

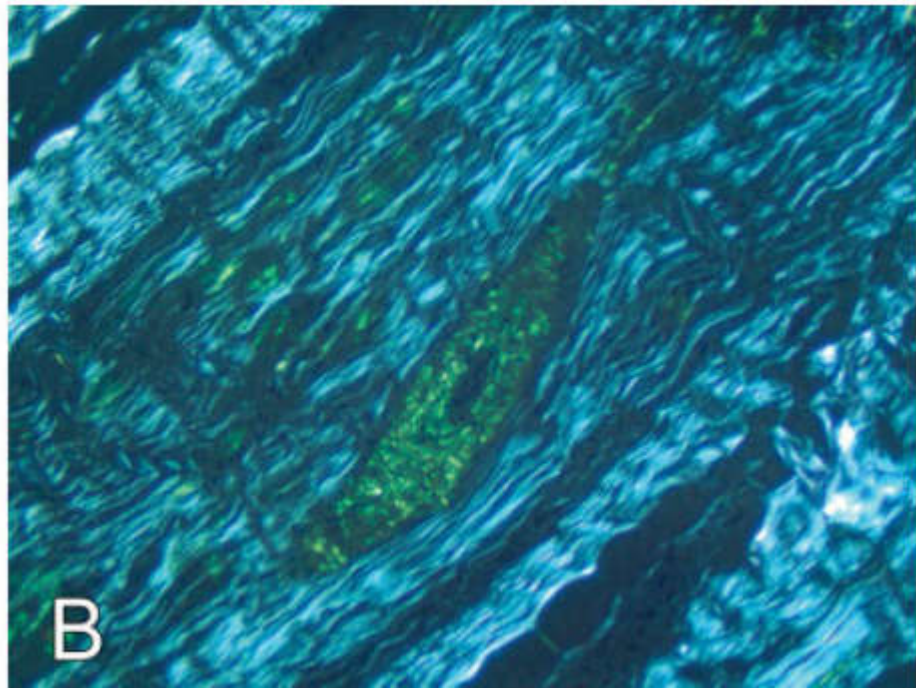
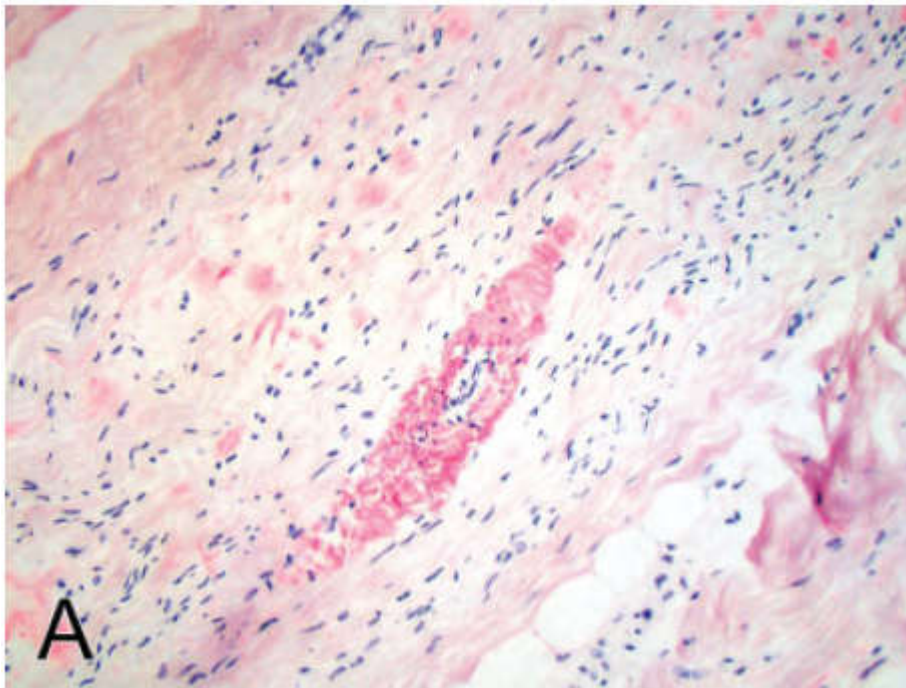
# Behandeling van polyneuropathie bij TTR amyloïdose

Dr. Alexander F.J.E. Vrancken, neuroloog

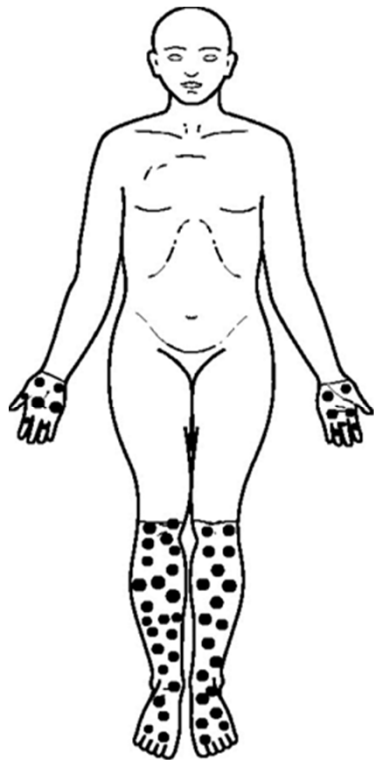
# TTR amyloïddepositie in zenuwstelsel

- Zenuwen
  - polyneuropathie
  - autonome neuropathie
- Hersenen (zeer weinig voorkomend)

# Amyloiddepositie in zenuwen

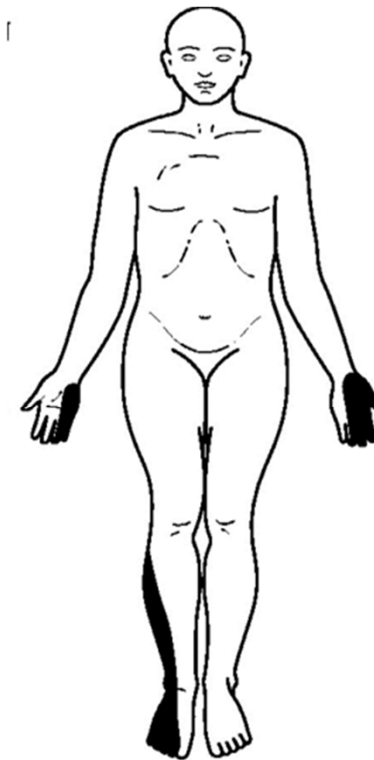


# ATTR: polyneuropathie



A

- progressief
- pijn
- ↓ spierkracht
- ↓ gevoel
  - temperatuur
  - aanraking
  - evenwicht

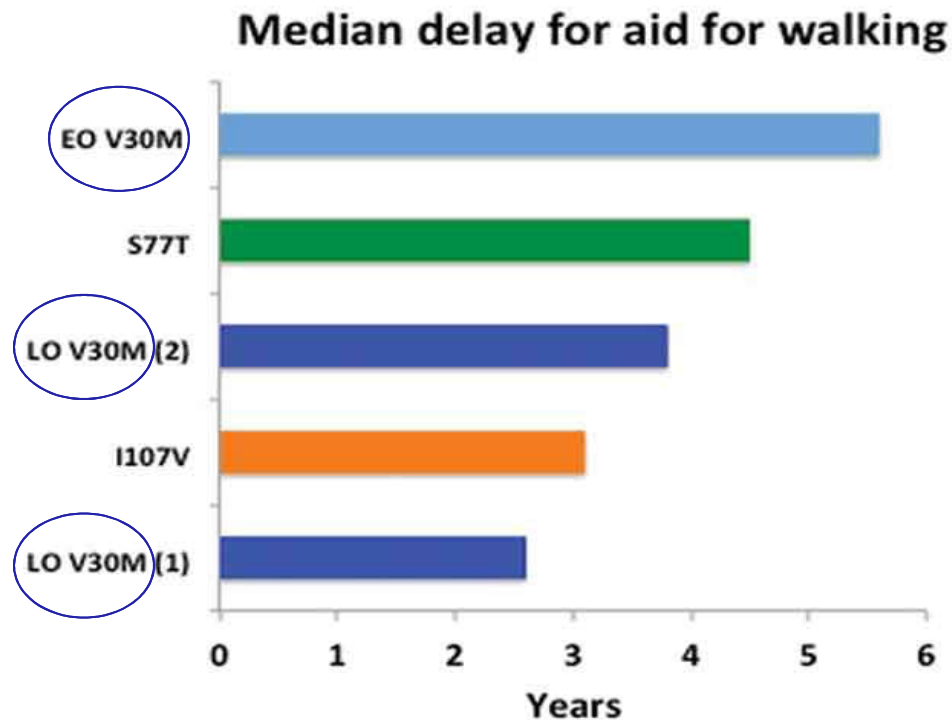


D



## ATTR: polyneuropathie

- mobiliteit: gebruik van loophulpmiddelen



## ATTR: autonome neuropathie

- progressief
- 2-5 jaar na begin ziekte
- bloeddrukdalingen
- mictieproblemen, impotentie
- obstipatie/diarree, ↓ maaglediging
- droge ogen/mond, ↓ zweetproductie
- hartritmestoornissen

# ATTR: behandeling polyneuropathie/autonome neuropathie

- geen genezing
- symptoombestrijding
- amyloiddepositiebestrijding
  - remmen progressie
  - voorkomen/uitstellen symptomen (carriers)
- niet-medicamenteus: fysio, ergo, revalidatie



REVIEW

Open Access

## Guideline of transthyretin-related hereditary amyloidosis for clinicians

Yukio Ando<sup>1,13\*</sup>, Teresa Coelho<sup>2</sup>, John L Berk<sup>3</sup>, Márcia Waddington Cruz<sup>4</sup>, Bo-Göran Ericzon<sup>5</sup>, Shu-ichi Ikeda<sup>6</sup>, W David Lewis<sup>7</sup>, Laura Obici<sup>8</sup>, Violaine Planté-Bordeneuve<sup>9</sup>, Claudio Rapezzi<sup>10</sup>, Gerard Said<sup>11</sup> and Fabrizio Salvi<sup>12</sup>

### SUPPLEMENT ARTICLE

OPEN



## First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy

David Adams<sup>a</sup>, Ole B. Suhr<sup>b</sup>, Ernst Hund<sup>c</sup>, Laura Obici<sup>d</sup>, Ivailo Tounev<sup>e,f</sup>, Josep M. Campistol<sup>g</sup>, Michel S. Slama<sup>h</sup>, Bouke P. Hazenberg<sup>i</sup>, Teresa Coelho<sup>j</sup>, from the European Network for TTR-FAP (ATTReuNET)





# ATTR: behandeling polyneuropathie/autonome neuropathie

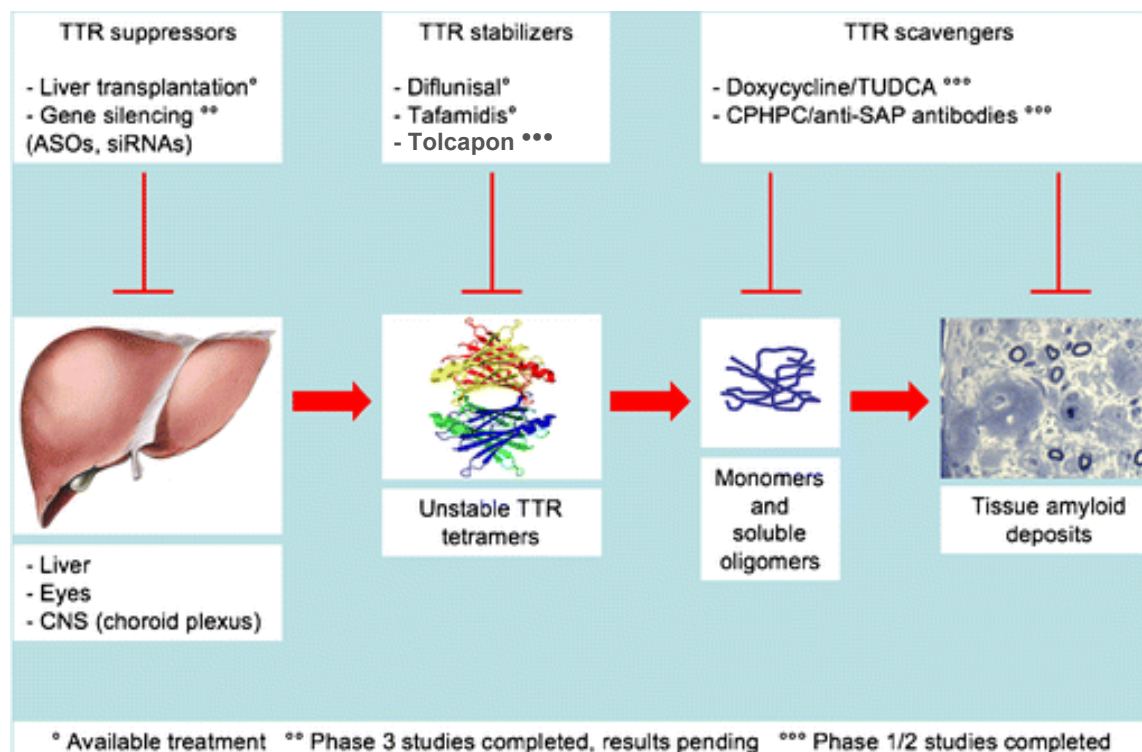
- Symptoombestrijding
  - neuropathische pijn
    - ✓ amitriptyline, duloxetine
    - ✓ gabapentine, pregabaline
    - ✓ tramadol, oxycodon
    - ✓ pijnteam

# ATTR: behandeling polyneuropathie/autonome neuropathie

- Symptoombestrijding
  - autonome klachten
    - ✓ lage bloeddruk: zout, steunkousen, midodrine, fludrocortison
    - ✓ misselijkheid: domperidon, metoclopramide, erytromycine
    - ✓ diarree: loperamide
    - ✓ obstipatie: laxeermiddelen
    - ✓ urine(in)continentie: diverse middelen, catheter
    - ✓ impotentie: diverse middelen (oraal, via plasbuis, injectie)
    - ✓ droge ogen/mond: kunsttranen/-speeksel

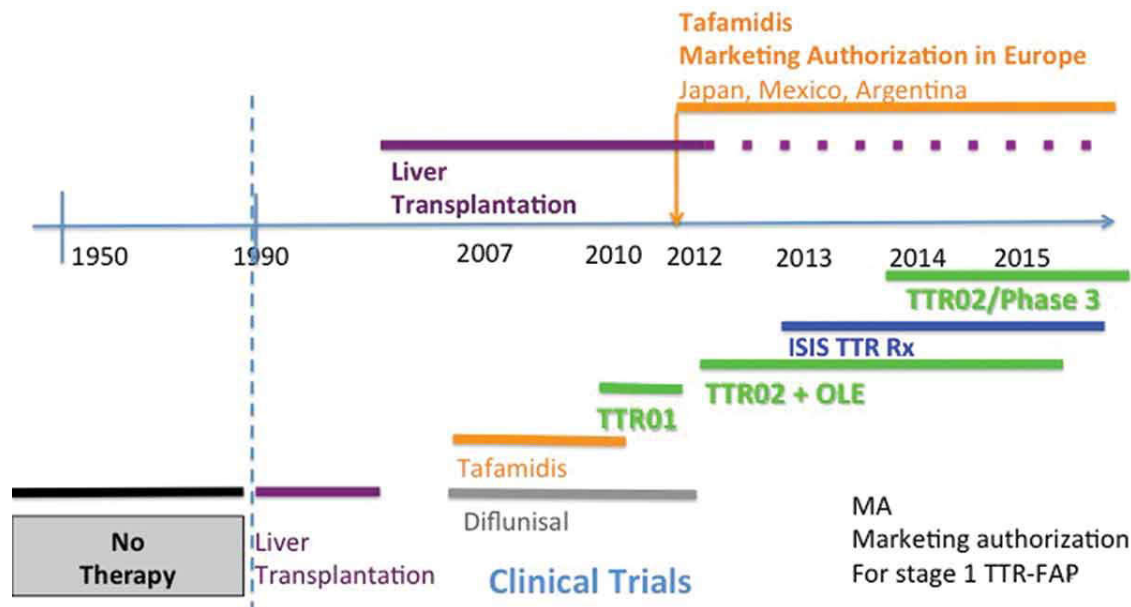
# ATTR: behandelning polyneuropathie/autonome neuropathie

- Bestrijding amyloid

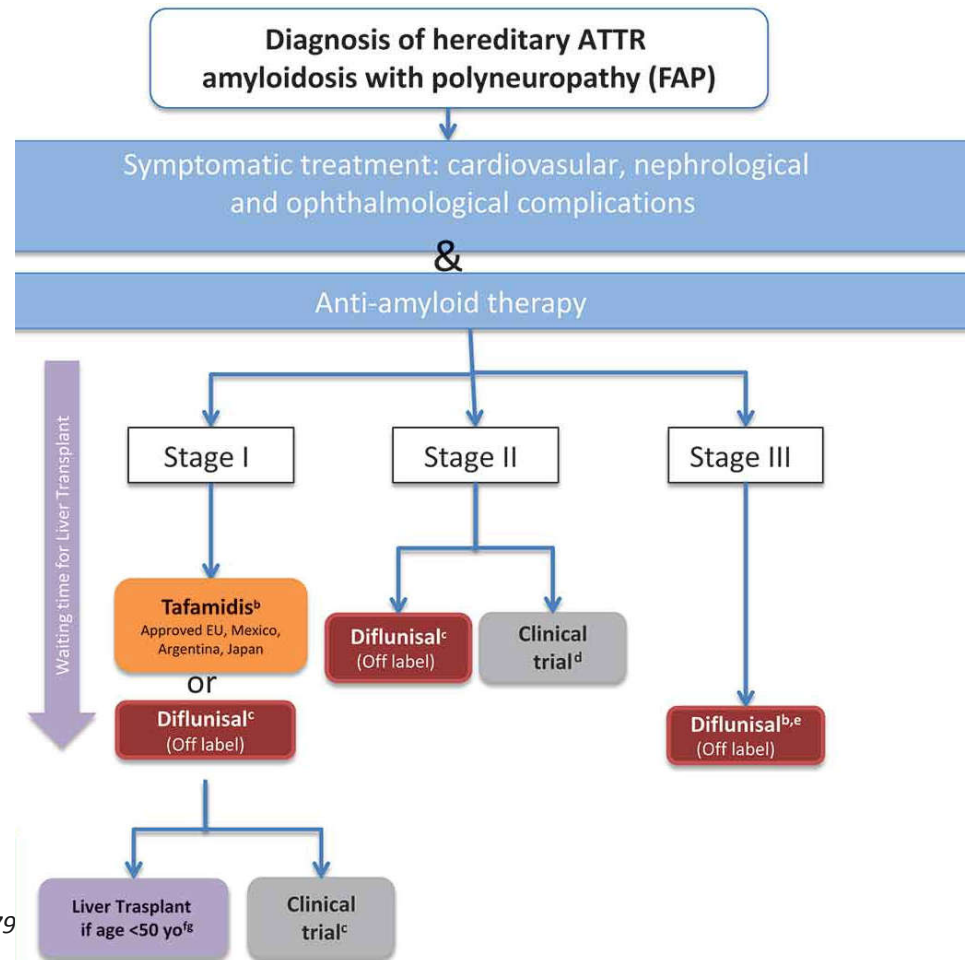


# ATTR: behandeling polyneuropathie/autonome neuropathie

- Bestrijding amyloid

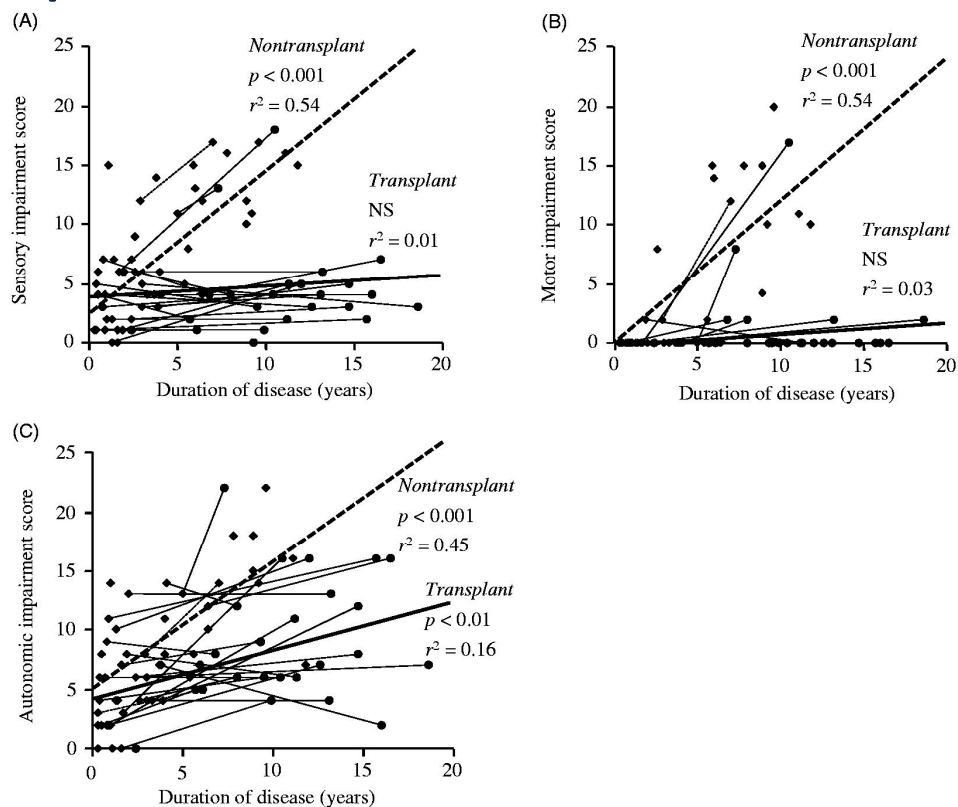


# ATTR: behandelning polyneuropathie/autonome neuropathie



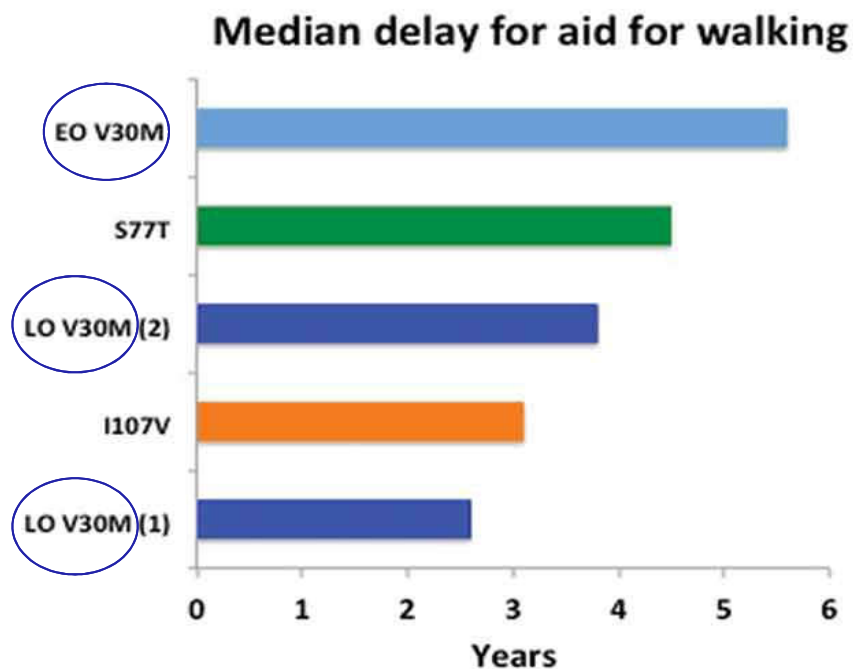
# ATTR: behandelning polyneuropathie/autonome neuropathie

## Levertransplantatie



# ATTR: behandeling polyneuropathie/autonome neuropathie

- Amyloiddepositiebestrijding



*Exp Opin Pharmacother 2016;17(6):791-802*



# ATTR: behandelning polyneuropathie/autonome neuropathie

## Tafamidis for transthyretin familial amyloid polyneuropathy

A randomized, controlled trial



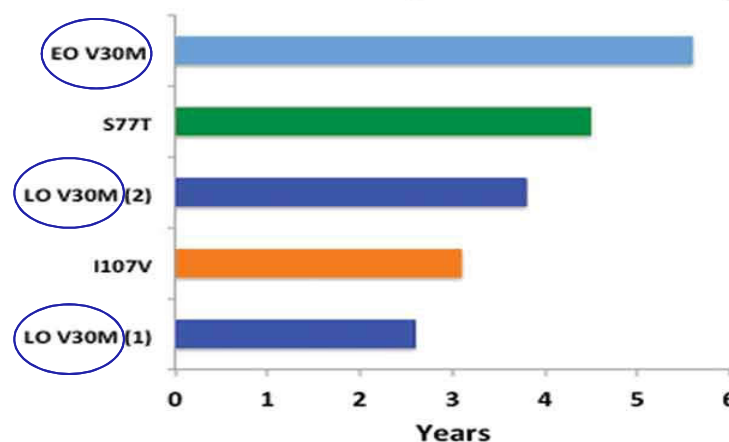
Neurology 2012;79:785-92

Teresa Coelho, MD  
Luis F. Maia, MD  
Ana Martins da Silva,

### ABSTRACT

**Objectives:** To evaluate the efficacy and safety of 18 months of tafamidis treatment in patients with early-stage V30M transthyretin familial amyloid polyneuropathy (TTR-FAP).

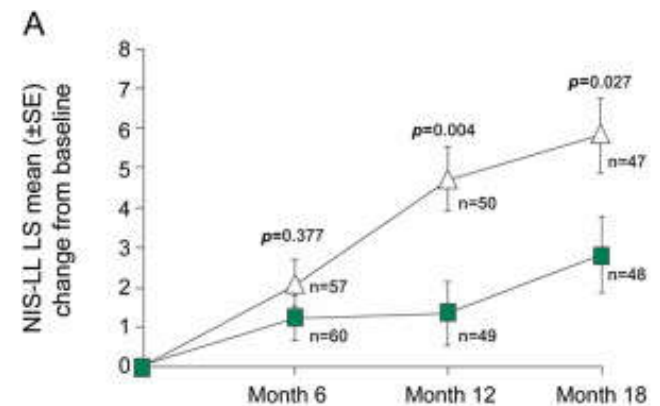
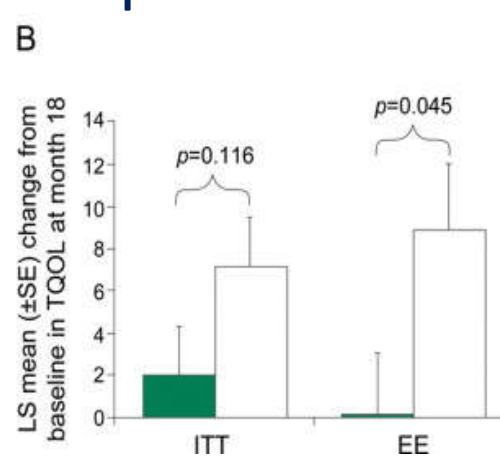
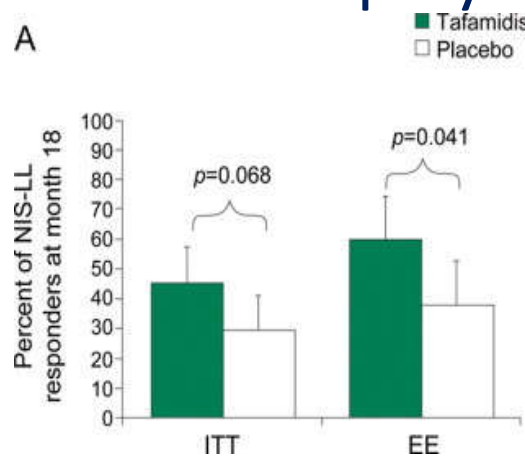
### Median delay for aid for walking



UMC Utrecht

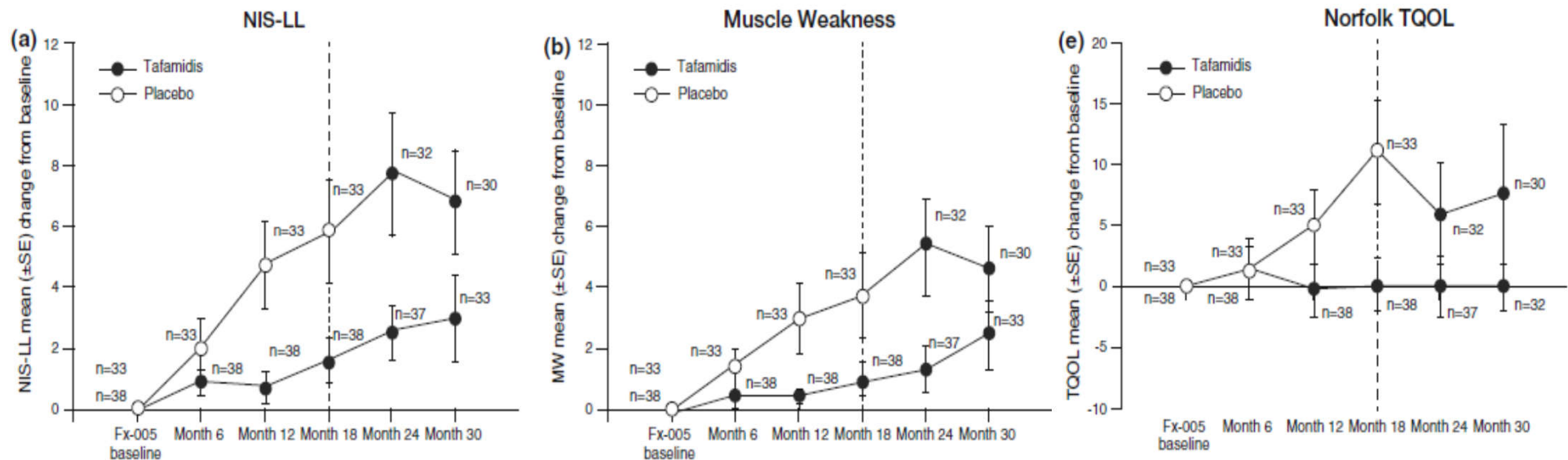
# ATTR: behandeling polyneuropathie/autonome neuropathie

- Tafamidis
  - minder achteruitgang spierkracht benen
  - ATTR polyneuropathie stadium 1



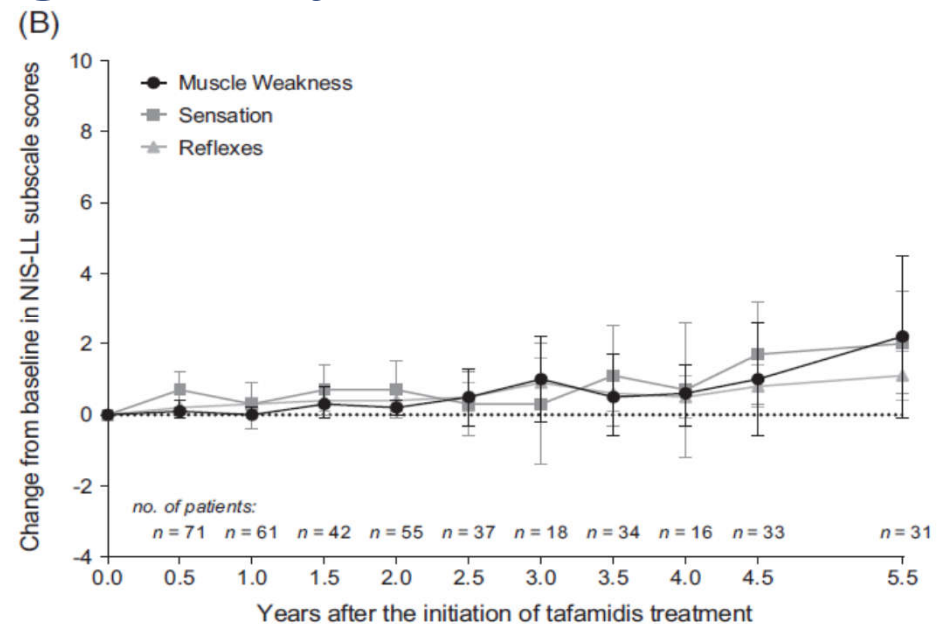
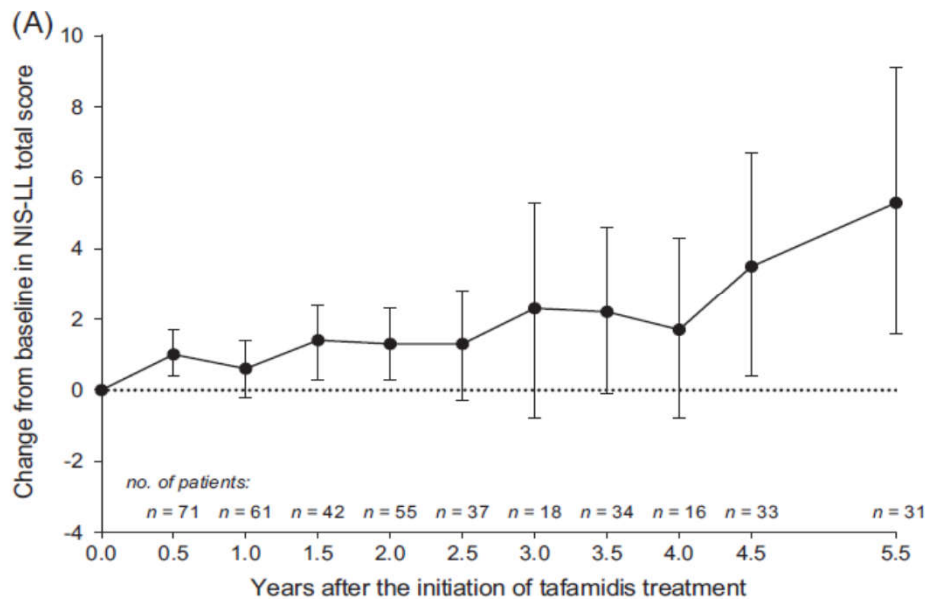
# ATTR: behandeling polyneuropathie/autonome neuropathie

- Tafamidis: effect op lange termijn



# ATTR: behandeling polyneuropathie/autonome neuropathie

- Tafamidis: effect op lange termijn



# ATTR: behandeling polyneuropathie/autonome neuropathie

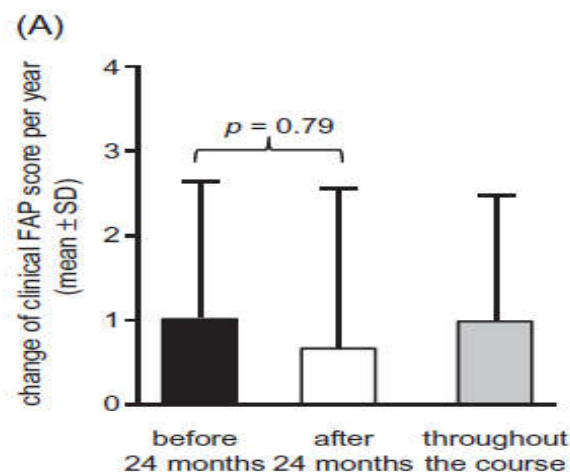
- Diflunisal

Outcomes	Mean (95% CI)			P Value
	Placebo Change From Baseline	Diflunisal Change From Baseline	Difference, Placebo-Diflunisal	
NIS+7 score				
At 1 year	12.5 (8.6 to 16.4)	6.2 (2.8 to 9.6)	6.4 (1.2 to 11.6)	.02
At 2 years	26.3 (20.2 to 32.4)	8.2 (2.9 to 13.6)	18.0 (9.9 to 26.2)	<.001
NIS score				
At 1 year	10.1 (6.9 to 13.3)	4.1 (1.2 to 6.9)	6.0 (1.7 to 10.3)	.007
At 2 years	23.2 (17.8 to 28.5)	6.4 (1.6 to 11.2)	16.8 (9.6 to 24.0)	<.001
NIS-LL score				
At 1 year	6.0 (3.9 to 8.2)	3.2 (1.3 to 5.2)	2.8 (-0.1 to 5.7)	.06
At 2 years	12.1 (8.9 to 15.3)	3.8 (0.9 to 6.6)	8.3 (4.1 to 12.6)	<.001
Kumamoto score				
At 1 year	4.1 (2.1 to 6.2)	1.9 (0.1 to 3.7)	2.3 (-0.5 to 5)	.10
At 2 years	8.0 (5.8 to 10.3)	3.1 (1.1 to 5.1)	5.0 (1.9 to 8.0)	.002
Modified BMI <sup>b</sup>				
At 1 year	-38.5 (-74.9 to -2.1)	-18.7 (-51.6 to 14.1)	-19.8 (-68.8 to 29.2)	.43
At 2 years	-67.9 (-108.1 to -27.7)	-33.7 (-69.3 to 1.8)	-34.1 (-87.8 to 19.5)	.21
SF-36 physical component score				
At 1 year	-1.9 (-3.9 to 0.2)	0.7 (-1.1 to 2.5)	-2.6 (-5.3 to 0.1)	.06
At 2 years	-4.9 (-7.6 to -2.1)	1.2 (-1.2 to 3.7)	-6.1 (-9.8 to -2.5)	.001



# ATTR: behandeling polyneuropathie/autonome neuropathie

- Diflunisal
  - ATTR polyneuropathie elk stadium
  - effect cardiomyopathie ondanks bijwerkingen
  - effect lange termijn (> 3-4 jaar)

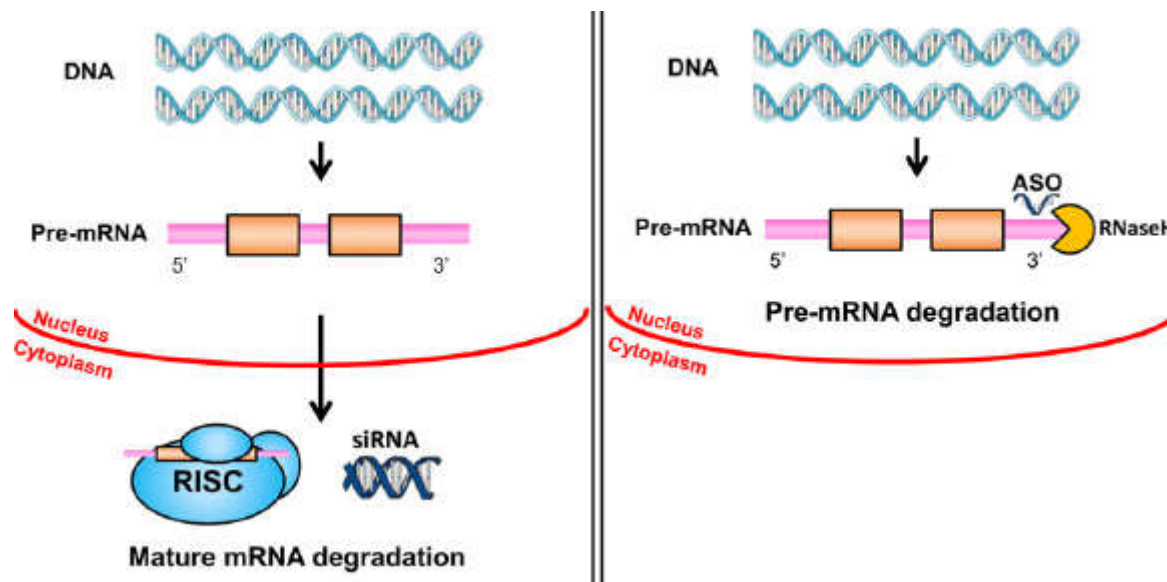


# ATTR: behandelning polyneuropathie/autonome neuropathie

- Gentherapie

- siRNA

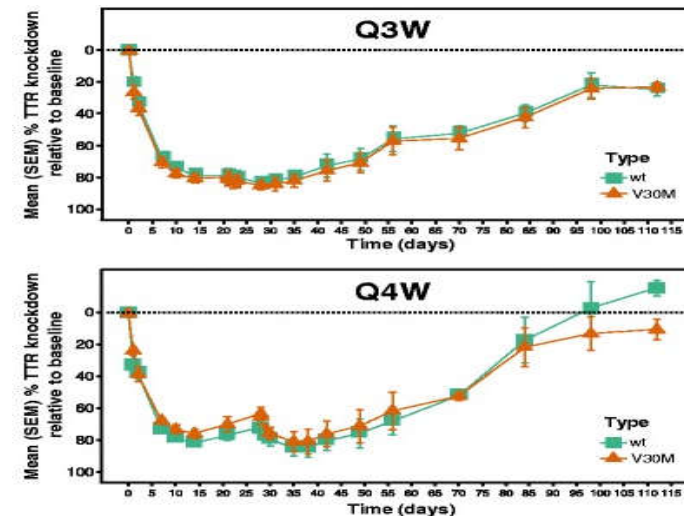
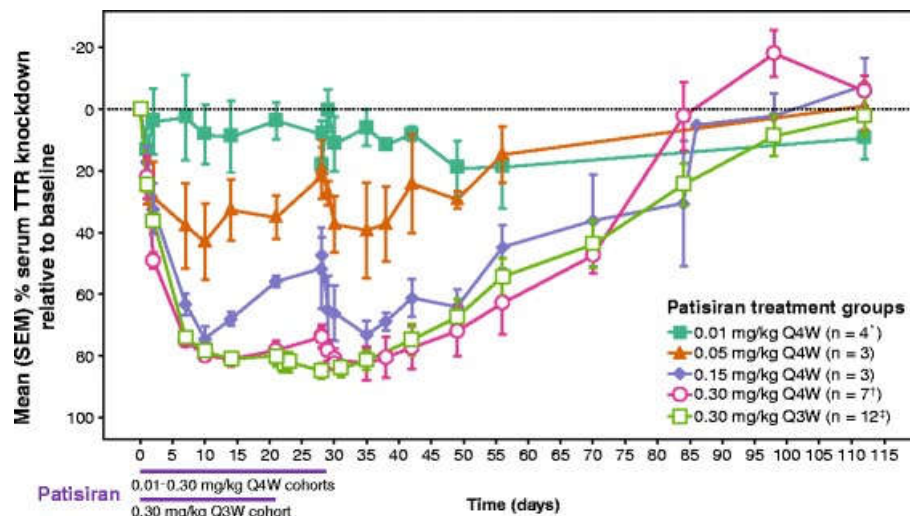
- antisense oligonucleotiden (ASO)





# ATTR: behandelning polyneuropathie/autonome neuropathie

- Gentherapie: patisiran siRNA
  - fase 1/2 studies

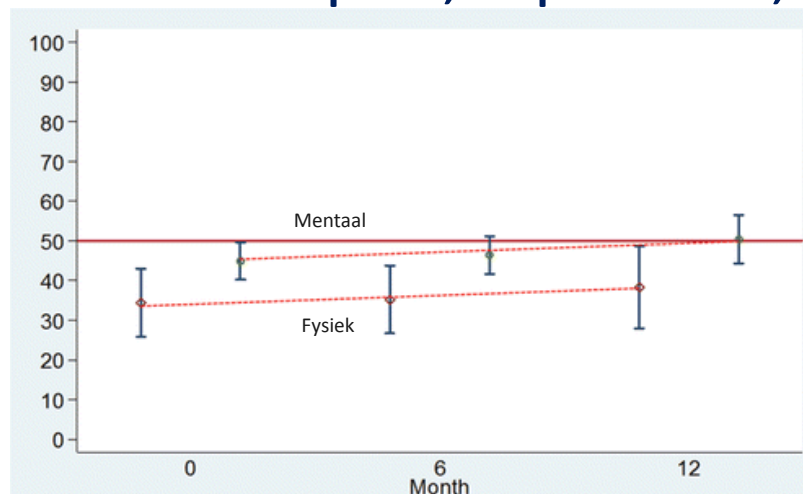


# ATTR: behandeling polyneuropathie/autonome neuropathie

- Gentherapie
  - patisiran siRNA
    - lopende fase 2 studie (open label)\*
  - IONIS-TTR<sub>RX</sub> (ISIS 420915) ASO, fase 1 studie\*\*
    - fase 1 studie: 80-96% afname TTR in plasma gezonden
    - effect ziekteprogressie?

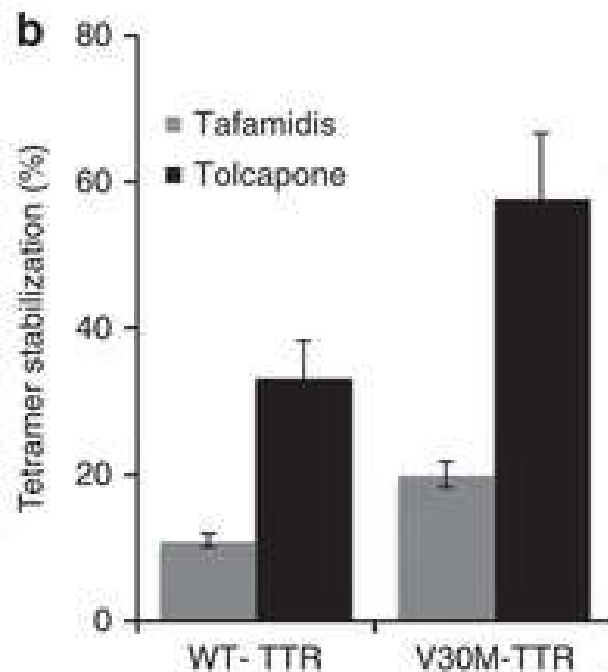
# ATTR: behandeling polyneuropathie/autonome neuropathie

- Doxycycline + tauroursodeoxycholzuur/TUDCA
  - antibioticum + middel tegen galstenen
  - fase 2 studie, 9 pt 6 maanden, 6 pt 12 maanden,
  - NIS-LL/Kumamoto: 4 pt =, 1 pt beter, 1 pt slechter
  - SF-36 QoL



# ATTR: behandeling polyneuropathie/autonome neuropathie

- Tolcapon/SOM0266 (ziekte v Parkinson)



- 3 gezond, 3 pat Val30Met
- effect op ziekteprogressie?

# ATTR: behandeling polyneuropathie/autonome neuropathie

Reig et al. *Orphanet Journal of Rare Diseases* 2015, **10**(Suppl 1):P9  
<http://www.ojrd.com/content/10/S1/P9>



**POSTER PRESENTATION**

**Open Access**

## SOM0226, a repositioned compound for the treatment of TTR amyloidosis

Núria Reig<sup>1\*</sup>, Salvador Ventura<sup>2</sup>, Maria Salvadó<sup>3</sup>, Josep Gámez<sup>3</sup>, Raúl Insa<sup>1</sup>

*From* First European Congress on Hereditary ATTR amyloidosis  
Paris, France. 2-3 November 2015

- 6 gezond, 15 asymptomatische carriers/patiënten
- duidelijke robuuste stabilisatie TTR in bloed
- effect op ziekteprogressie?



# ATTR: behandeling polyneuropathie/autonome neuropathie

- Tot slot...
  - hoe vroeger hoe beter, 3 pijlers
    - symptomatisch
    - anti-amyloiddepositie
    - revalidatie
  - asymptomatische carriers: wanneer starten?
- Vragen?