Amyloidosis

Herkennen en Behandeling

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Cardioloog

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The Netherlands

umcg cardiology research institute

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Disclosures

- Research grants: Pfizer, Vifor Pharma, Ionis, Astra Zeneca, Novo Nordisk, Pharma Nord
- Consultancy fees from: AstraZeneca, Vifor, Novo Nordisk, Ionis, PharmaNord, Pharmacosmos, BridgeBio, Pfizer and Novartis (all paid to the institute)
- Supported by an ERC Consolidator Grant of the EU.

Amyloidose

Diagnose vaak gemist

Slechte prognose

Slechte inspanningstolerantie

Beperkte behandelopties

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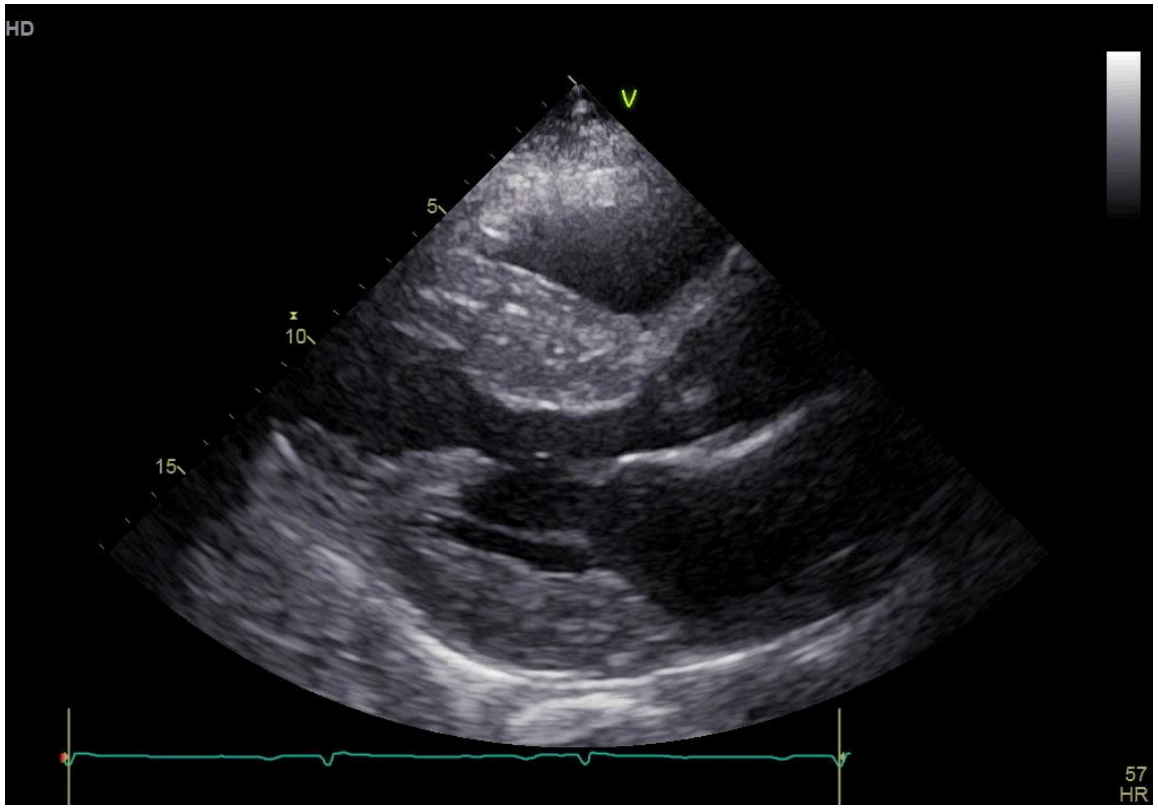
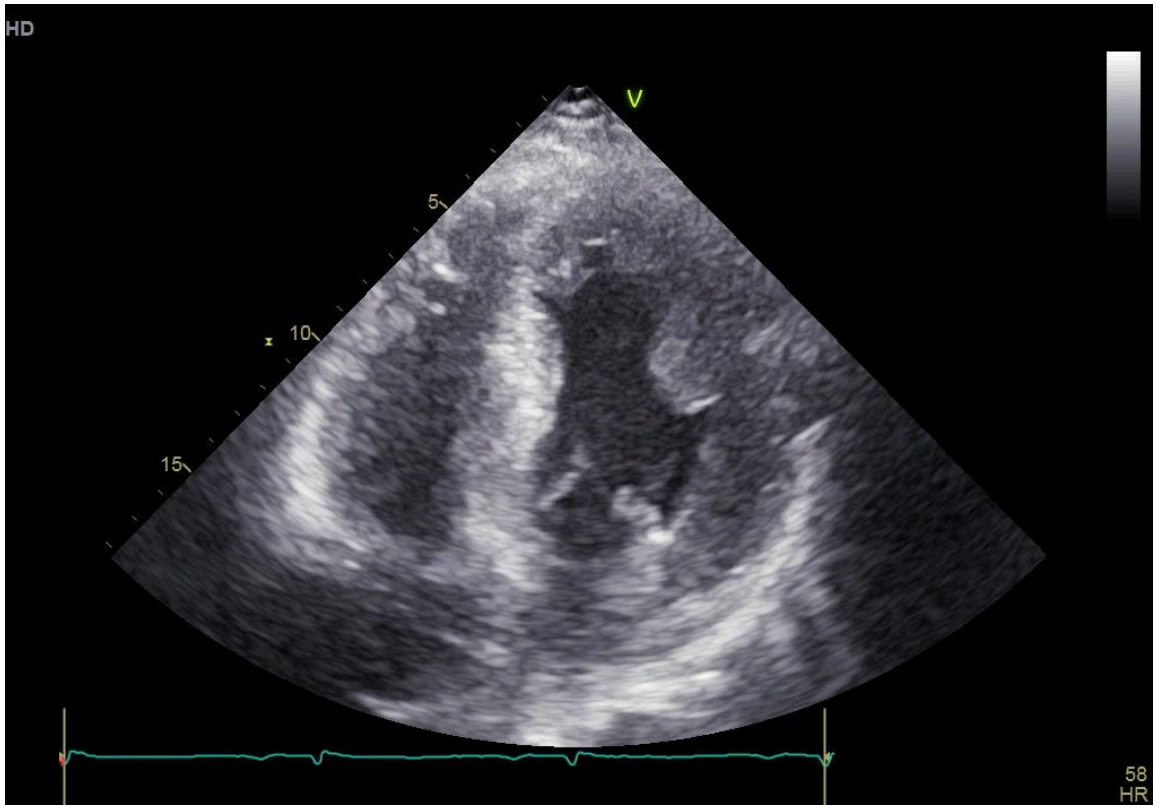
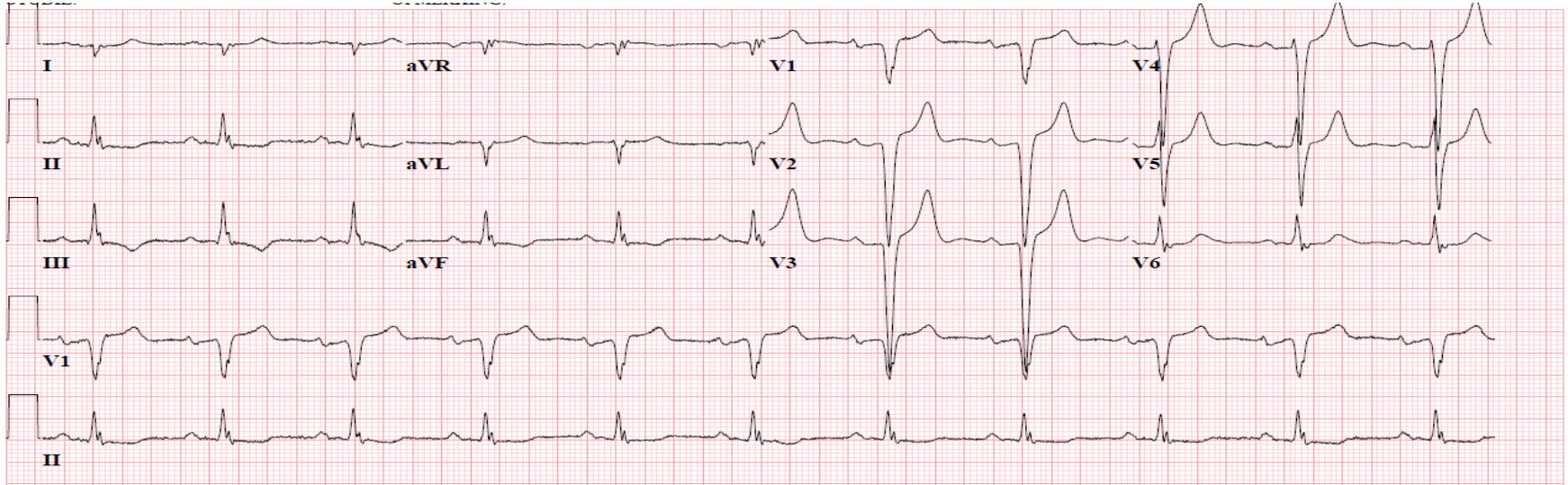
ATTR-CM, transthyretin amyloid cardiomyopathy. 1. Rozenbaum MH et al. *Cardiol Ther* 2021;10:141–159; 2. Ruberg FL et al. *J Am Coll Cardiol* 2019;73:2872–2891; 3. Singh A et al. *J Am Coll Cardiol* 2017;69:750–759; 4. Lane T. *Circulation* 2019;140:16–26; 5. Stewart M et al. *Neurol Ther* 2018;7:349–364; 6. Kittleson MM et al. *Circulation* 2020;142:e7–e22; 7. Garcia-Pavia P et al. *Eur Heart J* 2021;42:1554–1568

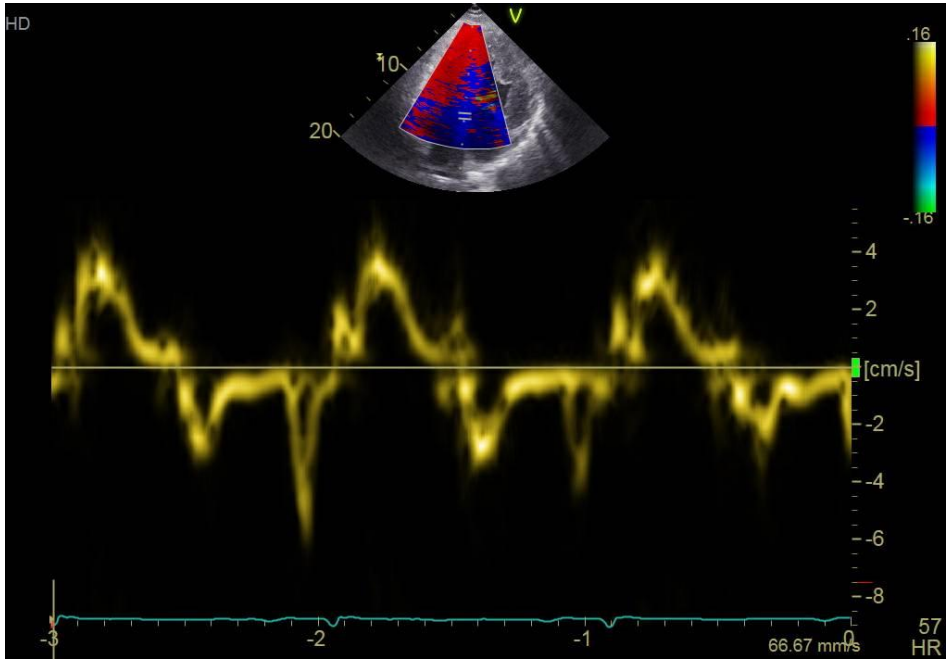




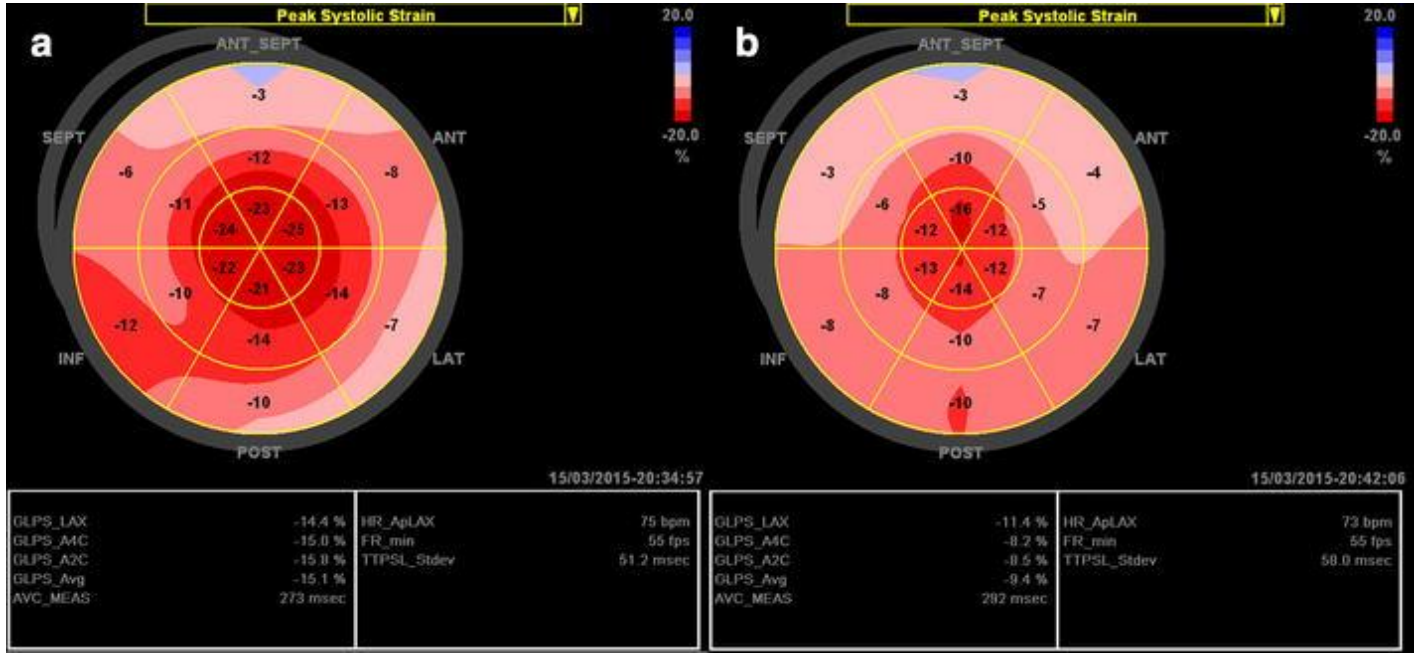


Man, 84 jaar

Door huisarts verwezen ivm dyspnoe

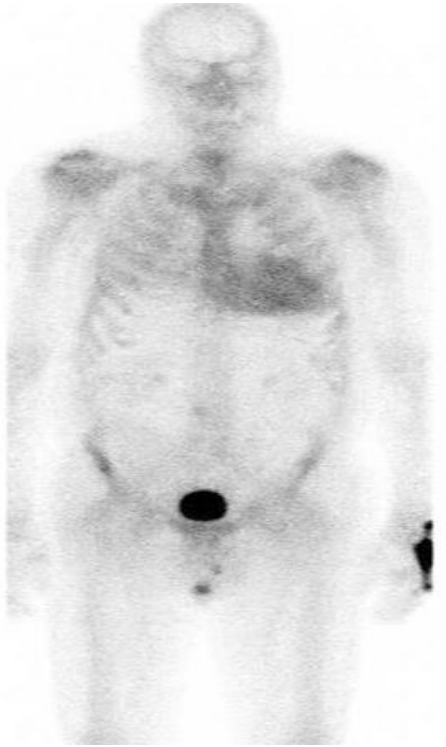


E' - lat 4.6 cm/s
E' - sept 3.5 cm/s
E/e' 19.8

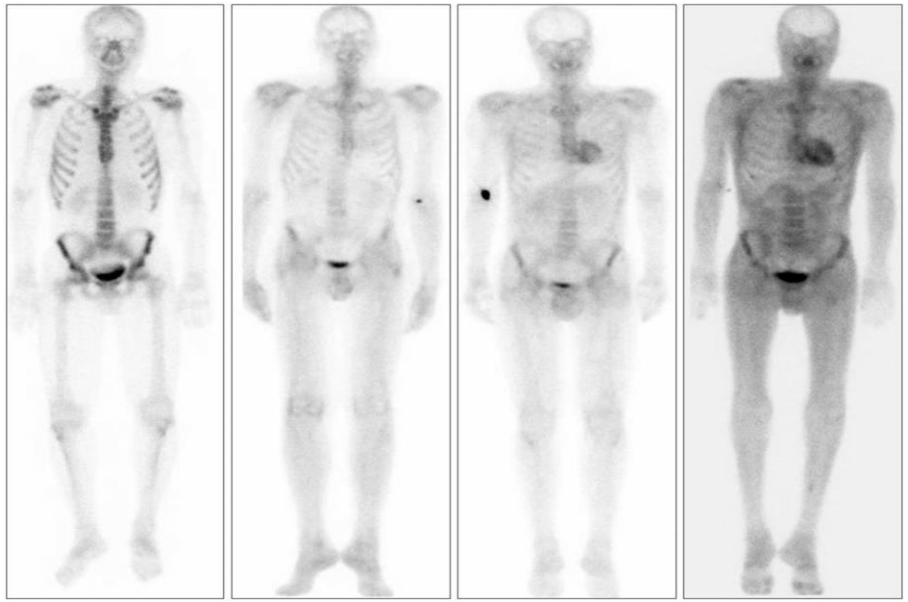


Strain meting (GLS)

Botscan: Tc-99m HDP



Patient



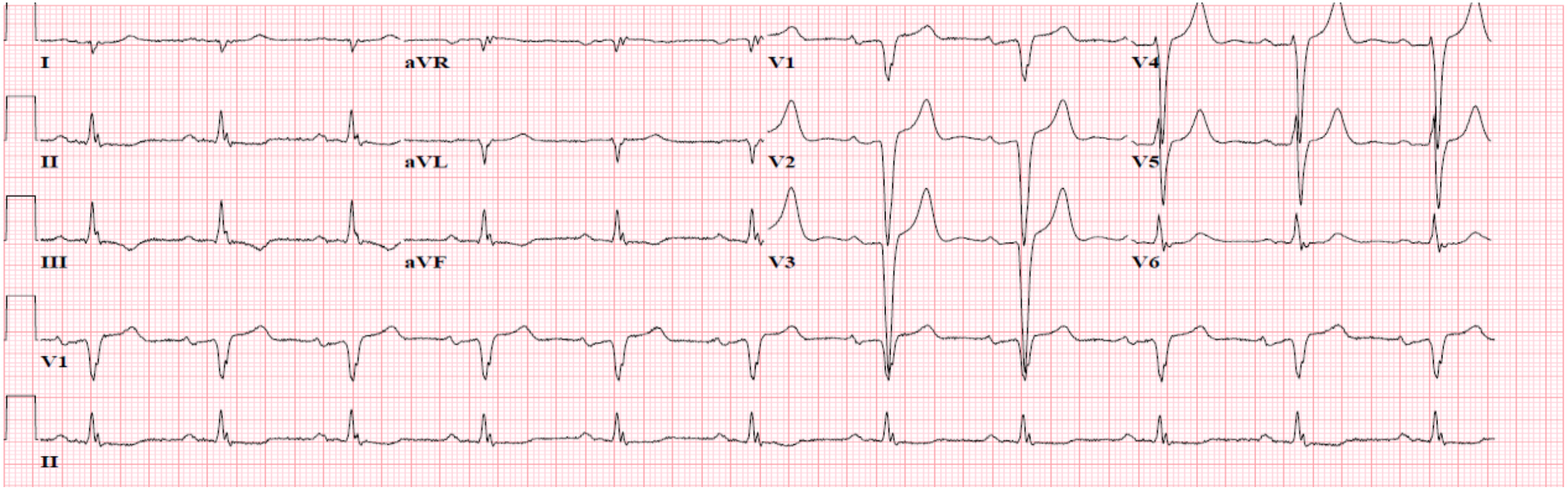
0 1 2 3

Visual grading score

Red flags:

- Discrepantie ECG voltage / LVMI
- Apical Sparing
- Carpaal tunnel syndroom
- AV block / pacemaker
- Oudere mannen (man:vrouw = 9:1)

ECG



Sinus rhythm: 65 bpm, 1st degree AV block
QRS: 131 ms
Rightward axis

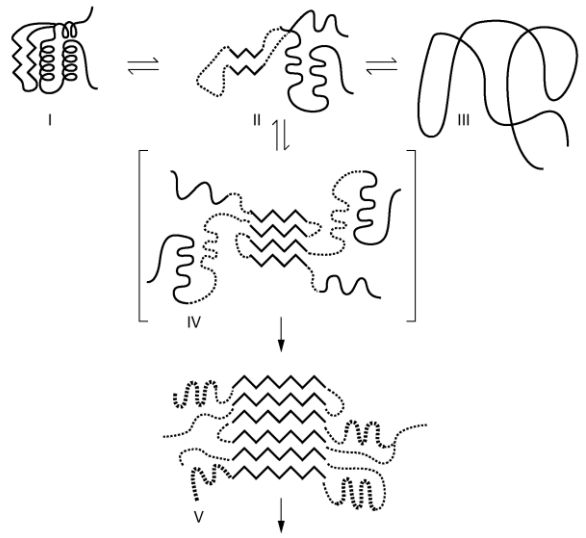
qs-pattern V1-3 and + lateral

AV, atrioventricular; bpm, beats per minute; ECG, electrocardiogram

Amyloïdose

Groep van ziekten gekenmerkt door stapeling van verkeerd gevouwen eiwitten in de vorm van amyloïdfibrillen

Deze fibrillen zijn resistent tegen proteolyse en hebben affiniteit voor Congo rood.



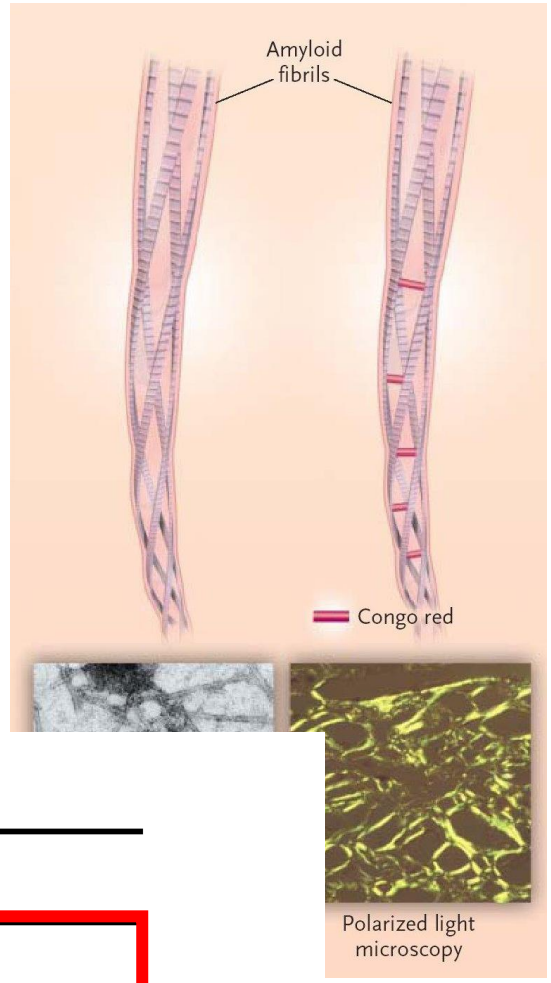


Table 1. Amyloid type and degree of heart involvement

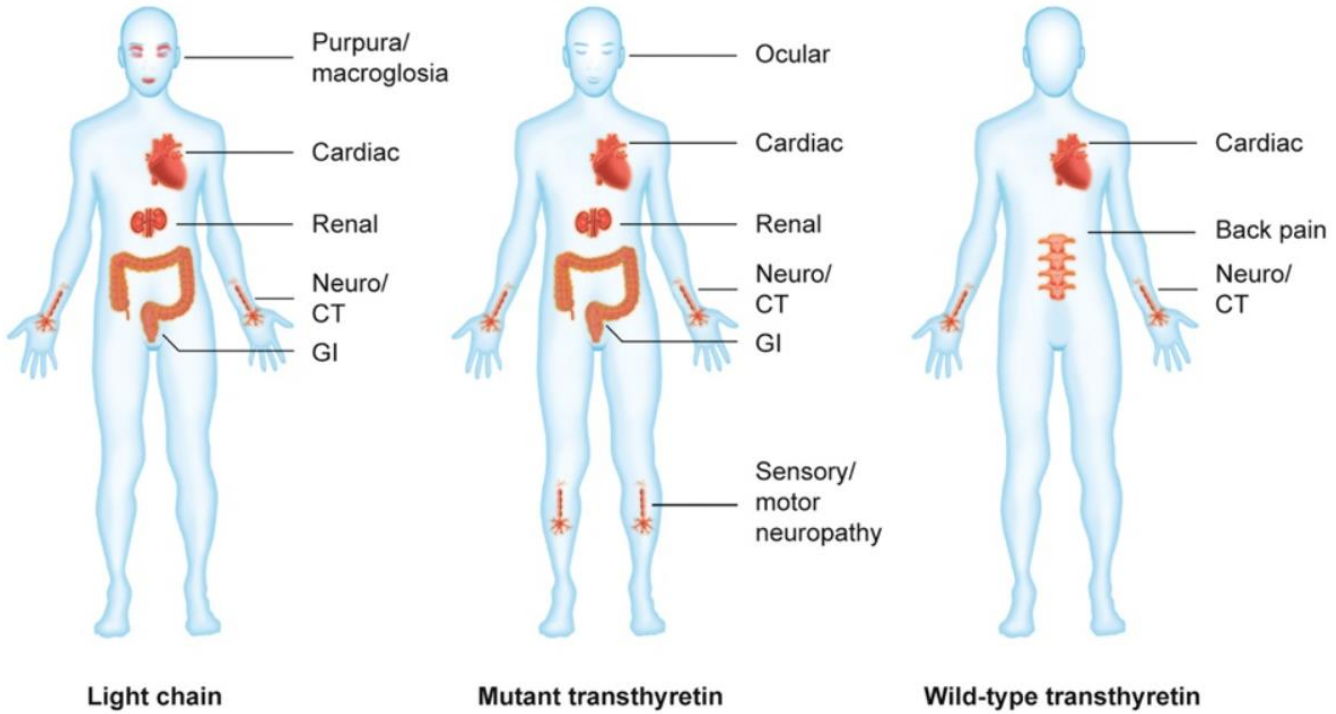
Amyloid type	Precursor protein	Extent of heart involvement
AL	Immunoglobulin light chains	Frequent and severe
ATTR (hereditary)	Mutant transthyretin	Frequent and severe
ATTR (wild type)	Wild type transthyretin	Frequent and severe
AA	Serum amyloid A	Severe heart involvement can occur
AFib (hereditary)	Mutant Fibrogen	Severe heart involvement can occur [1,2]
Apo A-I (hereditary)	Mutant apolipoprotein A-I	Severe heart involvement can occur [3-6]
Apo A-II (hereditary)	Mutant apolipoprotein A-II	Severe heart involvement can occur [7]
IAA	Atrial natriuretic peptides	Frequent and severe [8]

AL, amyloid light-chain amyloidosis; ATTR, transthyretin-related amyloidosis; Afib, fibrinogen amyloidosis; AA, amyloid A amyloidosis; Apo A-I, apolipoprotein A-I amyloidosis; Apo A-II, apolipoprotein A-II amyloidosis; IAA, Isolated atrial amyloidosis.

Onderscheid tussen AL and ATTR

heel belangrijk

AL vs ATTRwt vs ATTRv



Light chain | **Mutant transthyretin** | **Wild-type transthyretin**

Skin/soft tissue
- Purpura
- Macroglosia
- Back pain

Cardiac
- Fatigue
- Shortness of breath
- Edema
- Arrhythmias

Renal
- Renal insufficiency
- Proteinuria
- Edema

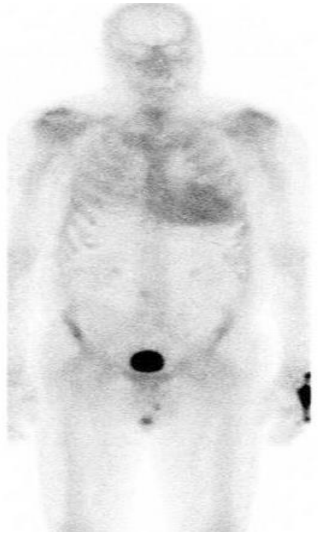
GI
- Diarrhea
- Constipation
- Nausea
- Early satiety

Neuro
- Carpal tunnel (CT)
- Peripheral neuropathy
- Orthostasis
- Weakness

Ocular
- Vitreous opacification
- Glaucoma
- Papillary abnormalities

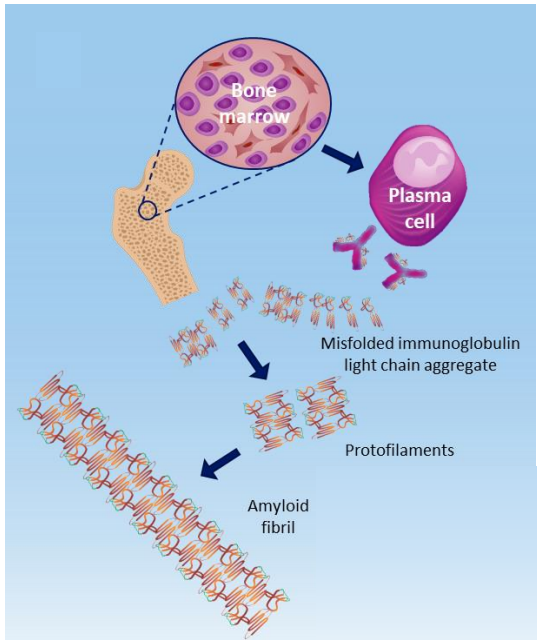
Important tools for diagnosis and typing[1]

Bone scintigraphy[2]



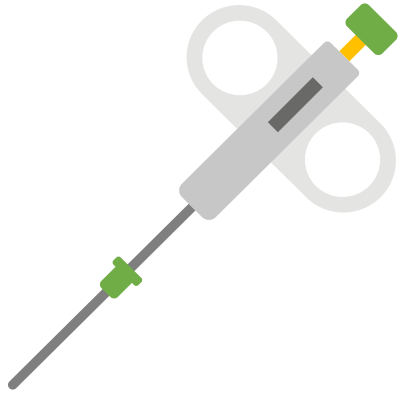
Blood + urine[3]

M protein, BJ protein and free light chains
Bone marrow if needed



Biopsy[2]

(Congo red and typing)

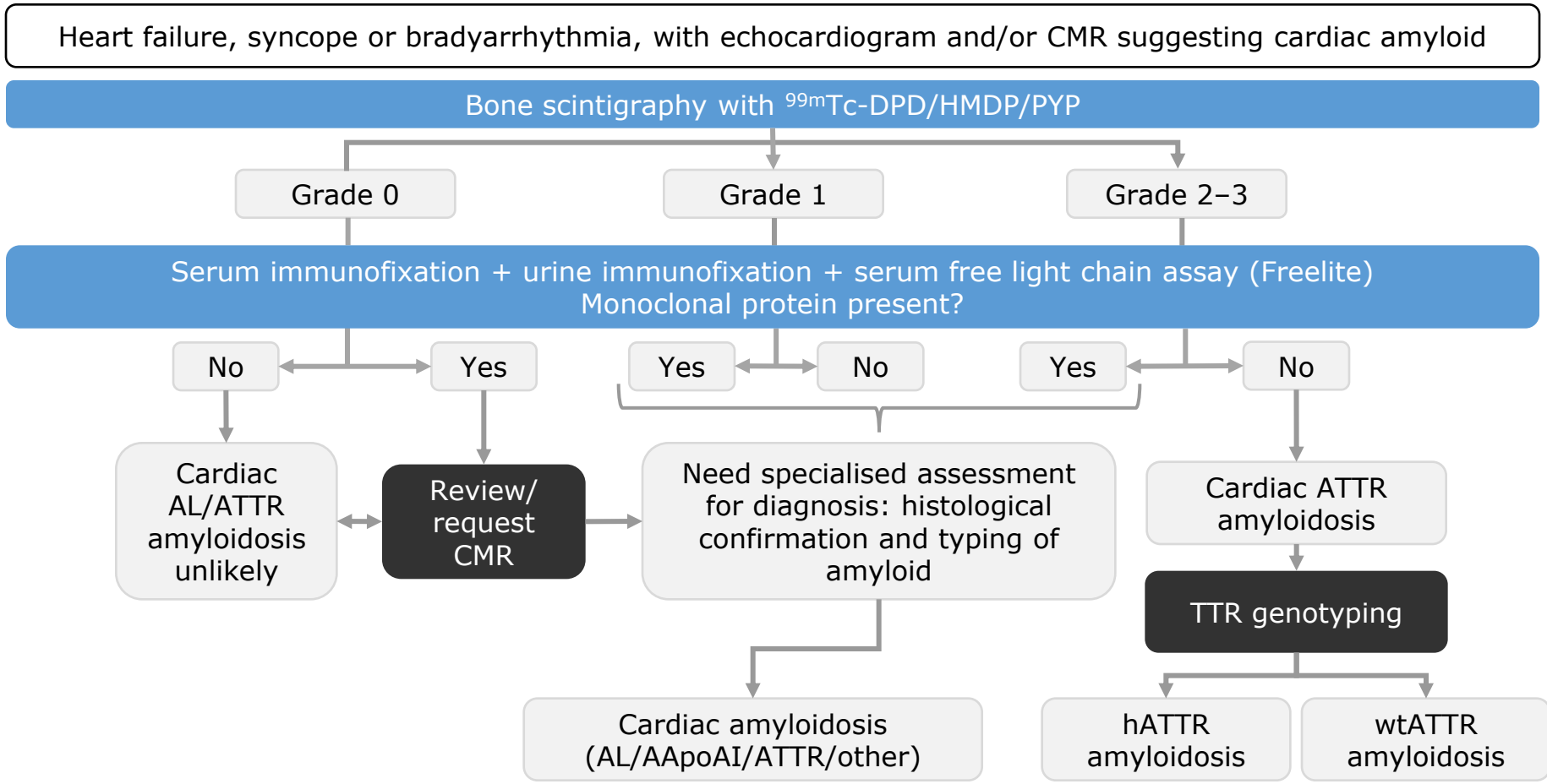


Genetic testing[1]

Wild-type vs hereditary

BJ, Bence Jones
1. Gillmore GD et al. *Circulation* 2016;133:2404–2412; 2. Provided by the speaker; 3. Donnelly JP, Hanna M. *Cleveland Clinic J Med* 2017;84:12–26

Diagnostic algorithm for patients with suspected amyloid cardiomyopathy



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99mTc-DPD/HMDP/PYP, 99mTc-diphosphono-1,2-propanodicarboxylic acid/hydroxymethylene diphosphonate/pyrophosphate; AApoAI, apolipoprotein AI; AL, amyloid light chain; ATTR, transthyretin amyloid; CMR, cardiac magnetic resonance; hATTR, hereditary transthyretin amyloid; wtATTR, wild-type transthyretin amyloid. Gillmore GD et al. *Circulation* 2016;133:2404–2412

Hoe vaak komt ATTR-CM voor?

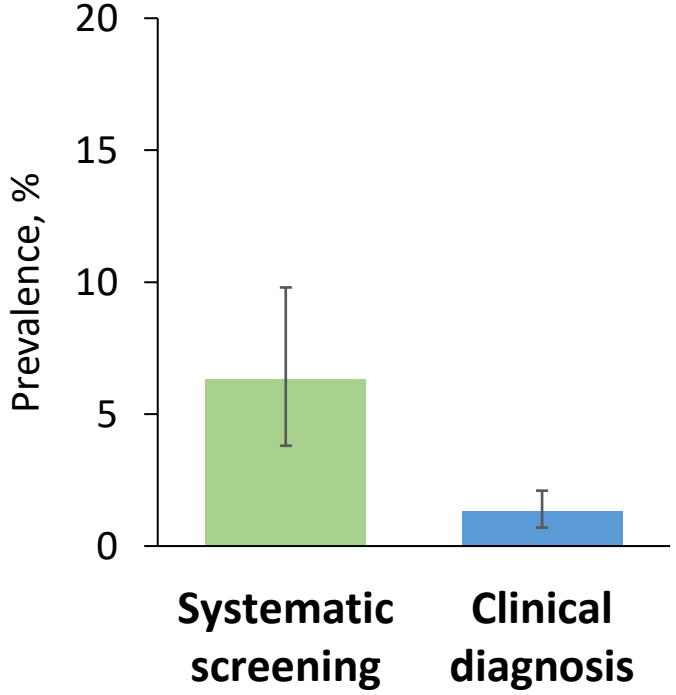
Amerikaanse studie

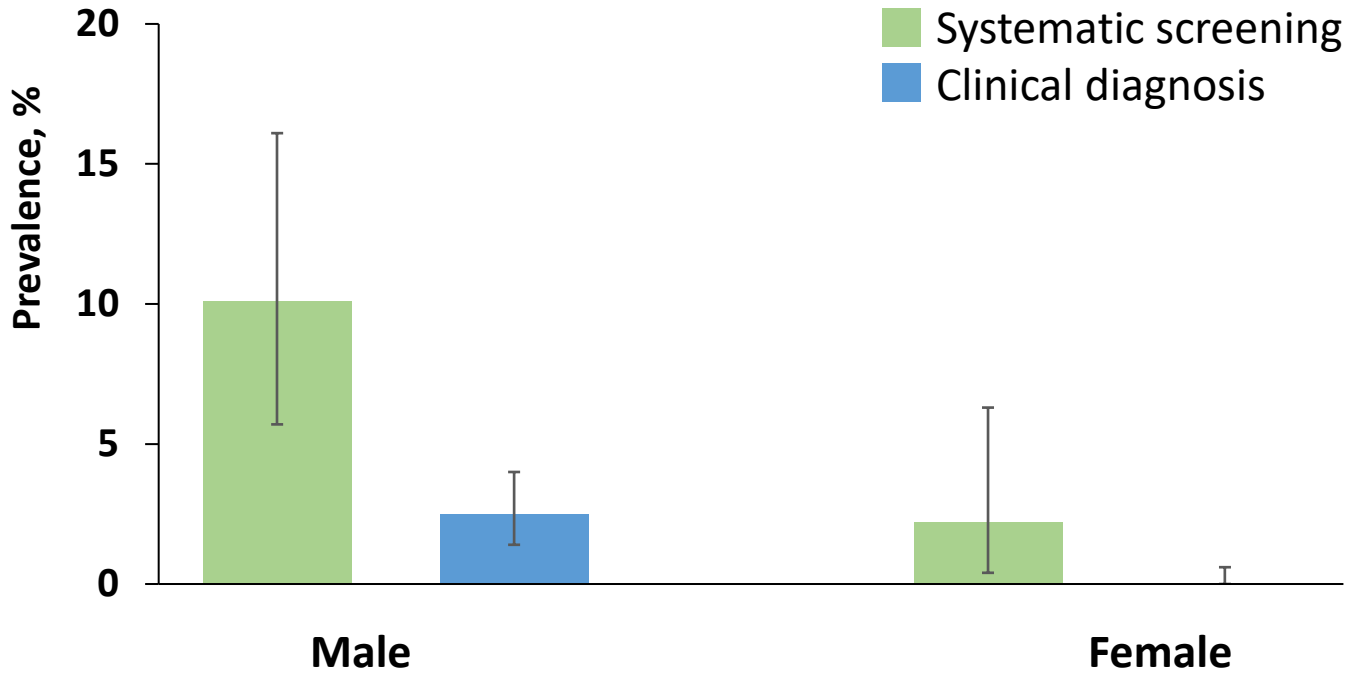
Screening study

Patiënten met HFpEF

N=286

Botscan





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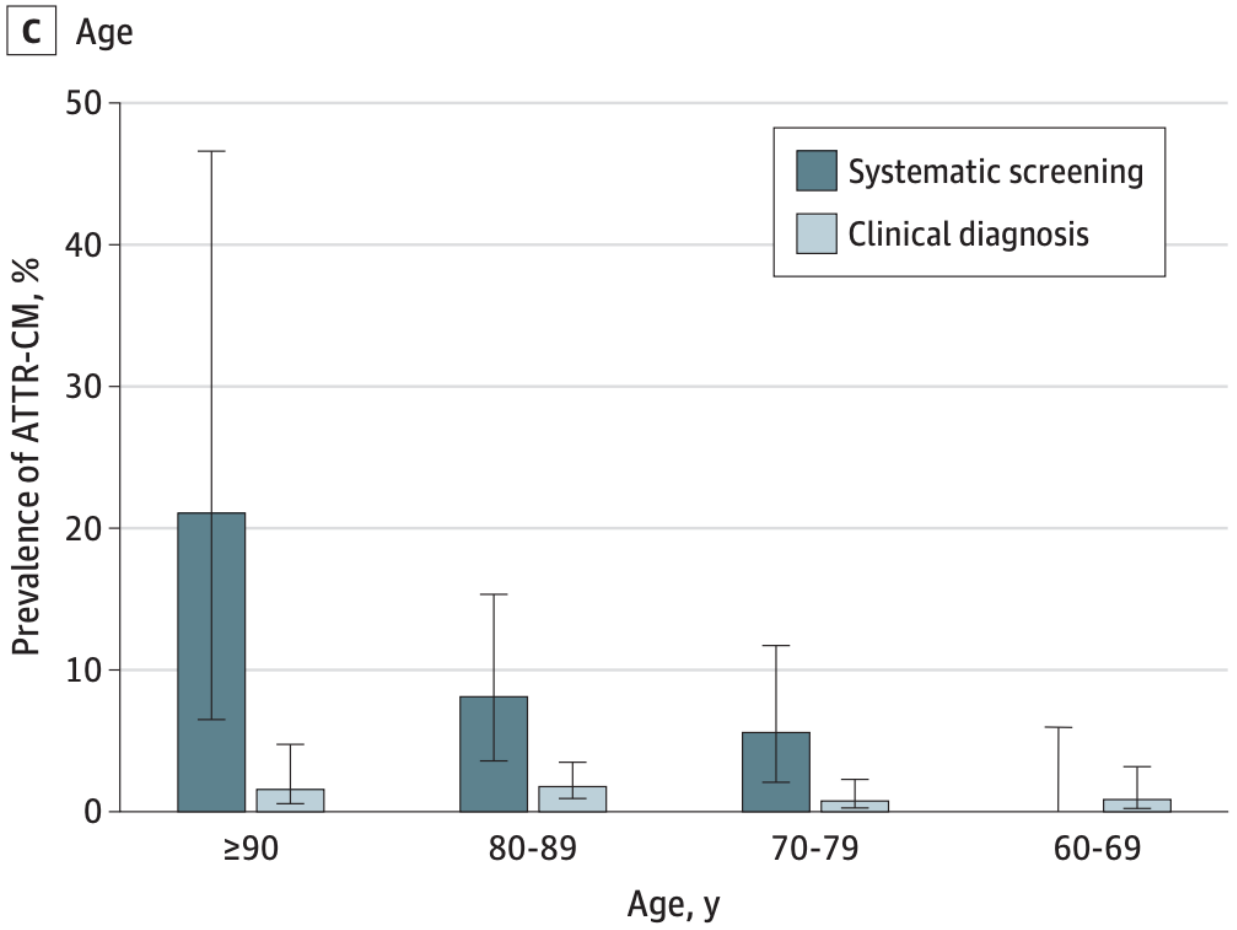
ATTR-CM, transthyretin amyloid cardiomyopathy
AbouEzzeddine OF et al. *JAMA Cardiol* 2021;6(11):1267–1274

Prevalentie hangt van leeftijd af



Screening study

N=286

Bonescintigraphy

Nederlandse data

	$HF^{ATTRwt-}$ (n=98)	$HF^{ATTRwt+}$ (n=5)	p-value	
Age at diagnosis, years ± SD	72.7 ± 7.8	73.9 ± 12.6	.720	
Men	49.0%	80.0%	.060	
Hypertension	79.2%	28.6%	.003	
Diabetes Mellitus type II	39.6%	42.9%	.860	
Myocardial Infarction	21.9%	14.3%	.640	
Rhythm			.830	
Sinus rhythm	62.5%	71.4%		
Atrial fibrillation	34.4%	28.6%		
Atrial flutter	3.1%	0.0%		
Clinical				
Systolic blood pressure (mmHg)	139.0 (125.0, 154.0)	139.0 (129.0, 160.0)	.610	
Diastolic blood pressure (mmHg)	73.0 (62.0, 82.0)	66.0 (62.0, 77.0)	.480	
IVSD (mm)	10.0 (9.0, 12.0)	12.5 (11.0, 13.0)	.032	
LVMi	95.0 (77.0, 121.0)	118.0 (108.0, 144.0)	.053	
LVEF (%)	55.0 (50.0, 58.0)	55.0 (55.0, 55.0)	.980	
Laboratory				
NTproBNP (ng/L)	1490.0 (687.0, 2490.5)	1275.0 (962.0, 1594.0)	.900	
eGFR (ml/min * 1.73 m2)	48.5 (37.0, 72.0)	52.0 (43.0, 58.0)	.930	
Creatinine (µmol)	106.0 (85.0, 143.0)	116.0 (104.0, 137.0)	.460	
ALAT (IU/L)	19.5 (14.0, 25.0)	22.0 (15.0, 29.0)	.380	

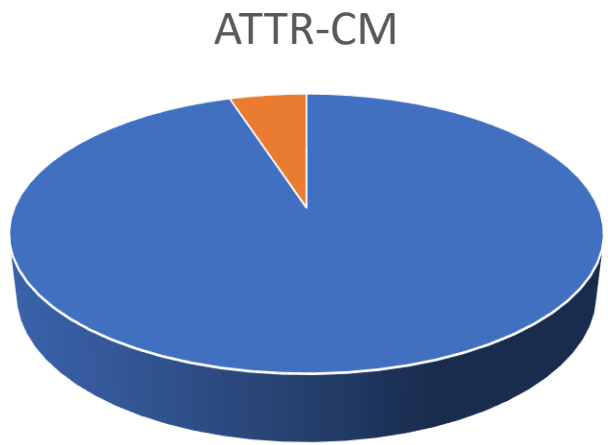
Prospective screening study

LVEF > 40%

Elevated NTproBNP

NYHA II-III + diuretics

Screening study



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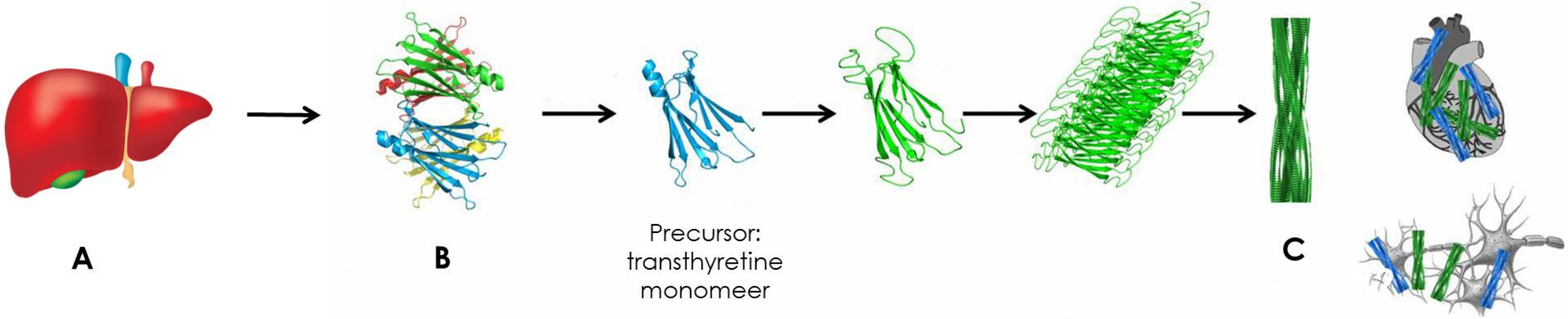
Tubben et al. Eur J Heart Failure 2024

Behandeling ATTR-amyloïdose



A. Productie transthyretine verminderen

B. Transthyretine tetrameer stabiliseren

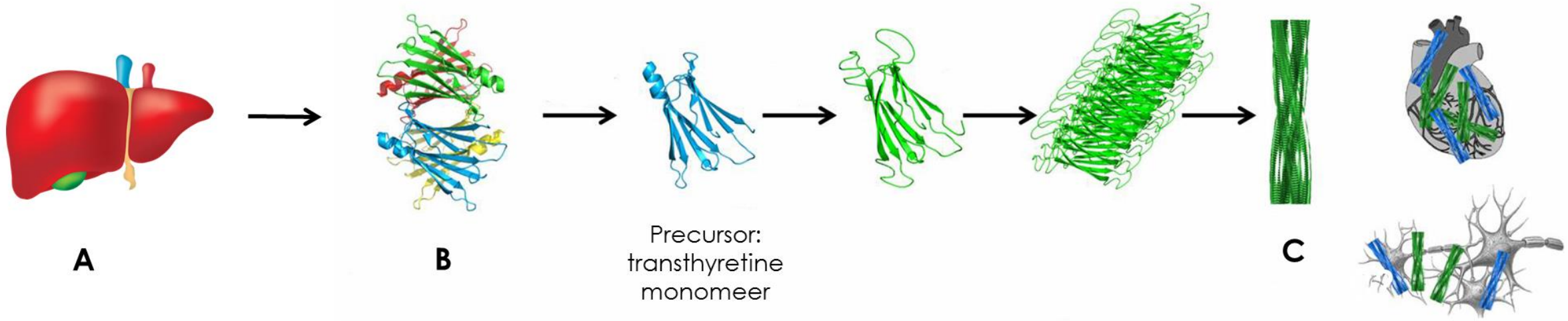
C. Amyloïd opruimen

Behandeling ATTR-amyloïdose

Liver transplant, patisiran*, inotersen*, vutrisiran*

Tafamidis AG-10*

NNC6019-0001*, NI006*



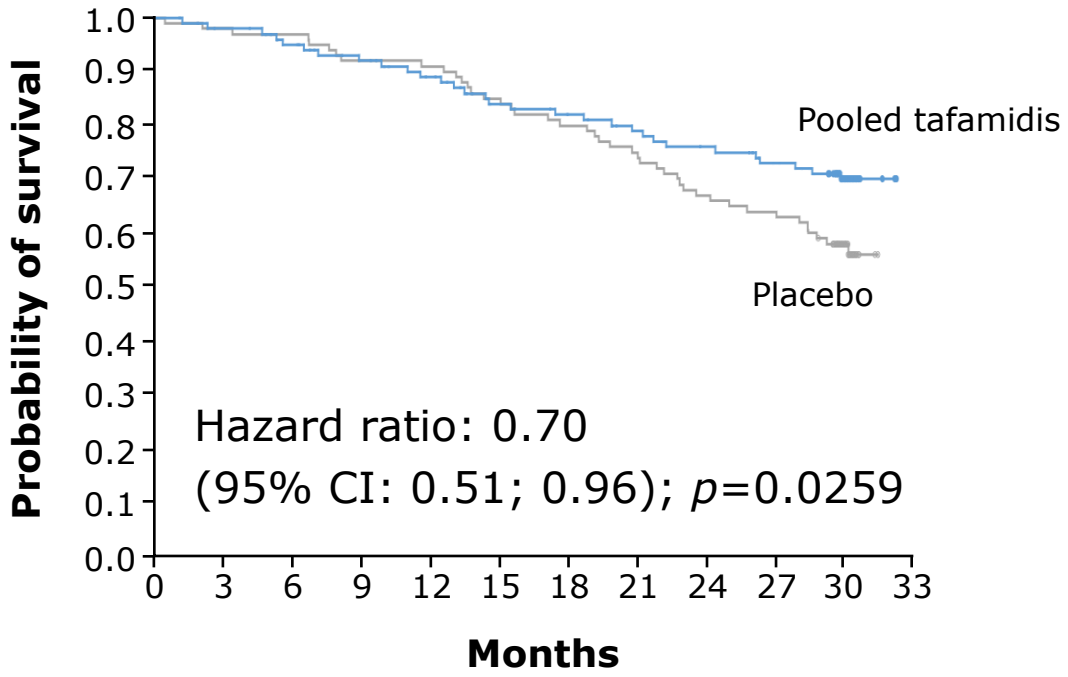
A. Productie transthyretine verminderen

B. Transthyretine tetrameer stabiliseren

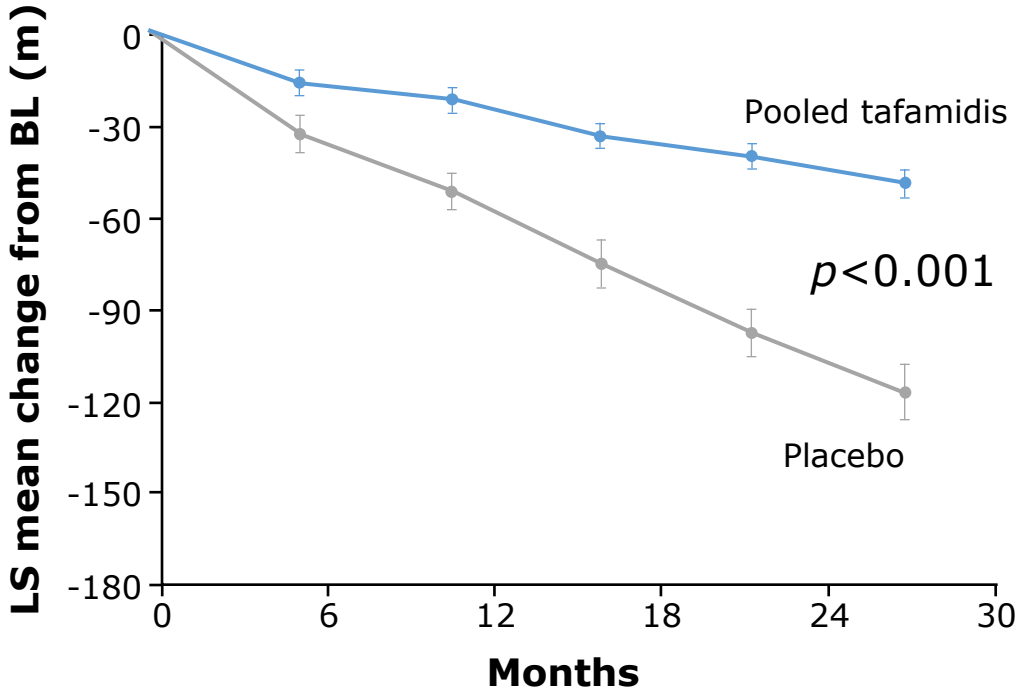
C. Amyloïd opruimen?

ATTR stabilisator (tafamidis)

Survival



Change from baseline in 6MWT



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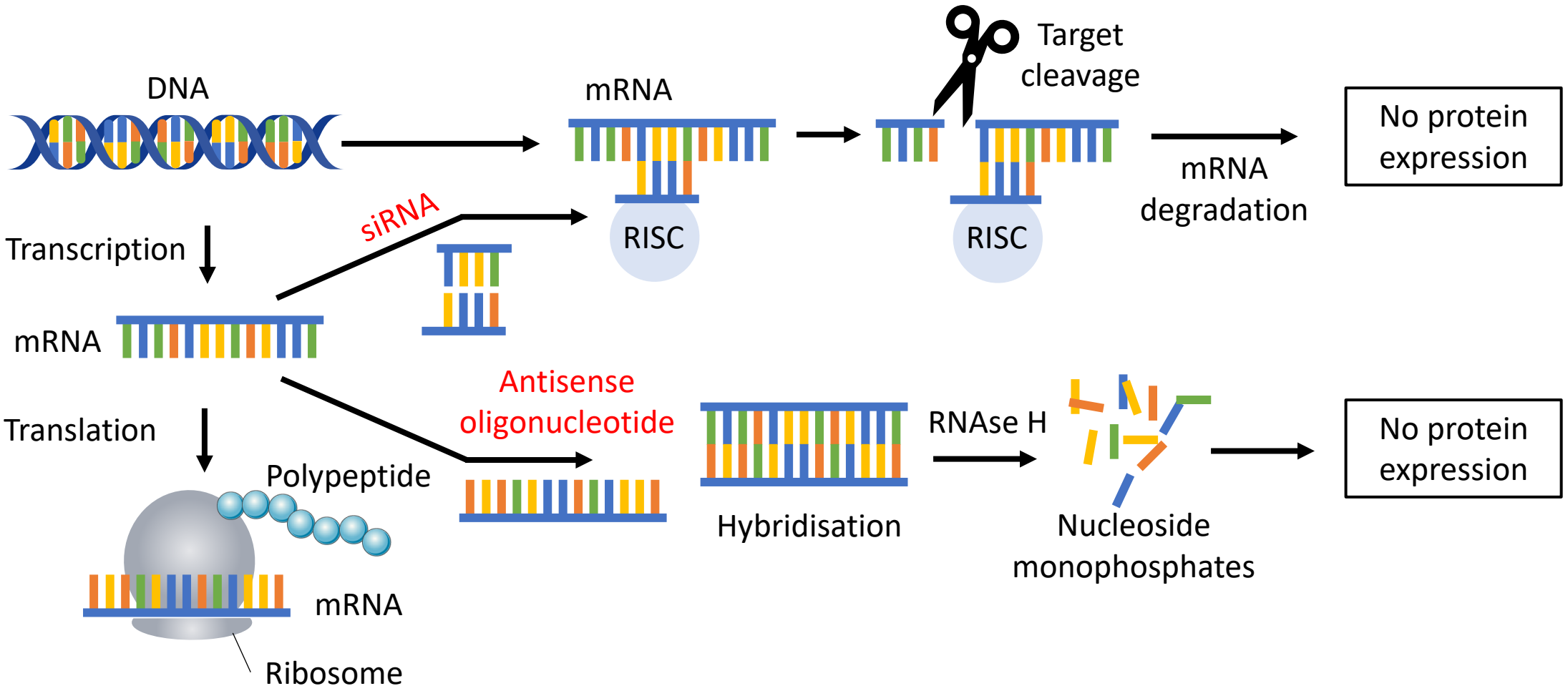
6MWT, 6-minute walk test; BL, baseline; CI, confidence interval; LS, least-squares

Maurer MS et al. *N Engl J Med* 2018;379:1007–1016

Productie transthyretine verminderen
RNA interference



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DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; RISC, ribonucleic acid-induced silencing complex; RNAse H, ribonuclease H; siRNA, small interfering ribonucleic acid

Sperry BW, Tang WHW. *Heart* 2017;103(11):812–817

The NEW ENGLAND JOURNAL of MEDICINE

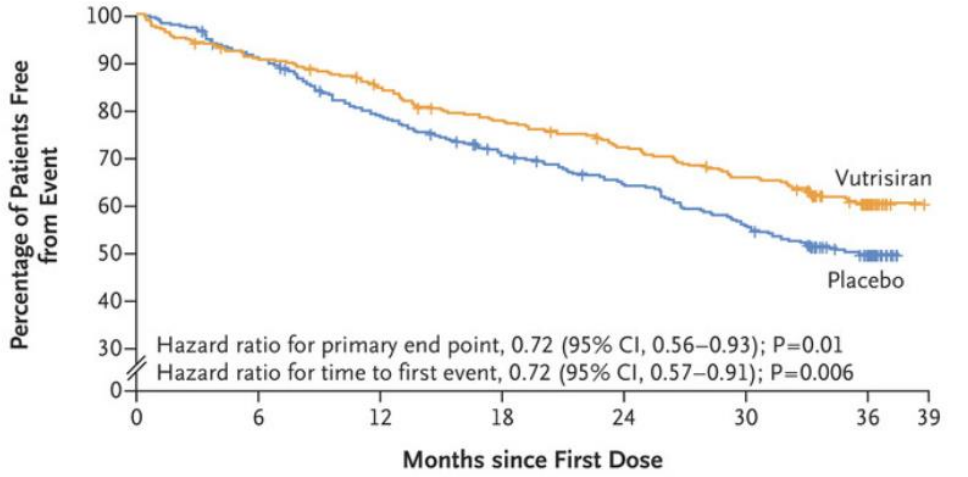
ORIGINAL ARTICLE

Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

M. Fontana, J.L. Berk, J.D. Gillmore, R.M. Witteles, M. Grogan, B. Drachman, T. Damy, P. Garcia-Pavia, J. Taubel, S.D. Solomon, F.H. Sheikh, N. Tahara, J. González-Costello, K. Tsujita, C. Morbach, Z. Pozsonyi, M.C. Petrie, D. Delgado, P. Van der Meer, A. Jabbour, A. Bondue, D. Kim, O. Azevedo, S. Hvitfeldt Poulsen, A. Yilmaz, E.A. Jankowska, V. Algalarrondo, A. Slugg, P.P. Garg, K.L. Boyle, E. Yureneva, N. Silliman, L. Yang, J. Chen, S.A. Eraly, J. Vest, and M.S. Maurer, for the HELIOS-B Trial Investigators*

HELIOS-B (Vutrisiran)=siRNA

A Time to First Event in the Overall Population

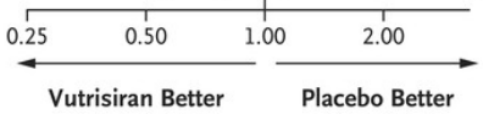


No. at Risk (cumulative no. of events)

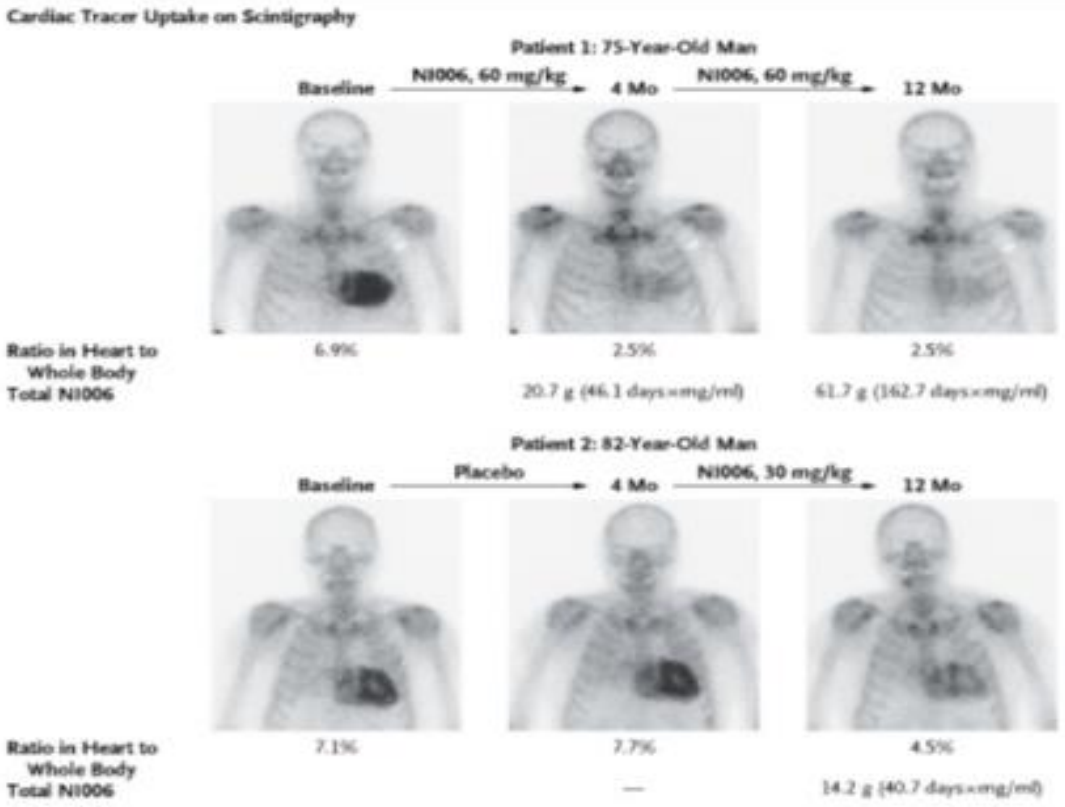
Vutrisiran	326 (0)	294 (30)	271 (50)	247 (72)	227 (90)	206 (110)	62 (125) 0 (125)
Placebo	328 (0)	295 (31)	253 (70)	221 (96)	199 (115)	172 (142)	52 (159) 0 (159)

C Subgroup Analyses of the Primary End Point (overall population)

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Overall	654	0.72 (0.56–0.93)
Age		
<75 yr	257	0.55 (0.35–0.85)
≥75 yr	397	0.81 (0.58–1.11)
Tafamidis use at baseline		
No	395	0.67 (0.49–0.93)
Yes	259	0.79 (0.51–1.21)
ATTR disease type		
Variant	76	0.92 (0.49–1.72)
Wild type	578	0.67 (0.51–0.90)
NYHA class		
I or II	592	0.73 (0.55–0.96)
III	62	0.68 (0.33–1.41)
Baseline NT-proBNP level		
≤2000 pg/ml	342	0.53 (0.35–0.79)
>2000 pg/ml	312	0.80 (0.56–1.13)



Amyloid opruimen?



ORIGINAL ARTICLE

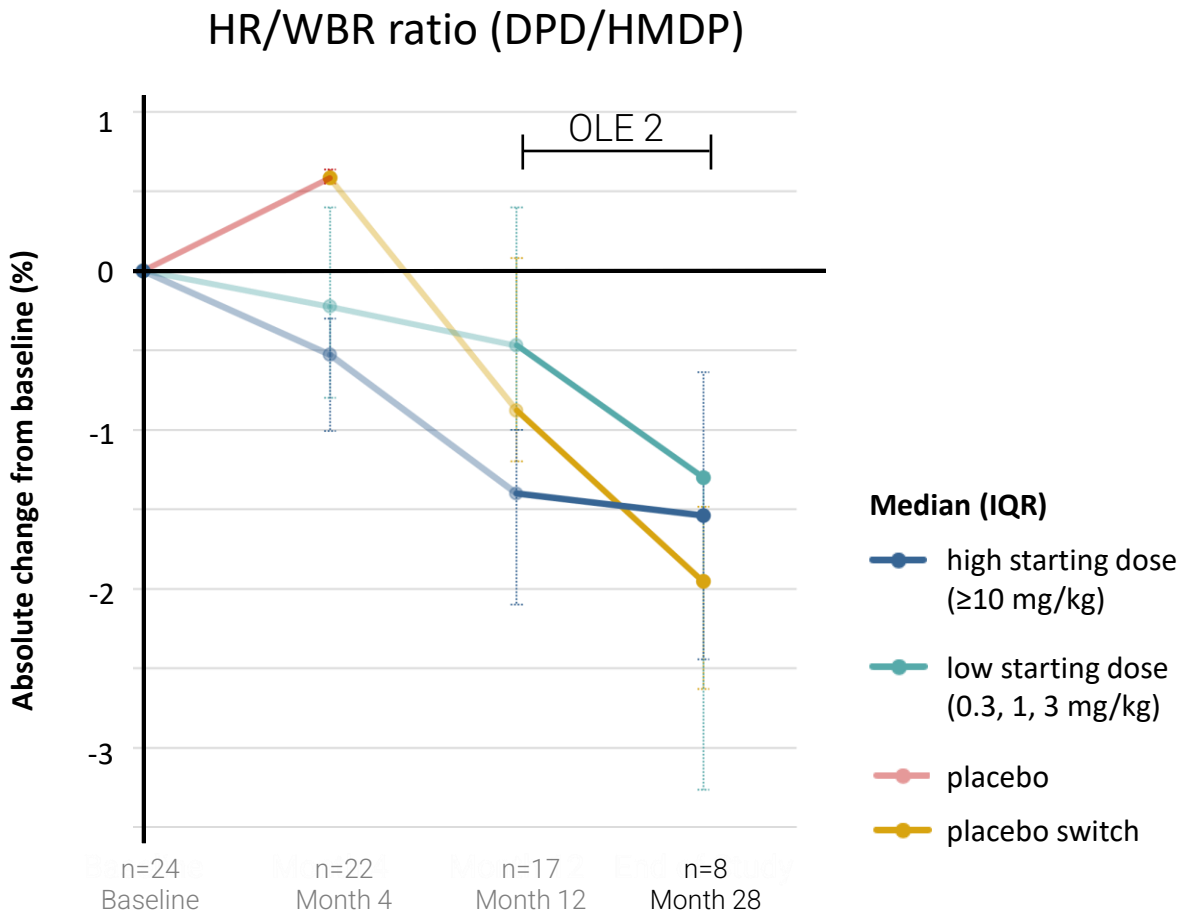
MEETING OF THE HEART FAILURE ASSOCIATION

Antibody NI006 for Depletion Cardiac Amyloid

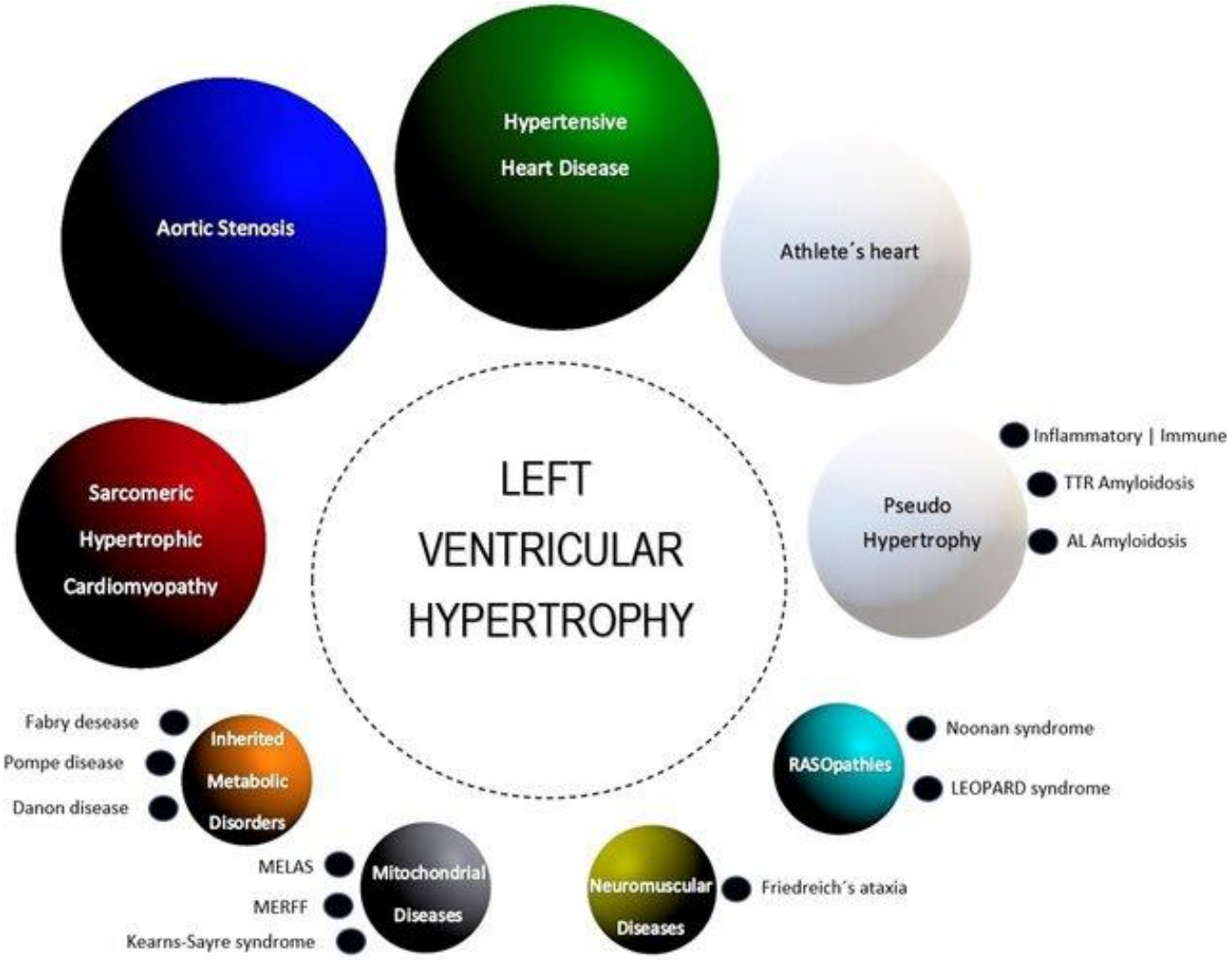
P. Garcia-Pavia and Others

Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph Hock, M.D., Peter C. Kahr, M.D., and Thibaud Damy, M.D., Ph.D.



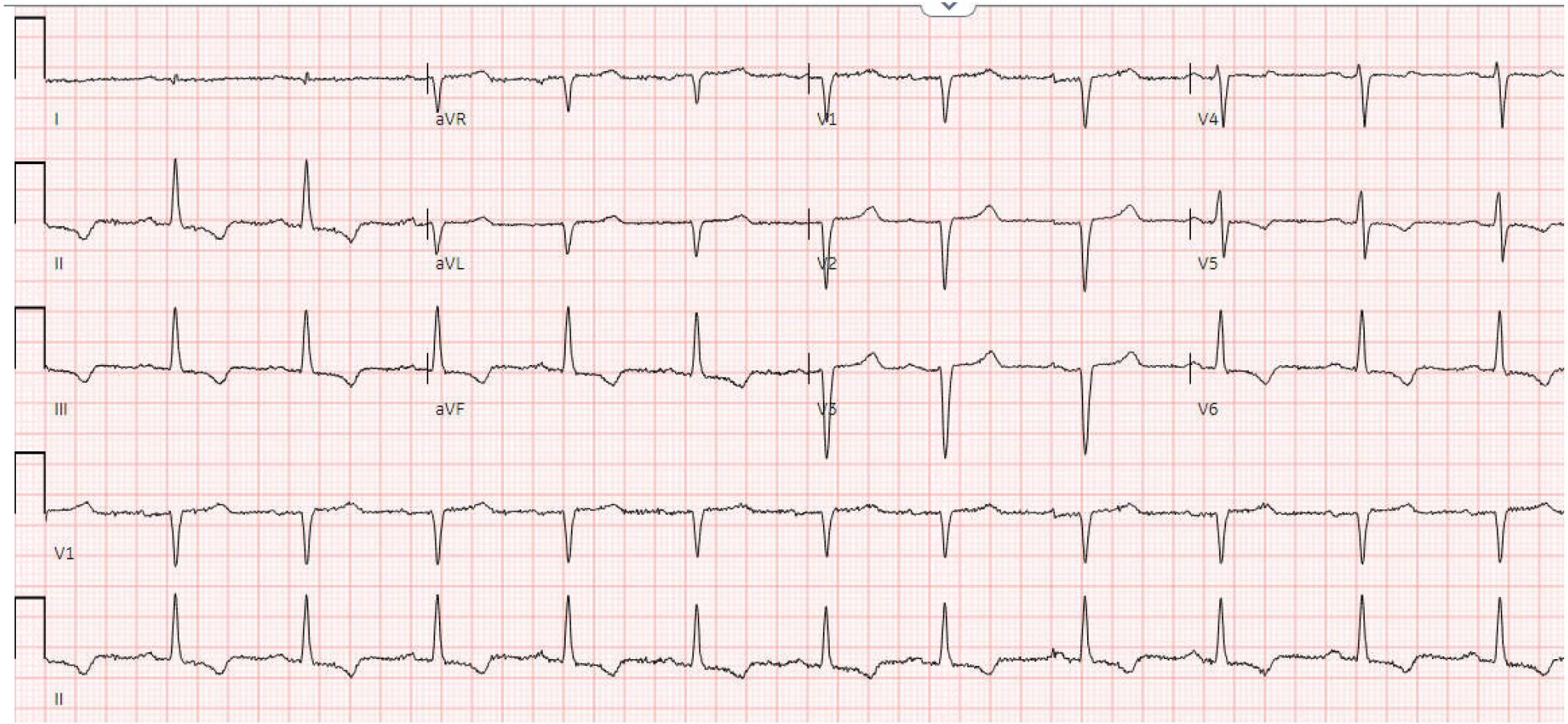
Soms is het lastiger om diagnose te stellen



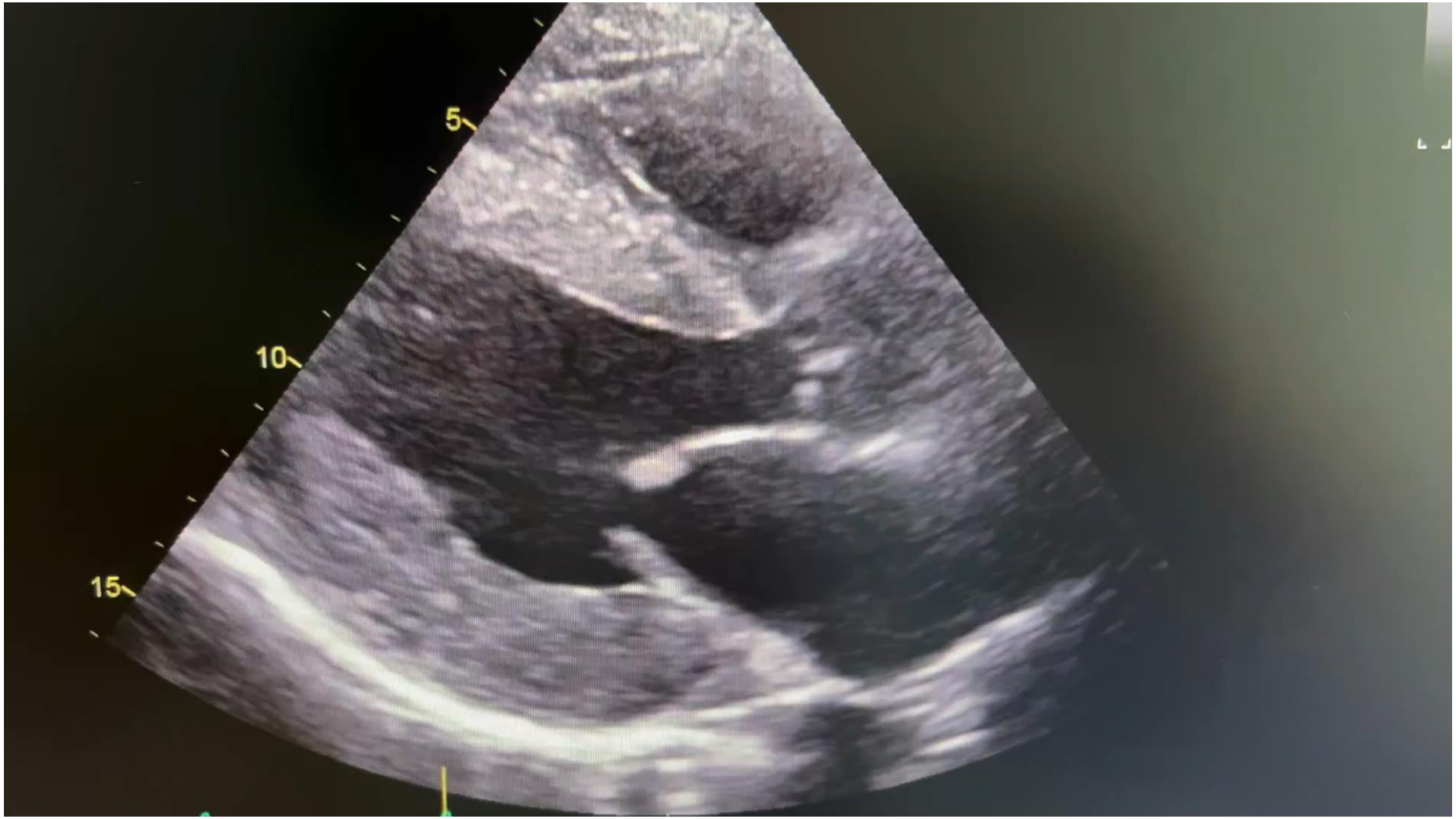
Vrouw 56jr

- Recente opname in verwijzend ziekenhuis ivm dec cordis
- Vermoeid en kortademig.
- Tintelingen en doof gevoel in de handen
- Duizelig bij opstaan en bukken.
- Heesheid.

ECG



Echocardiogram



Septum 18mm

Achterwand: 21mm

RV: 9mm

MRI: LVH en RVH. Verhoogde T1 waarde

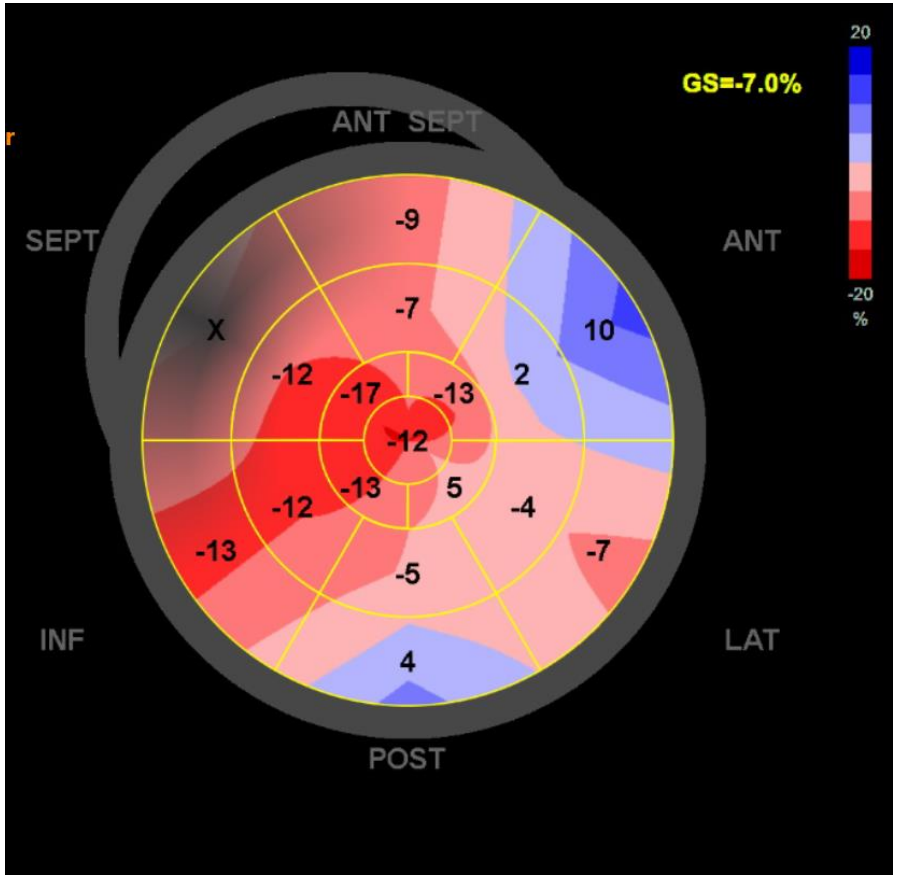
Genetica: geen bekende HCM of DCM mutaties

Lab: Geen M-proteïne, VLKs normaal,

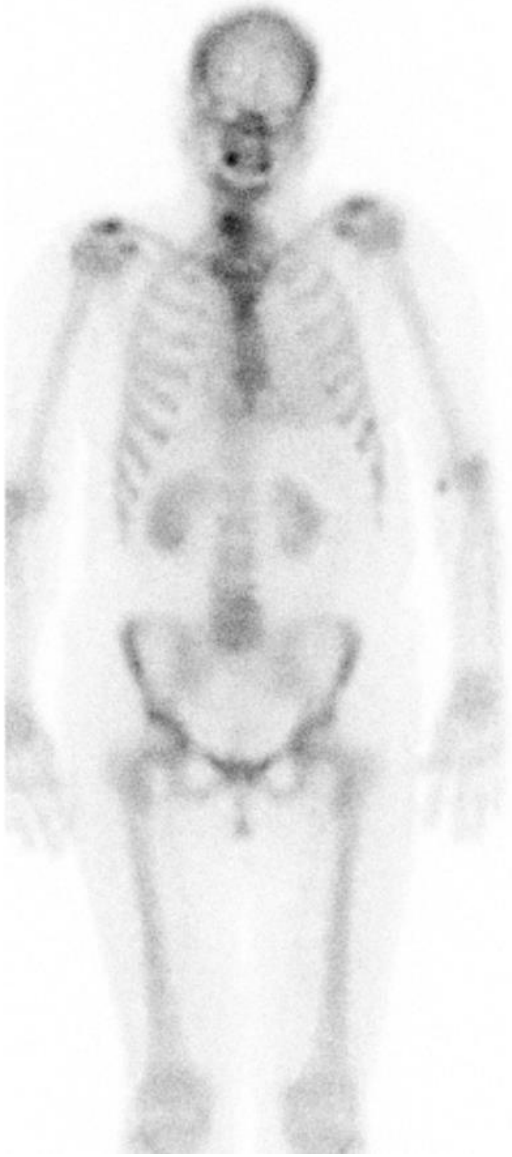
Beenmerg: Geen plasmaceldyscrasie

Verwijzing: analyse hypertrofie

Echocardiogram

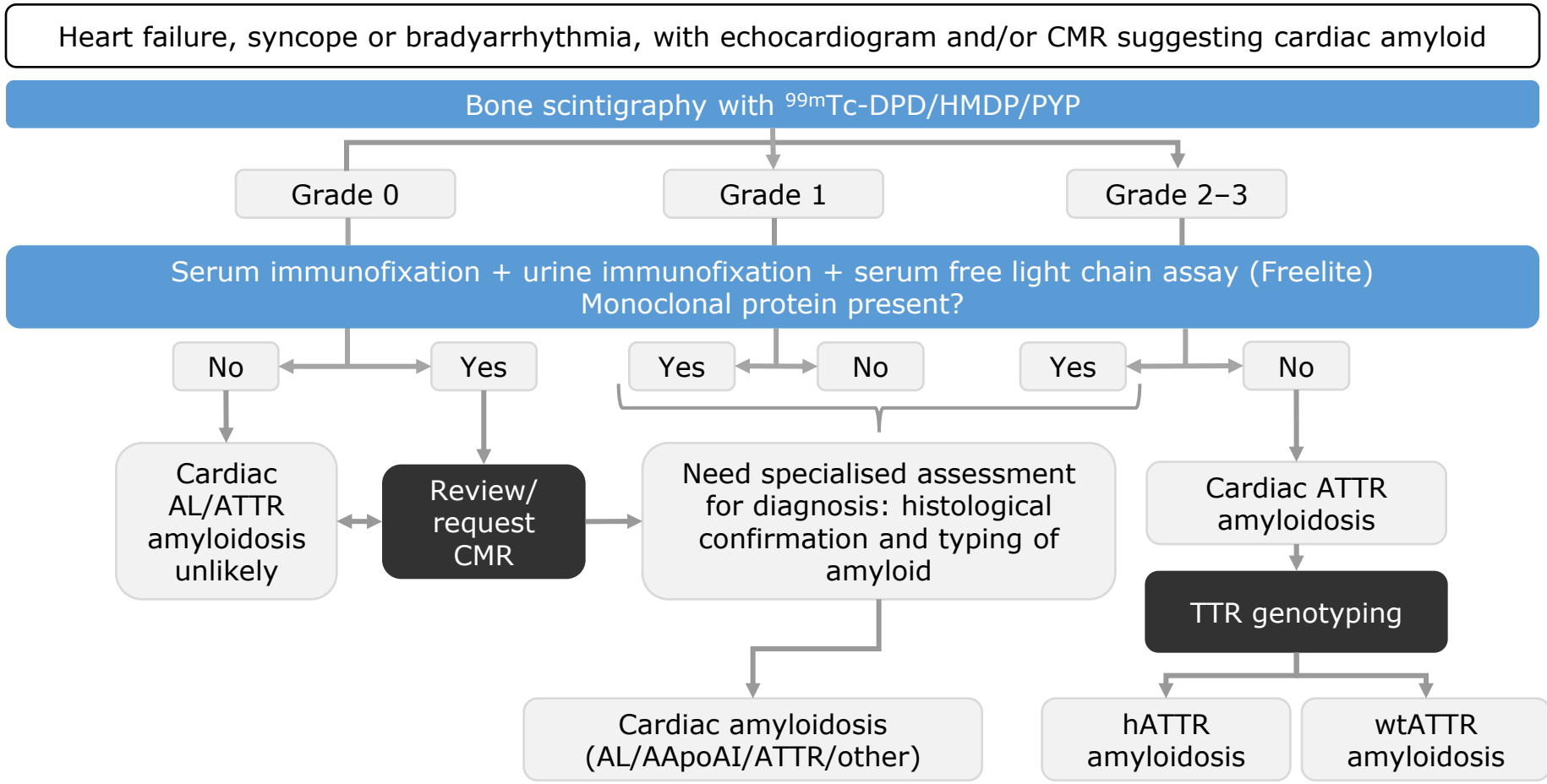


"Cherry on top?"



Graad 1 tracer uptake

Diagnostic algorithm for patients with suspected amyloid cardiomyopathy



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99mTc-DPD/HMDP/PYP, 99mTc-diphosphono-1,2-propanodicarboxylic acid/hydroxymethylene diphosphonate/pyrophosphate; AApoAI, apolipoprotein AI; AL, amyloid light chain; ATTR, transthyretin amyloid; CMR, cardiac magnetic resonance; hATTR, hereditary transthyretin amyloid; wtATTR, wild-type transthyretin amyloid. Gillmore GD et al. *Circulation* 2016;133:2404–2412

Vetbiopt: amyloid aantoonbaar, echter moeilijk te karakteriseren

KNO: Laryngoscopie: beeld van uitgebreide laryngeale amyloïddepositie

Genetisch onderzoek (genpanel amyloïdose): heterozygotie voor c.605T>C, p.(Leu202Pro) mutatie in het ***APOA1*-gen**

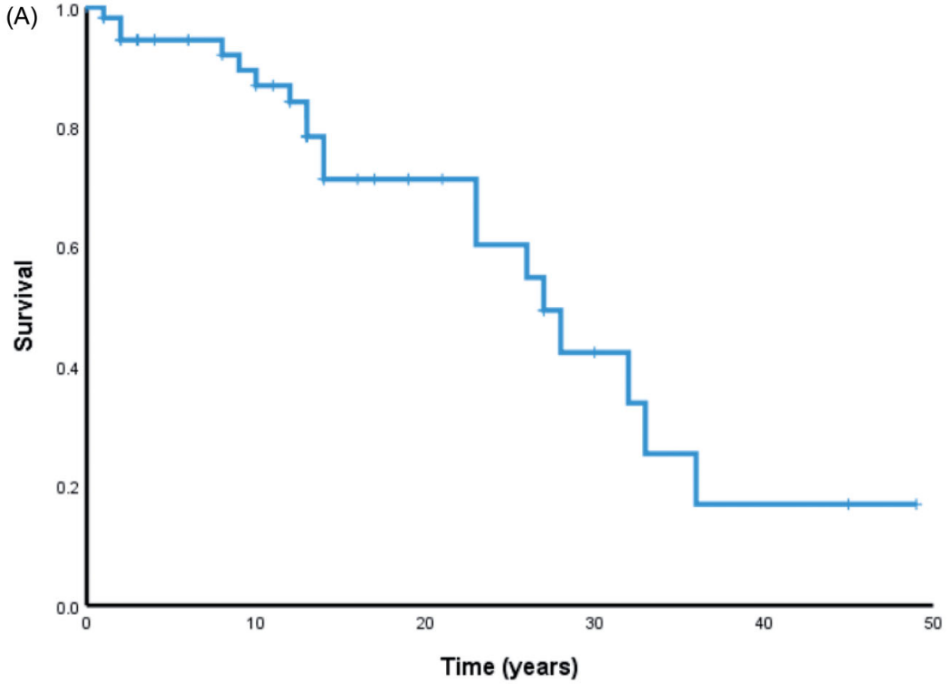
Conclusie: erfelijke Apolipoproteïne A1-amyloïdose gekenmerkt door myocardiale, hepatogene en laryngeale amyloïddepositie

Behandeling: symptomatische behandeling, afgezien van traject hart-levertransplantatie

ApoA1 mutaties: zeer zeldzaam, langzaam progressief

Table 1. ApoA1 Mutations Associated with AApoAI Amyloidosis

Variant (mature protein)	Clinical manifestations/found amyloid sites
p.Gly26Arg	Renal failure, gastrointestinal amyloid, peripheral neuropathy
p.Trp50Arg	Renal failure
p.Leu60Arg	Renal failure
p.Leu64Pro	Renal failure
p.Leu60_Phe71delinsValThr	Liver failure
p.Glu70_Trp72del	Renal failure
p.Asn74fs	Gastrointestinal amyloid, renal failure, amyloid detected in uterus, ovaries, pelvic lymph nodes
p.Leu75Pro	Renal failure, hepatic amyloid, gastrointestinal amyloid
p.Leu90Pro	Cardiomyopathy, cutaneous amyloid
p.Lys107del	Aortic intimal amyloid
p.Ala154fs	Renal amyloid
p.Leu170Pro	Amyloid in larynx
p.Arg173Pro	Cardiomyopathy, cutaneous and laryngeal amyloid
p.Leu174Ser	Cardiomyopathy
p.Ala175Pro	Laryngeal amyloid
p.Leu178His	Cardiomyopathy, cutaneous and laryngeal amyloid



Time (years)	0	10	20	30	40
n	57	37	18	6	2

Conclusions

- 5-10% van de patienten met HFpEF heeft amyloidose
- Botscan staat centraal in het stellen van de diagnose
- AL amyloidosis moet worden uitgesloten (vrije lichte ketens en M-proteine)
- Tafamidis is eerste geregistreerde medicijn voor de behandeling van ATTR-CM
- Er komen nieuwe middelen aan: remmen aanmaak en stimuleren afbraak
- Soms lastige diagnose; dan weefsel nodig om diagnose te stellen.

AL, amyloid light chain; ATTR-CM, transthyretin amyloid cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; TTR, transthyretin

Thank you!

Call for PhDs and PostDocs!

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