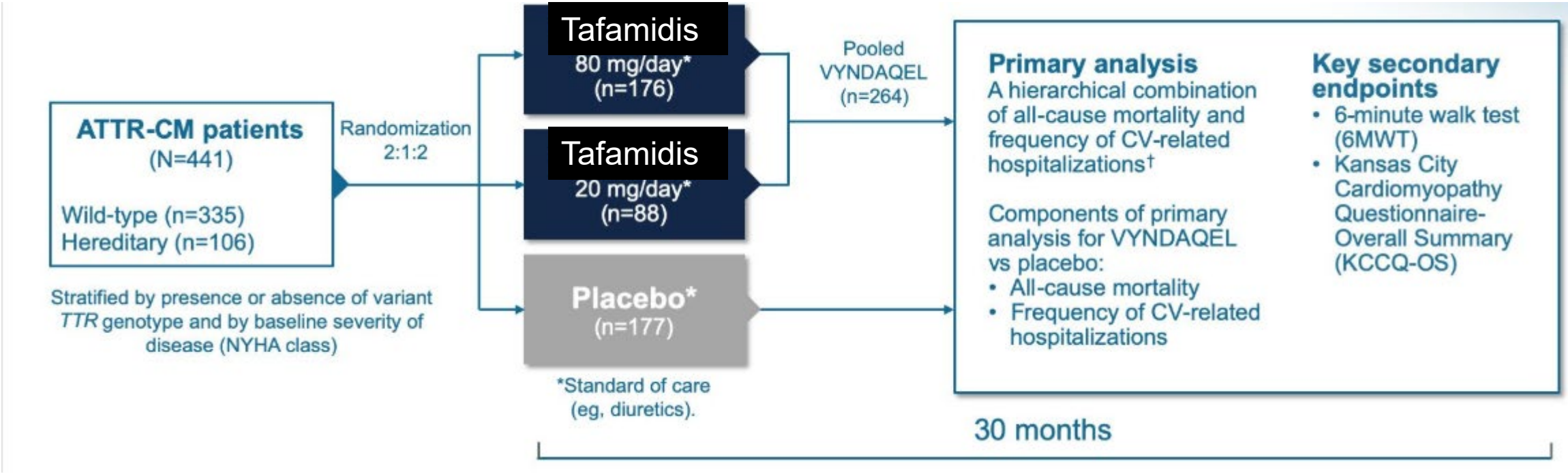
- This may reflect the young age and short disease duration of this cohort

Patients with an NIS of 10 or above, men and/or those reporting poor quality of life were more likely to be partial or nonresponders to tafamidis[1]

- NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire–Diabetic Neuropathy; TTR, transthyretin
- Monteiro C et al. JCI Insight 2019;4:e126526.

Tafamidis in wild-type or hereditary transthyretin amyloid cardiomyopathy

Tafamidis (61 mg soft capsules) is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy.[1] This indication is based on the evidence from ATTR-ACT phase 3 study in 441 patients with cardiomyopathy associated with either wild-type (n=335; 76%) or hereditary (106; 24%) ATTR amyloidosis[2]



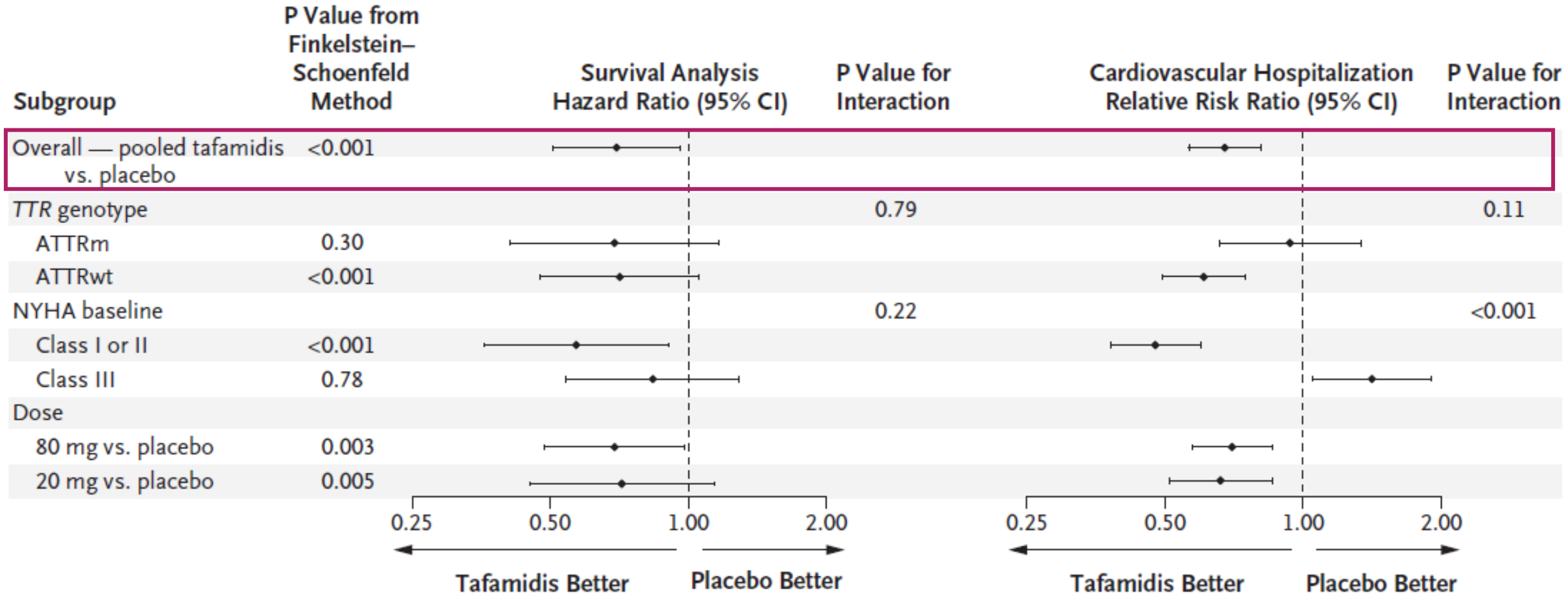
*The primary analysis was conducted using the Finkelstein–Schoenfeld method

6MWT, 6-minute walk test; ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; NYHA, New York Heart Association; TTR, transthyretin

1. Vyndaqel 61 mg soft capsules. SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/vyndaqel-epar-product-information_en.pdf [accessed September 29, 2020]; 2. Maurer MS et al. N Engl J Med 2018;379:1007–16.

ATTR-ACT – Combined primary outcome

At 30 months, tafamidis was associated with a reduction in all-cause mortality and CV-related hospitalizations vs placebo. The survival benefit from tafamidis was not apparent until 18 months

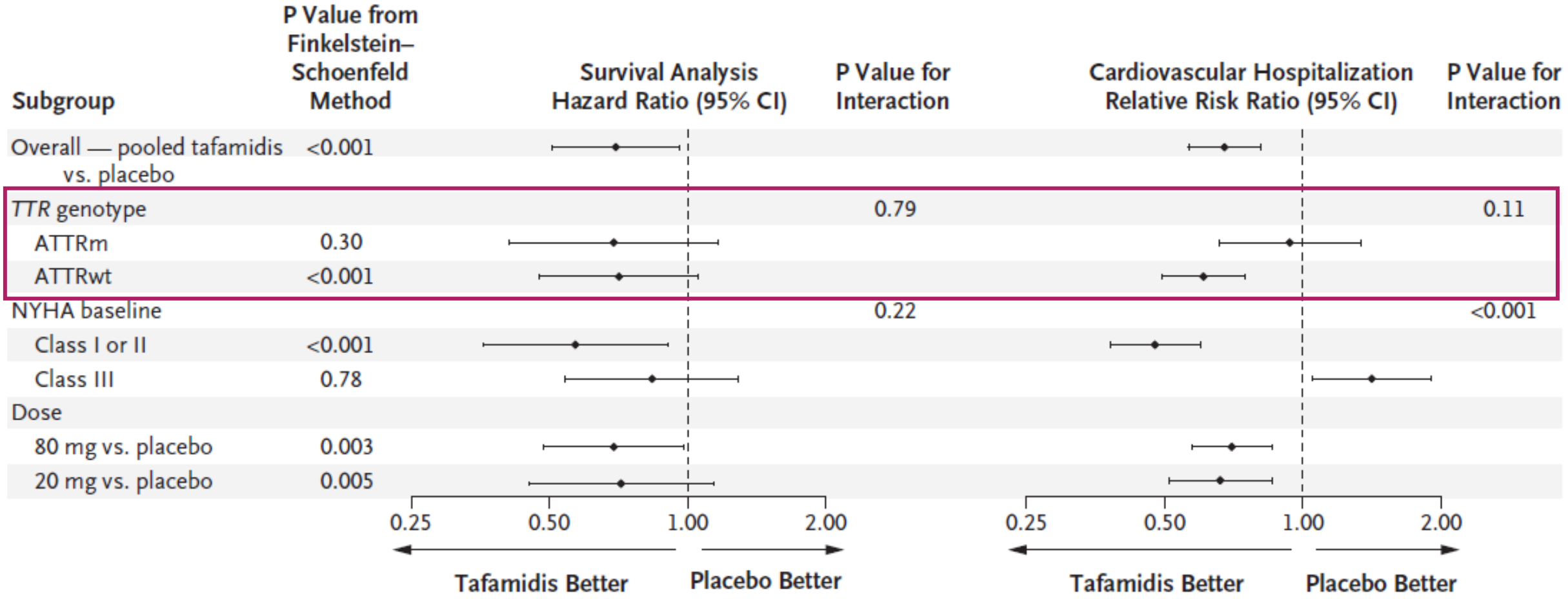


Over 30 months, tafamidis was associated with lower all-cause mortality vs placebo (29.5% vs 42.9%; HR 0.70 [95% CI 0.51–0.96]), and a lower rate of cardiovascular-related hospitalizations vs placebo with a relative risk ratio of 0.68 (0.48/year vs 0.70/year; 95% CI 0.56–0.81)

ATTRm, variant (mutated) transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; NYHA, New York Heart Association; TTR, transthyretin. Maurer MS et al. N Engl J Med 2018;379:1007–16.

ATTR-ACT

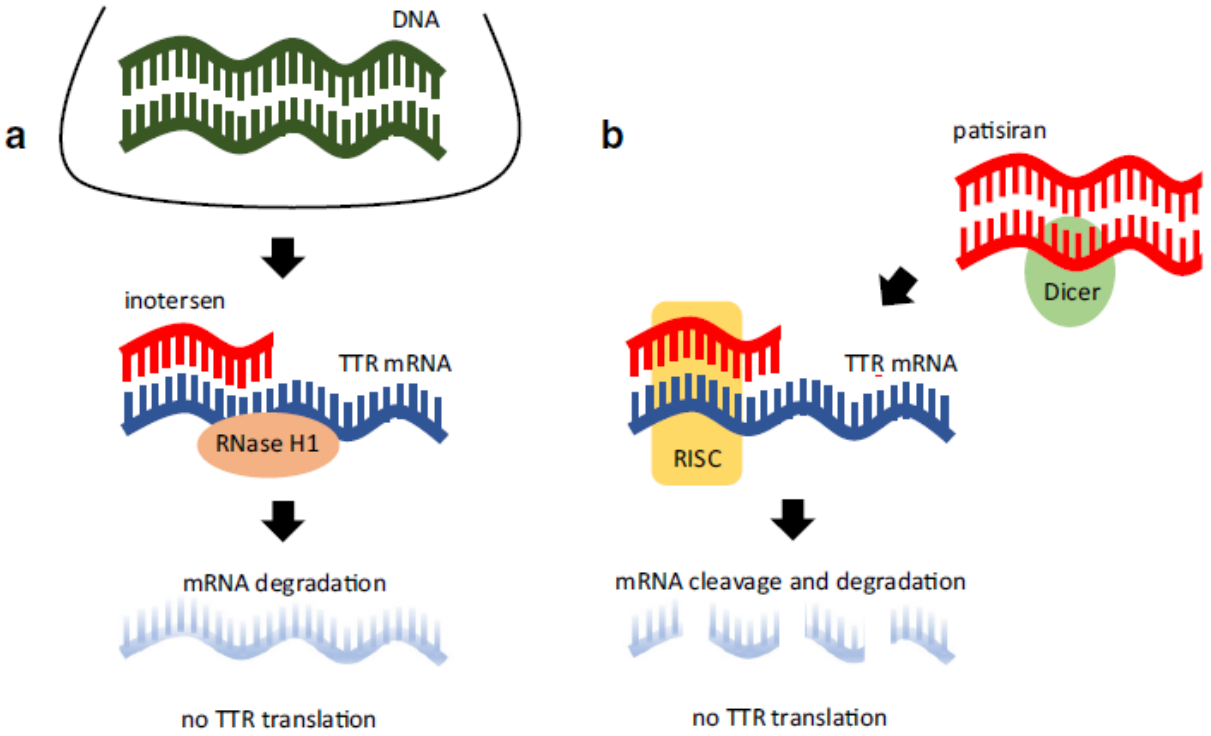
In the hATTR sub-population, all-cause mortality and CV-related hospitalizations were not statistically significantly different between tafamidis and placebo



ATTRm, variant (mutated) transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; hATTR, hereditary transthyretin amyloidosis; NYHA, New York Heart Association

Maurer MS et al. N Engl J Med 2018;379:1007–16.

Gene silencing (siRNA, ASO)



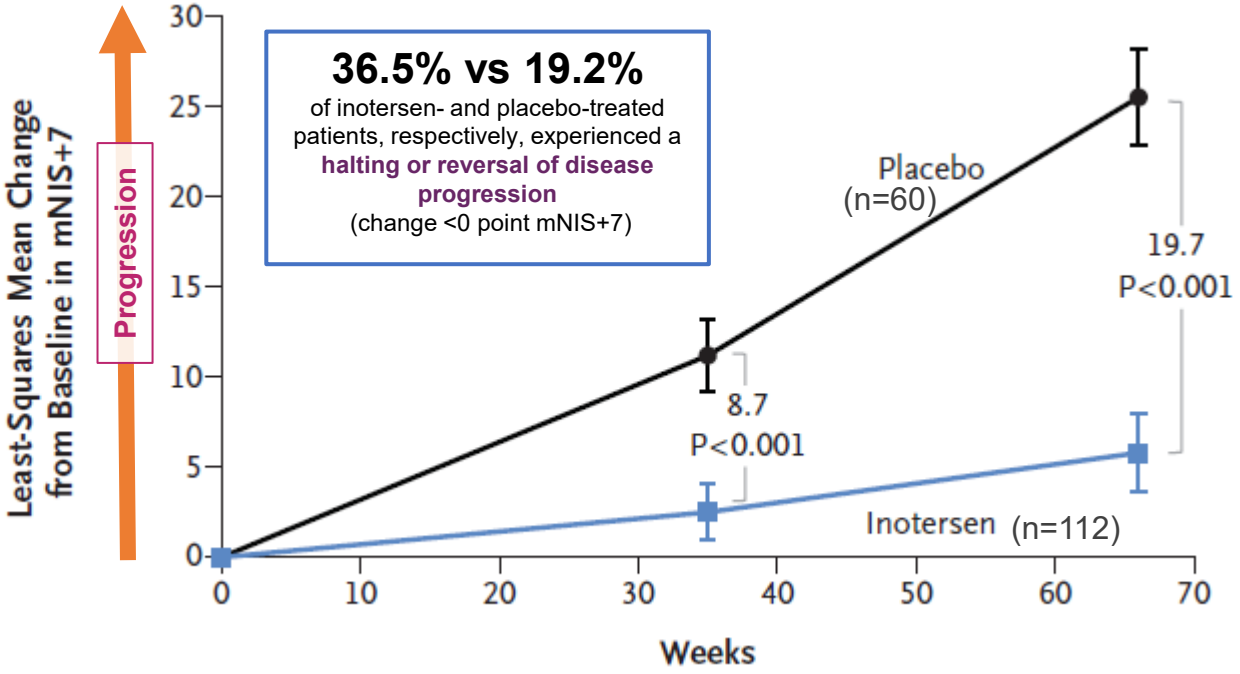
RNA-induced silencing complex

Inotersen

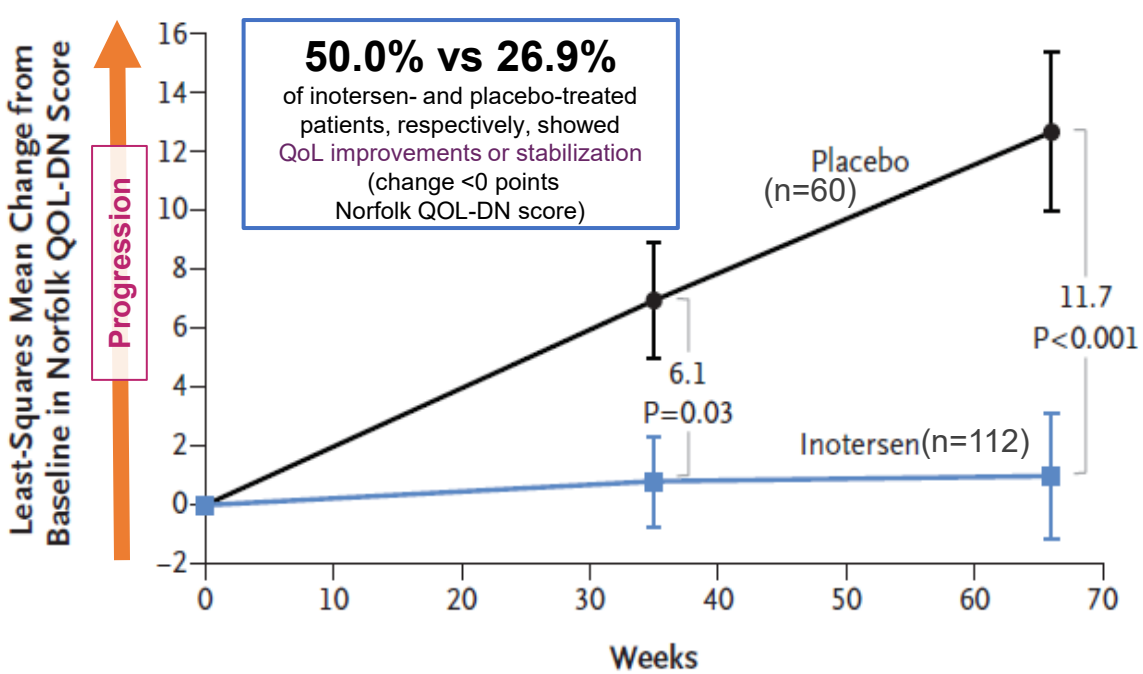
NEURO-TTR and open-label extension study

NEURO-TTR: Neurologic disease progression with inotersen slowed (relative to placebo) and QoL changes stabilized (relative to baseline)

NEURO-TTR: mNIS+7 IONIS change from baseline at 66 weeks (primary endpoint)



NEURO-TTR: Norfolk QoL-DN change from baseline at 66 weeks (primary endpoint)



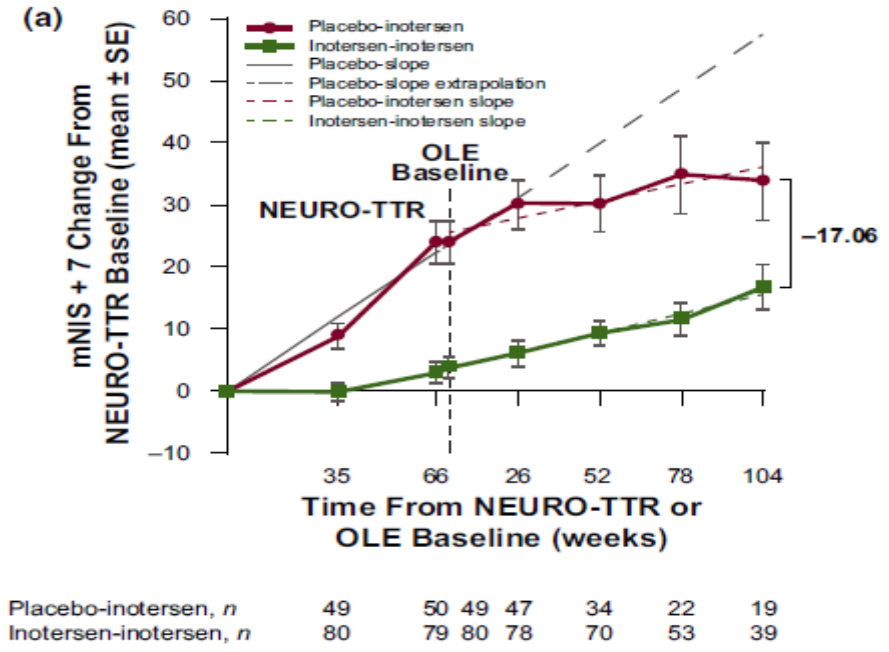
mNIS+7 mean change from baseline
NEURO-TTR (66 weeks): 5.8 points [inotersen] vs 25.5 points [placebo]

Norfolk QoL-DN mean change from baseline
NEURO-TTR (66 weeks): 1.0 points [inotersen] vs 12.7 points [placebo]

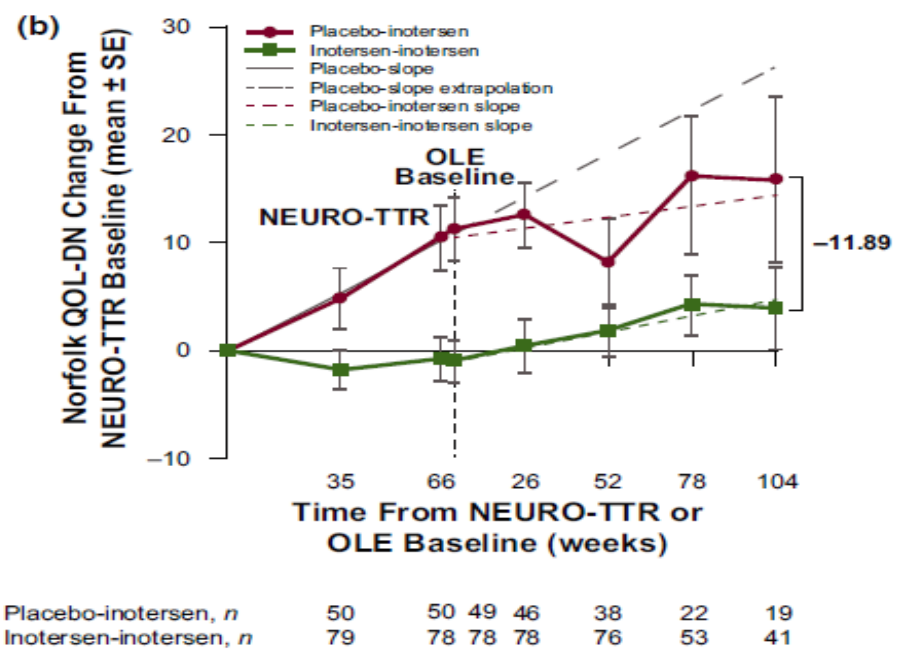
- Treatment effect = least-squares mean (±SE) change from baseline at Week 66 (15 months); Composite scores on the mNIS+7 scale range from −22.3 to 346.3 (the higher the score, the poorer the function)
- mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire–Diabetic Neuropathy; QOL, quality of life; SE, standard error
- Benson MD et al. N Engl J Med 2018;379:22–31.

NEURO-TTR OLE: Early intervention with inotersen provides greater long-term disease stabilization

NEURO-TTR: mNIS+7 IONIS change from OLE BL at 104 weeks



NEURO-TTR: Norfolk QoL-DN change from OLE BL at 104 weeks



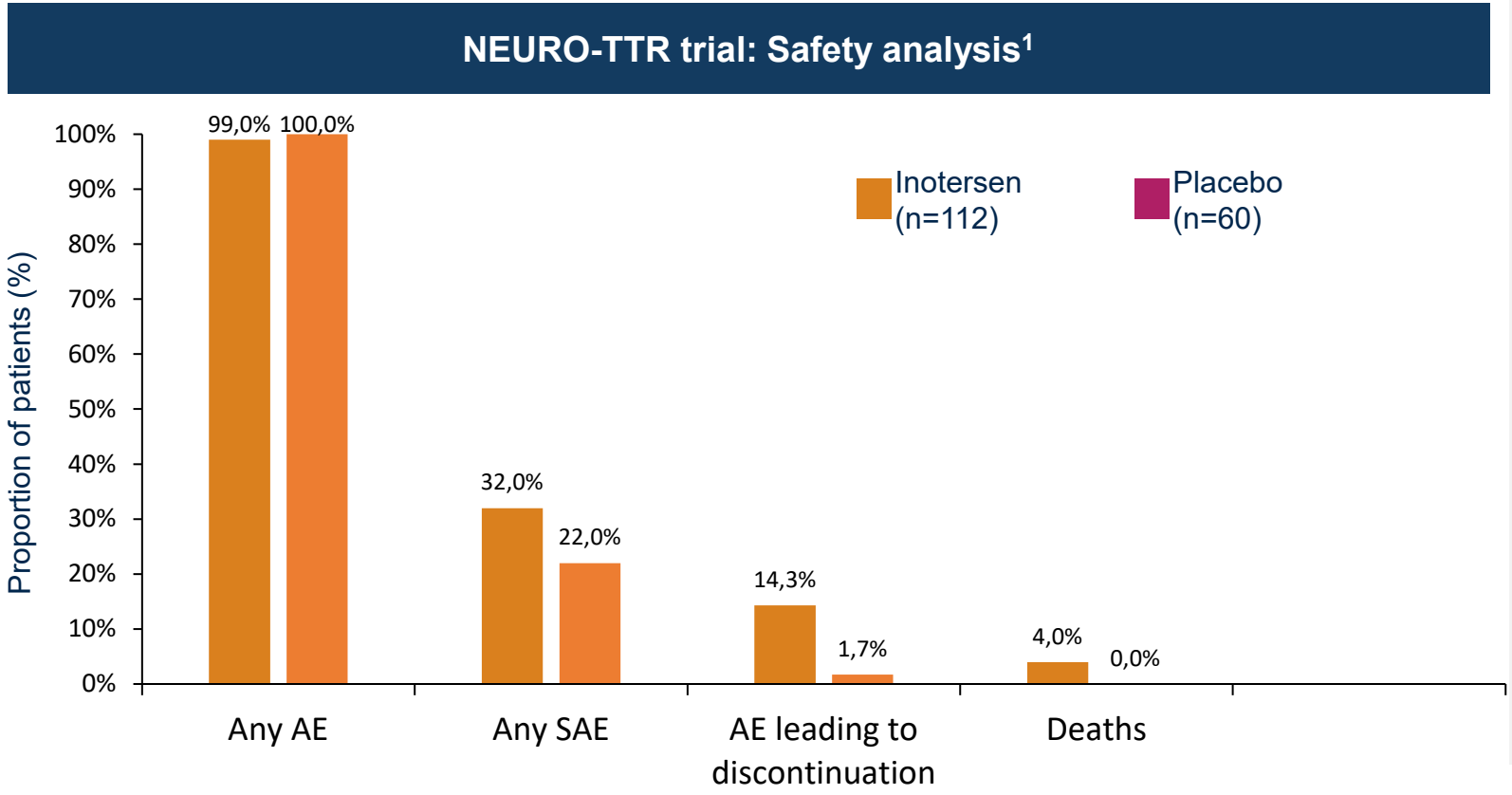
mNIS+7 improvement (<0-point change):
Inotersen: 24% of patients at 170 weeks from NEURO-TTR BL
Placebo-inotersen: 47% of patients at 104 weeks from OLE BL

Norfolk QoL-DN improvement (<0-point change):
Inotersen: 46% of patients at 170 weeks from NEURO-TTR BL
Placebo-inotersen: 42% of patients at 104 weeks from OLE BL

BL, baseline; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life Questionnaire–Diabetic Neuropathy; OLE, open-label extension; SE, standard error

Brannagan TH et al. Eur J Neurol 2020;27:1374–81.

NEURO-TTR: Safety findings



- Principal safety concerns for inotersen (SAEs) in the NEURO-TTR trial were:
  - **Thrombocytopenia (3 patients)** with platelet count of <25,000 per cubic millimeter[1]
  - **Glomerulonephritis (3 patients)**[1]
- Confirmed decrease in platelet count (<140,000 per cubic millimeter):[1] 54% inotersen vs 13% placebo
- One death in the inotersen group was treatment-related event (grade 4 thrombocytopenia); regular monitoring required[1]
- Other AEs (>10% and 2x placebo): nausea, pyrexia, chills, vomiting and anemia[1]

NEURO-TTR OLE (52 weeks)[2]

AE leading to discontinued treatment: 9% [inotersen-inotersen] and 4% [placebo-inotersen]

No evidence of increased risk for grade 4 thrombocytopenia or severe renal events with increased duration of exposure

AE, adverse event; OLE, open-label extension; SAE, serious adverse event

1. Benson MD et al. N Engl J Med 2018;379:22–31; 2. Brannagan TH et al. Blood 2018;132 (Supplement 1): 498.

Clinical trial and post-marketing surveillance: Management of thrombocytopenia in patients treated with inotersen

- During NEURO-TTR platelet monitoring increased:
  - From at least every 6 weeks, to every 2−3 weeks (February 2016), to weekly (May 2016)
  - Before weekly monitoring in NEURO-TTR **grade 4 thrombocytopenia** (<25,000 per cubic millimeter) occurred in 3% of patients[1]
  - After the introduction of **weekly monitoring**, there were **no cases of grade 4 thrombocytopenia** in the NEURO-TTR or the OLE studies[1–3]
- Recent post-marketing surveillance data (collected between October 2018 and August 2019) from the US:
  - REMS have confirmed that **weekly platelet monitoring has largely mitigated the risk of severe thrombocytopenia** with no cases of grade 4 thrombocytopenia or serious bleeding with severe thrombocytopenia reported[3]

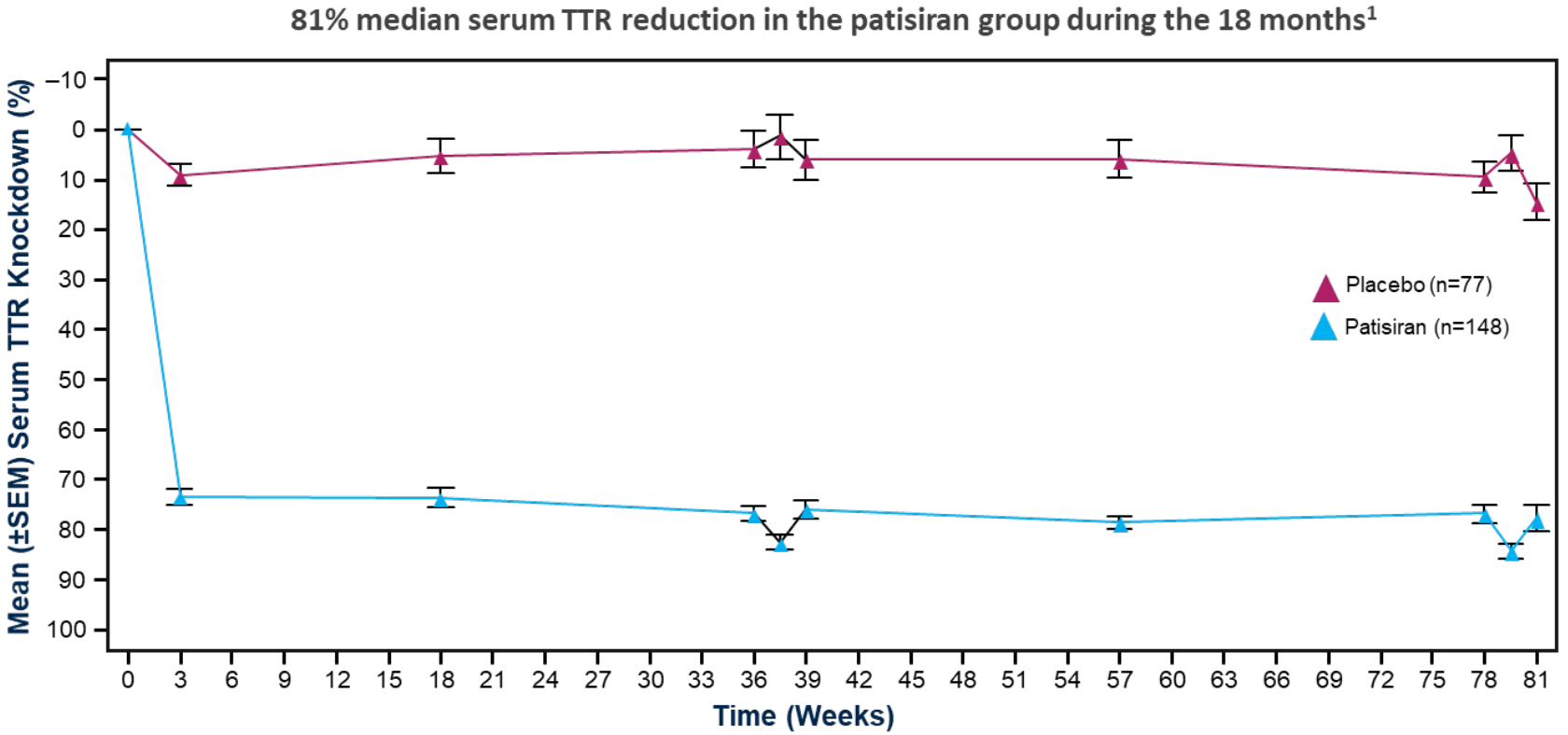
OLE, open-label extension; REMS; Risk Evaluation and Mitigation Strategy

1. Benson MD et al. N Engl J Med 2018;379:22–31; 2. Brannagan TH et al. Eur J Neurol 2020;27:1374–81; 3. Gertz M et al. Virtual presentation at European Academy of Neurology (EAN); May 2020; Abstract EPR2229.

Patisiran

APOLLO study

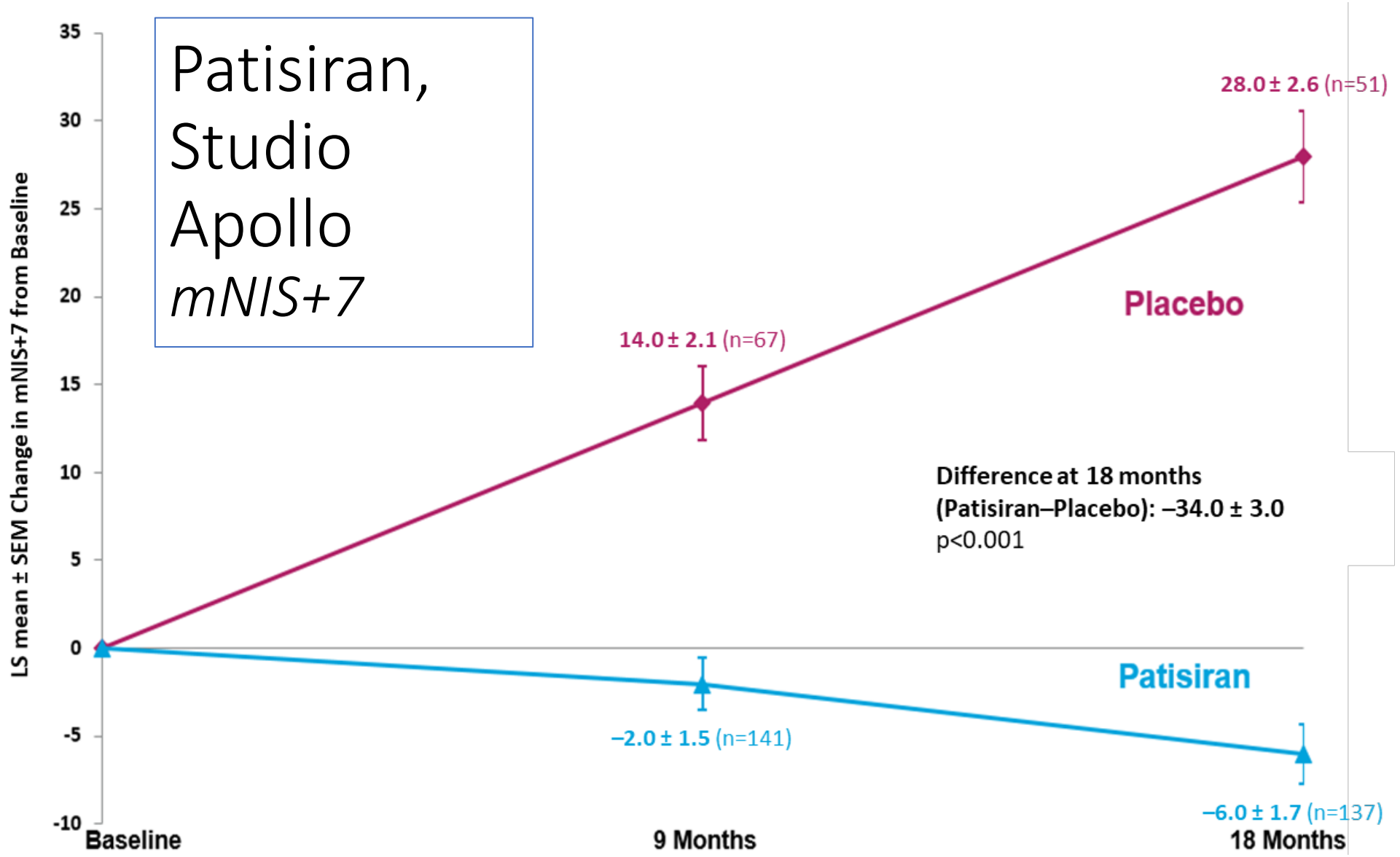
Effetti sui livelli di transitiretina

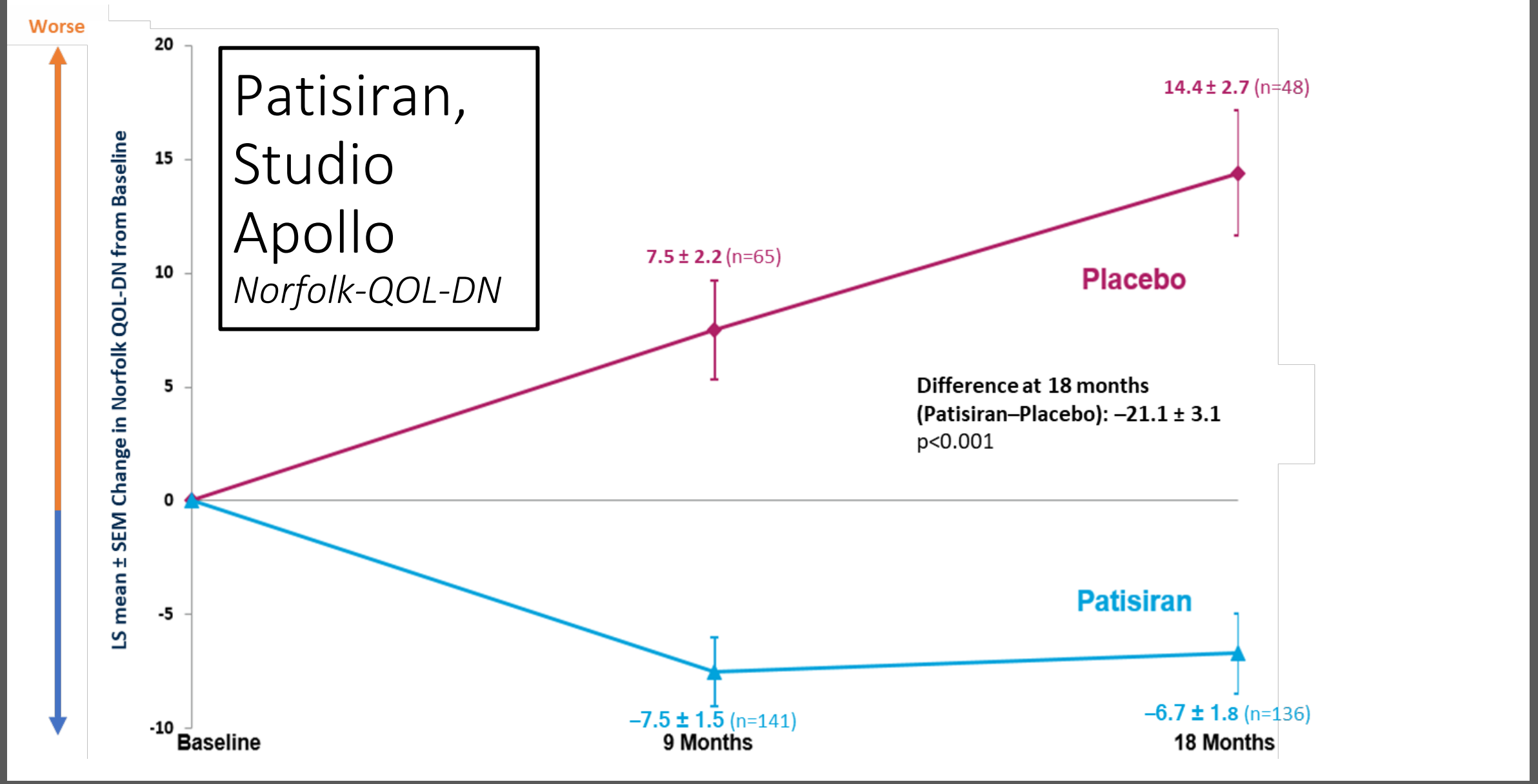


TTR Change	CFB at 9 months		CFB at 18 months	
	Placebo (n=77)	Patisiran (n=148)	Placebo (n=77)	Patisiran (n=148)
Mean (SEM) serum TTR knockdown[2]	1.5% (4.47)	82.6% (1.36)	4.8% (3.38)	84.3% (1.48)

- 1. Adams et al. *N Engl J Med* 2018;379:11–21; 2. Adams et al. *First European Meeting for ATTR Amyloidosis for Doctors and Patients* 2017 Oral Presentation O9

Patisiran, Studio Apollo *mNIS+7*

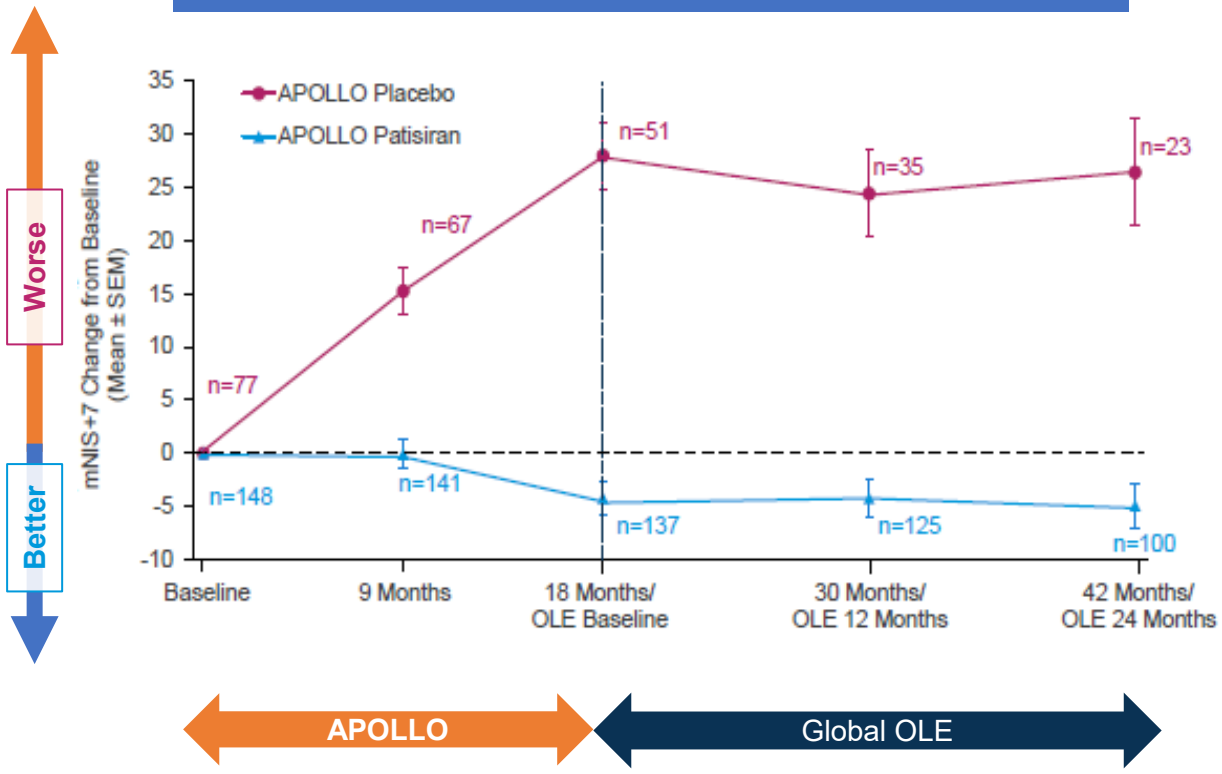



Worse
Patisiran, Studio Apollo
Norfolk-QOL-DN
LS mean ± SEM Change in Norfolk QOL-DN from Baseline
20
15
10
5
0
-5
-10
14.4 ± 2.7 (n=48)
7.5 ± 2.2 (n=65)
Placebo
Difference at 18 months
(Patisiran–Placebo): –21.1 ± 3.1
p<0.001
Patisiran
–7.5 ± 1.5 (n=141)
–6.7 ± 1.8 (n=136)
Baseline
9 Months
18 Months

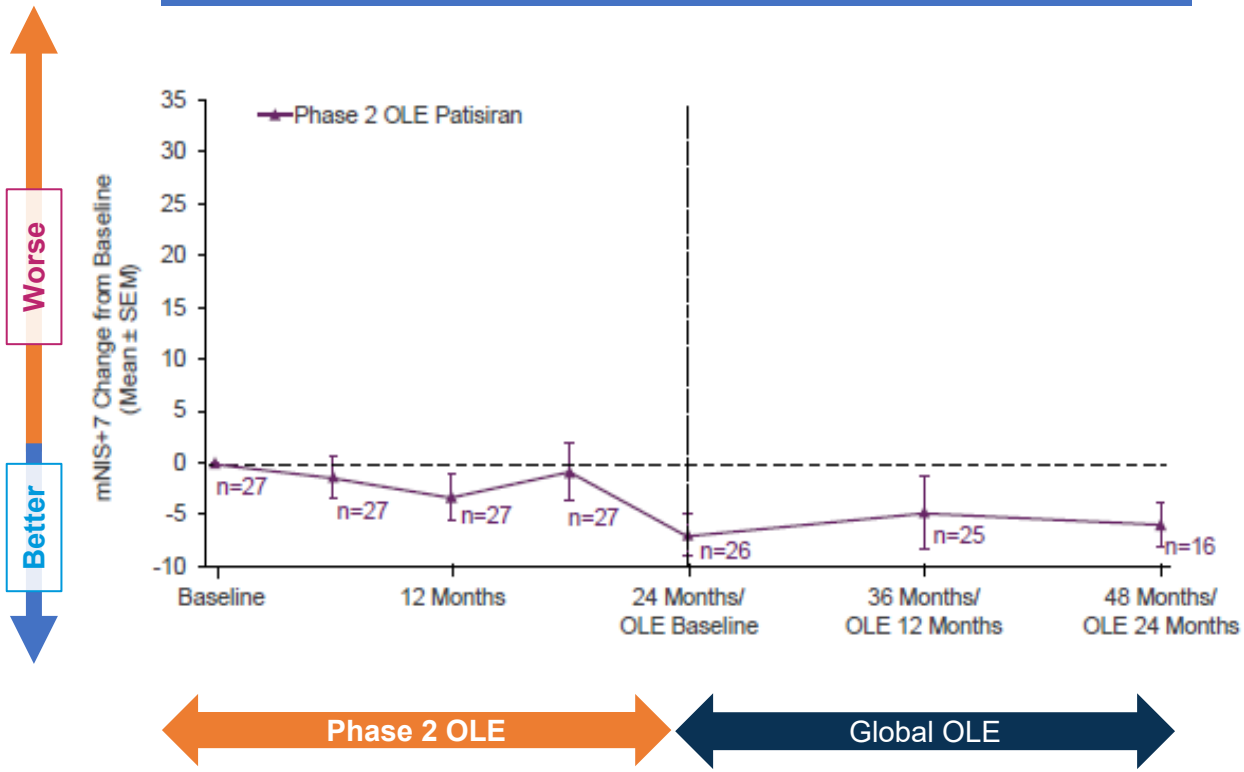
Improved neuropathy control (relative to baseline) was sustained with patisiran beyond the parent studies[a]

Change in mNIS+7 following patisiran treatment on Global OLE
(includes patients with more than 3 years of treatment)

APOLLO and Global OLE[a]



Phase 2 OLE

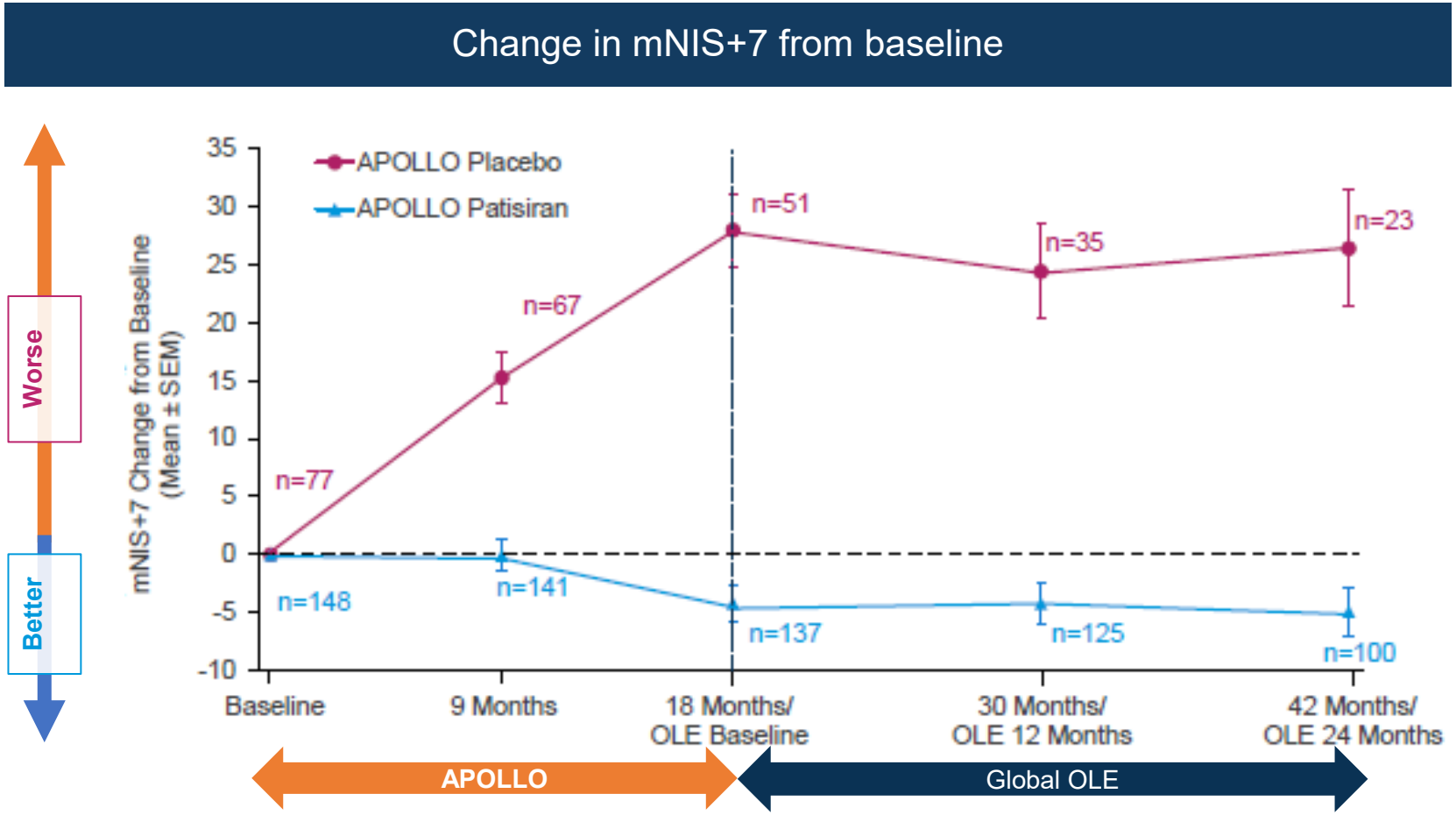


[a]Parent studies includes Phase 2 OLE and Phase 3 APOLLO trials. For APOLLO patients initiating alternative hATTR amyloidosis treatment, mNIS+7 assessments after alterative treatment are treated as missing

hATTR, hereditary transthyretin amyloidosis; mNIS+7, modified Neuropathy Impairment Score +7; OLE, open-label extension; SEM, standard error of mean

1. Adams D et al. Poster presented at European Academy of Neurology (EAN) Virtual Congress; May 23–26, 2020.

Delayed treatment was associated with an accumulating disease burden

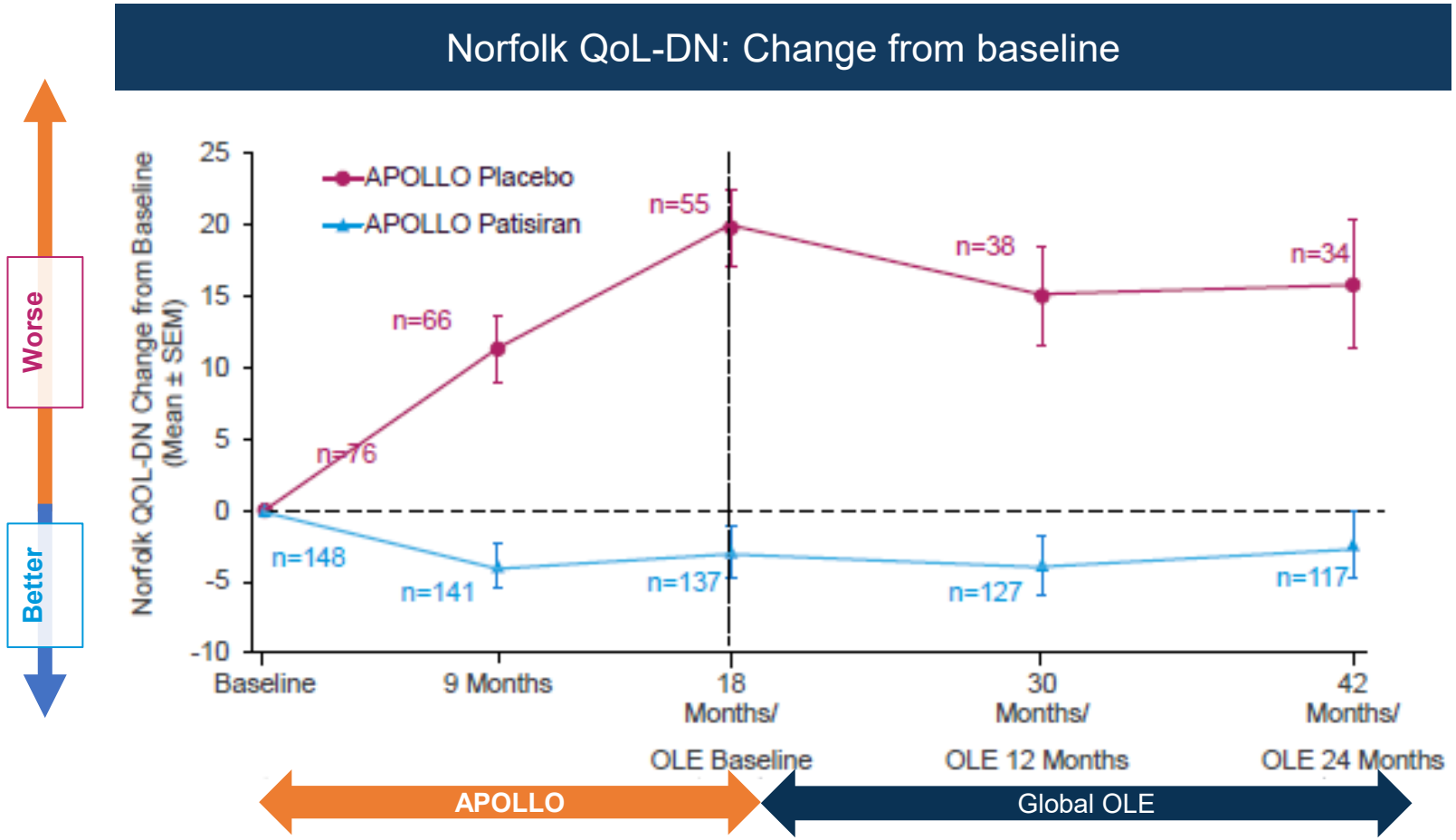


mNIS+7, modified Neuropathy Impairment Score +7; OLE, open-label extension; SEM, standard error of mean

1. Adams D et al. Presented at European Academy of Neurology (EAN) Virtual Congress; May 23–26, 2020.

Earlier intervention with patisiran prolonged the ability of people to remain active and engaged, and safeguarded QoL

Sustained improvement in QoL with patisiran treatment was observed in the OLE study



Norfolk QOL-DN, Norfolk Quality of Life Questionnaire–Diabetic Neuropathy; OLE, open-label extension; QOL, quality of life; SEM, standard error of mean

1. Adams D et al. Presented at European Academy of Neurology (EAN) Virtual Congress; May 23–26, 2020.

Nuovi scenari

Potenziamento farmaco-cinetico

Coniugazione con NAGal

Vutrisiran	GalNAc-siRNA	HELIOS-A[28]	Phase III, multicentre, randomized, open-label; 3:1 randomization to SC vutrisiran (25 mg) once every 3 months or IV patisiran (0.3 mg/kg) once every 3 weeks, for 18 months	164 patients with ATTRv-PN (vutrisiran $n = 122$; patisiran $n = 42$)	At 9 months, vutrisiran significantly improved neuropathy scores, QOL and gait speed	No serious adverse events	Evaluation ongoing
		HELIOS-B[67]	Phase III, multicentre, randomized, double-blind, placebo-controlled; SC vutrisiran (25 mg) or placebo once every 3 months	Patients with ATTRv-CM or ATTRwt-CM	NA		

Potenziamento farmaco-cinetico

Coniugazione con NAGal

Eplontersen	2′-MOE-modified, GalNAc3-conjugated ASO	Viney et al. (2021)[30]	Phase I, single-centre, randomized, placebo-controlled; 10:2 randomization (active versus placebo), one cohort receiving a single SC dose of eplontersen 120 mg and three cohorts receiving SC eplontersen 45 mg, 60 mg or 90 mg once every 4 weeks	Healthy volunteers (n=47; 20 women, 27 men)	Eplontersen produced an overall reduction of approximately 90% in circulating TTR levels in the multiple-dose cohorts	No serious adverse events	Evaluation ongoing

Editing genico

The NEW ENGLAND JOURNAL of MEDICINE

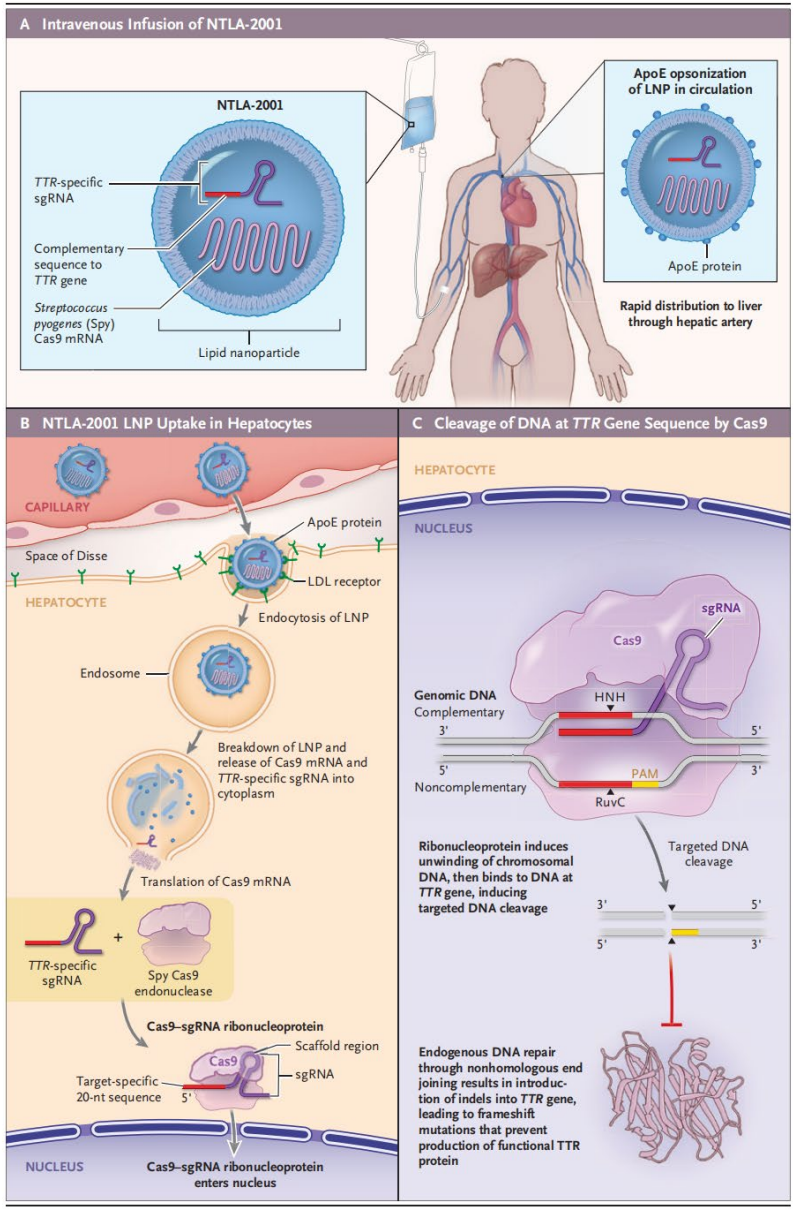
ORIGINAL ARTICLE

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Phase I, multicentre, randomized, open- label, placebo- controlled; single IV dose of NTLA-2001: 0.1 mg/kg (*n* = 3) or 0.3 mg/kg (*n* = 3)

6 patients with ATTRv- PN

Interim results from the first two single- dose groups of the trial: NTLA-2001- mediated dose- dependent and sustained reductions in serum TTR protein concentration



Obiettivo: diagnosi

- Aumentare la capacità di riconoscimento della patologia
- Ridurre il più possibile gli errori diagnostici
- Ridurre il più possibile il ritardo diagnostico


WANTED
hATTR


DENIX

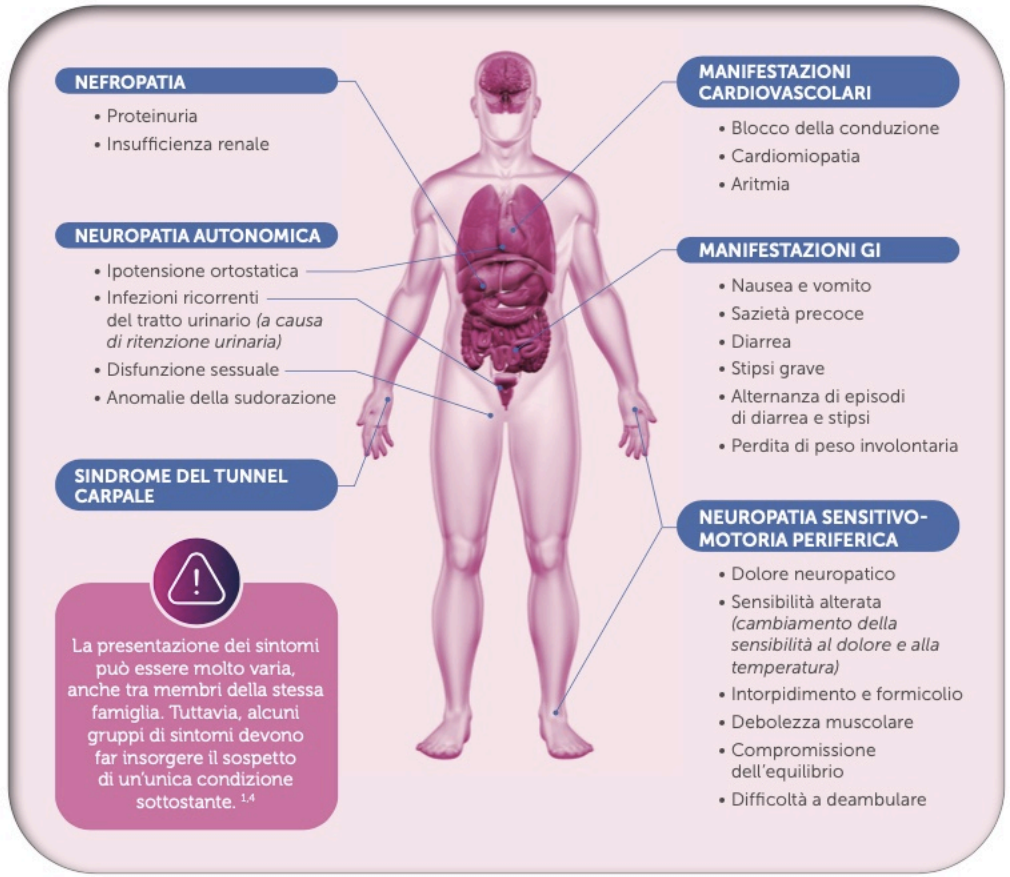
Strategie

- Aumentare insight sulla patologia per riconoscere i nuovi casi inviati.
- Costituzione di teams multidisciplinari.
- Iniziative per cercare casi ‘passati’ di cui è rimasta traccia, suggestivi: screening attivo
- Favorire la capacità del territorio di individuare sospetti.
  - Collegamento con MMG e specialisti territoriali
  - Formazione

«Conoscere per riconoscere»

Red flags

- Familiarità per neuropatia o cardiopatia
- Biopsia positiva
- Sindrome del tunnel carpale bilaterale e recidivante
- Polineuropatia sensitivo-motoria assonale
- Perdita di peso importante
- Disturbi gastrointestinali con svariate presentazioni cliniche dalla diarrea alla stipsi
- Disautonomia (disfunzione erettile nei maschi, ipotensione ortostatica, sincopi)
- Cardiomiopatia con pBNP e troponina elevati
- Captazione cardiaca alla scintigrafia ossea



Screening: sospetto diagnostico, le red flags

Test genetico

Progressive symmetric sensorimotor neuropathy

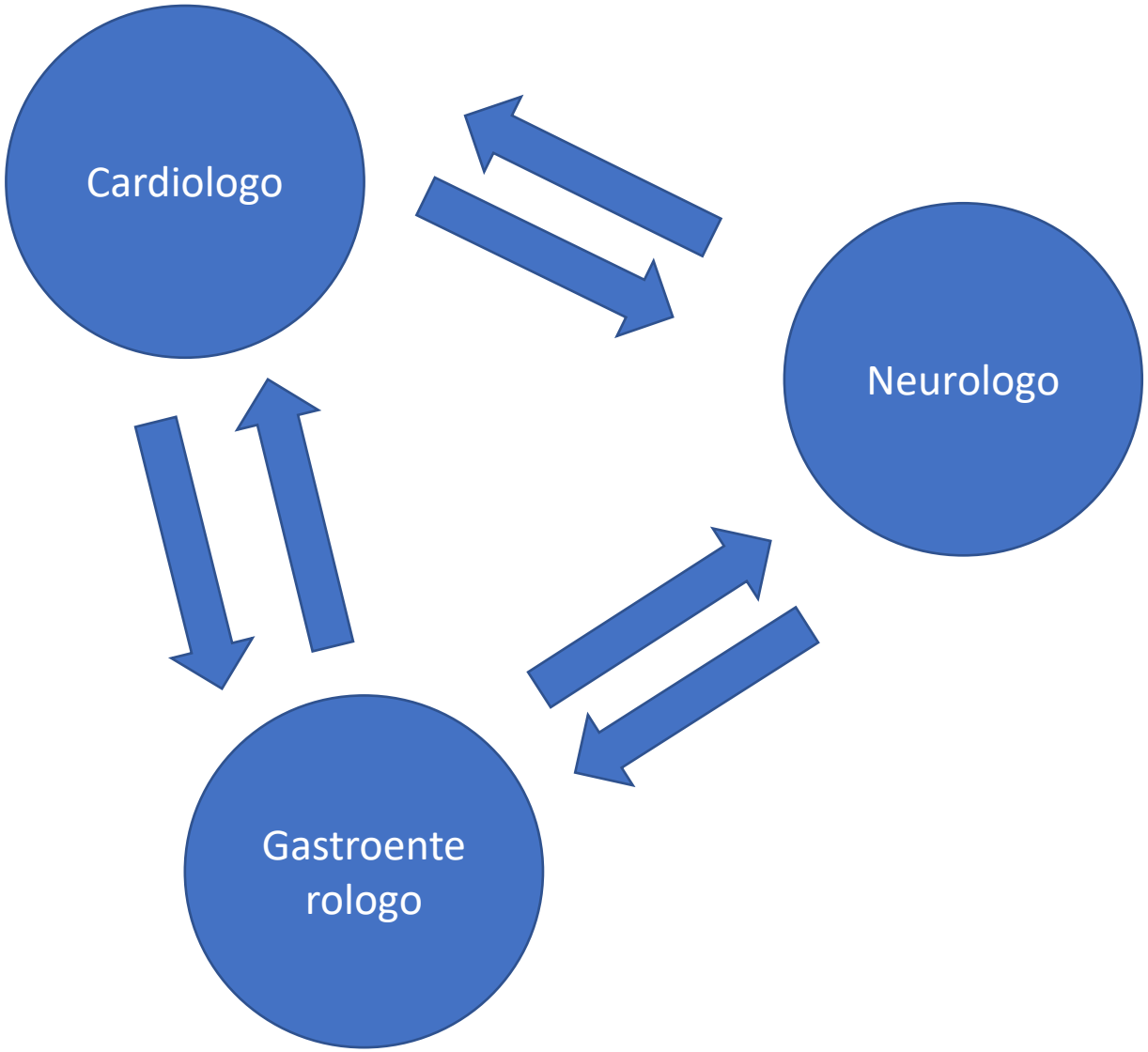
+ ≥1 of

- Family history of hATTR amyloidosis symptoms
- Neuropathy and sensory involvement
- Renal abnormalities
- Bilateral CTS
- Early autonomic dysfunction and GI complaints
- HFpEF (without hypertension)
- Cardiac hypertrophy, arrhythmias, ventricular blocks, right-sided or biventricular HF, or cardiomyopathy
- Vitreous opacities

HFpEF, heart failure with preserved ejection fraction

Based on Conceição et al. *J Peripher Nerv Syst* 2016;21:5–9

Team multidisciplinare



Management

Diagnosi

Teams multidisciplinari: algoritmi

Patologia internistica suggestiva

Condivisione del caso

Valutazione neurofisiologica

Se neuropatia
+
almeno una red flag

ESAME GENETICO

Screening genetico attivo

- Su **tunnel carpali bilaterali che recidivano** alla chirurgia;
- Su pazienti con **captazioni cardiache alla scintigrafia ossea**;
- Su pazienti con **biopsia positiva al Rosso Congo**;
- Su pazienti con **polineuropatia assonale idiopatica** evidenziata in ENG, anche in assenza di familiarità;
- **Familiari di I grado** dei pazienti affetti.

Approvato in data 13.7.20

Azienda Ospedaliera Universitaria
Policlinico Paolo Giaccone
di Palermo

Comitato Etico Palermo 1

Verbale N° 7/2020 Seduta del 13.07.2020

OMISSIS
STUDI

16. SCREENING GENETICO PER AMILOIDOSI EREDITARIA DA MUTAZIONE DELLA TRANSTIRETINA (HATTR) NEI PAZIENTI AFFETTI DA DISAUTONOMIA, POLINEURONEUROPATIA, CARDIOPATIA AMILOIDOSICA E SINDROME DEL TUNNEL CARPALE.

Sperimentatore: Prof. Filippo Brighina
Centro: U.O.C. di Neurologia e Neurofisiopatologia

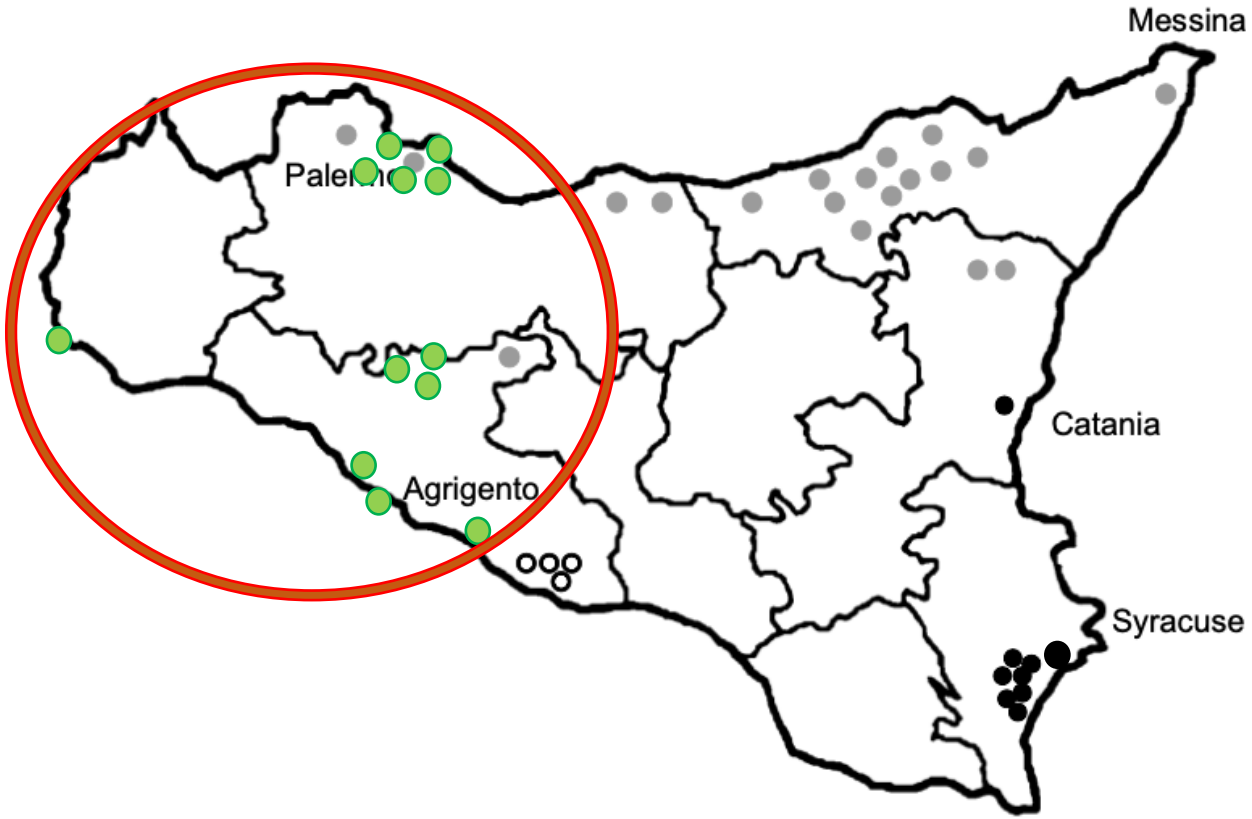
Il Comitato Etico esamina ed approva la sottoelencata documentazione:
- Protocollo
- Richiesta di autorizzazione studio -griglia
- Dichiarazione sul conflitto di interessi
- Dichiarazione di Helsinki
- Nulla osta del Responsabile della struttura
- Informativa e Manifestazione del consenso al trattamento dei dati personali

Il Comitato Etico fa presente che l'A.O.U.P. per lo svolgimento dello studio non sostiene spese aggiuntive e non copre eventuali danni che ne possano derivare.

Presidente
del Comitato Etico Palermo 1
Prof. Salvatore Lacorte

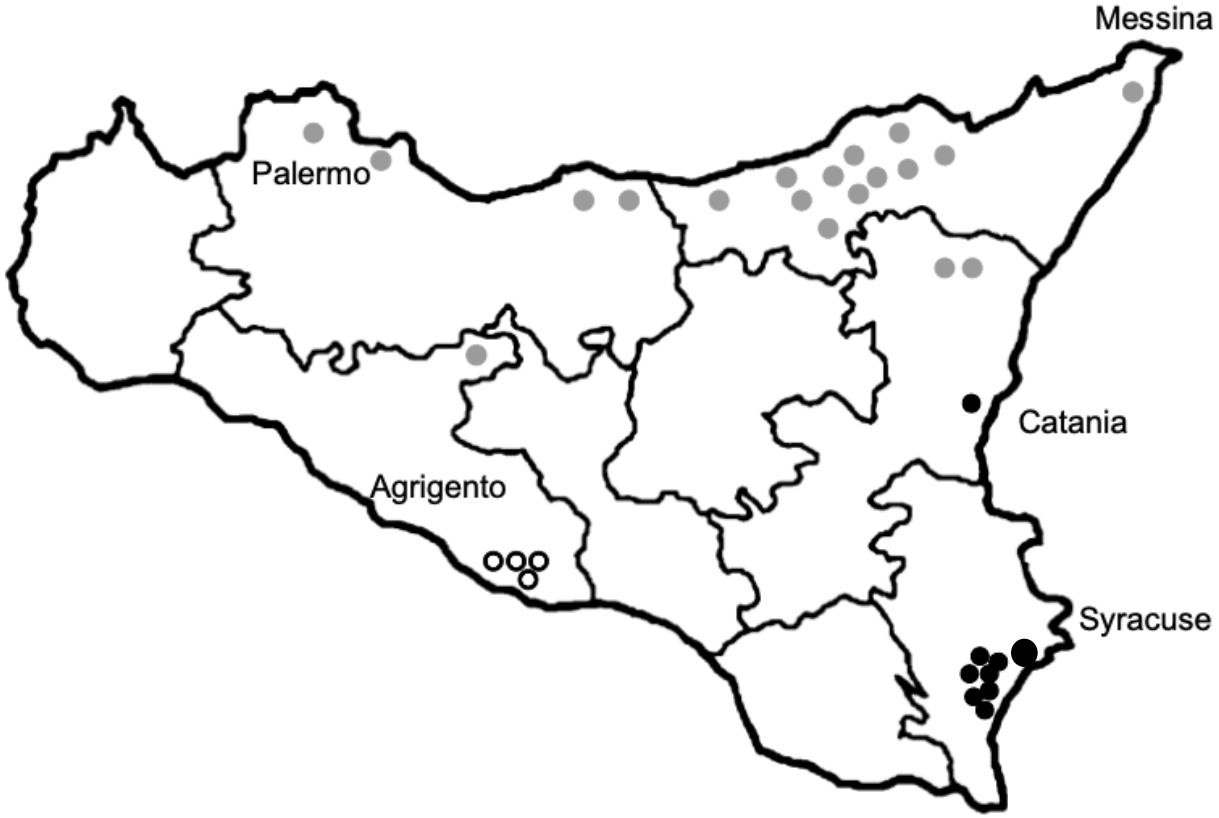
Palermo: oggi (24.4.2022)

- 185 test genetici effettuati
- *33 positivi (18%)*



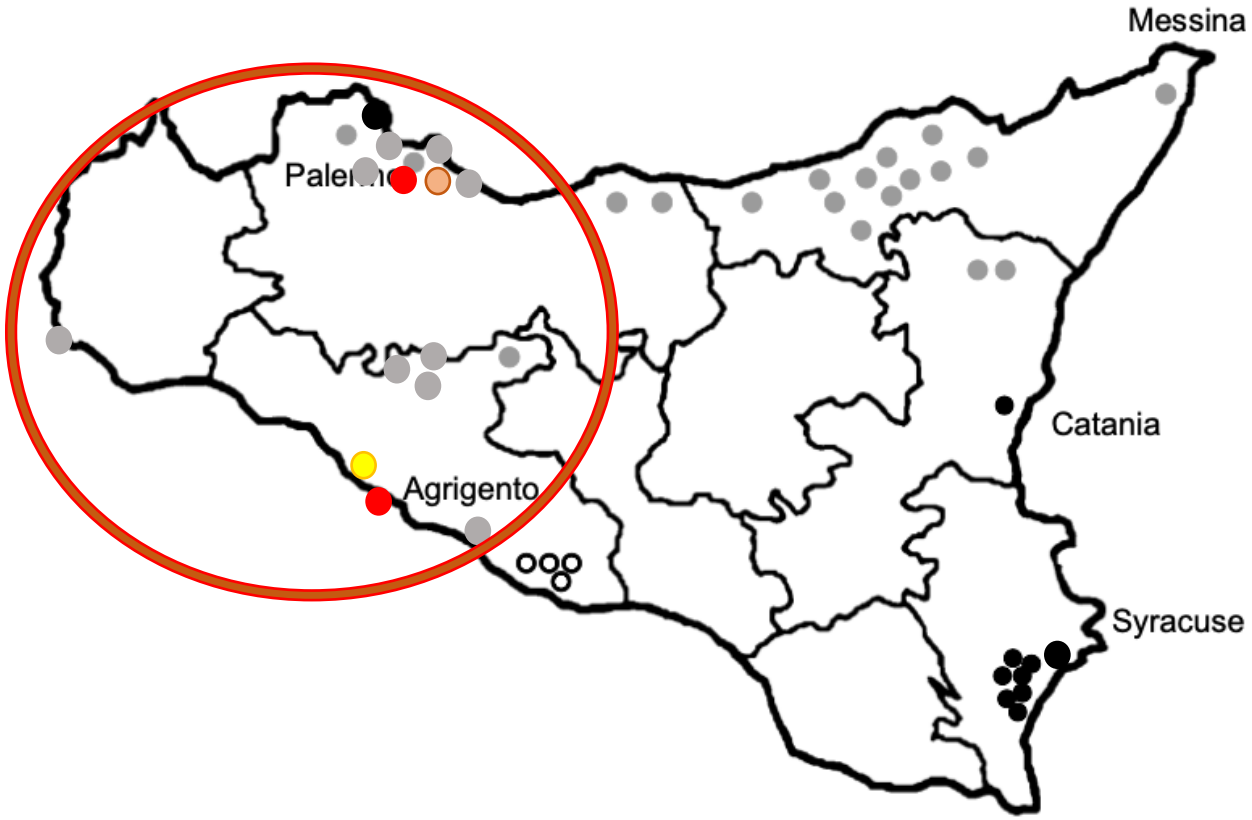
Casistica Sicilia Occidentale dopo screening: identificazione di 19 pazienti e 23 pre-sintomatici

- Phe84Leu
- Thr69Ala
- Glu109Gln
- Nuove diagnosi 2020-2022 (12 famiglie)



Casistica Siciliana da Mazzeo et al, 2015

- Phe84Leu
- Thr69Ala
- Glu109Gln



Pazienti ATTRv seguiti a Palermo
(23 pazienti, 28 pre-sintomatici):

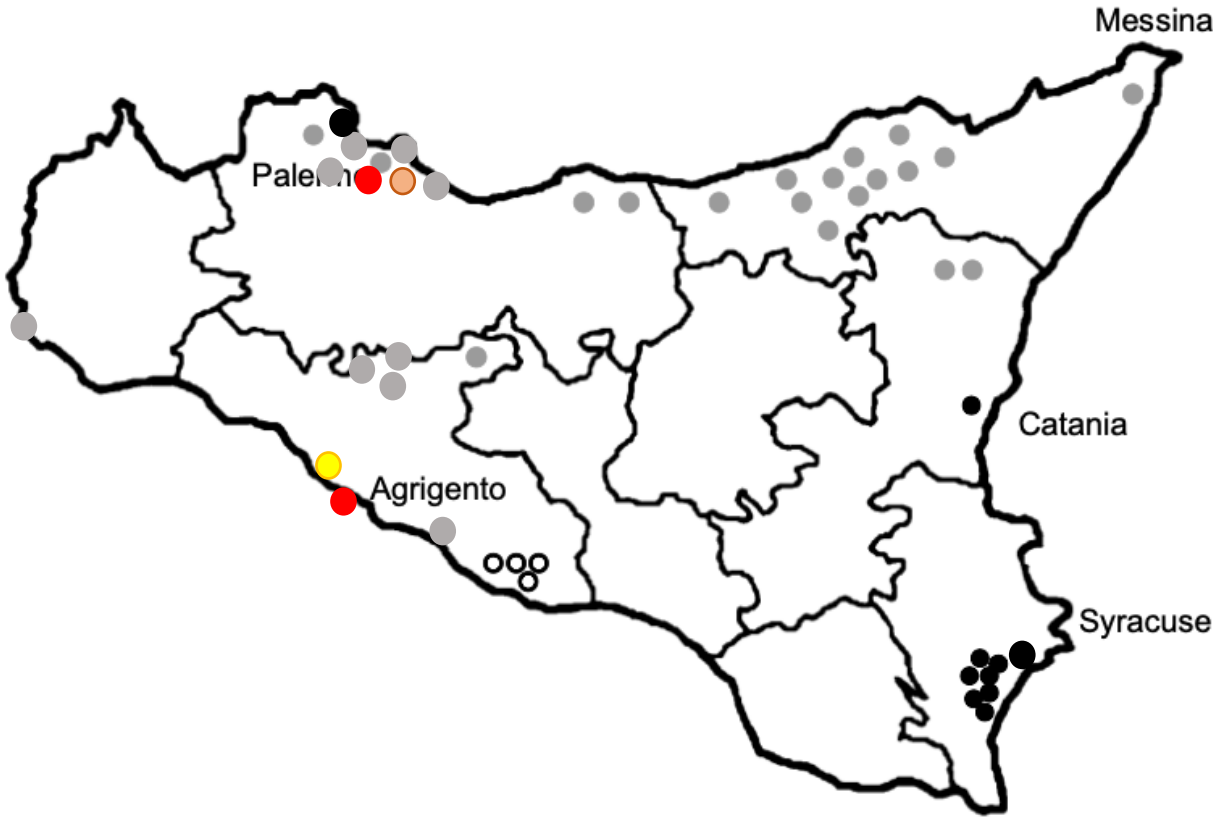
- Phe84Leu (17 pazienti, 14 carriers)
- Thr69Ala (0 pazienti)
- Glu109Gln (2 pazienti)
- His110Asn (1 paziente, 9 carriers)
- Val142Ile (2 pazienti, 3 carriers)
- Ser97Phe (1 paziente)

Casistica regionale?

Definizione nuovi dati di prevalenza in Sicilia

Famiglie:

- Phe84Leu
- Glu109Gln
- Thr69Ala
- His110Asn
- Val142Ile
- Ser97Phe



Ulteriori sviluppi:

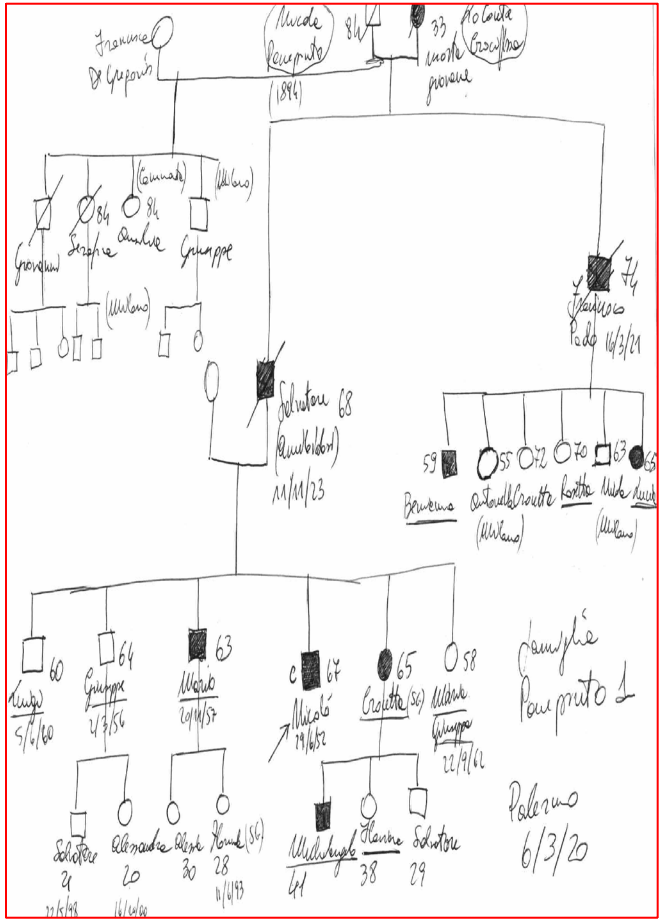
Potenziamento screening tramite algoritmi di machine-learning:

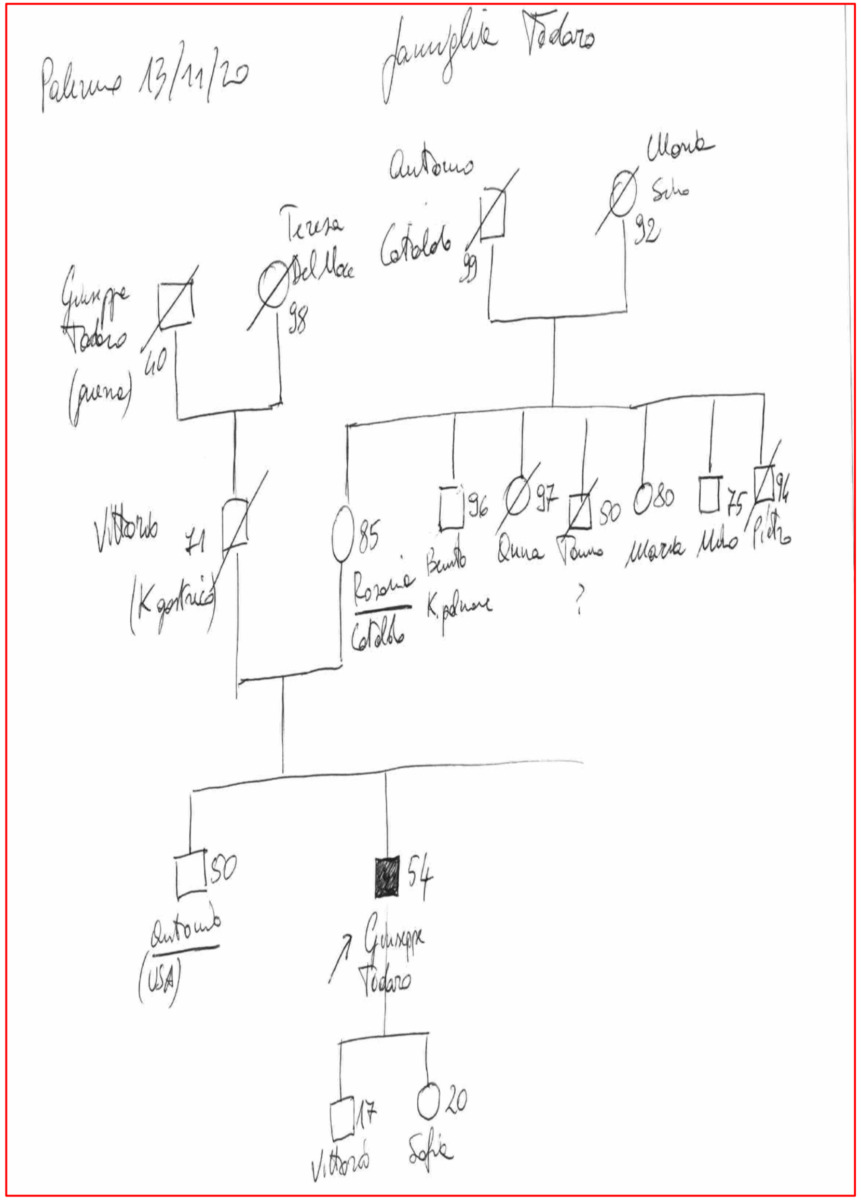
"Ricerca e sviluppo di nuovi biomarcatori e metodiche di valutazione del danno multi-organo per la diagnosi genetica precoce e il follow-up della polineuropatia amiloidosica ereditaria da transtiretina (hATTR)."

PON "Ricerca e Innovazione" 2014-2020, Asse IV "Istruzione e ricerca per il recupero" Azione IV.4 "Dottorati e contratti di ricerca su tematiche dell'innovazione"

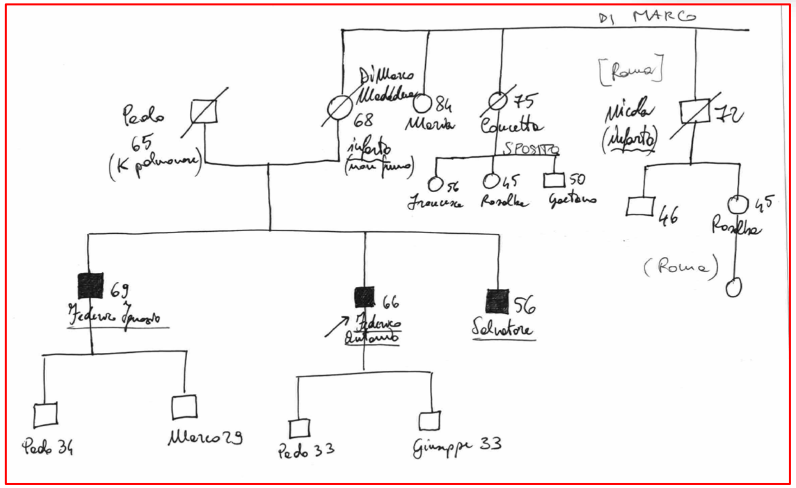
Partecipazione progetto nazionale Screen care:

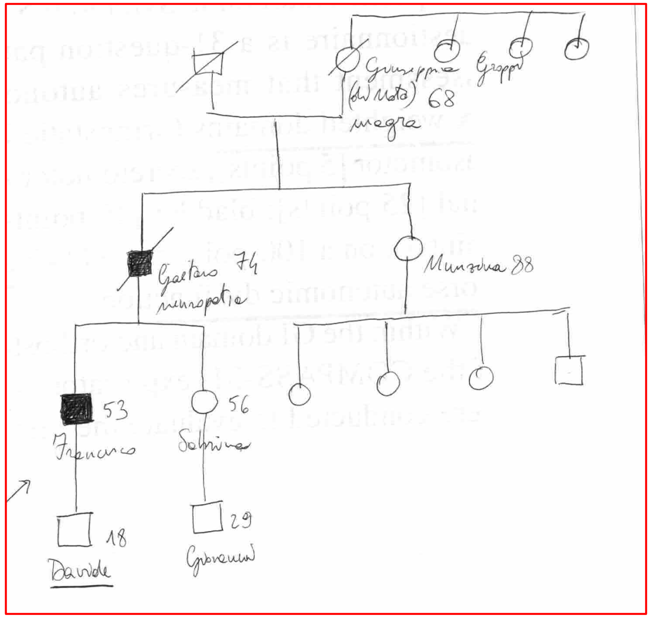
Screening attivo efficace da colleghi sul territorio: 3 nuovi casi (Agrigento, Trapani)

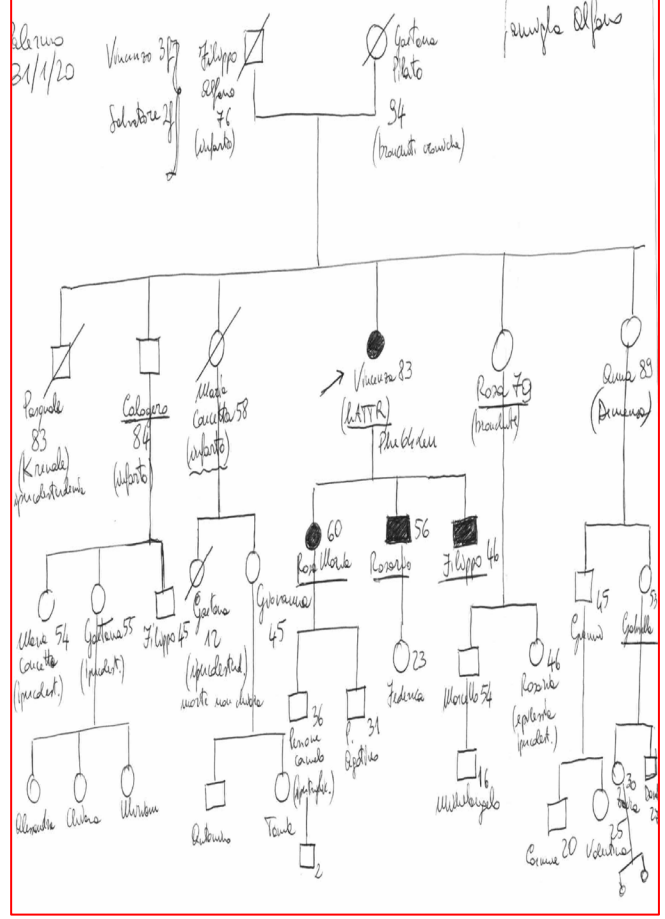

Famiglia Pomputo 1
Palermo 6/3/20

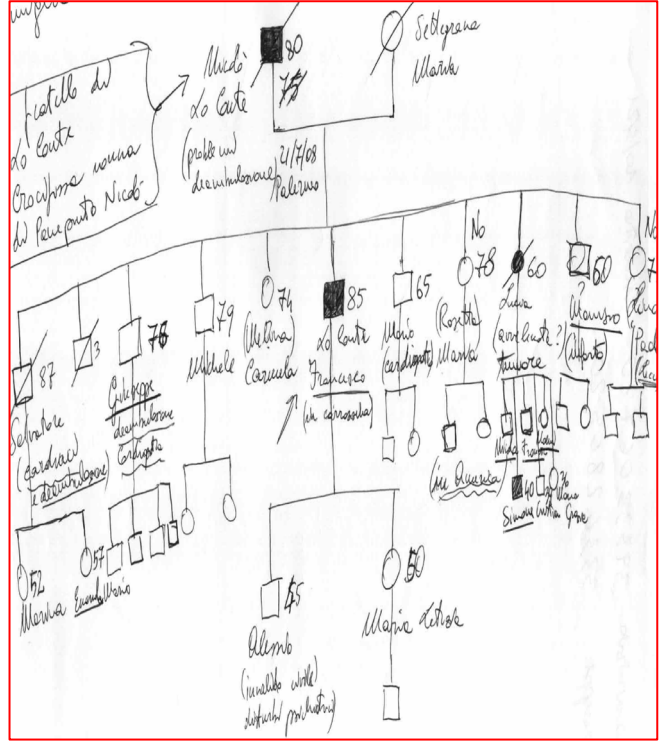

Palermo 13/11/20
Famiglia Todaro

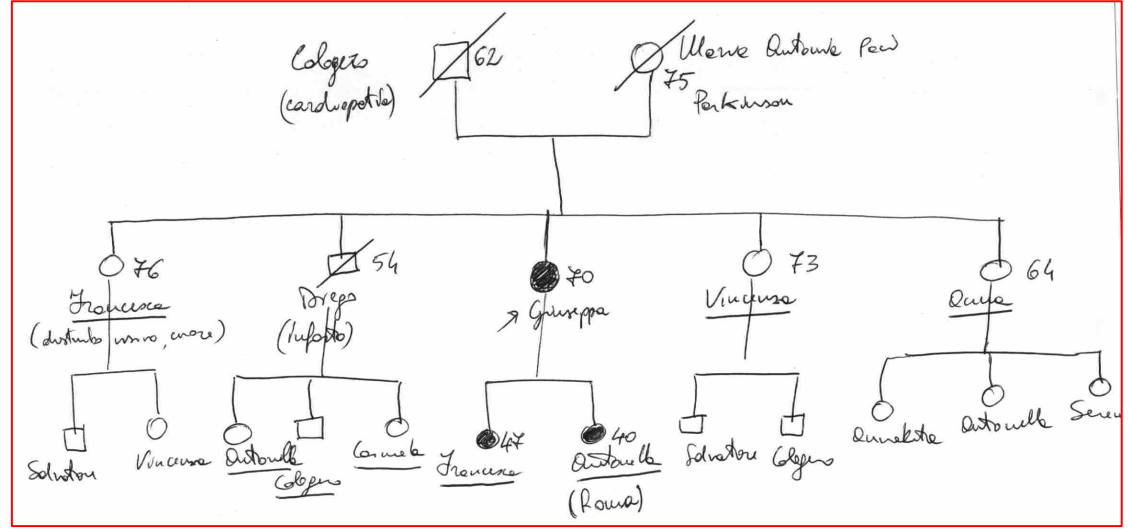

66° CONGRESSO NAZIONALE

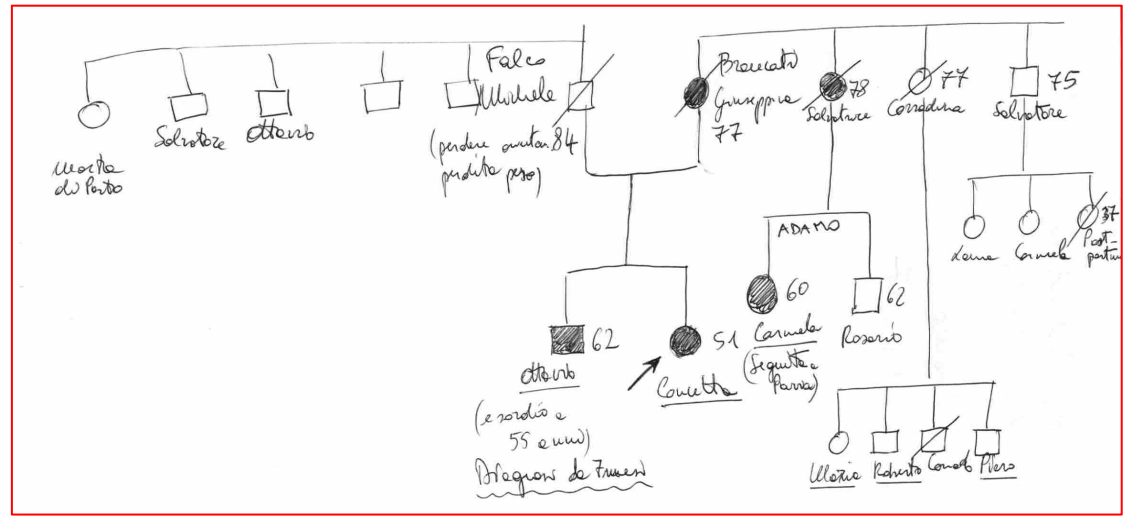

DI MARCO

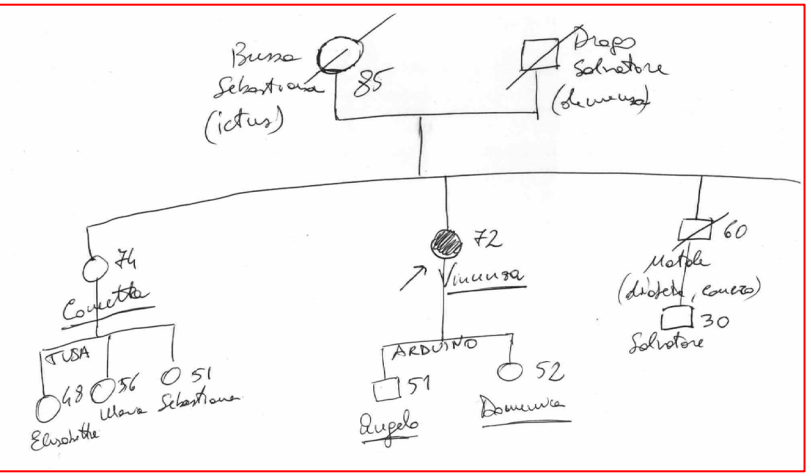


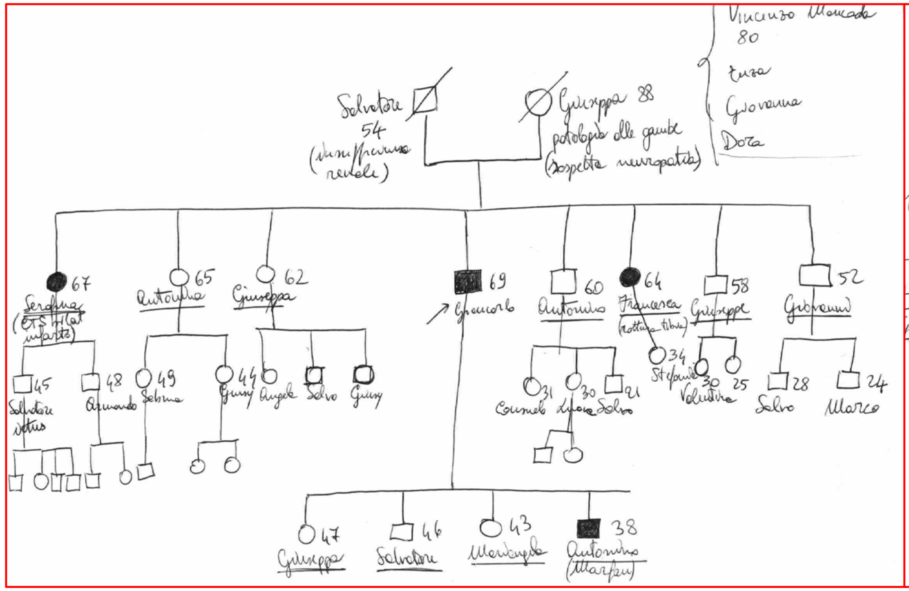


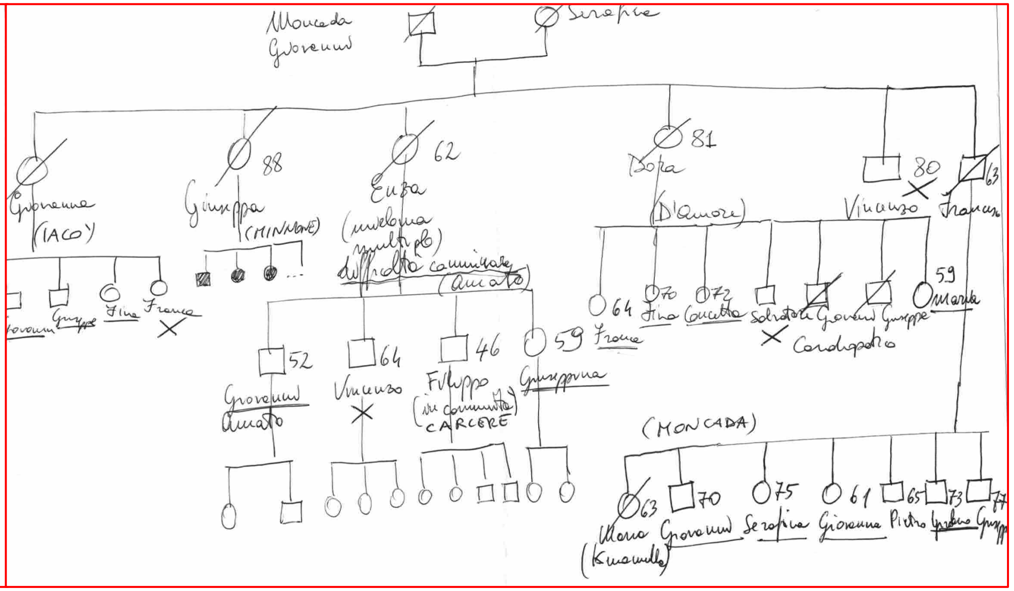


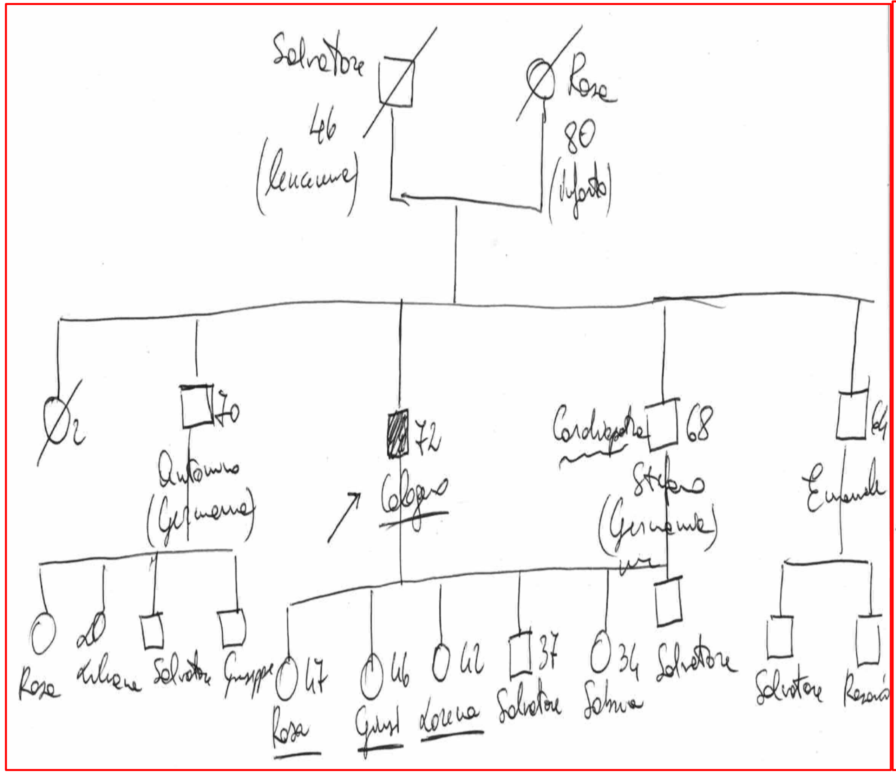


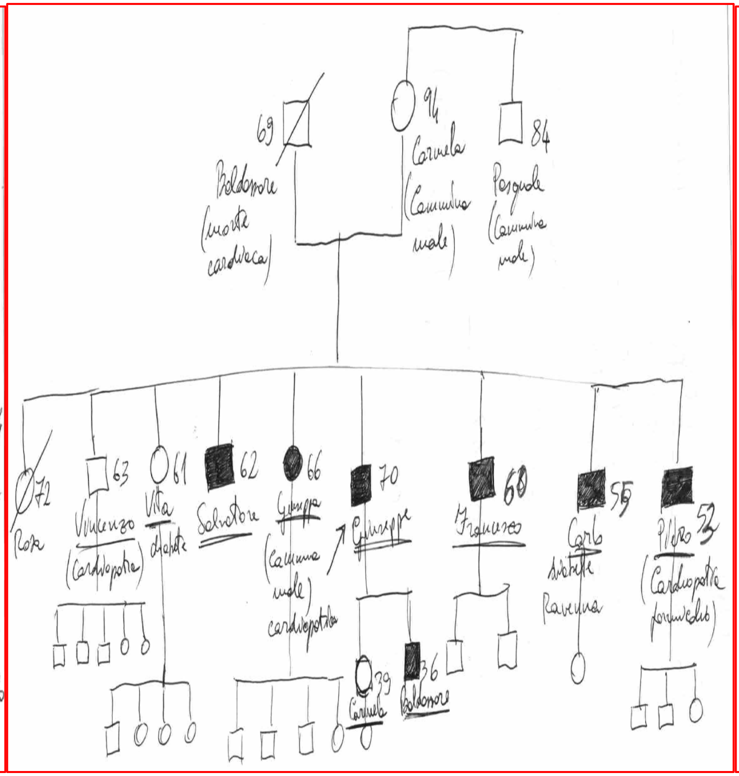


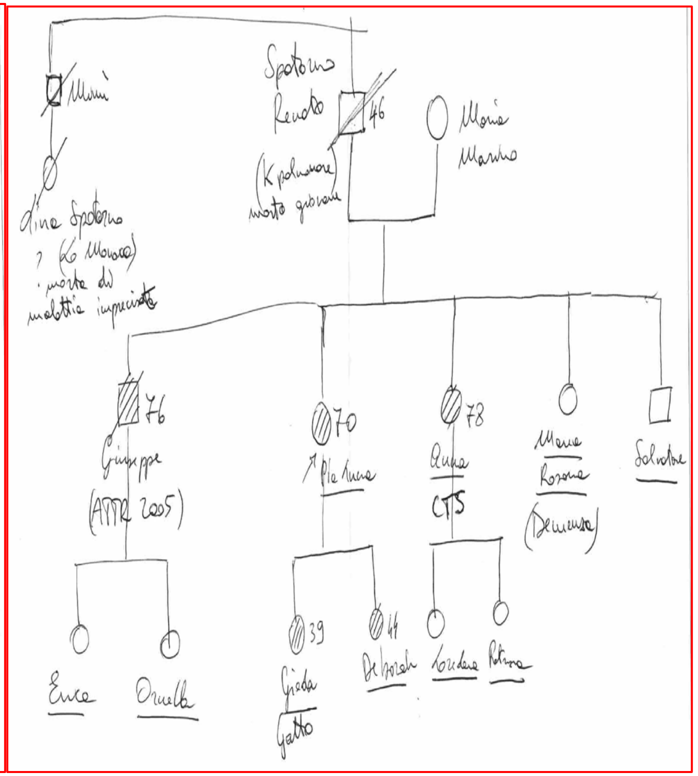



Salvatore 54
Giuseppa 88
Vincenzo Moncada 80
Enza
Giovanna
Dora
Serafina 67
Antonina 65
Giuseppa 62
Giacomo 69
Antonino 60
Francesca 64
Giuseppe 58
Giovanni 52
Giuseppe 47
Salvatore 46
Antonino 38


Moncada Giovanni
Serafina
Giovanna
Giuseppa 88
Enza 62
Dora 81
Vincenzo 80
Francesco 63
(MONCADA)
Giovanni 52
Vincenzo 64
Filippo 46
Giuseppina 59
CARCERE


Salvatore 46
Rosa 80
Antonino 70
Calogero 72
Stefano 68
Emanuele
Rosa
Salvatore


69
94 Carmela
84 Pasquale
Rosa
Vincenzo 63
Salvatore 62
Giuseppe 70
Francesco 68
Carlo 55
Pietro 52
Carmela 39
Baldassare 36


Spataro Renato 46
Giuseppe 76
Anna 78
Salvatore
Giada 39
Deborah 44

STC bil. trattata chirurgicamente;
Perdita di peso di 15 kg: attribuita ad anoressia da stato depressivo reattivo alla morte del coniuge

Ipoestesia tattile e dolorifica lieve distale
Ipotono distale lieve arti sup ed inf
Deficit stenico lieve distale (MRC:4)

Ipotrofia muscolare diffusa, paziente cachettica
Areflessia
Andatura lievemente atassica.

EMG/ENG: neuropatia assonale sensitivo-motoria con segni di denervazione all'EMG

Genetica positiva: Phe64leu

Inizia terapia con patisiran

Follow-up a 9 mesi di terapia

Grazie per l'attenzione!

Centro Diagnosi e Cura delle Malattie Rare Neuromuscolari

A.U.O. Policlinico "Paolo Giaccone" di Palermo

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Med. Interna

Prof. D. Noto
Prof. M. Averna

Cardiologia

Prof. G. Novo
Dott.ssa Di Lisi
Dott. L. Rossetto

Gastroenterologia

Prof. M. Cappello
Prof. A. Craxi

Radiodiagnostica

Dott. E. Grassedonio
Dott.ssa P. Toia
Dott. L. La Grutta

Anatomia Patologica

Prof. A. Florena
Prof. V. Rodolico
Dott. S. Bellavia

Med. Laboratorio

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Dott.ssa L. Agnello
Dott.ssa C. Gambino

Neurochirurgia

Prof. R. Maugeri
Dott. R. Giammalva
Prof. D. Iacopino