Nouvelles thérapeutiques dans les amyloses cardiaques

Pr T. **Damy** (Mondor)

Actualités Thérapeutiques dans les amyloses à transthyrétine CardioCONNECT

Pr Thibaud DAMY

APHP-CHU Henri Mondor,

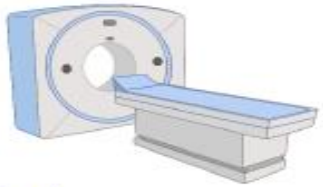
Paris, France

www.reseau-amylose.org

Les différents types d'amylose cardiaque

ACQUISES	HEREDITAIRE
ATTR-wt Sauvage (anciennement systémique sénile)	**ATTR-v** (V pour variant)
AL Chaine légère	Fibrinogen
AA Maladies inflammatoires	Gelsolin
	ApoA1
	ApoA2
	Lysozyme
	Cystatin C

ATTR prevalence in cardiologic « syndromes »

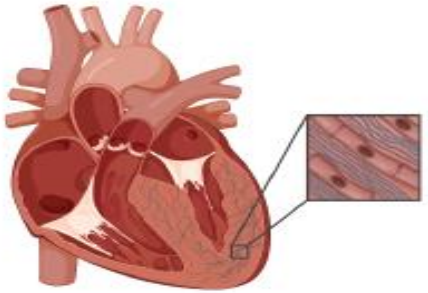


Bone scintigraphy
for non-cardiac reasons:
≥81 years: ~1.3% M, ~0.4% W

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

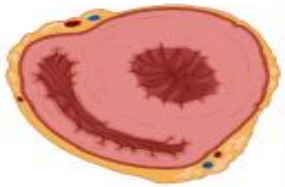
HFpEF: 12%
(95% CI 6-20%)
M 73% (39-100%)
77 years (66-86)
AL-CA 10% (0-40%)

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%

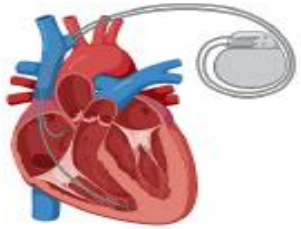
Prevalence of cardiac amyloidosis in screening studies



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

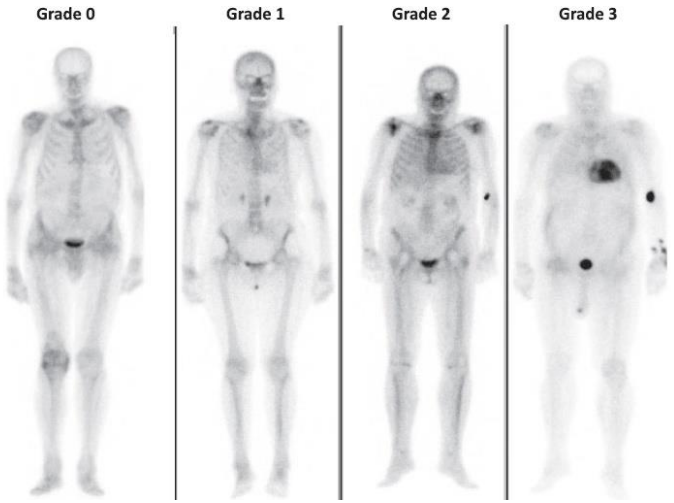
Surgery for carpal tunnel
syndrome: 7%
(95% CI 5-10%)
M 64% (33-100%)
76 years (73-79)
AL-CA 18% (0-33%)

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



Aimo A et al, Eur J Heart Failure 2022

Diagnosis algorithm



Signs & symptoms, ECG, echo or CMR suggestive of cardiac amyloidosis

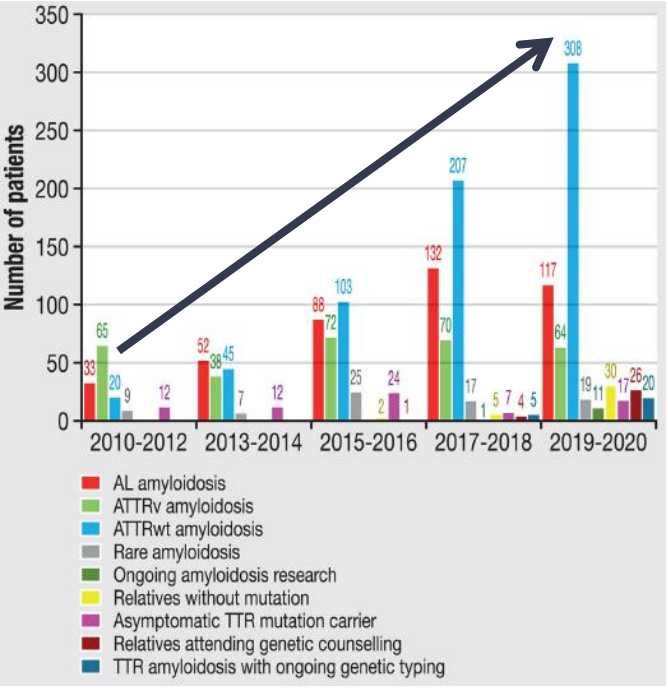
^{99m}Tc-DPD/PYP/HMDP Scintigraphy with SPECT **&** **Haematologic tests** (serum free-light chain quantification & serum and urine immunofixation)

- Scintigraphy grade 0, Haematologic tests - → **AL/ATTR cardiac amyloidosis unlikely** → If suspicion persists consider CMR followed by biopsy
- Scintigraphy grade 1-3, Haematologic tests - → Grade 2-3 → **Cardiac ATTR amyloidosis** → TTR genetic testing ATTRwt / ATTRv
- Scintigraphy grade 1-3, Haematologic tests - → Grade 1 → Histological confirmation (cardiac/extracardiac) **to diagnose**
- Scintigraphy grade 0, Haematologic tests + → AL amyloidosis? → CMR negative → Amyloidosis unlikely
- Scintigraphy grade 0, Haematologic tests + → AL amyloidosis? → CMR + or inconclusive → Histological confirmation (cardiac/extracardiac) **to diagnose**
- Scintigraphy grade 1-3, Haematologic tests + → Histological confirmation (usually cardiac) **to subtype**

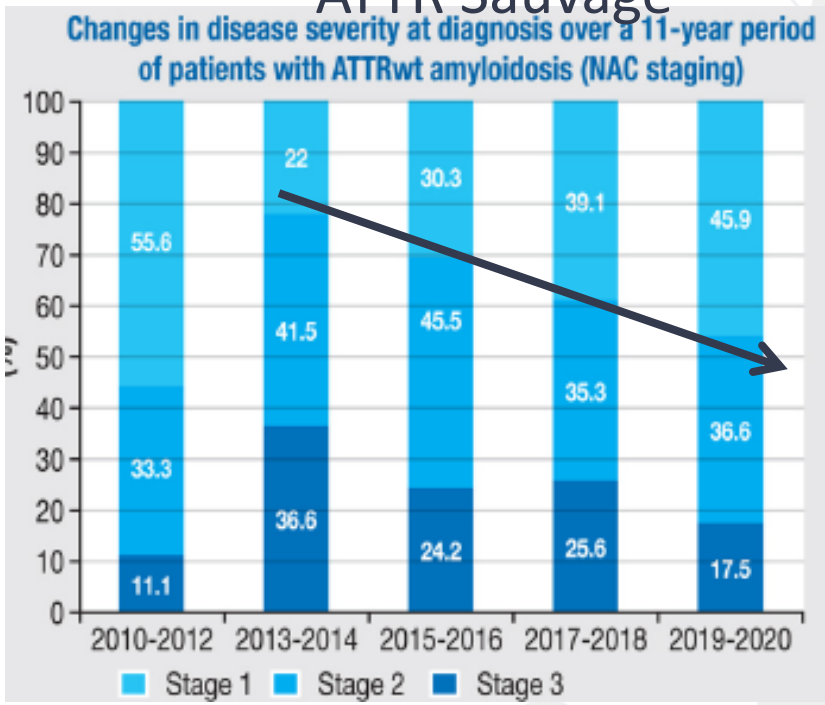
Garcia-Pavia P et al , 2021, 00, 1-15

Evolution du diagnostic et de la sévérité sur 11 ans d'expérience

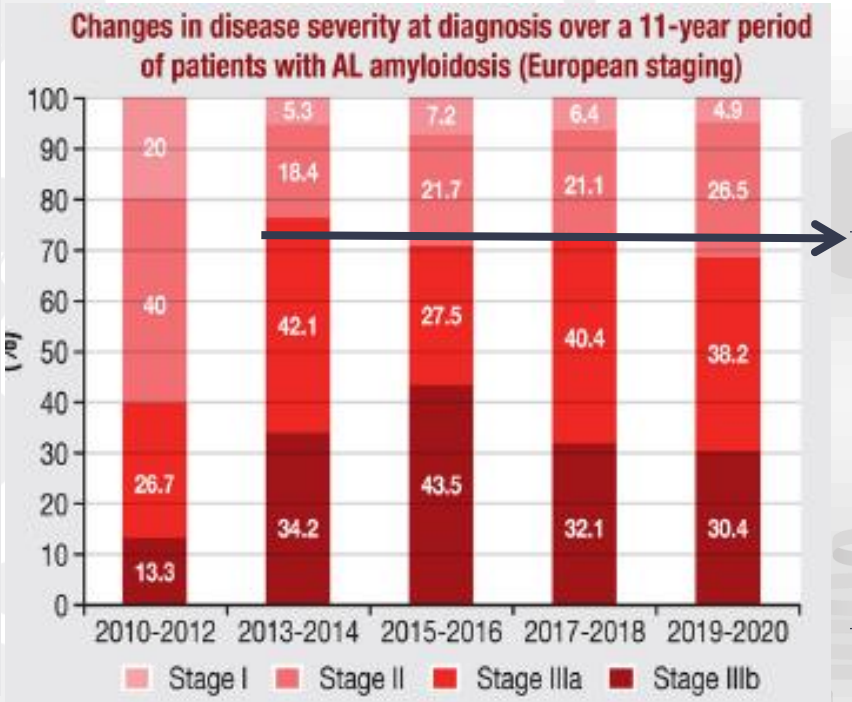
Réseau Amylose



ATTR Sauvage



AL



In 2023:
≈2500 Amyloses Cardiaques
>550 AL

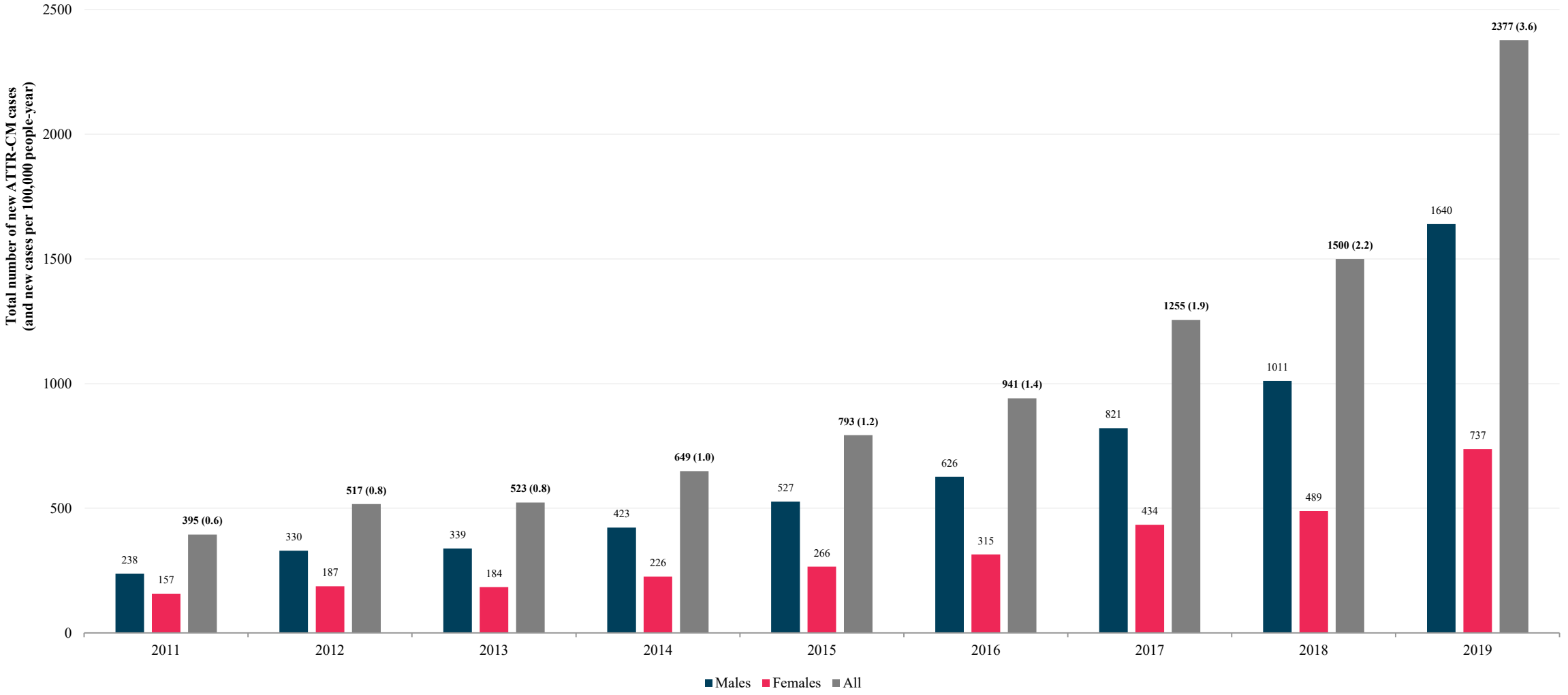
27 (9–51) **12 (4–7)** **17 (6–50)** **10 (2–25)**

-15 months **-7 months**

Temps entre le diagnostic et les symptômes cardiaques

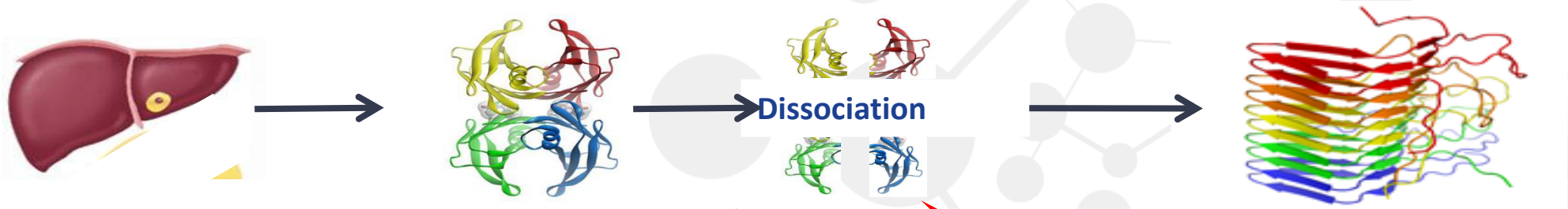
Damy T et al, ACVD 2023

Etude sur le SNDS (assurance maladie)



Damy T (…) Lairez O et al, Orphanet Journal of Rare Disease In press

Physiopathologie des amyloses à transthyrétine

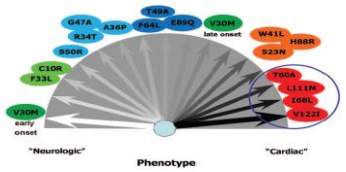


ATTRv

Autosomique dominante

120 mutations

CŒUR >>> Nerf



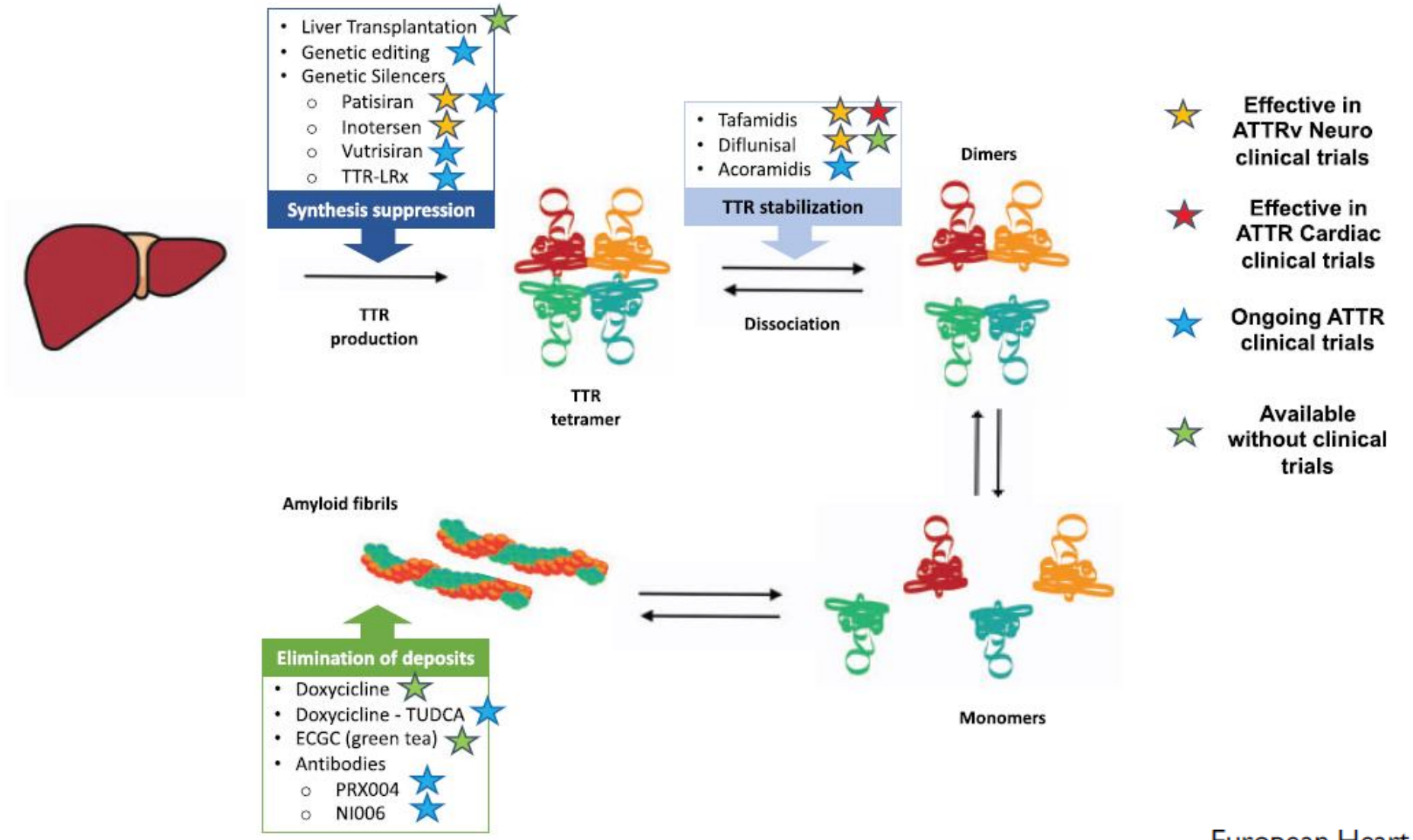
- Mutations cardiaques…
- ATTR V122I : présente chez 3,6% des africains/ afrocaribeens.

ATTRwt

Véritable « Alzheimer Cardiaque »

25% des hommes de plus de 80 ans ont des dépôts d'amylose TTR dans le coeur

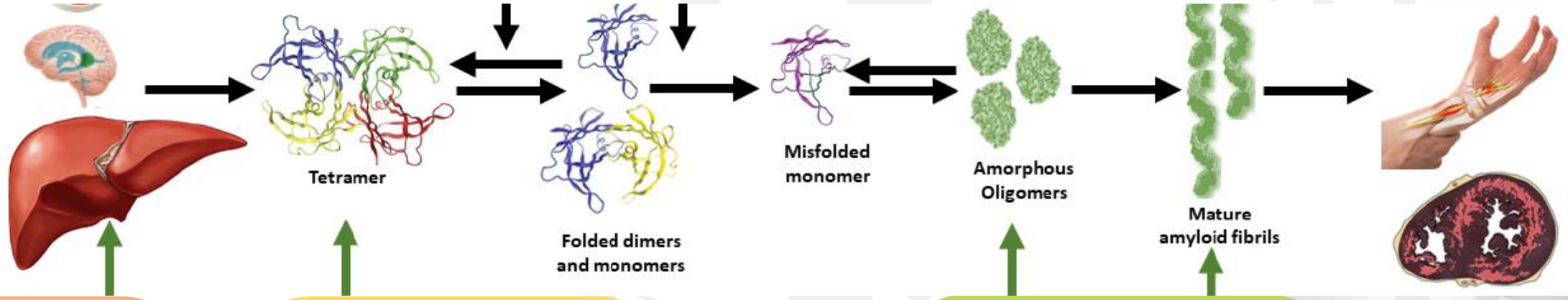
Les thérapies développées ou en développement pour les amyloses ATTR



European Heart Journal (2021) **00**, 1–15

Les mécanismes d'action des nouveaux traitements

Réseau Amylose



Liver Transplantation

TTR Gene Silencing

-siRNA and ASO : Patisiran, Revusiran, Vutrisiran, Inotersen, Eplontersen

-Crispr Cas 9

ATTR Stabiliseurs

-Tafamidis,

-Acoramidis,

-Diflunisal

Dépléteurs - Anticorps

-NI006

-PRX004

Adapted from Carroll A, et al. J Neurol Neurosurg P 2022

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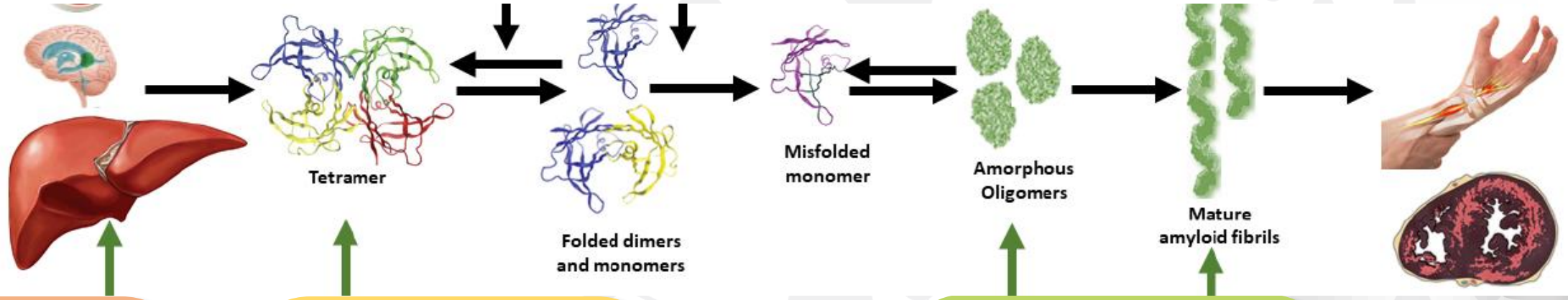

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Antibodies to clear Amyloidosis Deposits

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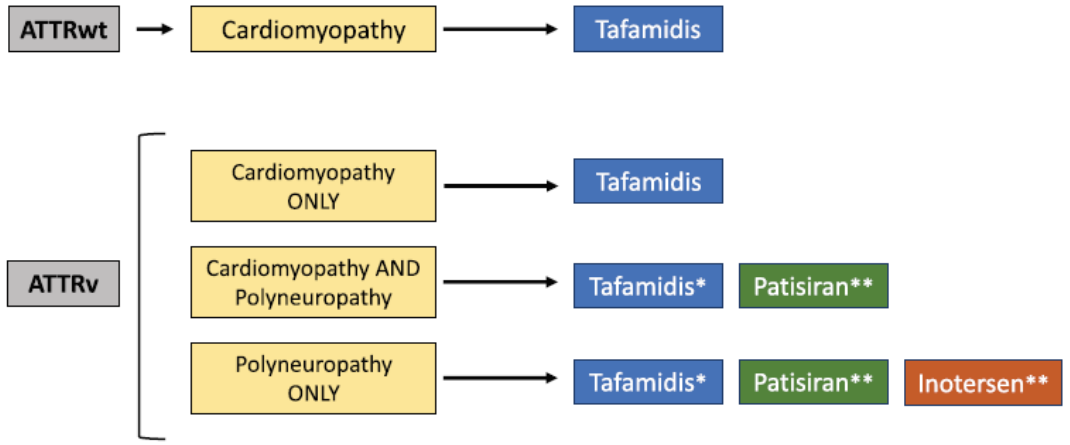
-PRX004

Adapted from Carroll A, et al. J Neurol Neurosurg P 2022

New recommendation for the treatment of transthyretin amyloidosis-cardiac amyloidosis

Recommendations	Class[a]	Level[b]
Tafamidis is recommended in patients with genetic testing proven hereditary hTTR-CMP and NYHA class I or II symptoms to reduce symptoms and CV hospitalization and mortality.	I	B
Tafamidis is recommended in patients with wtTTR-CA and NYHA class I or II symptoms to reduce symptoms and CV hospitalization and mortality.	I	B



* Polyneuropathy Stage 1
** Polyneuropathy Stage 1 & 2

European Heart Journal (2021) **00**, 1–15

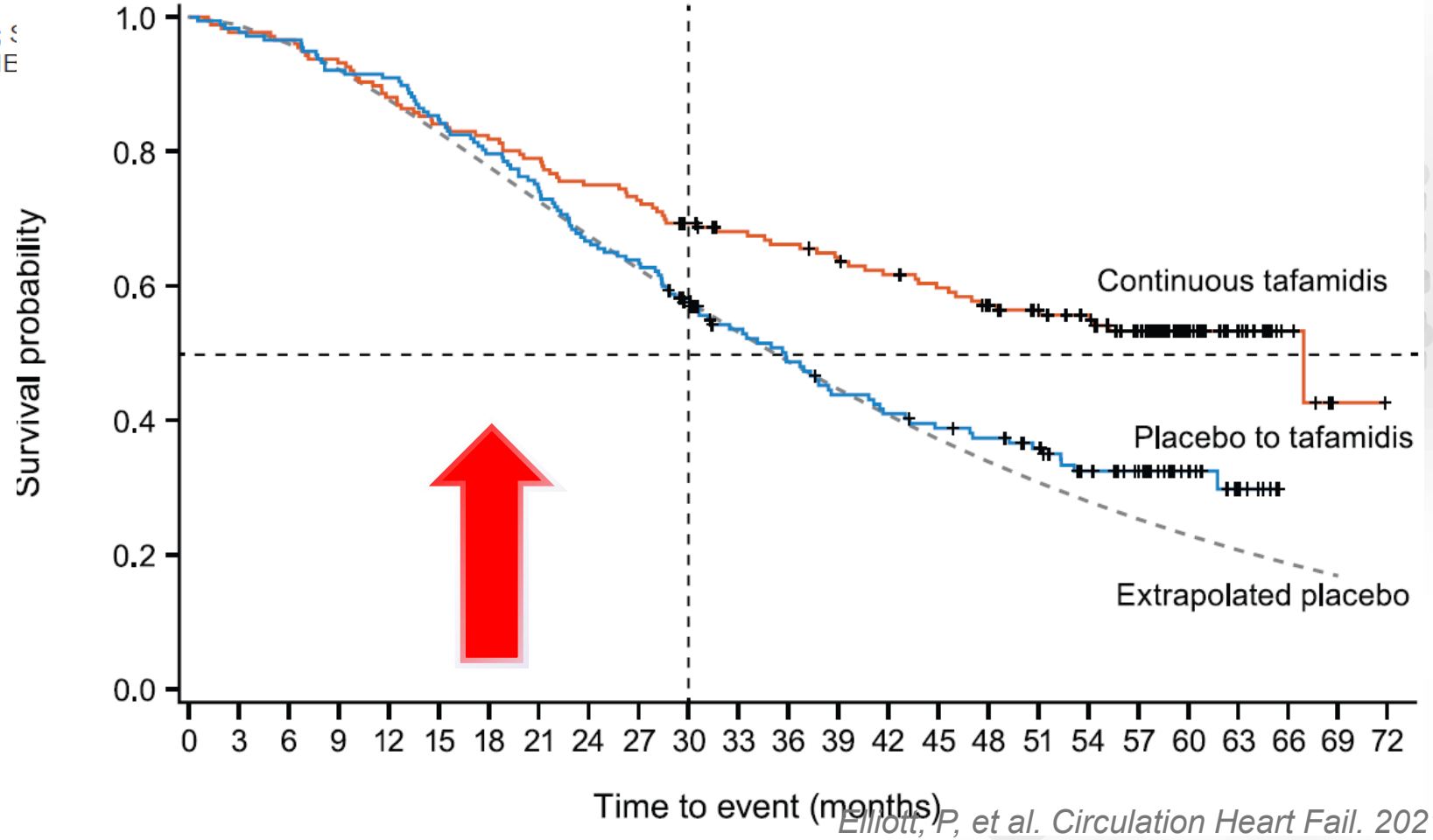
[a]Class of recommendation. [b]Level of evidence

Impact du tafamidis à long terme

Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy

Perry Elliott, MD; Brian M. Drachman, MD; S
Daniel J. Lenihan, MD; Ben Ebede, MS, ME
Sanjiv J. Shah, MD

- Median follow-up was 58.5 months in the continuous tafamidis group (n=176) and 57.1 months in the placebo to tafamidis group (n=177).
- 79 (44.9%) deaths with continuous tafamidis and 111 (62.7%) with placebo to tafamidis (hazard ratio, 0.59 [95% CI, 0.44–0.79]; *P<0.001)*.



Elliott, P, et al. Circulation Heart Fail. 2021

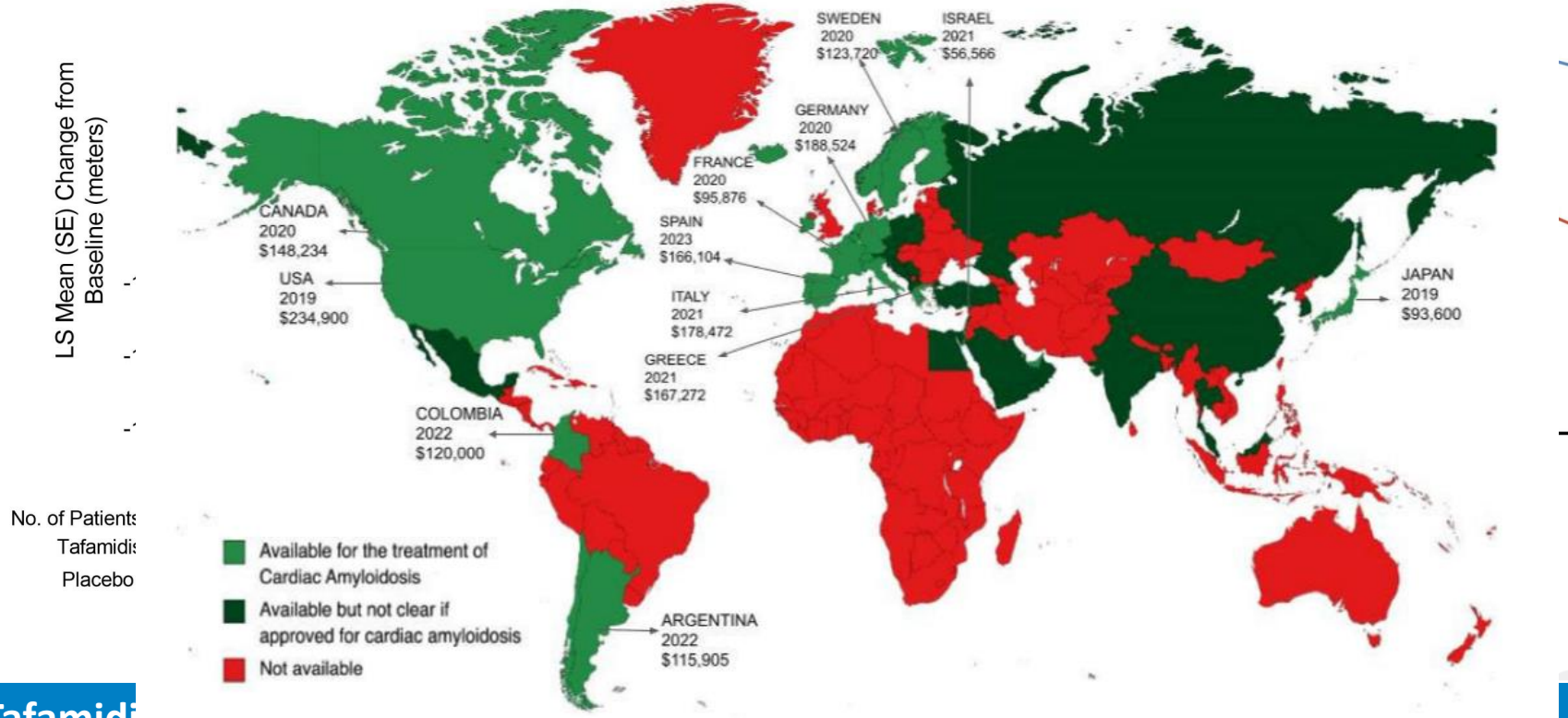
> Amyloid. 2023 Oct 3:1-3. doi: 10.1080/13506129.2023.2263620. Online ahead of print.

Ta

Heterogeneous worldwide access and pricing of Tafamidis

Abdirahman Wardhere [1], Dimitrios Bampatsias [1], Nowell Fine [2], Pablo Garcia-Pavia [3], Martha Grogan [4], Arnt V Kristen [5], Thibaud Damy [6], Yoshiki Sekijima [7], Mathew S Maurer [1]

A



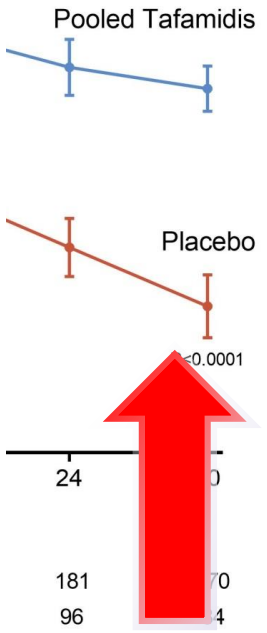


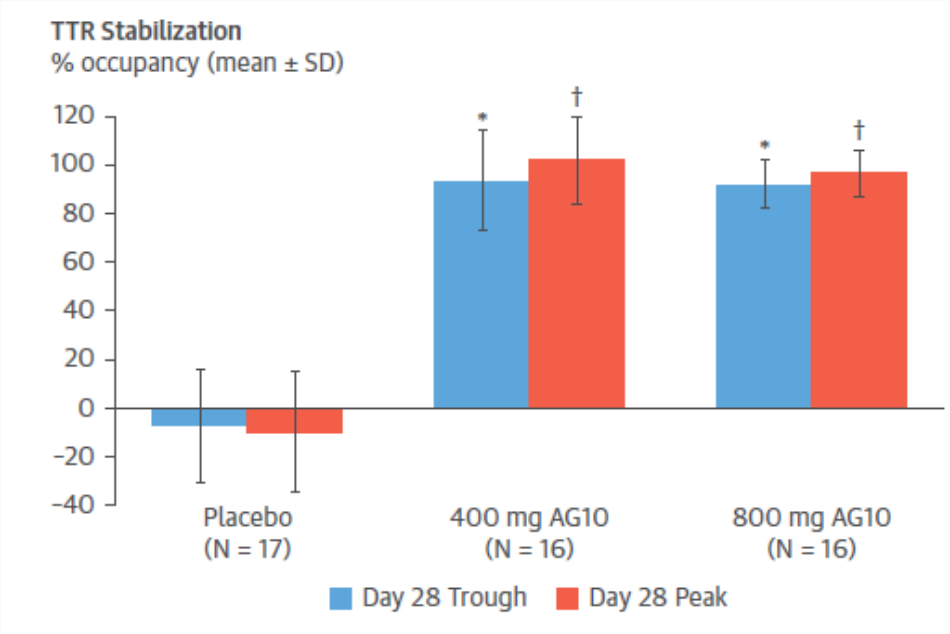
Figure 1. A world map illustrating Tafamidis availability for the treatment of ATTR cardiac amyloidosis. Green indicates countries where Tafamidis is available with labels for specific countries indicating the annual price list of Tafamidis where it is available for the treatment of ATTR cardiac amyloidosis. Dark green indicates countries where Tafamidis is available but not clear if approved for cardiac amyloidosis (list provided by the manufacturer). red indicates countries where Tafamidis is not available. Data for prices shown was obtained from experts in respective countries and or data from the following sources: USA Canada Italy Spain France Sweden Argentina Greece.

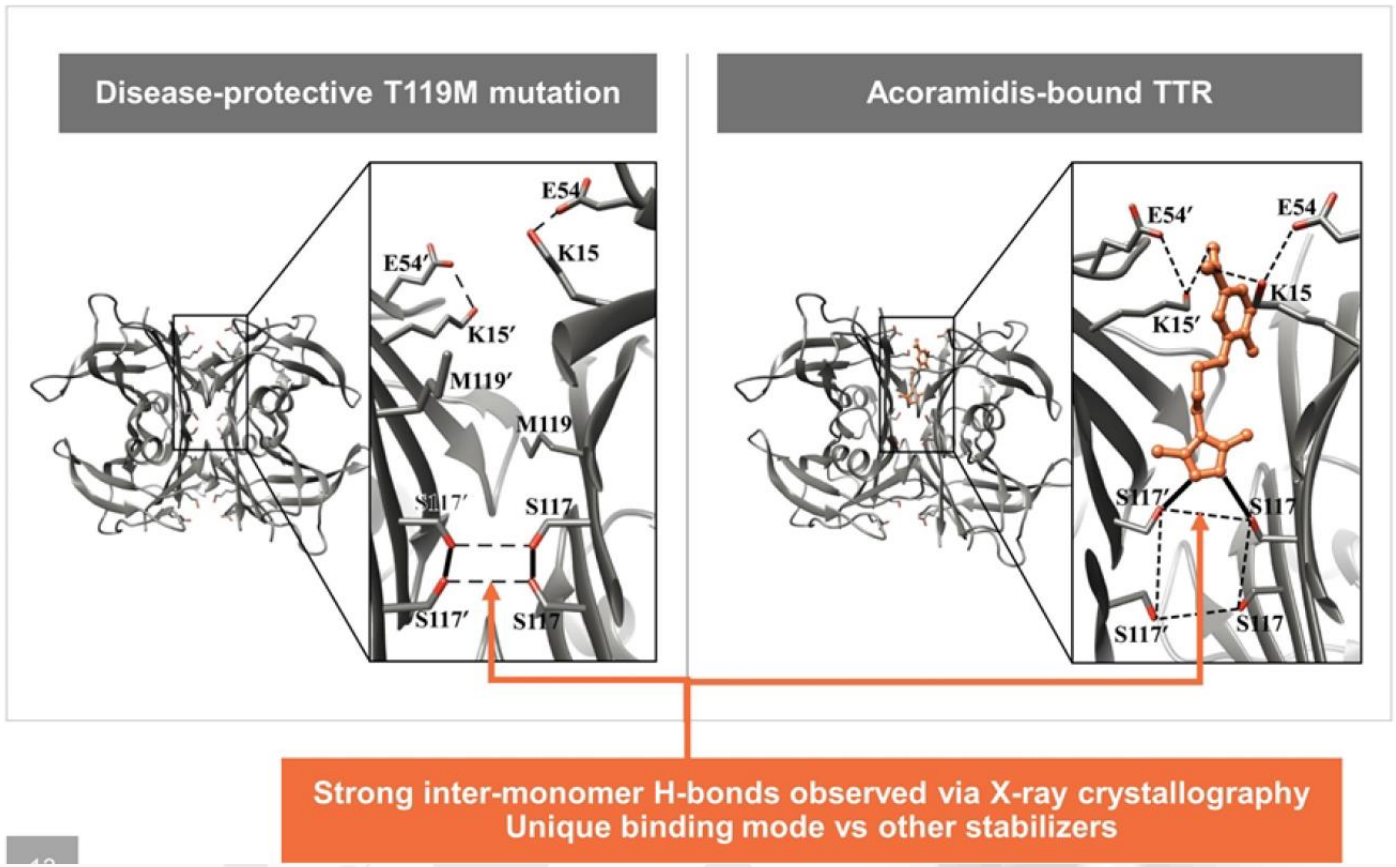
Tafamidi		At 30 months
NTpro		−2180.54
Least-square mean difference	[95% CI, −1249.10 to −221.13]	[95% CI, −3326.14 to −1034.95]

Maurer M et al , New England Journal of Medicine 2018

Acoramidis : Un nouveau stabilisateur

- Promising mechanism of action by mimicking th protective mutation ATTR Thr119Met





https://ir.eidostx.com/static-files/

J udge D et al, JACC 2 0 1 9 : 2 8 5 – 9 5

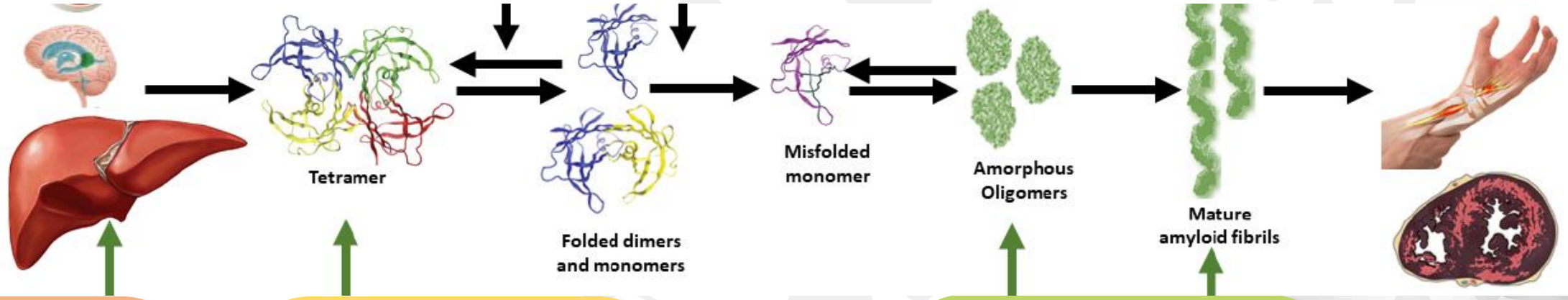
ATTRibute-CM : Critère principal combiné.

Subgroup	No. of Patients	Win Ratio [95% CI]	FS test P-value
Overall	611(100.0)	1.772 [1.417, 2.217]	<0.0001
ATTR-CM Genotype			
ATTRm-CM	59(9.7)	2.529 [1.303, 4.911]	0.0061
ATTRwt-CM	552(90.3)	1.756 [1.396, 2.208]	<0.0001
NT-proBNP (pg/mL)			
<= 3000	401(65.6)	1.787 [1.373, 2.325]	<0.0001
> 3000	210(34.4)	1.678 [1.160, 2.426]	0.0060
eGFR (mL/min/1.73m2)			
< 45	94(15.4)	1.410 [0.849, 2.341]	0.1841
>= 45	517(84.6)	1.797 [1.452, 2.226]	<0.0001
Age (years)			
< 78	299(48.9)	2.052 [1.489, 2.829]	<0.0001
>= 78	312(51.1)	1.499 [1.098, 2.045]	0.0107
NYHA Class			
I, II	512(83.8)	1.892 [1.479, 2.419]	<0.0001
III	99(16.2)	1.150 [0.652, 2.030]	0.6292

FS = Finkelstein-Schoenfeld; CI = Confidence interval.

Les mécanismes d'action des nouveaux traitements

Réseau Amylose



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Antibodies to clear Amyloidosis Deposits

-NI006

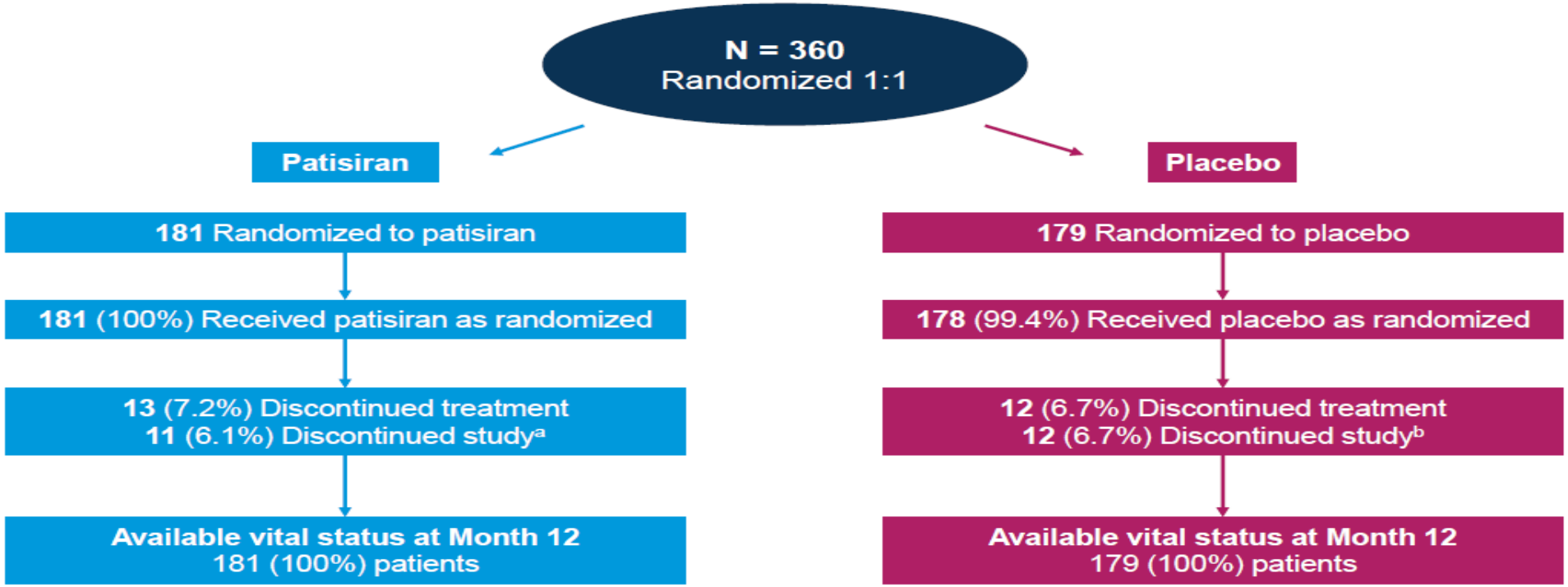
-PRX004

Adapted from Carroll A, et al. J Neurol Neurosurg P 2022

APPOLO-B design : Patisiran IV injection every 3 weeks

Patient Disposition

12-Month Double-Blind Treatment Period in APOLLO-B + Open Long term Extension (OLE)



[a]Reasons for discontinuing patisiran treatment: AE (4 [2.2%]), death (3 [1.7%]), other (6 [3.3%]). [b]Reasons for discontinuing placebo treatment: AE (5 [2.8%]), death (3 [1.7%]), physician decision (1 [0.6%]), other (3 [1.7%]). Other excludes A death, lost to follow-up, physician decision, pregnancy, protocol deviation, study terminated by sponsor, and non-compliance to study drug. **Abbreviation:** AE, adverse event.

Maurer MS et al, ISA Heidelberg meeting Abstract : ***OPLB001 08_09_2022***

Appolo B : parue le 26 octobre

Réseau Amylose

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 26, 2023 VOL. 389 NO. 17

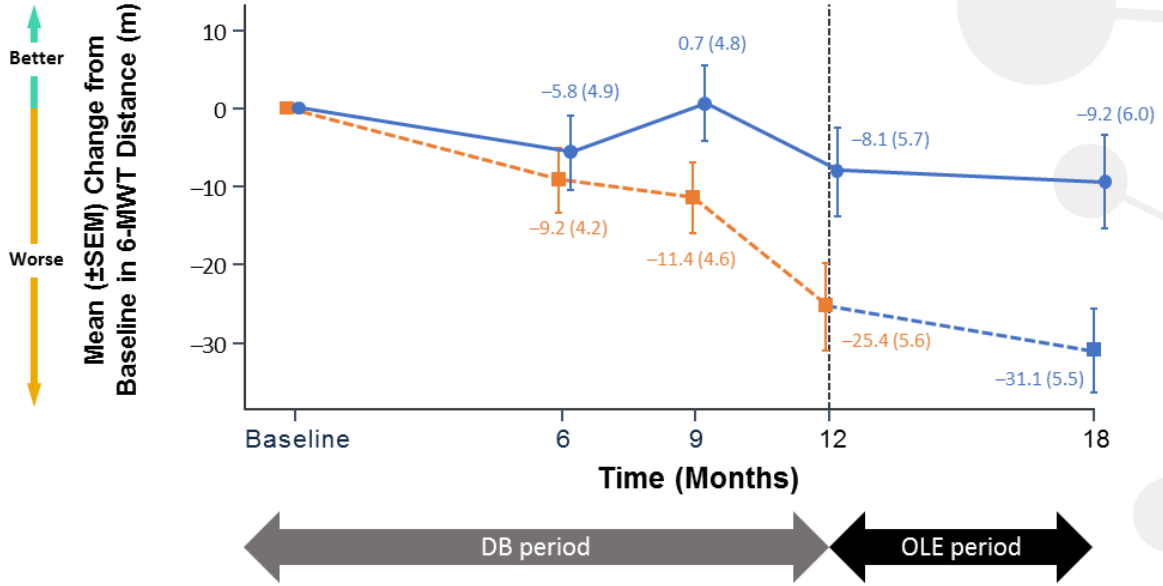
Patisiran Treatment in Patients with Transthyretin Cardiac Amyloidosis

M.S. Maurer, P. Kale, M. Fontana, J.L. Berk, M. Grogan, F. Gustafsson, R.R. Hung, R.L. Gottlieb, T. Damy, A. González-Duarte, N. Sarswat, Y. Sekijima, N. Tahara, M.S. Taylor, M. Kubanek, E. Donal, T. Palecek, K. Tsujita, W.H.W. Tang, W.-C. Yu, L. Obici, M. Simões, F. Fernandes, S.H. Poulsen, I. Diemberger, F. Perfetto, S.D. Solomon, M. Di Carli, P. Badri, M.T. White, J. Chen, E. Yureneva, M.T. Sweetser, P.Y. Jay, P.P. Garg, J. Vest, and J.D. Gillmore, for the APOLLO-B Trial Investigators*

Résultats Appolo-B : ATTR-CA

Critère primaire

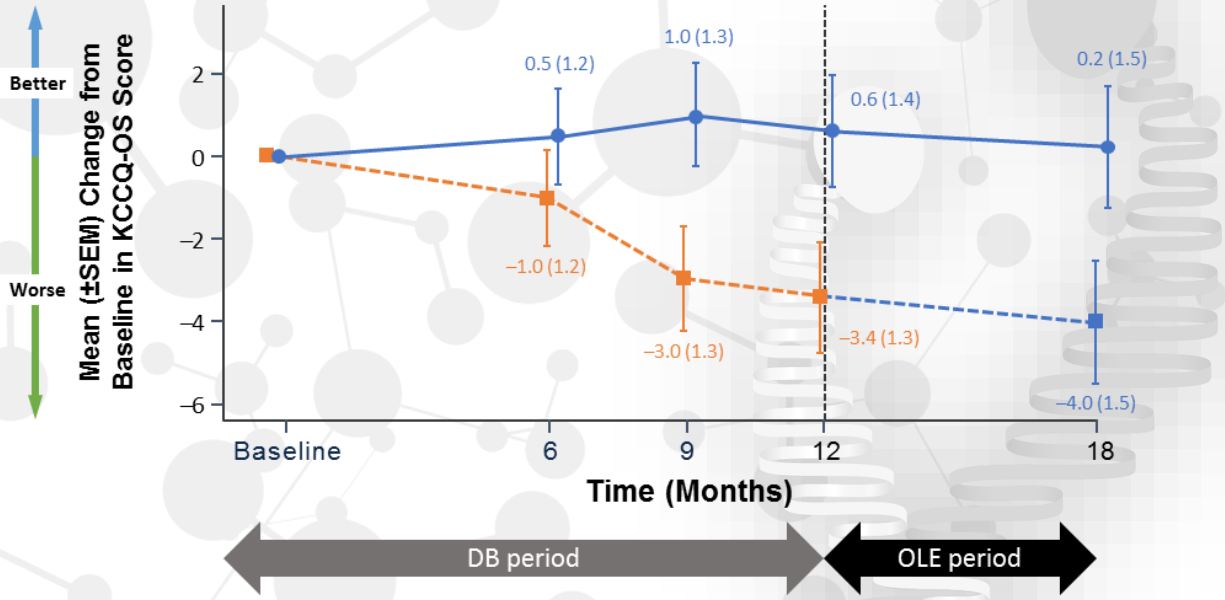
Mean Change from Baseline in 6-MWT



No. of patients					
Placebo	178	165	165	164	146
Patisiran	181	162	167	167	149

Critère secondaire

Mean Change from Baseline in KCCQ-OS



No. of patients					
Placebo	178	171	168	167	155
Patisiran	181	170	171	171	157

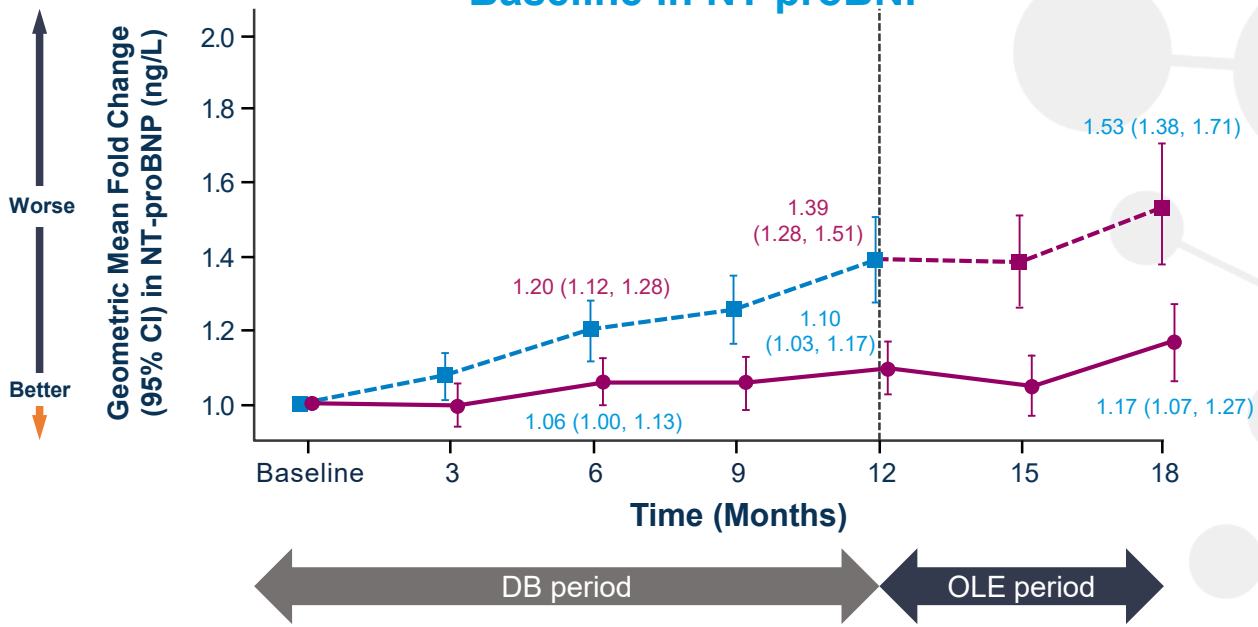
Patisiran Placebo

Présentation de Maurer M, ISA 2022

Résultats Apollo-B: Biomarqueurs Cardiaques

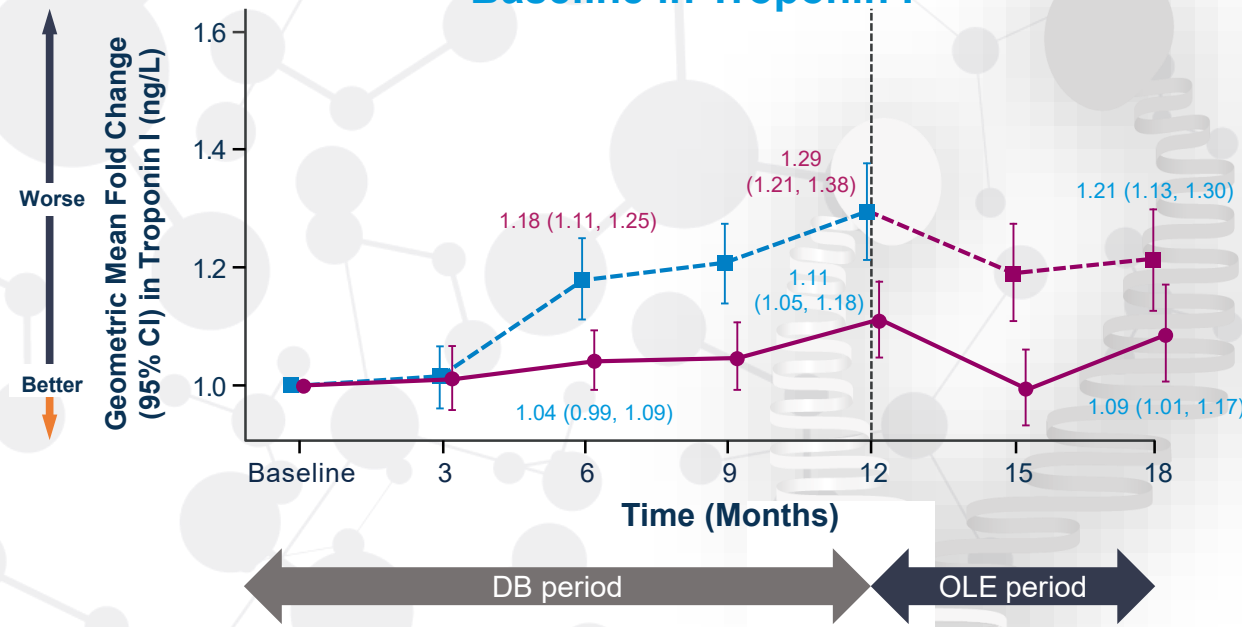
Réseau Amylose

Geometric Mean Fold Change from Baseline in NT-proBNP[a]



No. of patients							
Placebo	178	168	165	164	163	156	152
Patisiran	181	171	169	169	167	157	157

Geometric Mean Fold Change from Baseline in Troponin I[a]



No. of patients							
Placebo	172	158	162	156	155	150	145
Patisiran	174	161	162	160	158	146	147

Patisiran Placebo

D'après la présentation de Maurer M, ISA 2022 et HFA

[a]Visits with number of patients on both treatment arms ≥60 are presented. Baseline is defined as the last non-missing value available on or before the date of first dose of study drug in the DB period. All patients received patisiran after Month 12. **Abbreviations:** CI, confidence interval; DB, double-blind; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; OLE, open-label extension.

HELIOS B : Sub-cutaneous injection every 3 months.

Réseau Amylose

HELIOS·B

HELIOS·B

Randomized, double-blind trial in patients with ATTR-CM

N = 655
Patient population

- Amyloidosis ATTR; wtATTR or ATTRv regardless of mutation
  - **≤ 30% use of tafamidis at baseline**
- Confirmed cardiomyopathy and history of symptomatic heart failure
- NYHA ≤ III;
- PND I or II at baseline

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary endpoint
Composite outcome of all-cause mortality and recurrent CV hospitalizations (when the last patient reaches month 30).

Secondary endpoints

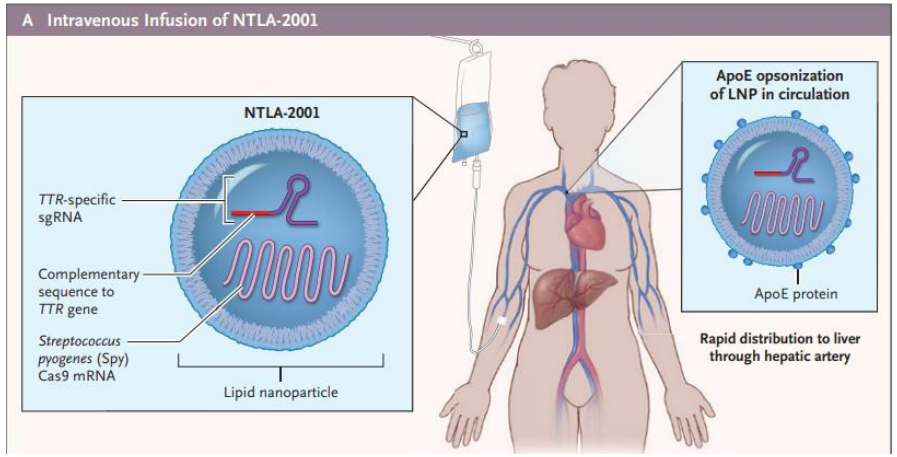
- Distance to 6-MWT
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score.
- Average wall thickness of the left ventricle (LV)
- Global longitudinal strain
- Composite endpoint of all-cause mortality and recurrent all-cause hospitalizations
- All-cause mortality
- Recurrent CV hospitalizations
- NT-proBNP

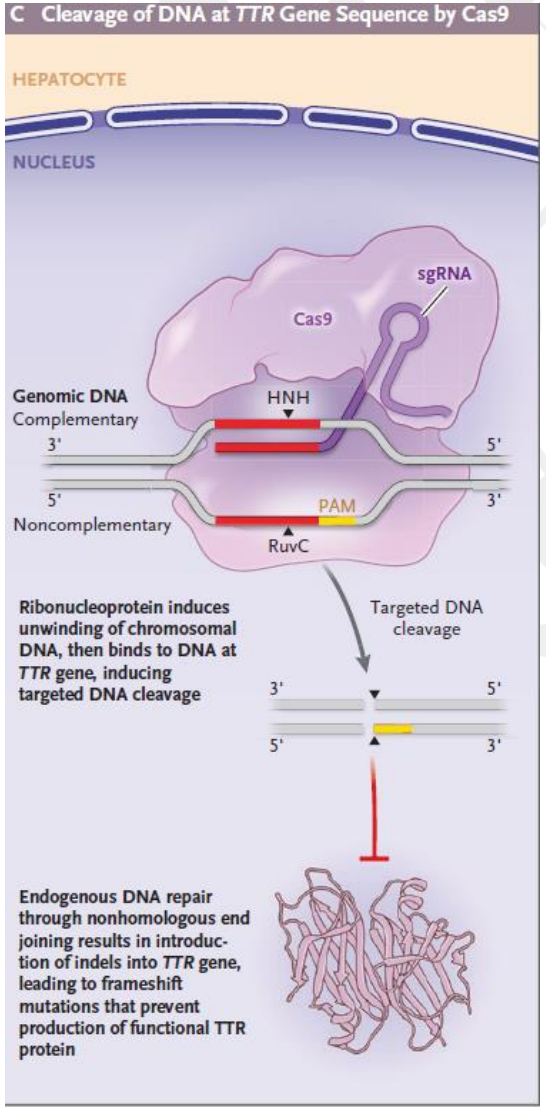
https://www.clinicaltrials.gov/ct2/show/NCT04153149

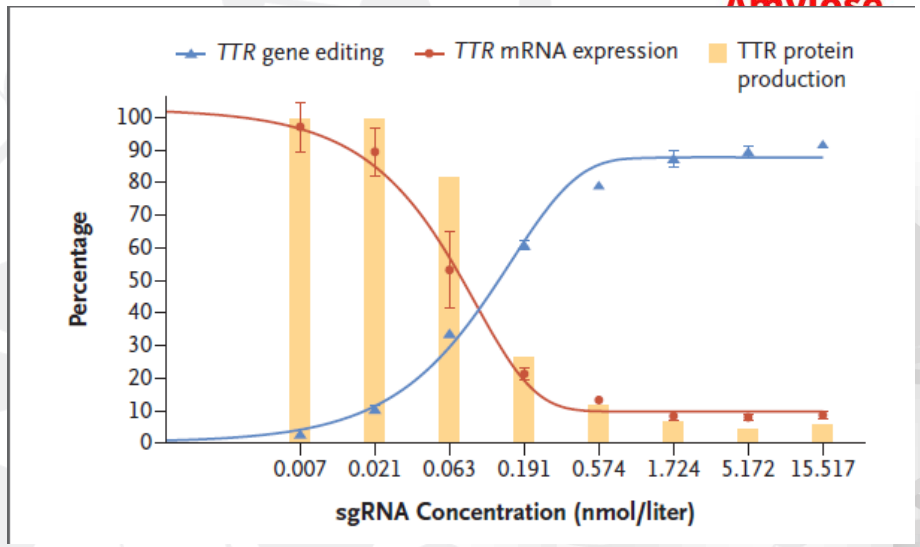
CrisprCas9: First gene therapy results for ATTR : Only one injection

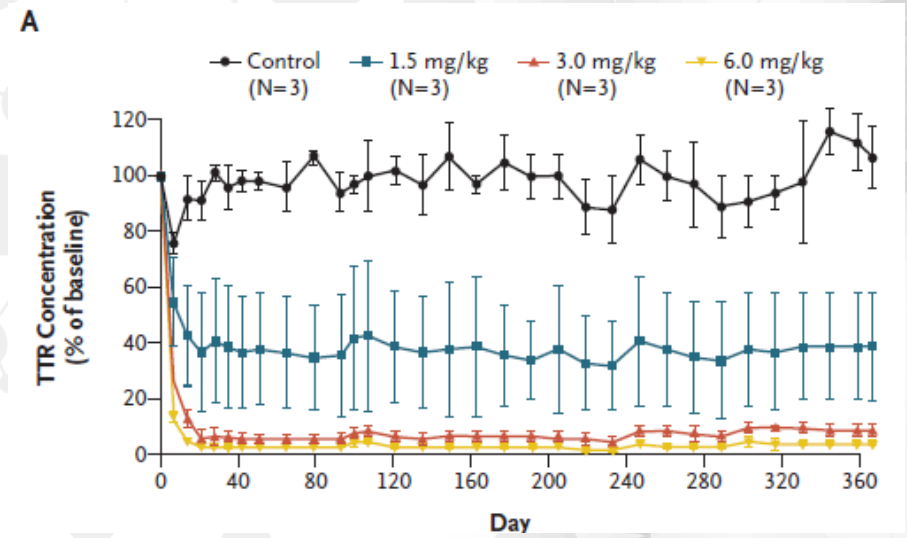
ORIGINAL ARTICLE

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis



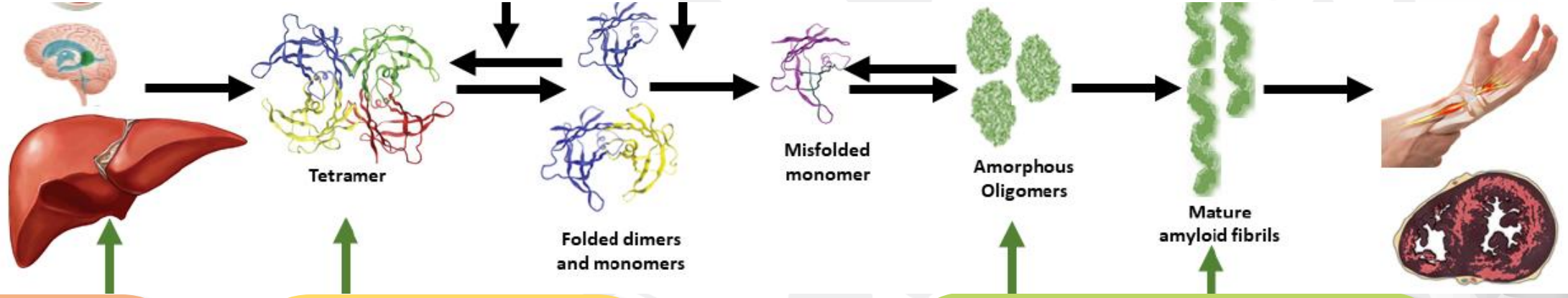






Gillmore J et al, NEJM 2021

Les mécanismes d'action des nouveaux traitements



Transplantation Hépatique

Thérapie génique
-siRNA and ASO : Patisiran, Revusiran, Vutrisiran, Inotersen, Eplontersen
-Crispr Cas 9

Stabilisateurs
-Tafamidis,
-Acoramidis,
-Diflunisal

Dépléteurs = Rétirer les dépots
-NI006 : ALXN2220
-PRX004 : NN6019-4940

Adapted from Carroll A, et al. J Neurol Neurosurg P 2022

ORIGINAL ARTICLE

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

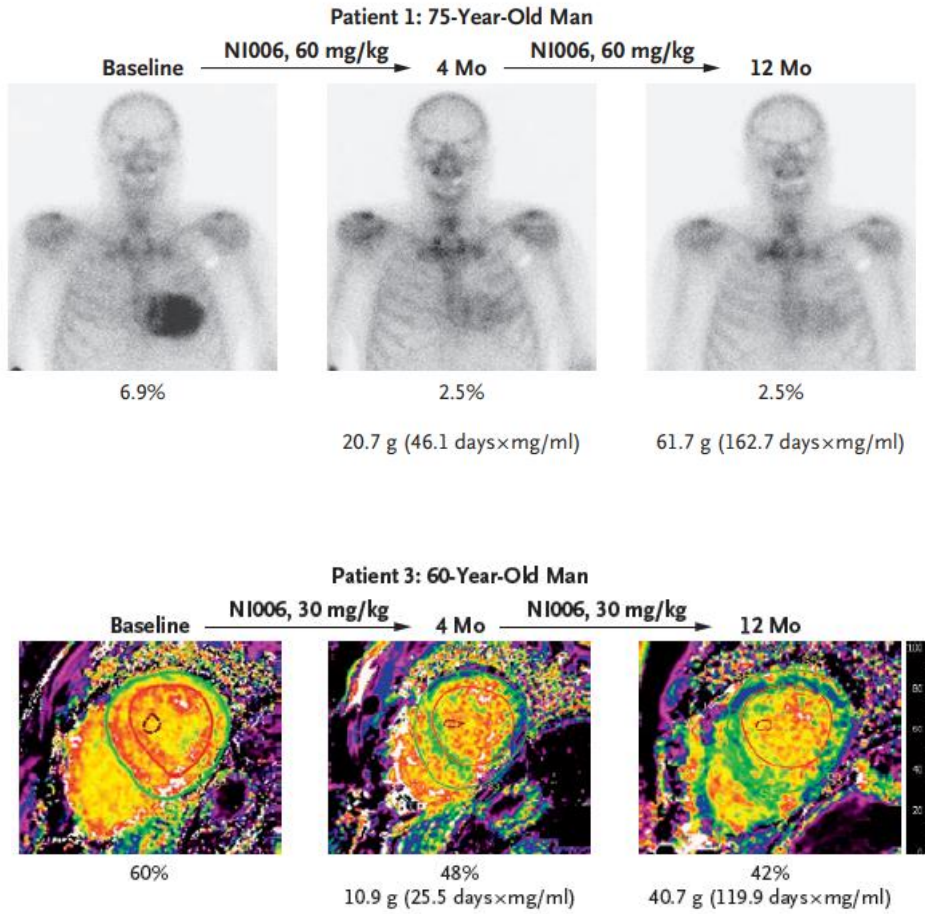
Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph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

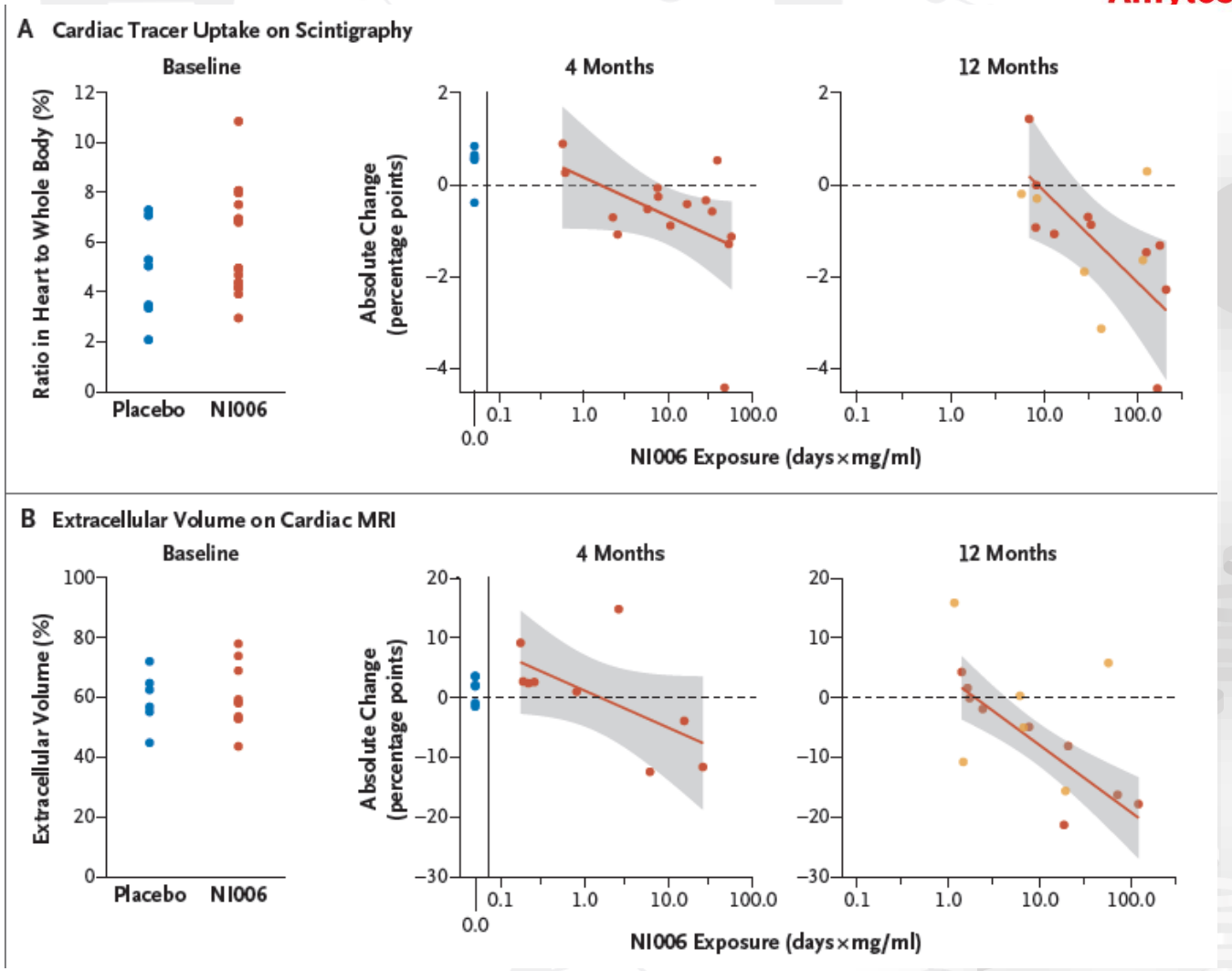
Réseau Amylose

- Double-blind, placebo-controlled, international, multicenter, combined single-ascending-dose and multiple-ascending dose, randomized clinical trial with an openlabel extension phase.
- NI006 or placebo every 4 weeks for 4 months.
- The 4-month placebocontrolled, ascending-dose phase was followed by an 8-month open-label extension phase in which all participating patients (including those randomly assigned to receive placebo) received NI006 with stepwise increases in the dose.

Michalon A et al , Nat com 2021
Pablo Garcia-Pavia et al, NEJM 2023, NEJM 2023

Changes in Cardiac Fixation (Bone Scintigraphy and ECV (Cardiac MRI)

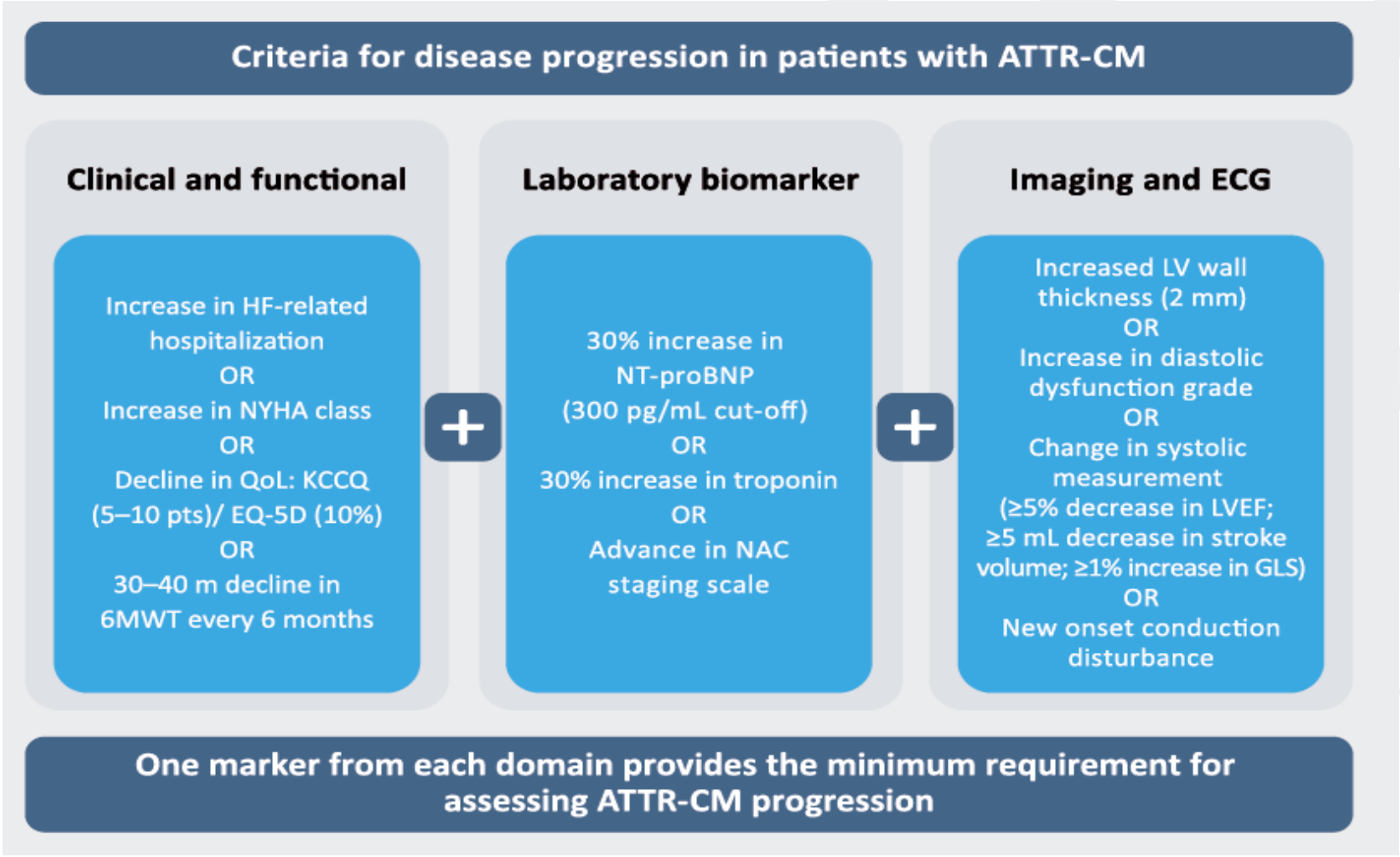




Pablo Garcia-Pavia et al, NEJM 2023, NEJM 2023

Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy

Pablo Garcia-Pavia[1,2,3]*, Frank Bengel[4], Dulce Brito[5], Thibaud Damy[3,6], Franz Duca[7], Sharmila Dorbala[8], Jose Nativi-Nicolau[9], Laura Obici[10], Claudio Rapezzi[11,12], Yoshiki Sekijima[13], and Perry M. Elliott[14]



Garcia Pavia P et al Eur HF J 2021

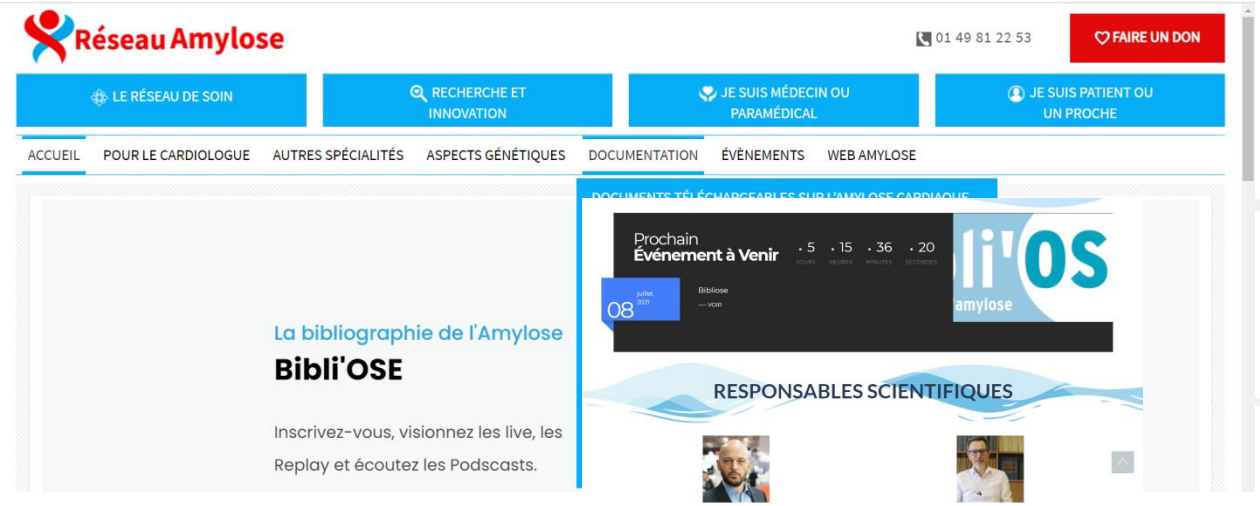
Conclusion

- ATTR Treatment : Tafamidis and lot of new options are coming *if we can offer them*
- AL amyloidosis are rare, underestimated and fatal multisystemic disease : Diagnostic emergency+++ = AL Treatment : Chemotherapy / Immunotherapy.
- Don’t forget that…ATTR+ Gammopathy are frequent…

- *“The evolution of targeted treatment options, holds much promise for improving the outcomes of patients”*

Hawkins P et al , Annals of Medicine 2015

www.reseau-amylose.org



www.bibliose.org

Triptyques pour les professionnels

Ce que doit savoir le cardiologue :

Nom du Triptyque	Objectif	Lien
Les amyloses cardiaques	Présenter les amyloses cardiaques, leurs symptômes et examens et les traitements	Téléchargez ICI
Amylose héréditaire cardiologique Val122Ile	Aider le cardiologue à comprendre la génétique des amyloses et la prise en charge particulière de la mutation ATTR Val122Ile	Téléchargez ICI
Amylose héréditaire cardiologique ValMet30	Aider le cardiologue à comprendre la génétique des amyloses et la prise en charge particulière de la mutation ATTR ValMet30	Téléchargez ICI
La scintigraphie osseuse	Comment réaliser et interpréter une scintigraphie osseuse pour le diagnostic de l'amylose cardiaque	Téléchargez ICI
L'anatomopathologie pour le diagnostic des amyloses cardiaques	Description des différents types d'amylose – Comment analyser un tissu pour suspicion d'amylose	*en cours*
Le prise en charge de l'hypotension orthostatique	Comprendre les mécanismes et la prise en charge de l'hypotension orthostatique dans les amyloses cardiaques	Téléchargez ICI
Prendre en charge la fragilité dans l'amylose	Expliquer la fragilité liée à l'amylose et les bénéfices de sa prise en charge au cardiologue	*en cours*
Prendre en charge les atteintes ORL	Expliquer les atteintes ORL (Surdité ou Trouble de la Voix ou du goût ou macroglossie) au cardiologue	Téléchargez ICI
Chirurgie canalaire et amylose cardiaque	Expliquer les atteintes orthopédiques de l'amylose cardiaque au cardiologue	*en cours*
Canal carpien, canal lombaire et tendinopathies dans l'amylose	Expliquer les atteintes rhumatologiques (syndrôme du canal carpien, canal lombaire étroit et tendinopathies) et leur prise en charge au cardiologue	*en cours*
	Expliquer les atteintes digestives de l'amylose cardiaque au	