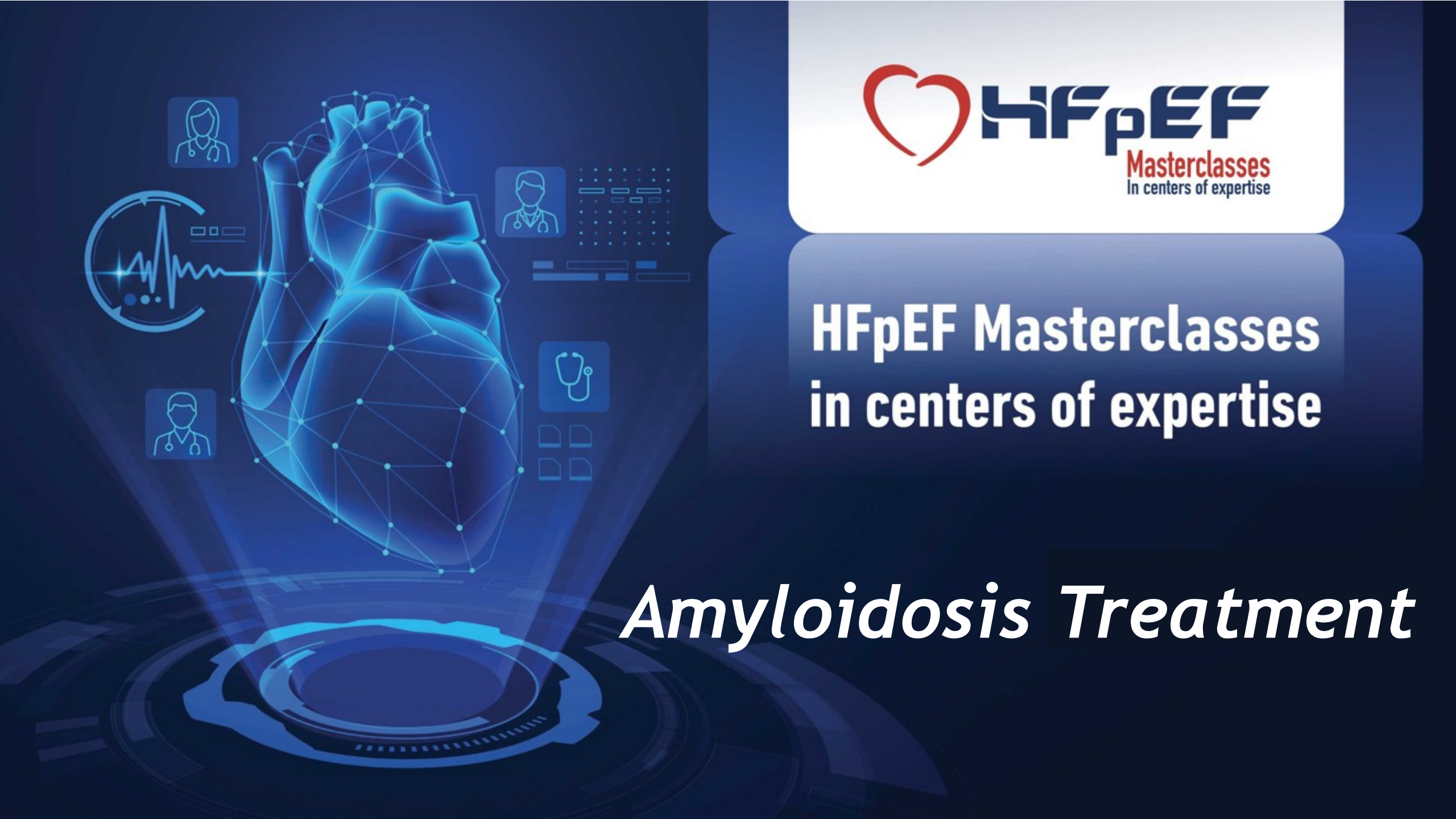

HFpEF
Masterclasses
In centers of expertise
HFpEF Masterclasses
in centers of expertise
Amyloidosis Treatment

HFpEF Masterclasses
in centers of expertise

FRANCE

7th November 2024 - DAY 1

8th November 2024 - DAY 2

Pr Thibaud DAMY

Referral Center for Cardiac Amyloidosis
Cardiology Department
CHU Henri Mondor, Créteil, France

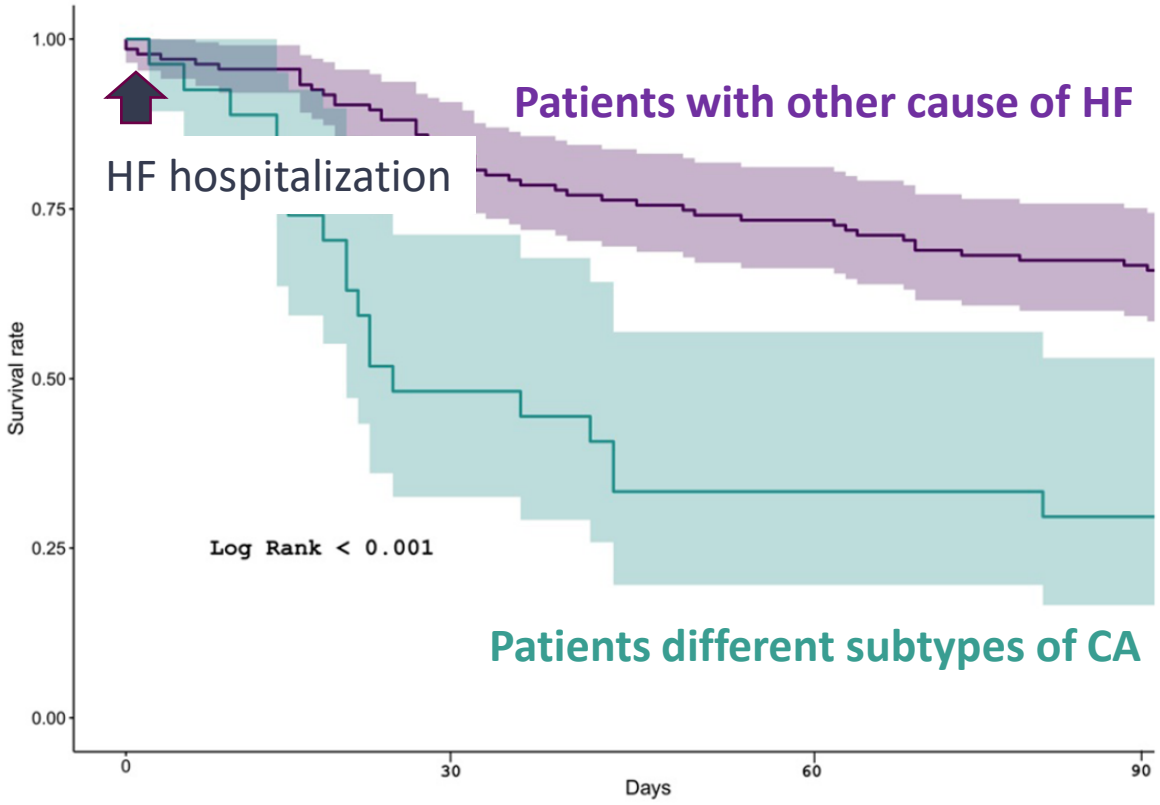
www.reseau-amylose.org

Declaration of Interest

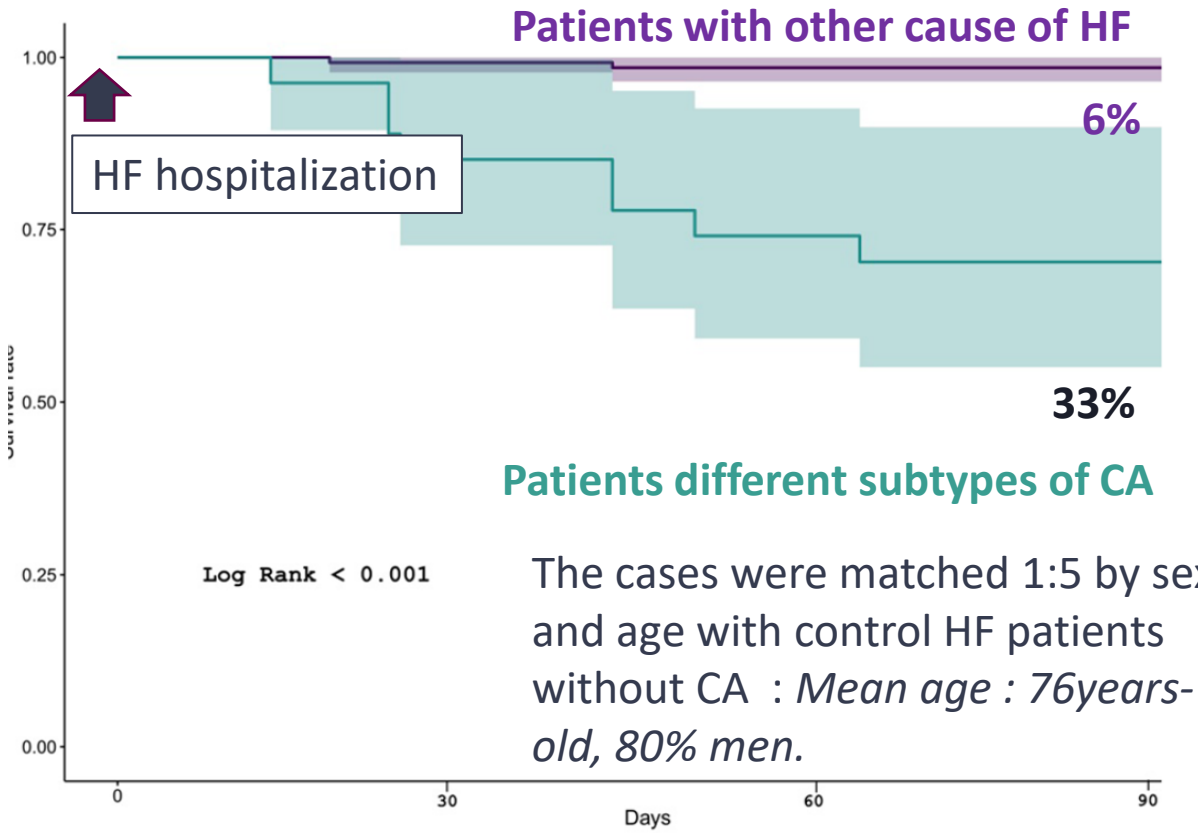
- Alexion, Alnylam, Akcea, Astra Zeneca, Bayer Pfizer, Prothena, GSK, Neurimmune, Novonordisck.

CA is associated with a 3-fold greater risk of death and a 2-fold of all-cause hospital readmission days after discharge.

Mortality and all causes rehospitalisation



All cause mortality

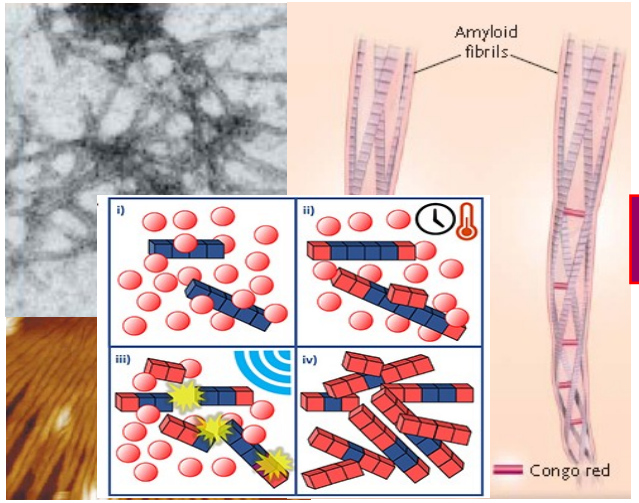


The cases were matched 1:5 by sex and age with control HF patients without CA : *Mean age : 76years-old, 80% men.*

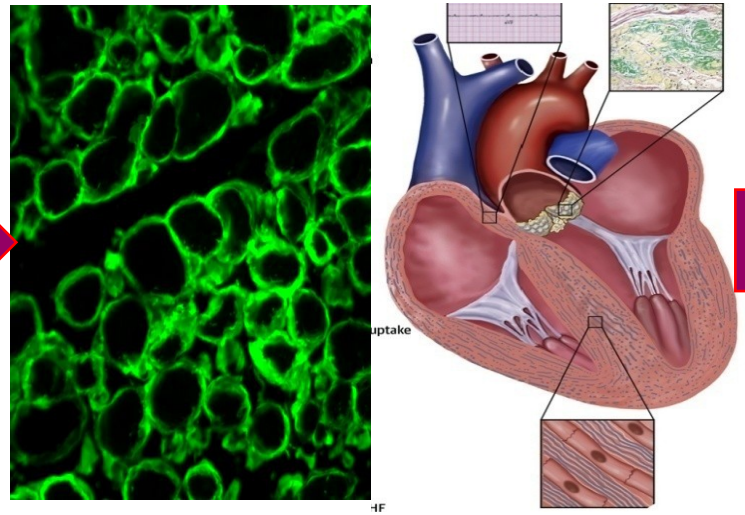
Berthelot E et al. Patients with cardiac amyloidosis are at a greater risk of mortality and hospital readmission after AHF, ESC-HF 2023

Amyloidosis: Definition and physiopathology

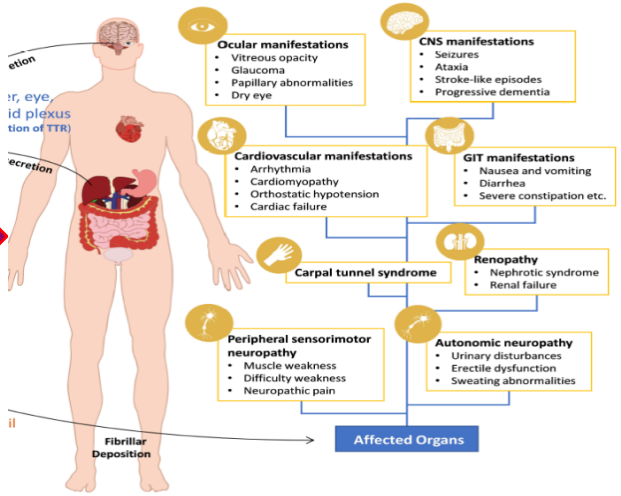
Amyloid Fibrills



Organs infiltration



Human Disease



Amyloid fibrills : >36 Proteins
Non Immunogenic++++
Associated with Aging-Process

Dynamic progress+++

Extracellular infiltration
↗ Cellular death

↗ Stiffness : CMR
↗ Thickness : LVH

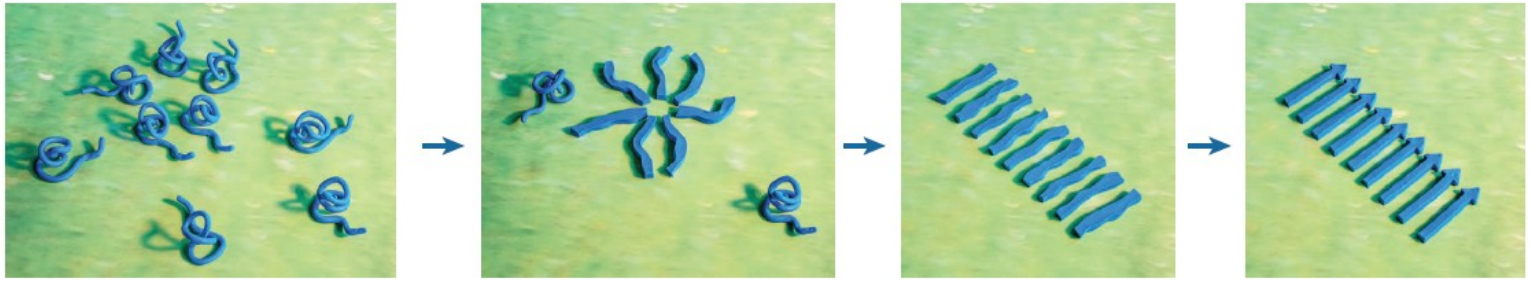
↘Stroke volume
↘Cardiac Output

Extracardiac Sd

Heart Failure
Conduction D
Rhythm D
Death

Merlini, NEJM 2003
Ternacle J, JACC 2019

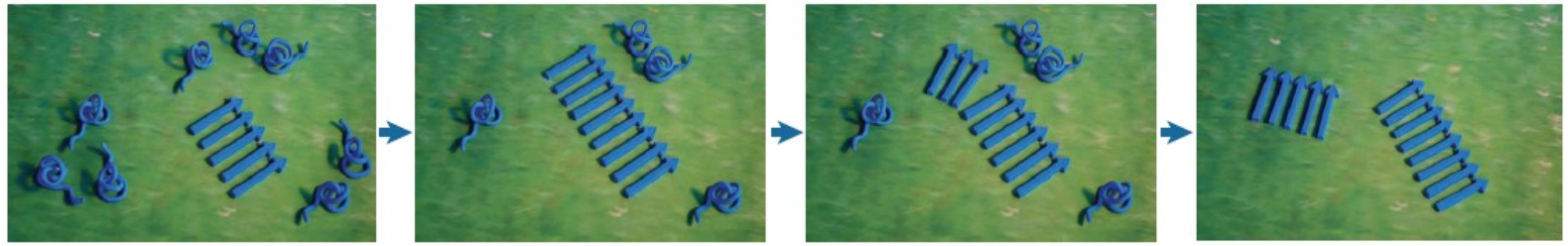
Amyloid agregation to its replication: *A dynamic process!*



Peptides unfolded, misfolded or intrinsically disordered

Nucleus (unstable)

Addition of monomers becomes faster, favouring growth of the aggregate

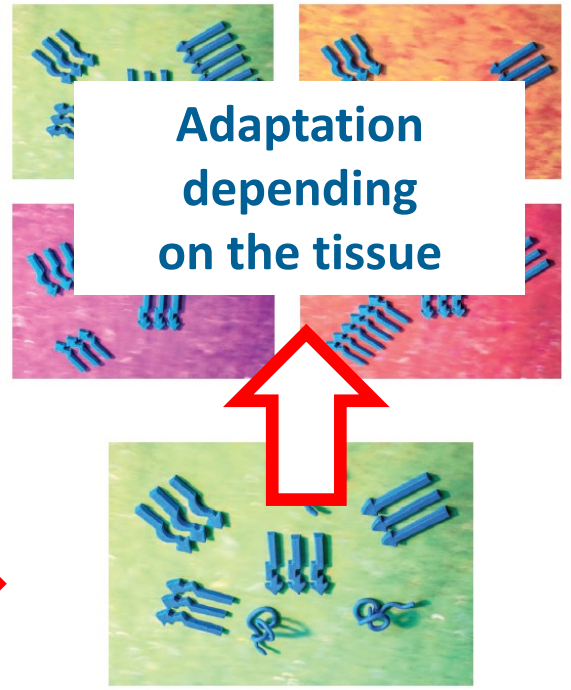


Amyloid seed

Recruitment

Replicative entities

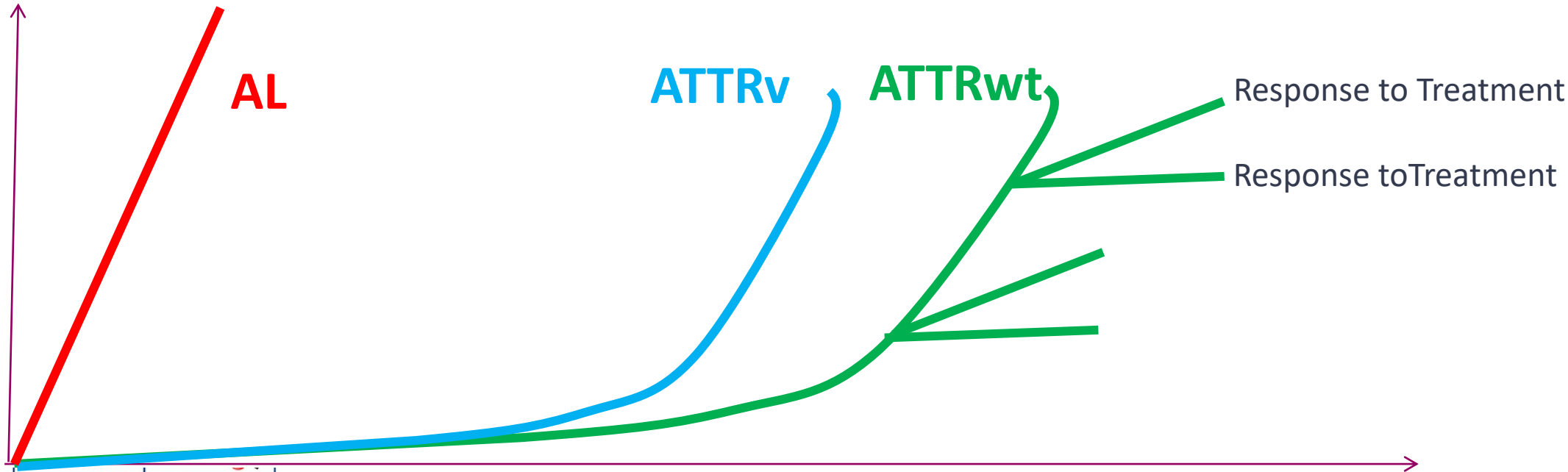
Replicative entities



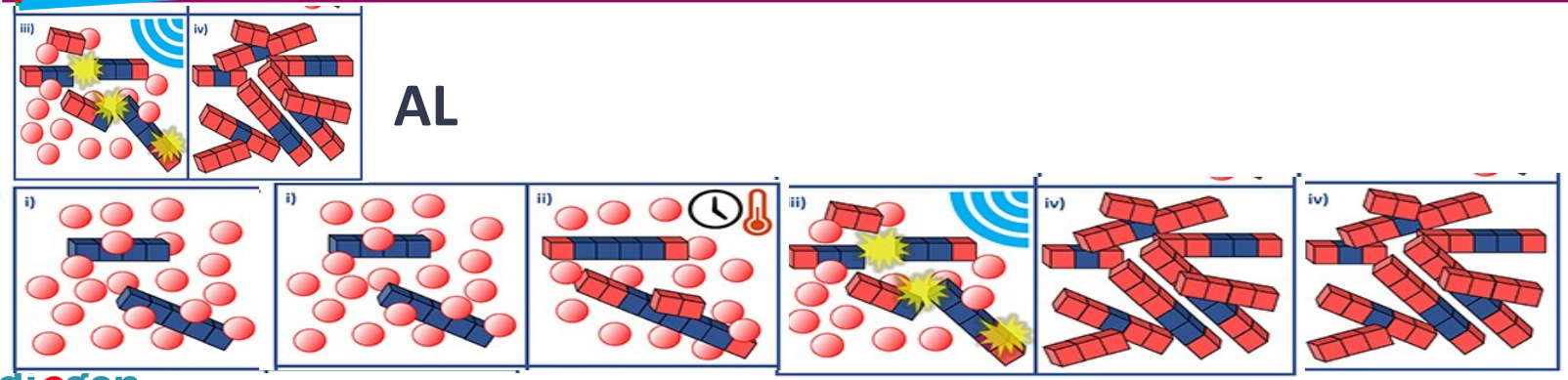
- *Riek R and Eisengberg, Nature 2016*

Kinetic of amyloid fibrills multiplication and infiltration.

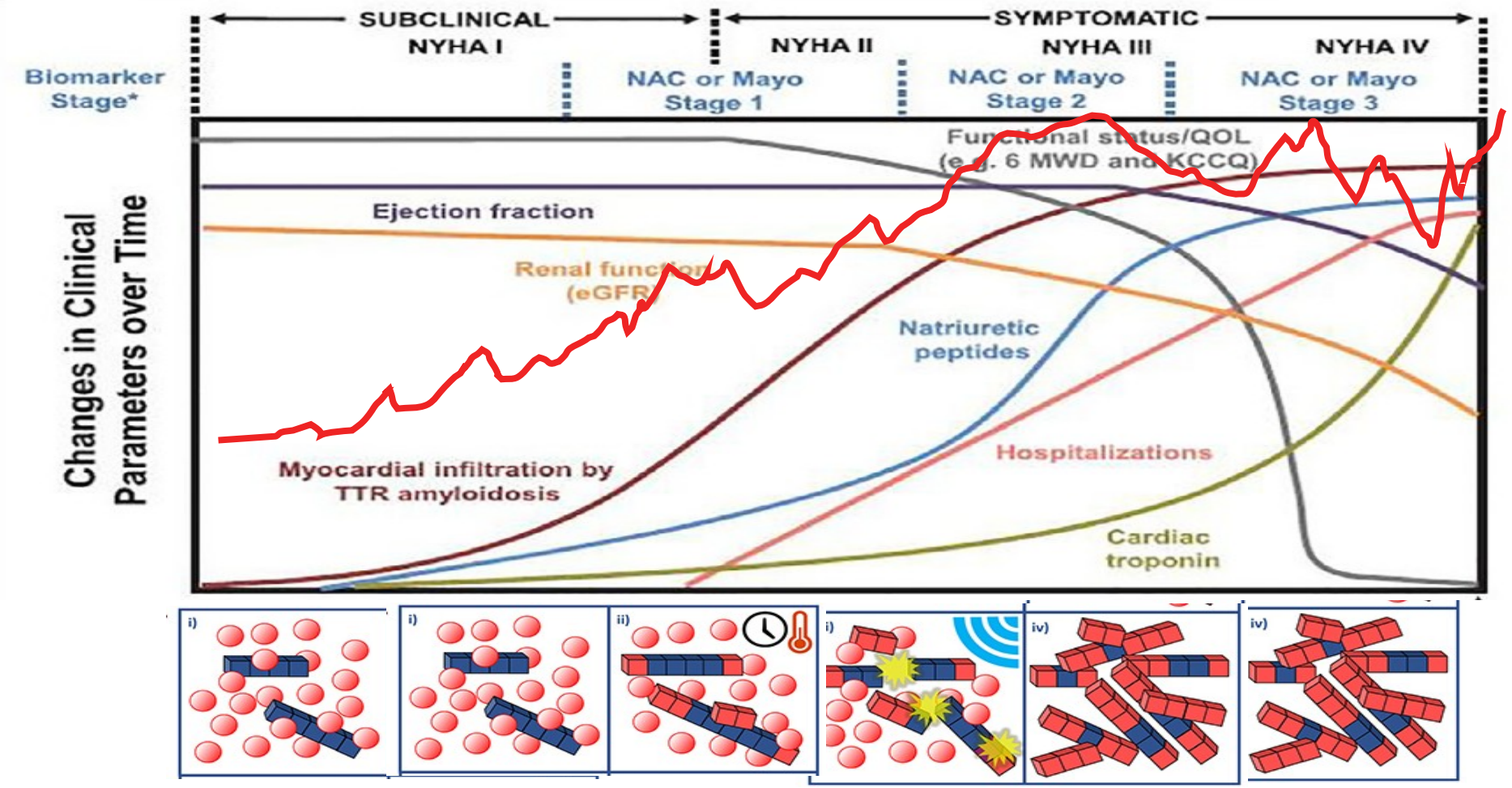
Amyloid fibrills multiplication



Amyloid fibrills Infiltration



ATTR-CM Natural history of the disease before Tafamidis



Modified from Griffin JM and Maurer M, Trends in Cvar Medicine 2019

Réseau Amylose

CA TREATMENT

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–15
doi:10.1093/eurheartj/ehab072

SPECIAL ARTICLE
Heart Failure and Cardiomyopathies

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases

maladies rares

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

Garcia Pavia P and al, EHJ 2021

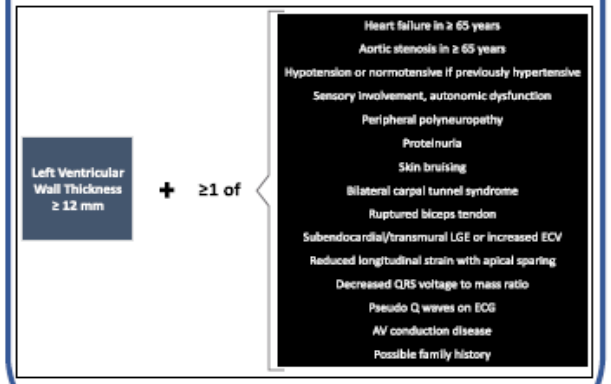
Cardiac amyloidosis

ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario



DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

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

Diagnosis made or proceed to **CMR and/or biopsy** according to results

TREATMENT

Cardiac complications and comorbidities

- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

Disease modifying treatment

- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

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

Cardiac Management of ATTR Cardiac Amyloidosis

Aortic Stenosis

- Severe AS confers worse prognosis.
- Concomitant ATTRwt risk factor for periprocedural AV block.
- TAVR improves outcome in amyloid-AS.

Thromboembolism

- High risk, common.
- Anticoagulate if AF, consider in selected cases in SR.
- Anticoagulate independent of CHADS-VASC score.

Conduction disorders

- PPM according to standard indications.
- Consider CRT if high paced burden expected.

Heart failure

- Control fluid.
- Diuretics.
- [redacted]
- LVAD not suitable for most patients.
- Heart transplant for selected cases.

Atrial Fibrillation

- Amiodarone, preferred AA.
- Use digoxin cautiously.
- Electrical CV has significant risk of complications and AF recurrence is frequent.
- Exclude thrombi before electrical CV.
- AF ablation data scarce and controversial.

Ventricular arrhythmias

- ICD for secondary prevention.
- ICD in primary prevention usually not recommended.
- Transvenous ICD preferred over subcutaneous ICD.

Garcia-Pavia P and al, EHJ 2021

Cardiac Treatment of CA = CHAD-S-TOP!

CHADS-TOP
Conduction
High Heart Rate
Anticoagulation
Diuretic
S-TOP BB….

- C: Prevent conduction disorders/rhythm : **PM/ ICD / CRT**?
- H: Maintenance of **HIGH HEART RATE…even** if PM needed
- A: Prevent cardiac embolism (PE/Stroke…) : ANTICOAGULATION
- D: **DIURETIC :** adapt the dose to volemia.
- **S-TOP:** betablocker, ivabradine, calcium blocker…(+/-ACE).Digoxin: dangerous?

Ternacle J et al, JACC 2019

Heart Failure and CA

Réseau Amylose

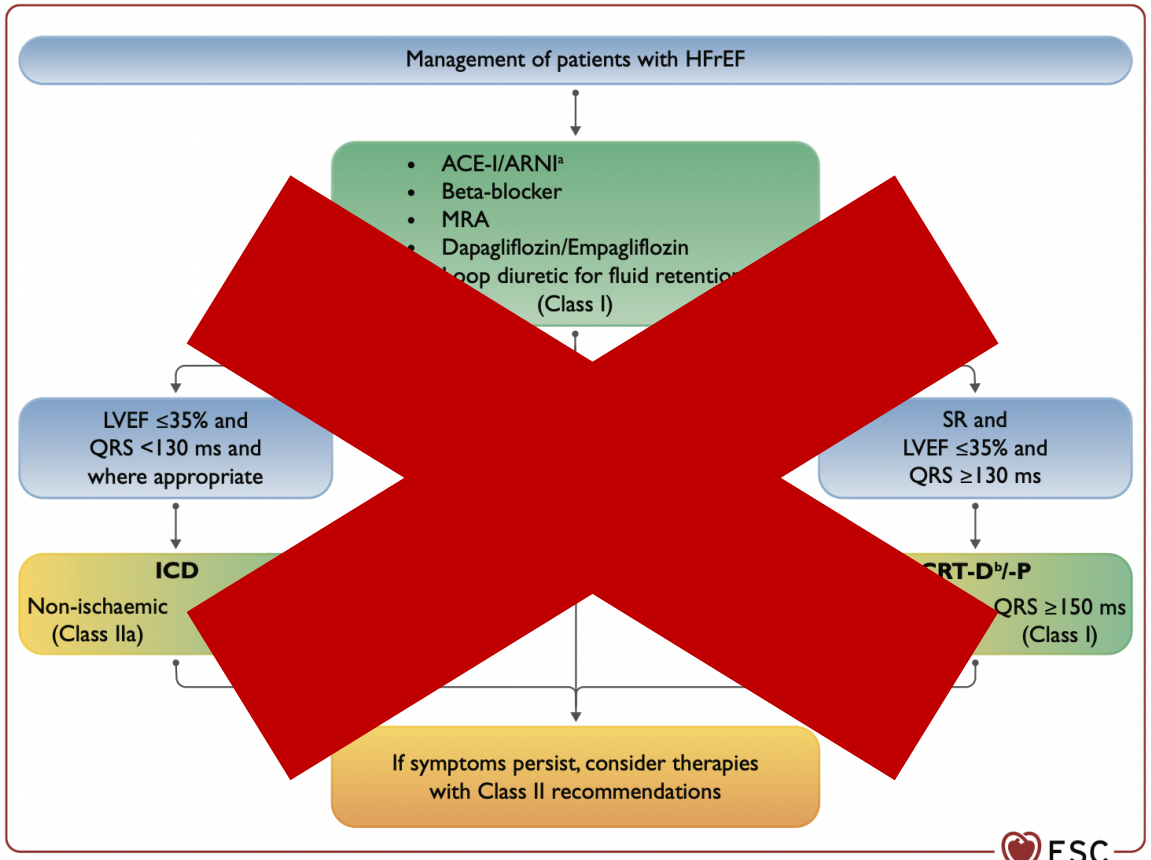
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

DO NOT USED IN CARDIAC AMYLOIDOSIS



↘HeartRate x SV (CA ↘)
= ↘ Cardiac-Output

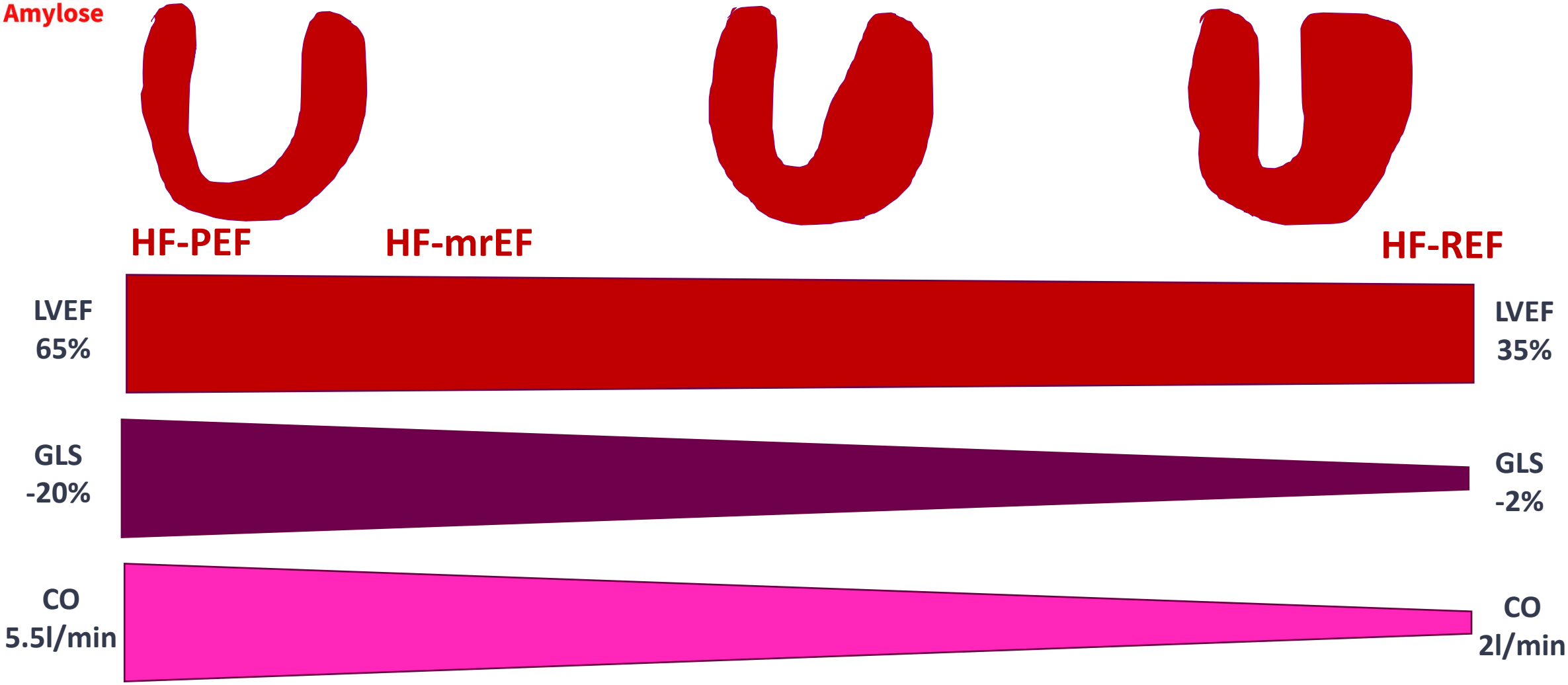
Do not apply ESC HF Guidelines

AND WORSE in LVEF <35%

maladies rares

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

Cardiac amyloidosis: natural history and systolic function

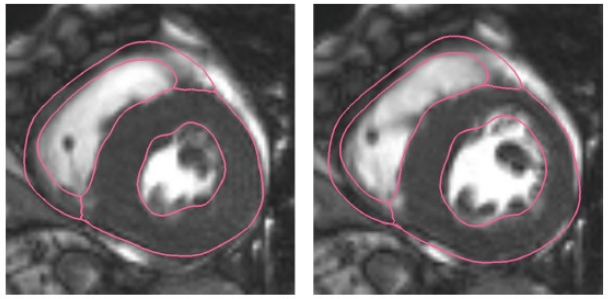


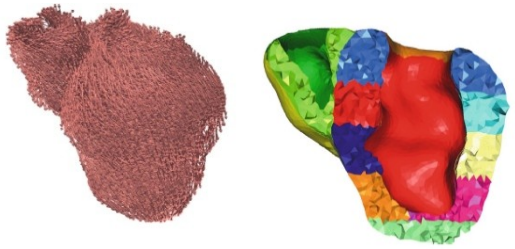
Patient – Specific Biomechanical Modeling of Cardiac Amyloidosis, A case Study

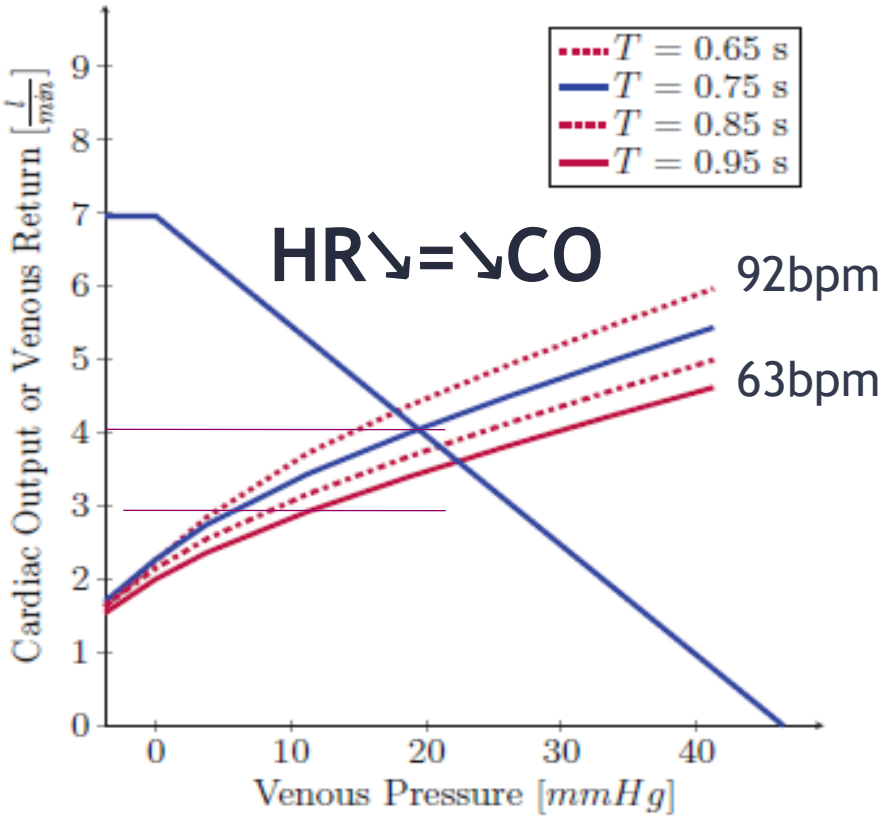
D. Chapelle, A. Felder, R; Chabiniok, A. Guellich, J-F Deux and T. Damy

- Low Stroke Volume
- No preload reserve
- HR dependency

CardiacOutput = HeartRate x SV

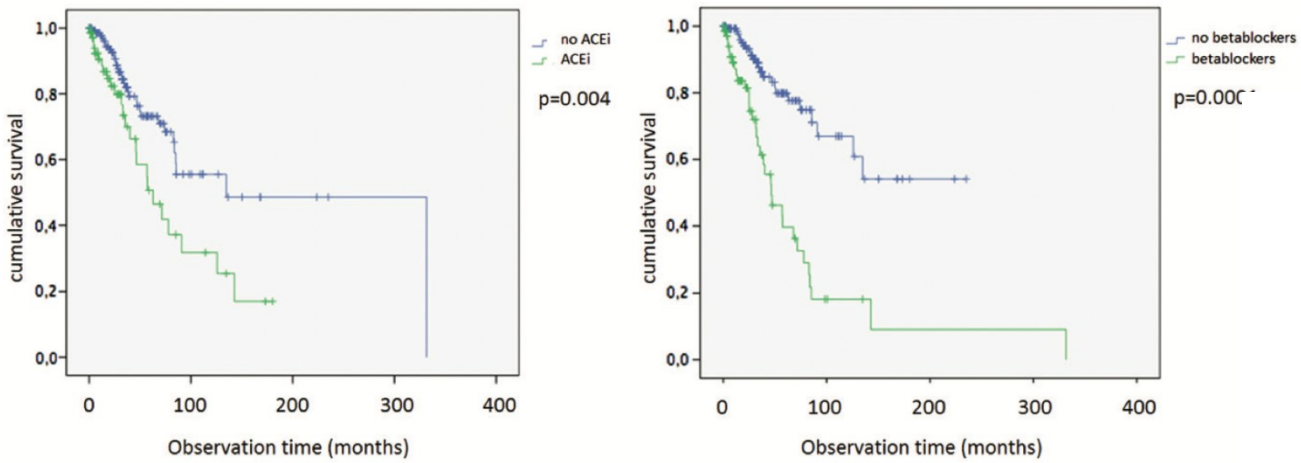




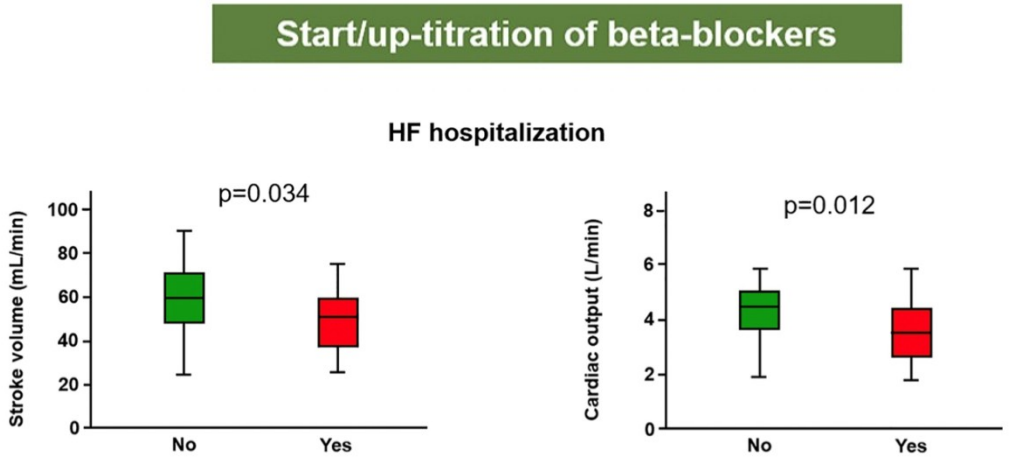


- Chapelle et al FIMH 2015

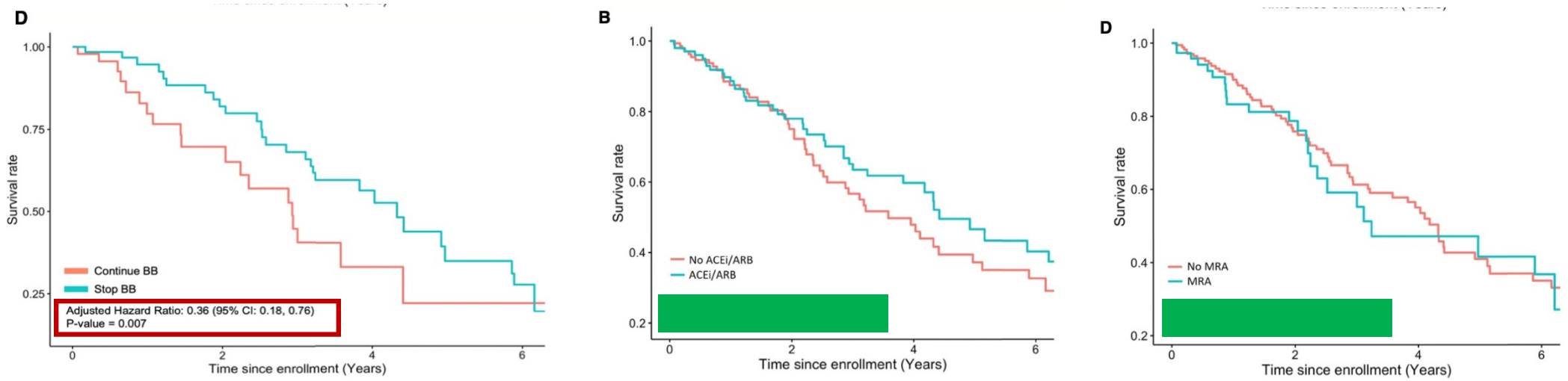
Betablocker as HF therapies and CA



Aus dem Siepen et al, Amyloid 2017



Aimo et al, Eur J of Int Medicine 2020



Cheng et al., JAHA 2021

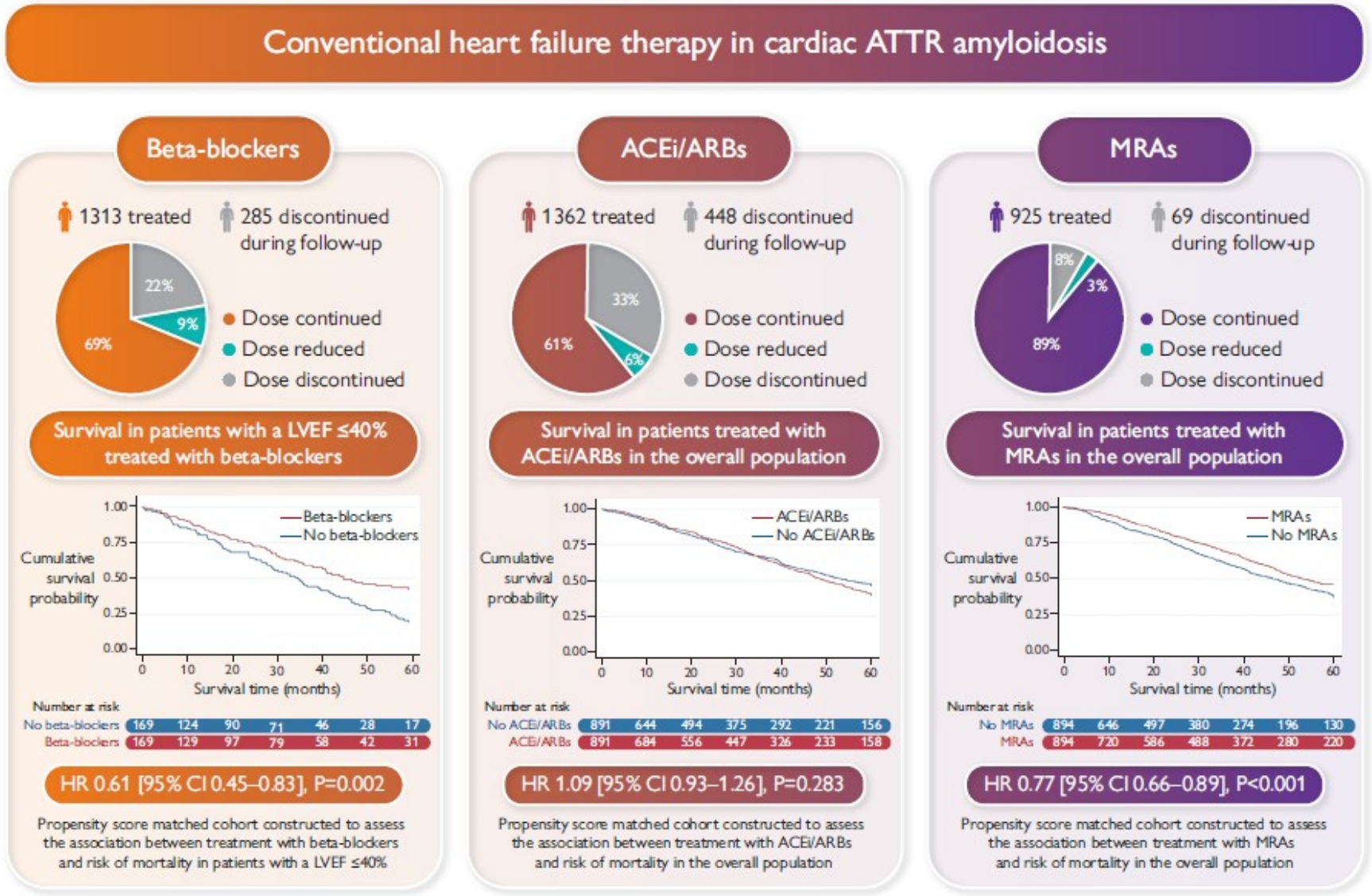
maladies rares

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

Beta-blocker?

- Restrospective
- Betablockers stopped or reduced in 31%
- Difficult to conclude…
- with bisoprolol ≤2.5 mg per day in *61.9%*

Conventional heart failure therapy in cardiac ATTR amyloidosis

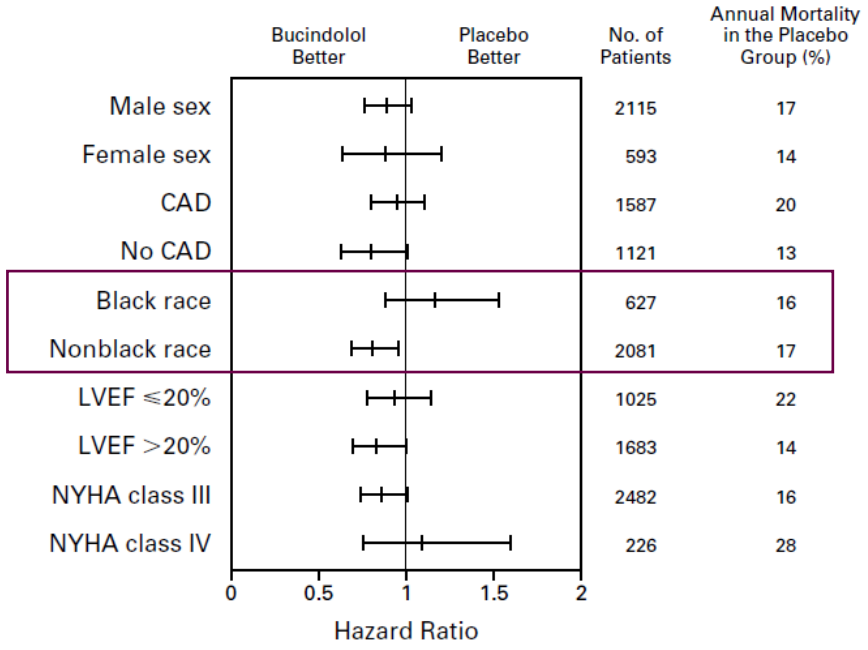


No convincing differences were found for treatment with ACEi/ARBs.

Ionnaou A, EHJ 2023

Betablocker and Cardiac Amyloidosis : Foe or Friend?
Etude BEST avec le Bucindolol dans LVEF<35%

A TRIAL OF THE BETA-BLOCKER BUCINDOLOL IN PATIENTS WITH ADVANCED CHRONIC HEART FAILURE



Transthyretin V122I in African Americans With Congestive Heart Failure

Table 1. Prevalence of the Amyloidogenic Transthyretin V122I Allele in Individuals Without Clinically Apparent Amyloidosis

Sample	Number	Age (yrs)	Prevalence (%)	Allele Frequency
Caucasian (convenience) (2)	86	Not noted	<1.2 (0/86)	<0.006
Caucasian (3)	453	Newborn	0.4 (2/453)	0.002
African American*	1,219	Newborn	3.3 (40/1219)	0.016
African American (3)	1,000	Newborn	3.0 (30/1000)	0.015
African American (CHS)*	802	Community >65	2.12 (17/802)	0.011
BEST: NYHA class III and IV heart failure*	207	19–93	6.3 (13/207)	0.032
Under age 60 yrs	116	<60	3.5 (4/116)	0.018
Age 60 yrs or over	91	>60	10 (9/91)	0.05

There is no longer any doubt that beta-blockers have a role in the treatment of mild-to-moderate (NYHA class II to III) chronic heart failure. as well as about the equivalency of beta-blockers. In doing so, it makes clear the need for studies that examine the mechanism of the heterogeneity of response to beta-blockers and for clinical trials that directly evaluate beta-blockers in blacks and in patients with NYHA class IV heart failure.

Etude négative du fait des sujets “noirs” probablement inclus avec amylose ATTRv et FEVG<35% = les plus graves!

Eichhorn EJ et al Engl J Med. 2001 May 31;344(22):

Y-a-t-il une place pour les bétabloquants dans les amyloses cardiaque?

Bétabloquants et amyloses cardiaques	
Qui prescrit?	Décision de centres experts
A quelle dose?	A doses minimes+++ / Sous surveillances
Les indications possibles	**Les "contres-indications" ou non justification**
Cardiopathie ischémique symptomatique	D'autant plus que la FEVG est basse!!! (FEVG<50%) Surtout pas dans les FEVG <35%
FA rapide non ralentie par la cordarone ET symptomatique : FC>120/bpm	FC<70bpm(?)
Obstruction intraVG symptomatique	Trouble conductif
FEVG altérée SI et SEULEMENT la cause de l'altération de la FEVG n'est pas l'amylose	La pose d'un PM… effet I-

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees

the sacubitril–valsartan group had a higher incidence of hypotension and angioedema and a lower incidence of hyperkalemia. Among 12 prespecified subgroups, there was suggestion of heterogeneity with possible benefit with sacubitril–valsartan in patients with lower ejection fraction and in women.

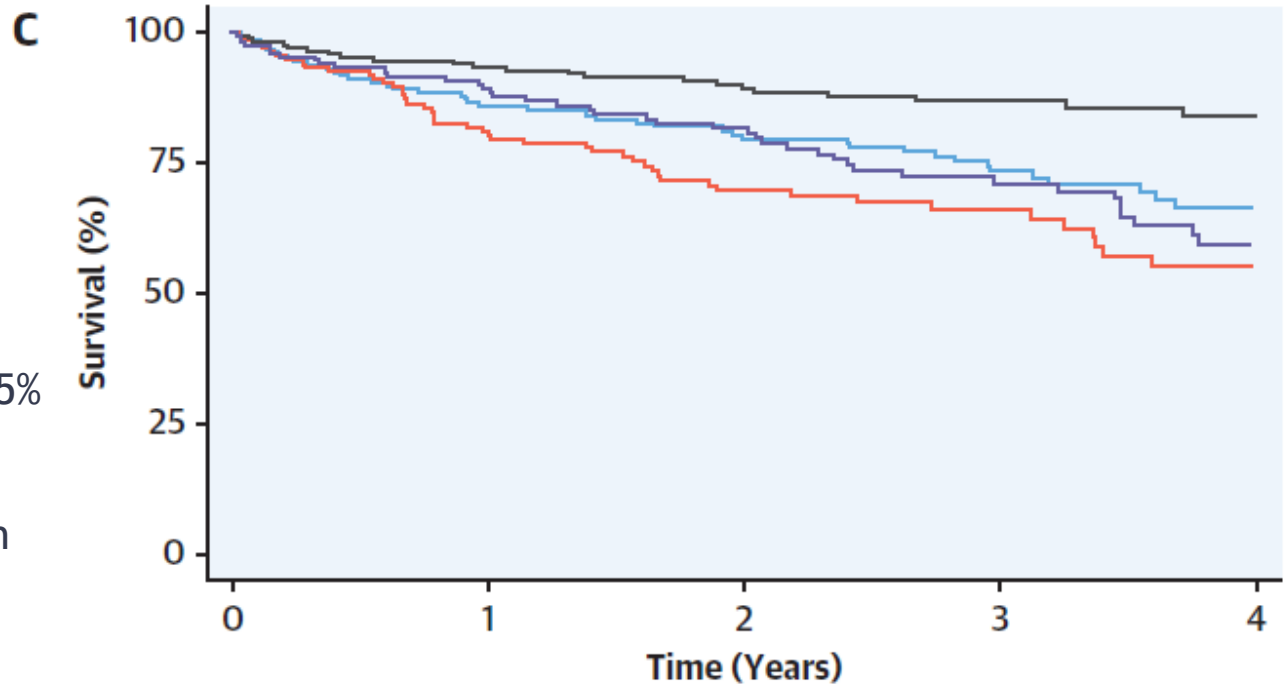
fraction. [illegible]er diseases, such as amyloid cardiomyopathy, may account for the reduced responsiveness with higher ejection fraction[illegible]. The pres-

Solomon SD, NEJM 2019

Spironolactone in Patients With an Echocardiographic HFpEF Phenotype Suggestive of Cardiac Amyloidosis

Results From TOPCAT

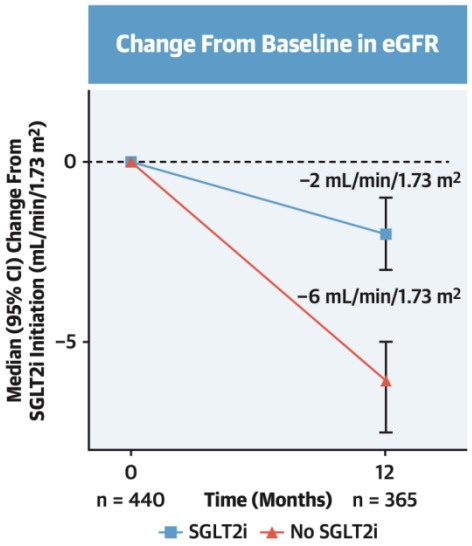
- Essai thérapeutique randomisée (Spiro versus Placebo
- Analyses Post-hoc
- Identification “potentielle” des amyloses en fonction de IVS≥12mm et S ≤6cm.sec : 25% des patients.
- Spironolactone associée à un meilleure pronostic.

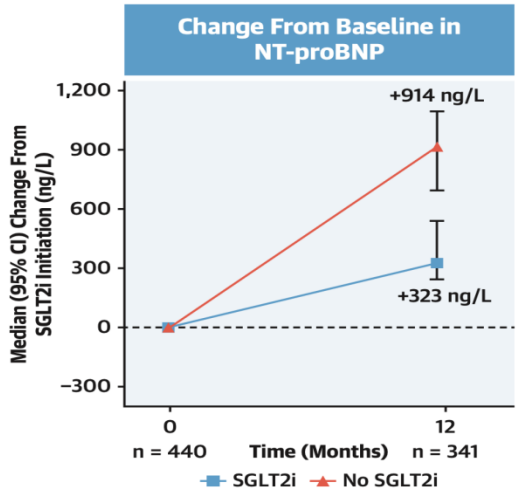


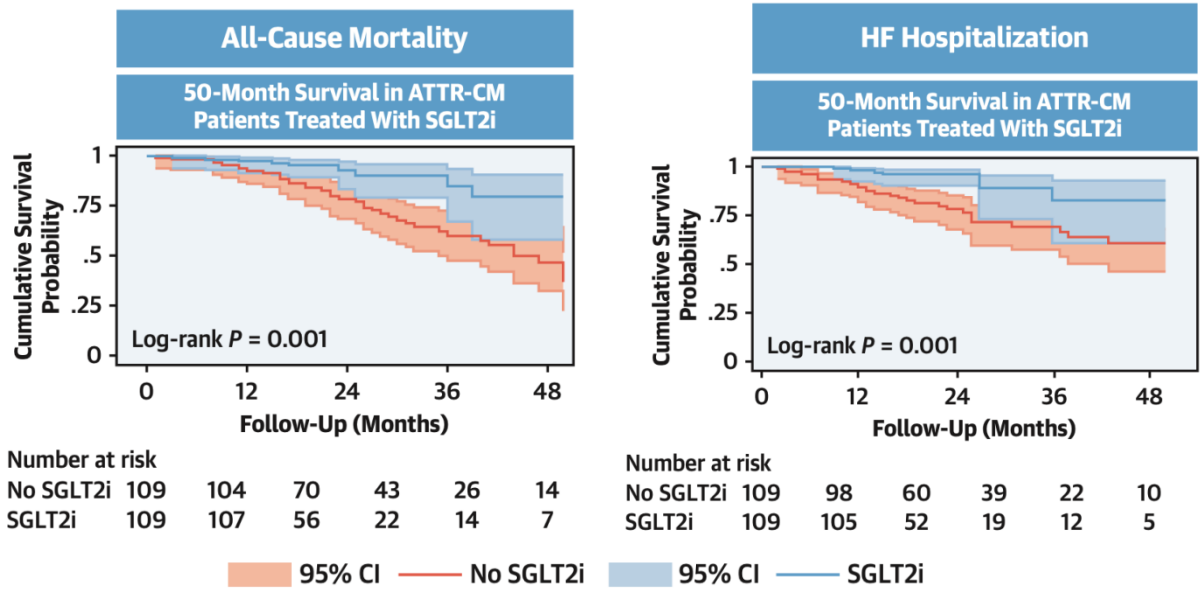
Number at risk					
s' velocity ≤6 cm/s, IVS <1.2 cm	157	131	104	69	37
s' velocity ≤6 cm/s, IVS ≥1.2 cm	135	105	70	41	19
s' velocity >6 cm/s, IVS <1.2 cm	165	152	121	77	42
s' velocity >6 cm/s, IVS ≥1.2 cm	133	113	84	53	27

Sperry, B.W. et al. J Am Coll Cardiol HF. 2021;9(11):795-802.

Heart failure and CA : SGLT2i







Safe treatment: 4.5% discontinuation rate over 28 months

- All-cause mortality
- Cardiovascular mortality
- HF hospitalization
- Cardiovascular mortality and HF hospitalization

- Slower decline in eGFR
- Attenuated rise in NT-proBNP
- Lower loop diuretic requirement
- Stable blood pressure profile

Porcari A, et al. J Am Coll Cardiol. 2024;83(24):2411-2422.

Porcari et al., JACC 2024

Heart failure and CA : diuretics

Diuretic Dose and NYHA Functional Class Are Independent Predictors of Mortality in Patients With Transthyretin Cardiac Amyloidosis

Richard K. Cheng, MD, MSc,[a] Wayne C. Levy, MD,[a] Alexi Vasbinder, RN,[b] Sergio Teruya, MD,[c] Jeffeny De Los Santos, MD,[c] Douglas Leedy, MD,[a] Mathew S. Maurer, MD[c]

- 309 patients, between 2002 and 2018
- Median follow-up = 1,92±1,8 years
- 33% deaths, 39% death or heart transplantation

After adjustment for age, sex, SBP, hereditary vs. WT, LVEF, eGFR, BNP or NTproBNP elevation, troponin I or T elevation and NYHA functional class

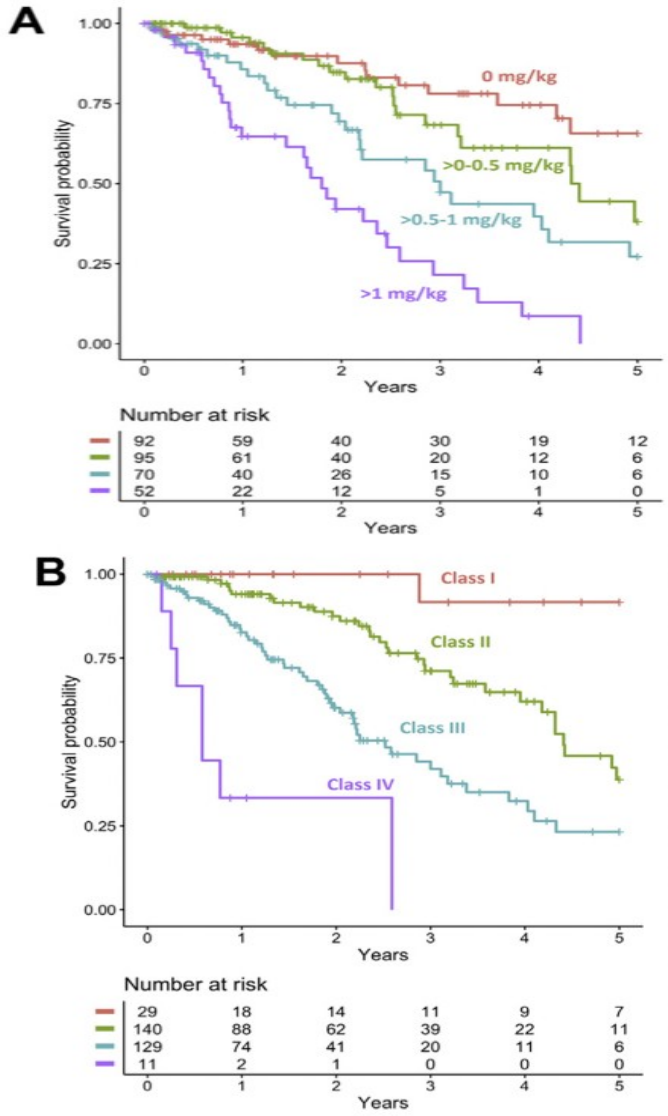
Cheng et al., JACC CardioOncol 2020

TABLE 2 Daily Diuretic Dose as Predictor of All-Cause Mortality and Mortality or Heart Transplantation

Model*	Hazard Ratio (95% CI) per 1 mg/kg Increase (Continuous Scale)	p Value
All-cause mortality		
Adjusted 1	1.80 (1.38-2.34)	<0.001
Adjusted 2	1.49 (1.11-2.01)	0.009
Mortality or heart transplantation		
Unadjusted	2.09 (1.72-2.54)	<0.001
Adjusted 1	1.73 (1.37-2.19)	<0.001
Adjusted 2	1.49 (1.15-1.93)	0.003
Adjusted 3	1.35 (1.03-1.77)	0.031

*Adjusted 1 = adjusted for age, sex, SBP, hereditary vs. wild type, LVEF; Adjusted 2 = adjusted for age, sex, SBP, hereditary vs. wild type, LVEF, and also adjusted for eGFR, BNP or NT-proBNP elevation, and troponin I or T elevation; Adjusted 3 = adjusted for age, sex, SBP, hereditary vs. wild type, LVEF, eGFR, BNP or NT-proBNP elevation, and troponin I or T elevation, and also adjusted for NYHA functional class.

CI = confidence interval; other abbreviations as in Table 1.



Anticoagulation et amylose cardiaque

8.2.1 L'anticoagulation

Le risque élevé continu d'événements thromboemboliques chez les patients atteints d'une amylose cardiaque justifie de discuter pour chaque patient des bénéfices (prévention de la thrombose) et des risques hémorragiques (atteinte cutanée importante ou gastrique) d'une anticoagulation à dose efficace. Il est nécessaire de demander un avis au centre expert le plus proche.

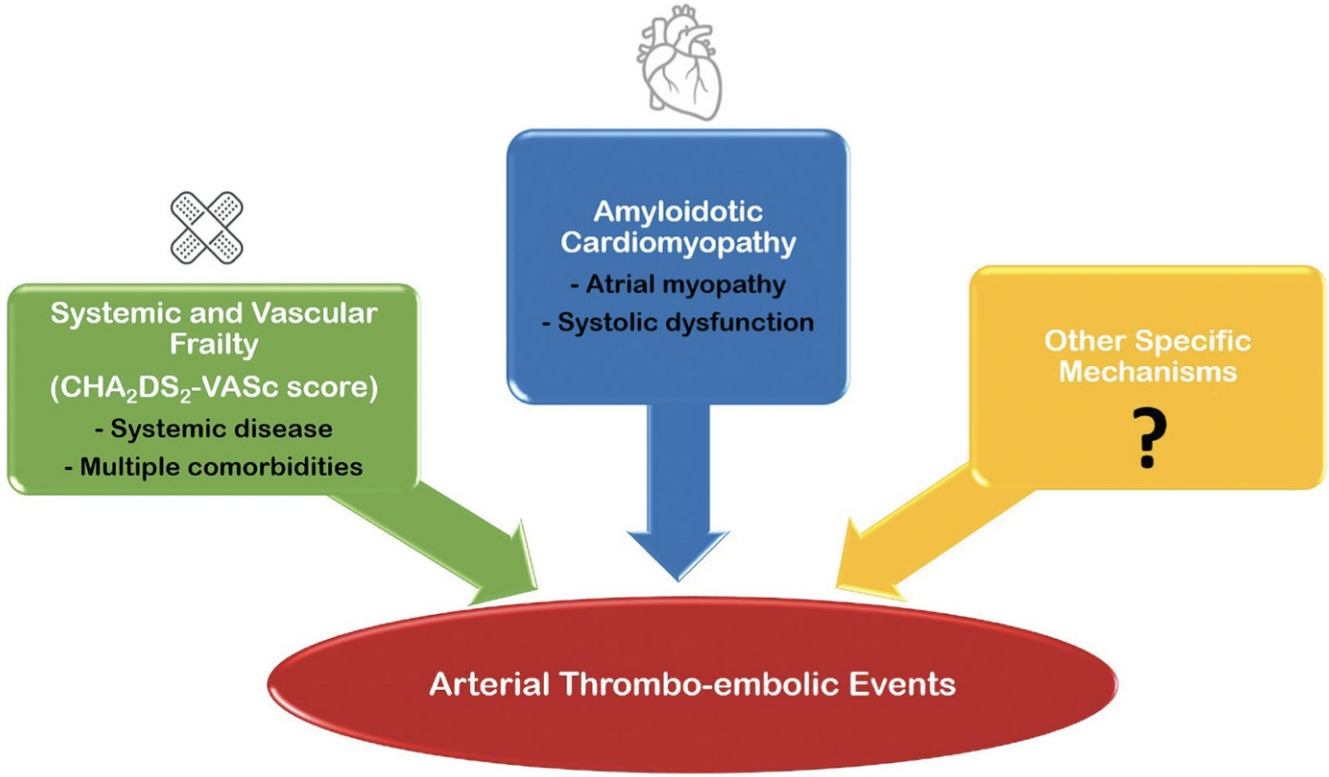
	Risques Thrombotiques	Risques Hémorragiquse
AL	-Profil transmitral restrictif -Onde E unique avec onde A absente sur le flux transmitral -Hyperexcitabilité atriale ou fibrillation atriale -Dysfonction VG	-Lésions cutanées ou muqueuses importantes -Déficit en facteur X
ATTRwt		
ATTRv		-Lésions digestives avec antécédents de saignement. -Mutation ATTR Val30Met p.(Val50Met) avec antécédent de greffe hépatique

Tableau 7 : Anomalies associées au risque thrombotique ouhémorragique dans les amyloses cardiaques

Anticoagulation and CA

Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation

Francesco Cappelli[a,b], Giacomo Tini[c,d], Domitilla Russo[e], Michele Emdin[f,g], Annamaria Del Franco[f,g], Giuseppe Vergaro[f,g], Gianluca Di Bella[h], Anna Mazzeo[h], Marco Canepa[c,d], Massimo Volpe[e,i], Federico Perfetto[a], Camillo Autore[e], Carlo Di Mario[b], Claudio Rapezzi[j,k] and Maria Beatrice Musumeci[e]



Cappelli et al, Amyloid 2020

AF and Electrical Cardioversion and amyloidosis

- Electrical Cardioversion: yes but significant risk of thrombus even on anticoagulant.
- Need to perform cardiac imaging (TEE/CT scan/MRI) before Electrical Cardioversion even if anticoagulant treatment is well conducted.
- High recidivism rate. Redo Electrical Cardioversion only if symptoms improved at the first Electrical Cardioversion.
-

French Referral Center for Cardiac Amyloidosis –opinion
HAS-PNDS Amyloses Cardiaques –Online "www.reseau-amylose.org"

Outcome of patients with cardiac amyloidosis admitted to an intensive care unit for acute heart failure

421 CA patients between 2009 and 2015

AL	WT-TTR	M-TTR
132 (31%)	94 (22%)	173 (41%)

Cardiac ICU: 46 CA patients admitted for AHF

AL	TTR
n=30, **65%**	n =16 ; **35%** 8 WT-TTR 8 hTTR

IN A CARDIOLOGIC ICU+++

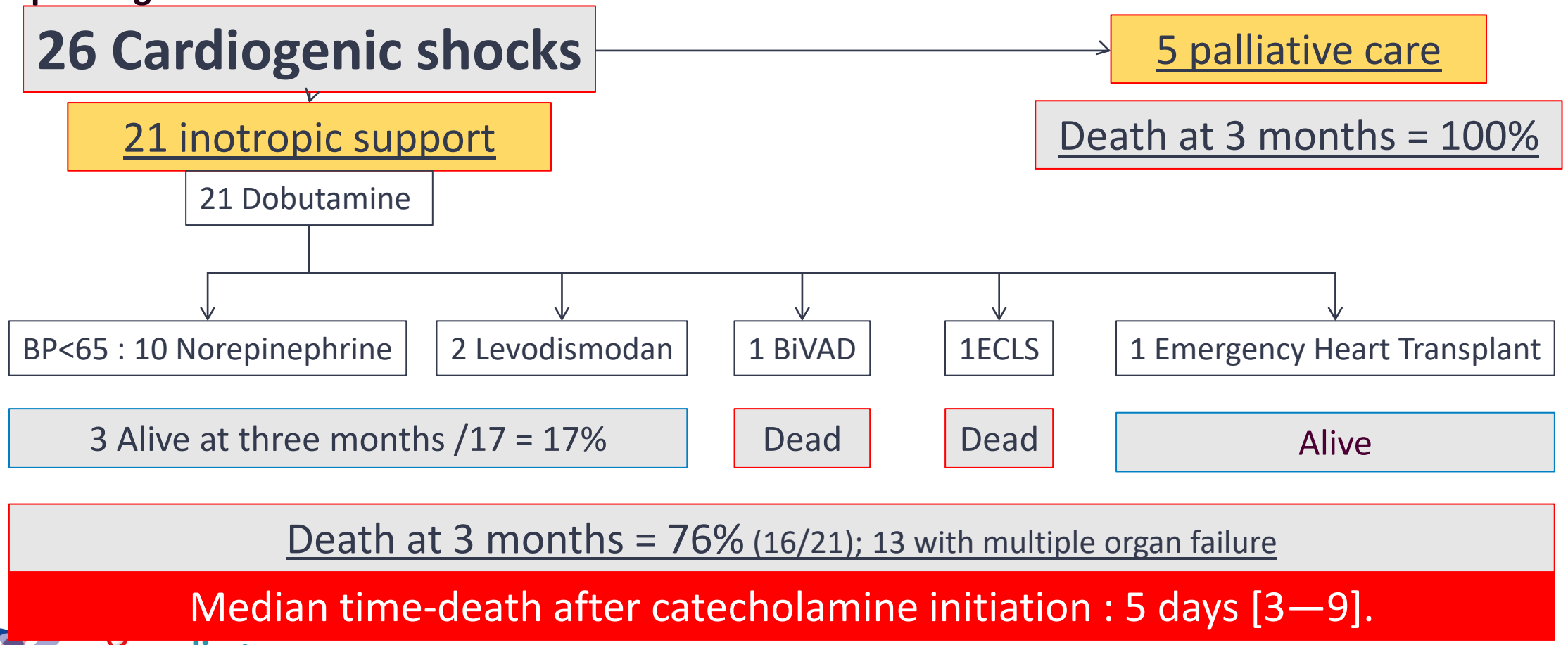
46 AHF

20 Severe AHF	26 Cardiogenic shock
Death <3month **n=3, 15%**	**Death <3month** **n= 21, 81%**

d'Humières et al. ACVD 2018

CS in CA : “Amyloid-Heart” team decision

- **Amyloid Heart Team : ICU+Cardiac Amyloid Experts+Surgeons+Hematologists+Anesthesiologists+ Nephrologists...**



d’Humières et al, ACVD 2018

Heart failure and CA : Heart transplantation

Outcomes in Patients With Cardiac Amyloidosis Undergoing Heart Transplantation

Christopher D. Barrett, MD,[a] Kevin M. Alexander, MD,[b] Hongyu Zhao, MD,[c] Francois Haddad, MD,[b] Paul Cheng, MD, PhD,[b] Ronglih Liao, PhD,[b] Matthew T. Wheeler, MD,[b] Michaela Liedtke, MD,[b] Stanley Schrier, MD,[b,*] Sally Arai, MD,[b] Dana Weisshaar, MD,[c] Ronald M. Witteles, MD[b]

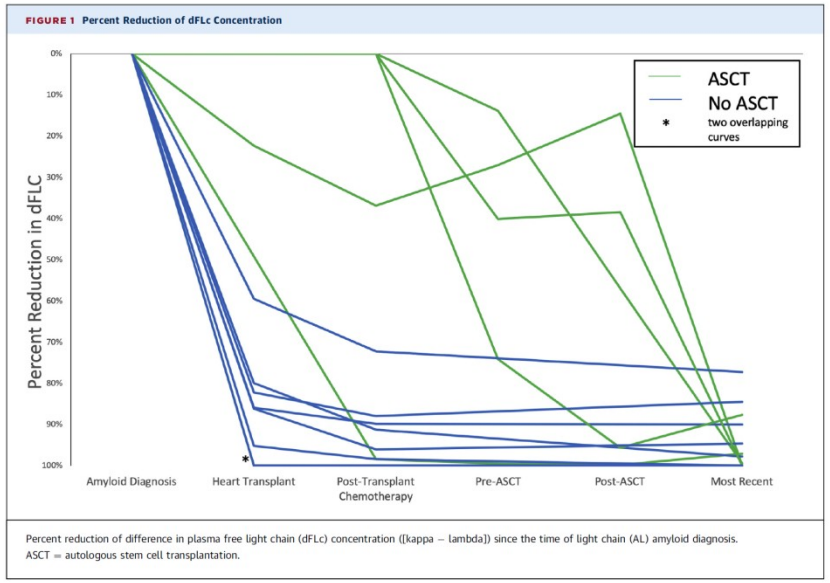
TABLE 1 Baseline Characteristics

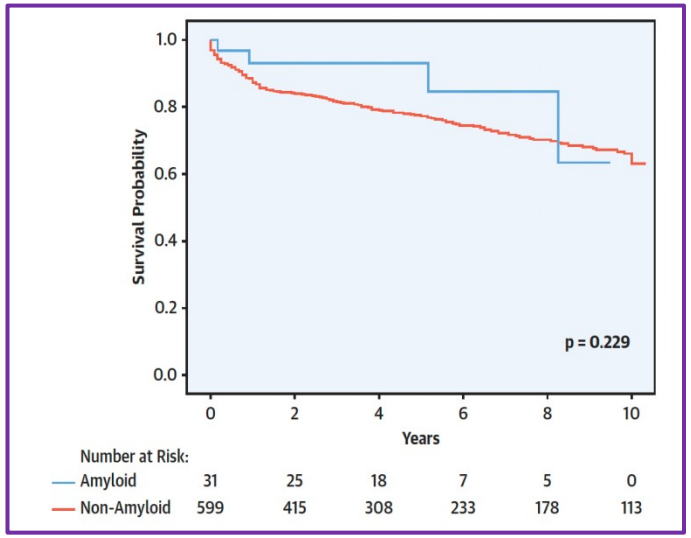
	All Amyloid Patients (N = 31)	AL (n = 13)	ATTR (n = 18)	p Value
Age at diagnosis (yrs)	61 (56–67)	56 (49–61)	66 (60–69)	<0.001
Age at transplant (yrs)	61 (57–67)	57 (49–61)	66 (61–70)	0.042
Male	22 (71)	6 (46)	16 (89)	0.017
Median pre-transplant labs				
Troponin I (ng/ml)	0.10 (0.04–0.20)	0.10 (0.05–2.00)	0.10 (0.02–0.20)	0.964
BNP (pg/ml)*	436 (254–757)	680 (366–1,205)	260 (182–453)	0.023
NT-proBNP (pg/ml)*	4,828 (3,223–7,530)	4,828 (4,300–10,349)	5,506 (2,158–8,399)	0.635
Creatinine (mg/dl)	1.3 (1.0–1.7)	0.9 (0.7–1.1)	1.6 (1.4–1.9)	<0.001
Alk phos (IU/l)	108 (78–157)	98 (75–129)	112 (77–161)	0.708
Albumin (g/dl)	3.7 (3.1–4.0)	3.7 (2.9–4.1)	3.7 (3.1–3.9)	0.953
Total bilirubin (mg/dl)	1.0 (0.8–1.2)	0.8 (0.7–1.1)	1.1 (0.9–1.3)	0.022
Days to transplantation	42 (19–108)	23 (16–41)	81 (24–144)	0.01

No significant difference in days to transplantation between CA and others cardiomyopathies (42 days)

Barrett et al., JACC HF 2020

- 31 patients with CA and HT (13 AL ; 18 ATTR) ; in case of AL : 2 Mayo II, 5 Mayo III, 6 Mayo IV
- 1 center in USA between 2004 and 2017





Complete response of dFLC was not necessary before heart transplantation

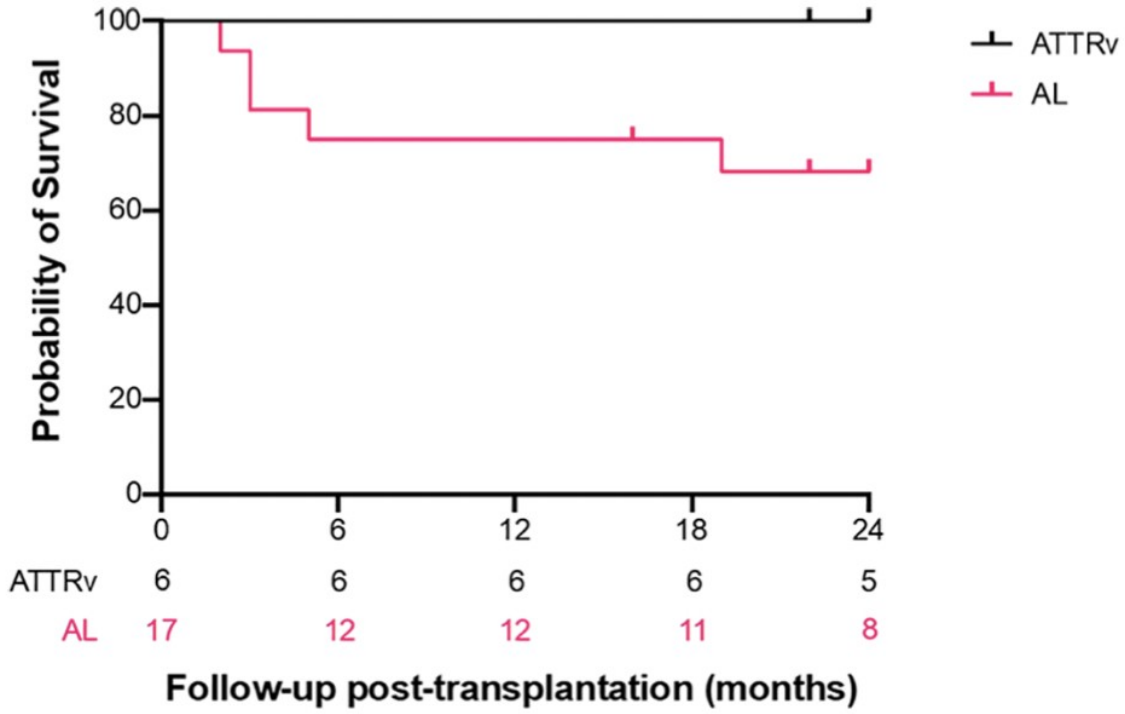
- **It's possible and it works +++**
- **2 words : BE FAST !**
- Don't wait chemotherapy response to start screening and prepare the patient…

Heart failure and CA : Our practise

Heart Transplantation, Either Alone or Combined With Liver and Kidney, a Viable Treatment Option for Selected Patients With Severe Cardiac Amyloidosis

Soulef Guendouz, MD,[1,2,3] Philippe Grimbert, MD, PhD,[4,5] Costin Radu, MD, PhD,[6] Daniel Cherqui, MD, PhD,[7] Chady Salloum, MD,[7] Nicolas Mongardon, MD, PhD,[5,8] Sami Maghrebi, MD,[8] Karim Belhadj, MD,[1,3,9] Fabien Le Bras, MD,[1,3,9] Emmanuel Teiger, MD, PhD,[2] Jean-Paul Couetil, MD, PhD,[6] Adriana Balan, MD,[6] Mounira Kharoubi, MSc,[1,2,3] Mélanie Bézard, MSc,[1,2,3] Silvia Oghina, MD,[1,2,3] Diane Bodez, MD, PhD,[10] Luc Hittinger, MD, PhD,[1,2,3] Vincent Audard, MD, PhD,[1,3,4,5] Violaine Planté-Bordeneuve, MD, PhD,[3,11] Alexandre De la Taille, MD, PhD,[12] Eric Bergoend, MD,[6] Valerie Frenkel, MD, PhD,[1,3,13] Pascale Fanen, MD, PhD,[1,3,14] Vincent Leroy, MD, PhD,[15] Christophe Duvoux, MD, PhD,[15] Maryvonnick Carmagnat, PharmD,[16] Thierry Folliguet, MD, PhD,[6] and Thibaud Damy, MD, PhD[1,2,3]

- 23 with CA and HT : 17 AL and 6 ATTRv
- 1 center at Henri Mondor (Creteil) between 2005 and 2018
- 57% male ; age at HT 60 years
- 14 heart only (12 AL ; 1 ATTRv) ; 5 heart and kidney (5 AL) ; 5 heart and liver (5 ATTRv)



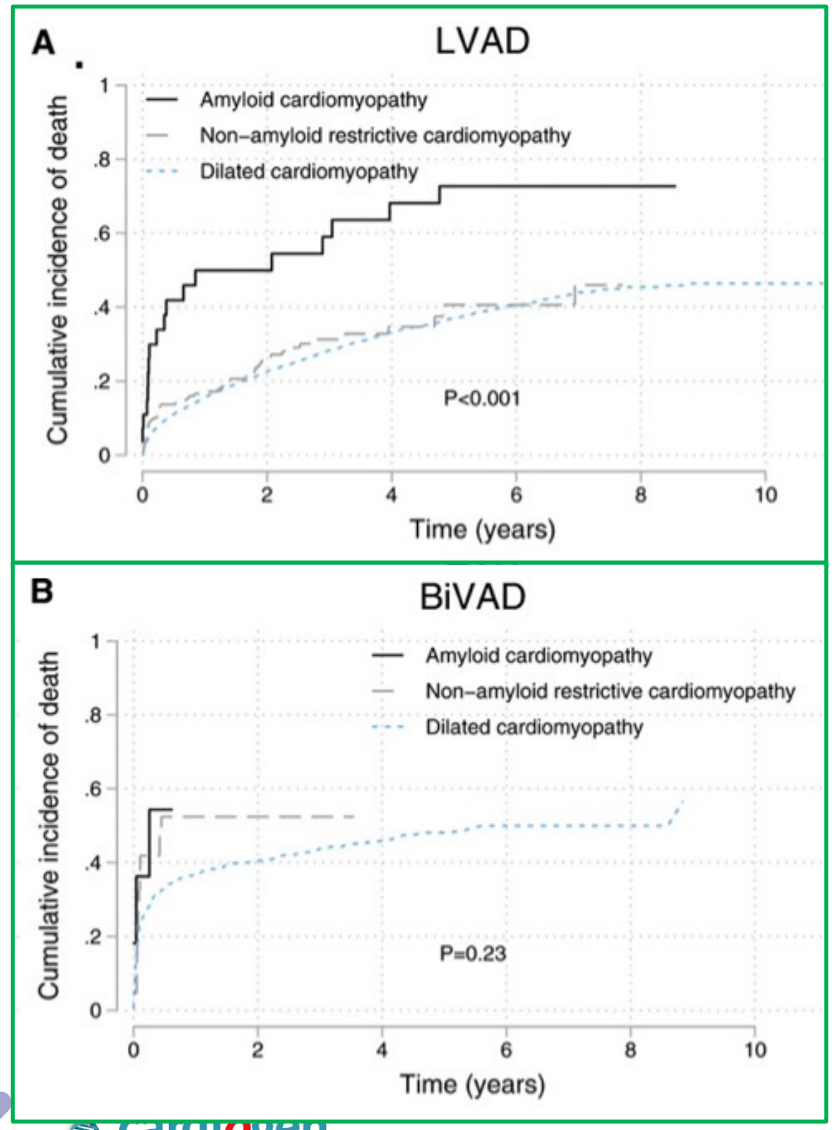
Guendouz S et al., Transplant Direct 2022

Heart Transplantation and CA

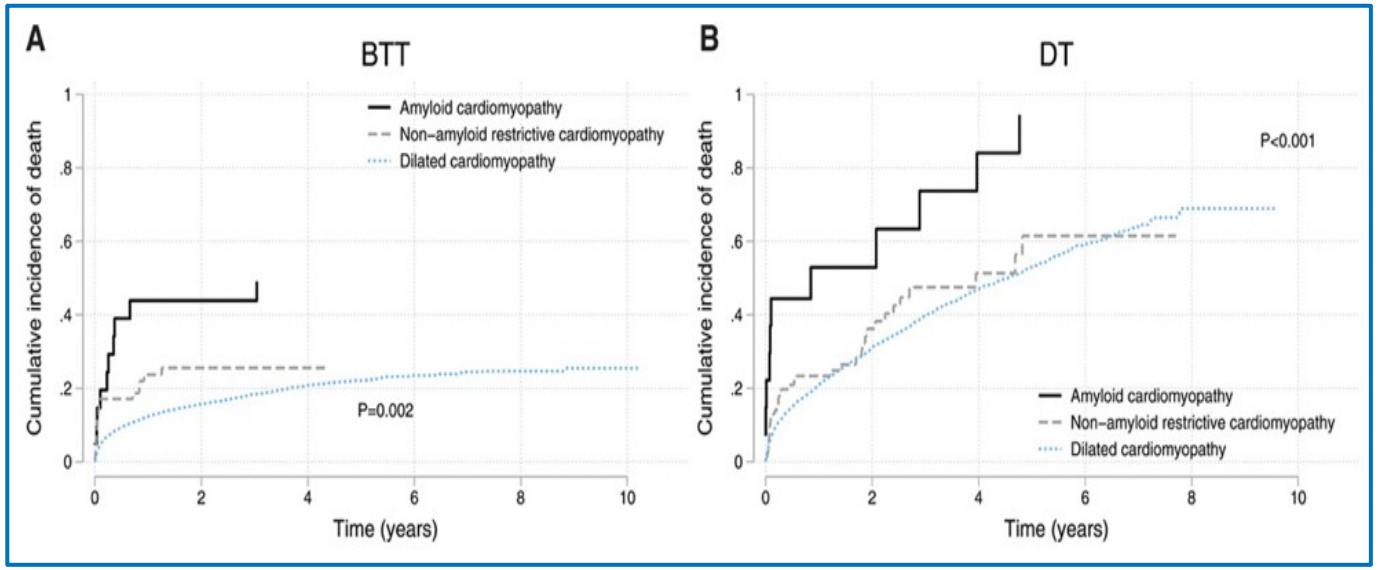
Ideal criteria	High risk not a good indication
< 65 yo	> 65 yo
Healthy / No comorbidity	Comorbidities / Denutrition
Amyloidosis with only cardiac involvement	Amyloidosis with cardiac involvement and Vascular dysautonomia+++ Nephrotic Syndrome Gastric –Intestinal Cutaneous « bullous »
Gammapathy isolated	Positive score CRAB/ bone infiltration - myeloma
Ambulatory HF	Cardiogenic shock (Intermacs 1,2,3)
Response to chemotherapy/immunotherapy if AL	No response to any AL-Treatment

French Referral Center for Cardiac Amyloidosis –opinion
HAS-PNDS Amyloses Cardiaques –Online "www.reseau-amylose.org"

Durable MCS and CA



- 19.921 DCM ; 248 RCM ; 46 ACM
- INTERMACS database, between 2005 and 2017



Michelis K et al, Circ Heart Fail 2020

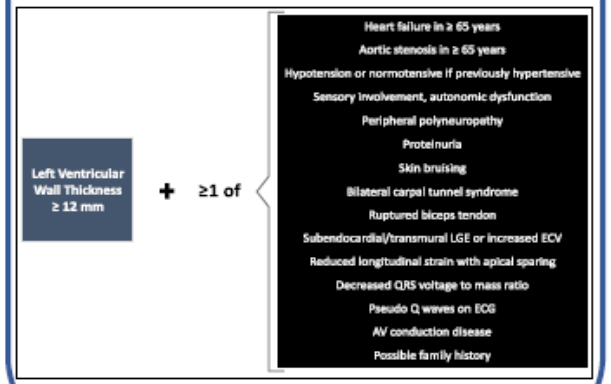
Cardiac amyloidosis

ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario



DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

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

Diagnosis made or proceed to **CMR and/or biopsy** according to results

TREATMENT

Cardiac complications and comorbidities

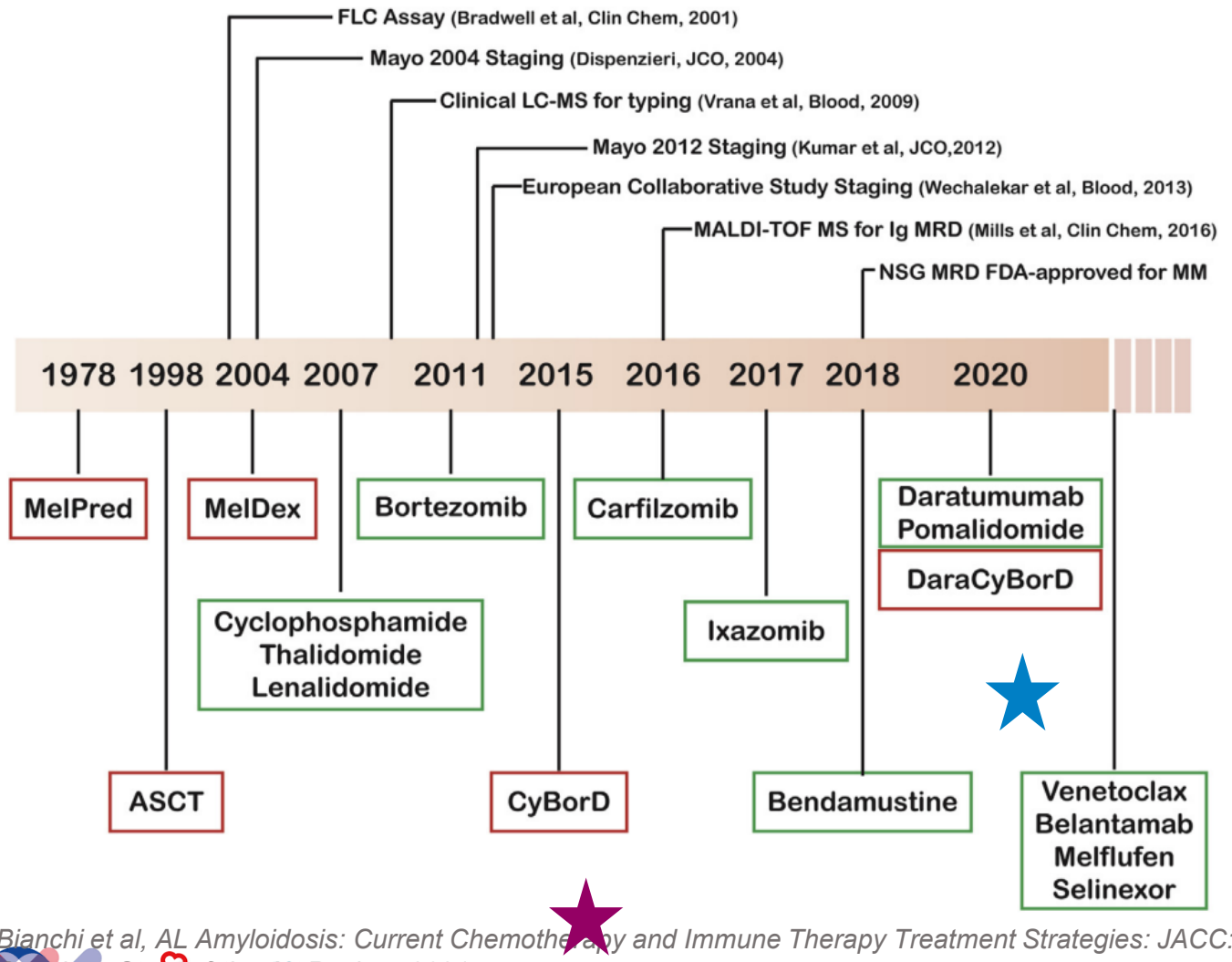
- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

Disease modifying treatment

- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

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

AL amyloidosis treatment: chemotherapy and immunotherapy



Giada Bianchi et al, AL Amyloidosis: Current Chemotherapy and Immune Therapy Treatment Strategies: JACC: CardioOncology State-of-the-Art Review, 2021

★ **« CyBorD »**

*Melphalan + **Cyclophosphamide***

Proteasome inhibitor: ***Bortezomid***

Dexaméthasone

Juin 2020

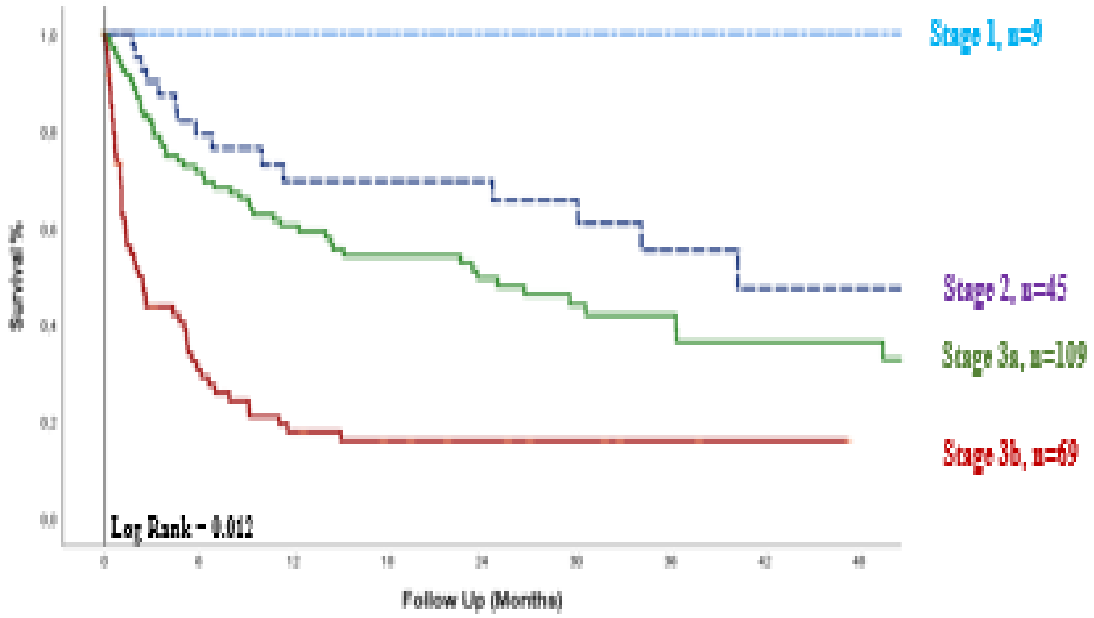
★ **DaraCyBorD ou « Andromeda »**

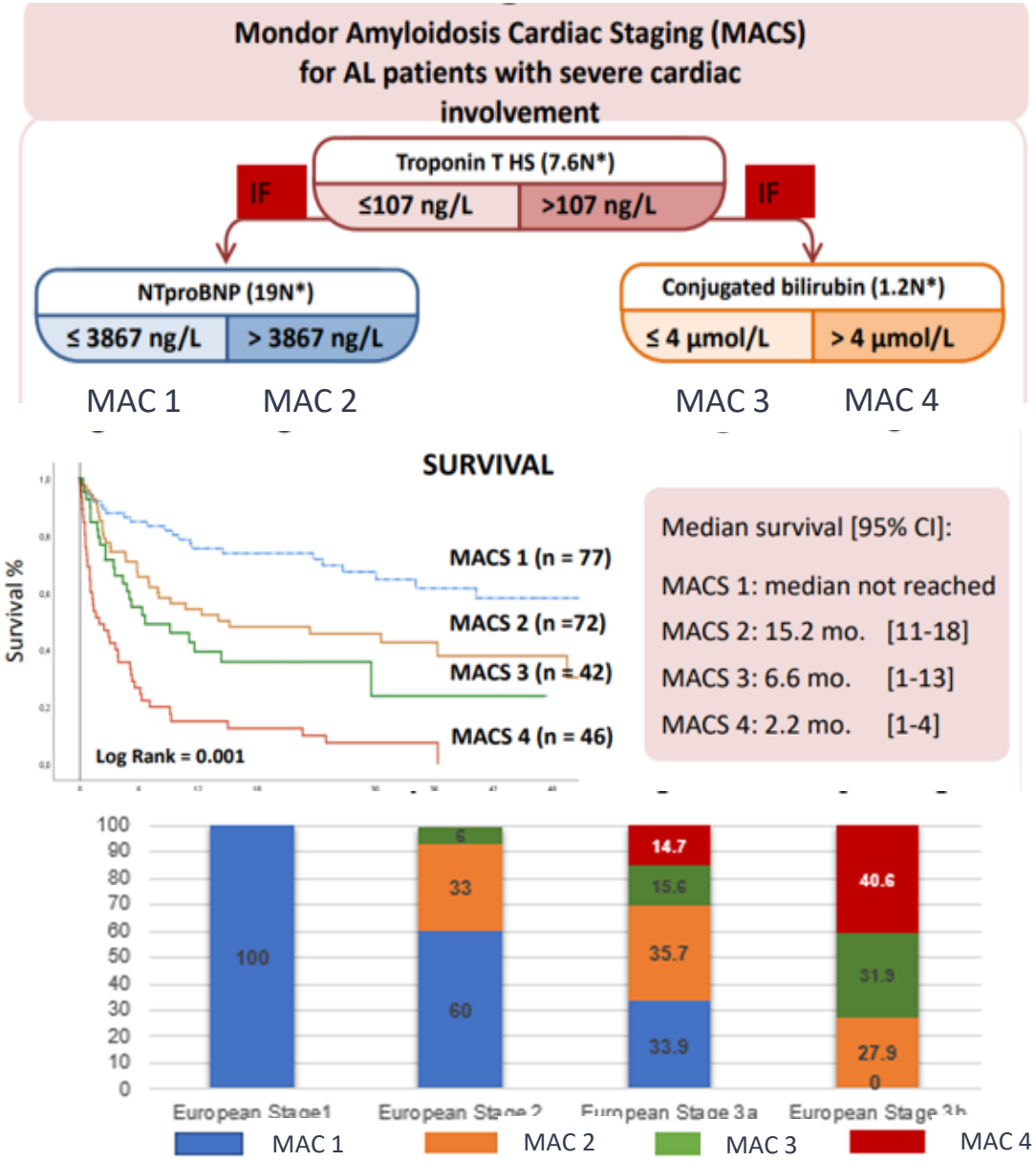
CyBorD : *Cyclophosphamide, Bortezomib, Dexaméthasone*

Monoclonnal anti body anti-CD 38 : **DARATUMUMAB**

Cardiac AL amyloidosis: Staging

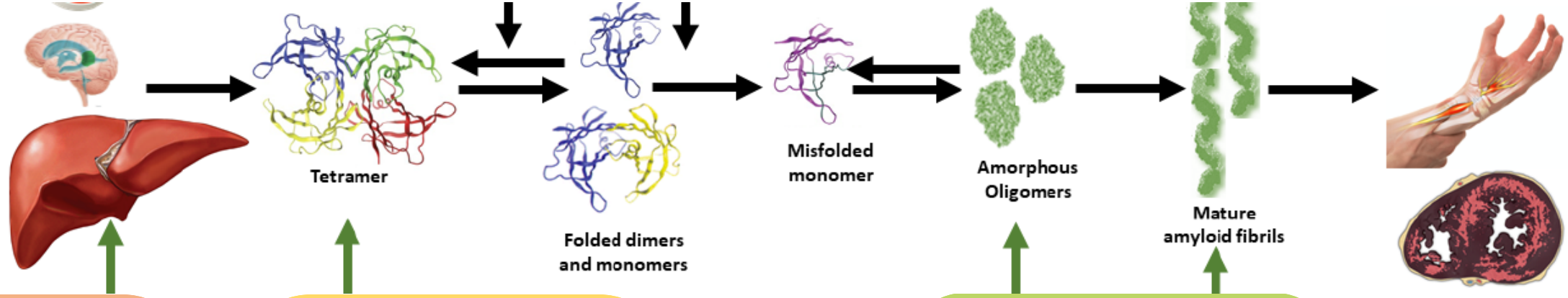
	Troponin T US ≥50 ng/l	NTproBNP ≥332 pg/ml
I	0	0
II	1 criteria	
IIIa	1	1
IIIb	1	NTproBNP≥ 8500 pg/ml





Zaroui et al ESC-HF 2024

ATTR Cardiac Amyloidosis Treatments : A new area in cardiology



Liver Transplantation

TTR Gene Silencing

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

-Crispr Cas 9

TTR Stabilizers

-Tafamidis,

-Acoramidis,

-Diflunisal

Antibodies to clear Amyloidosis Deposits

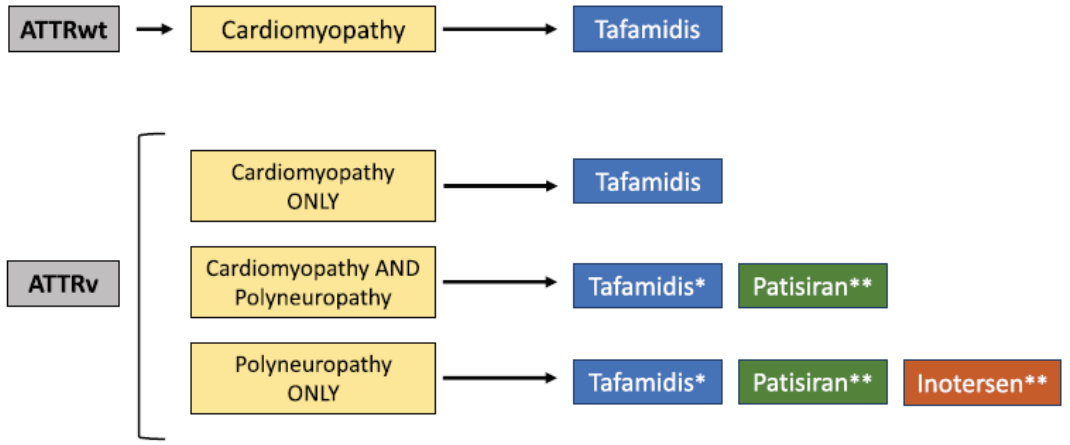
-NI006

-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

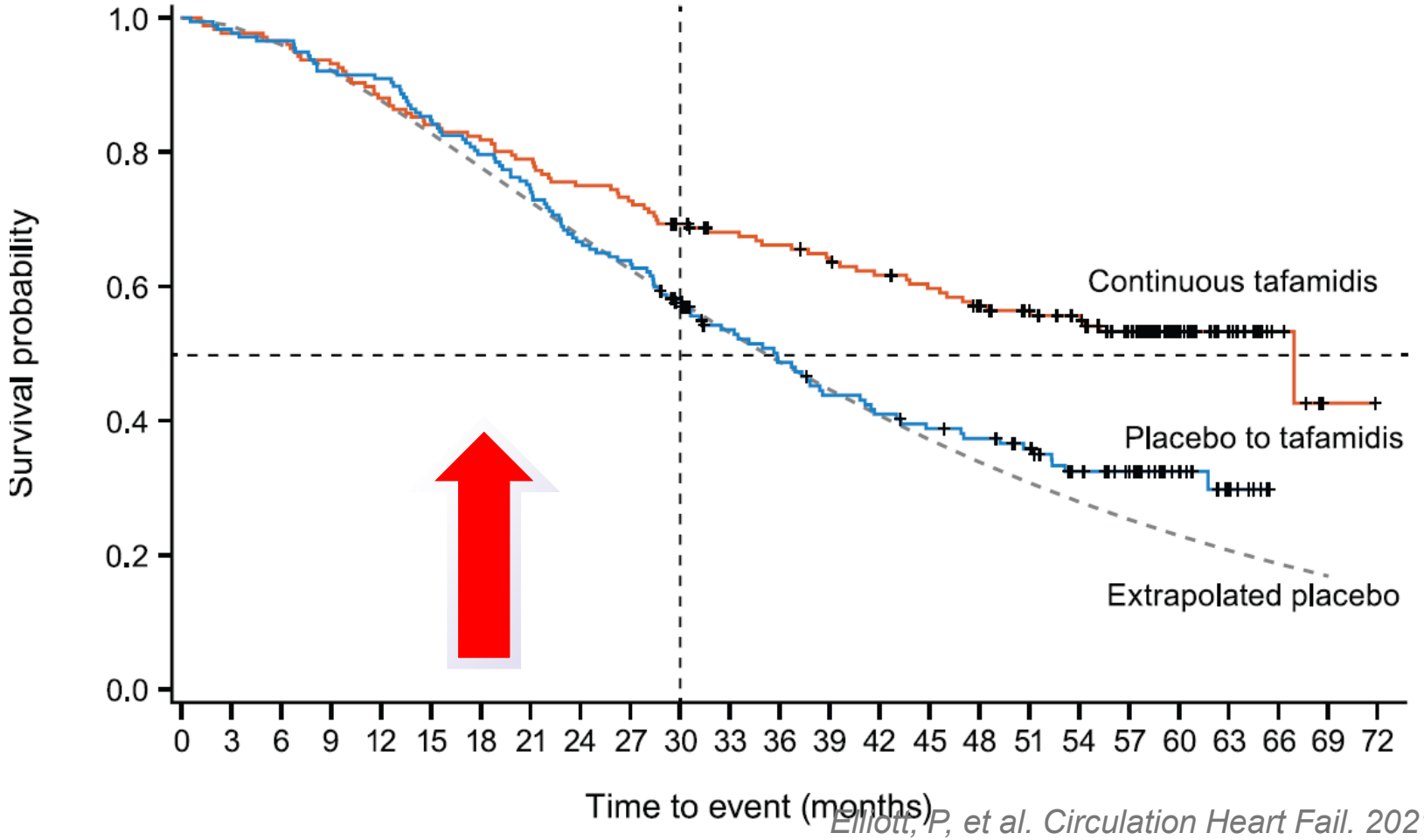
European Heart Journal (2021) **00**, 1–15

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

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

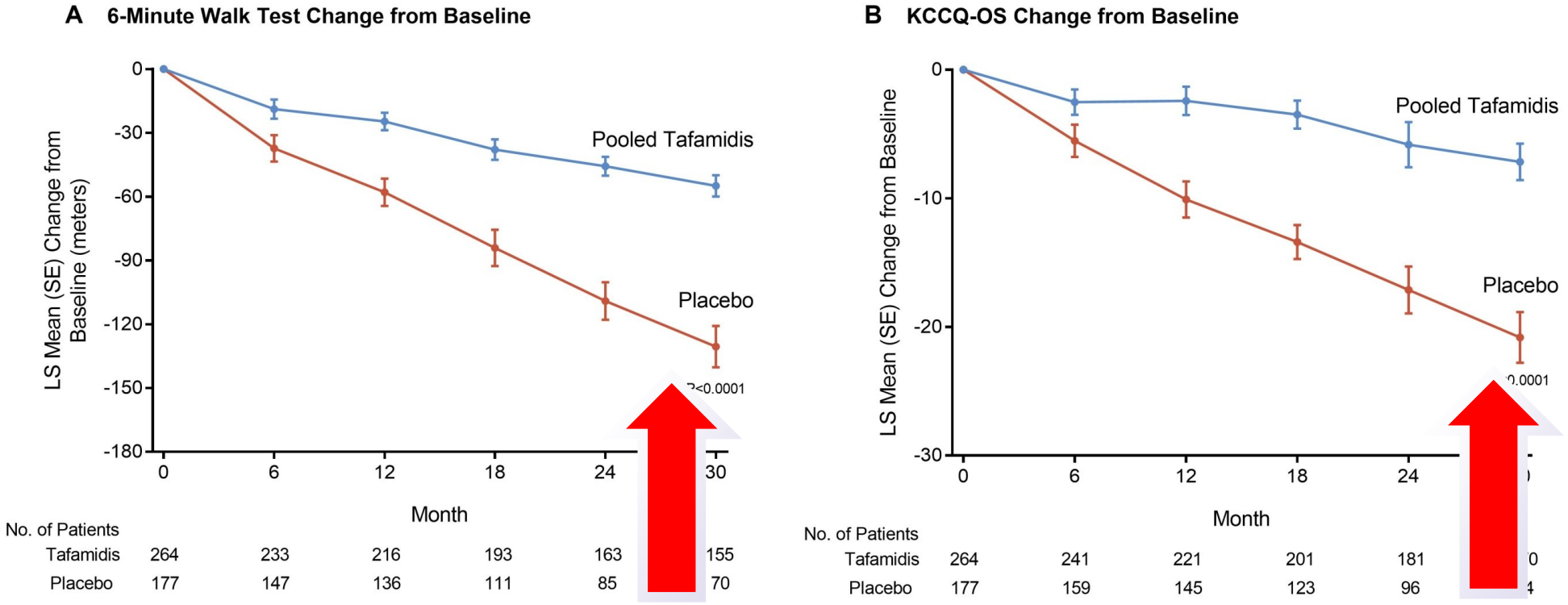
Perry Elliott, MD; Brian M. Drachman, MD; Stephen S. Gottlieb, MD; James E. Hoffman, MD; Scott L. Hummel, MD; Daniel J. Lenihan, MD; Ben Ebede, MS, MBA; Balarama Gundapaneni, MS; Benjamin Li, MS; Marla B. Sultan, MD, MBA; Sanjiv J. Shah, MD

- 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

Tafamidis reduces the decline in the 6MWT distance and KCCQ-OS score at 30 months



Tafamidis vs Placebo	At 12months	At 30 months
NTproBNP **Least-square mean difference**	−735.14 [95% CI, −1249.16 to −221.13]	−2180.54 [95% CI, −3326.14 to −1034.95]

Maurer M et al , New England Journal of Medicine 2018

Comparative change of NTproBNP and HS-cTnT before and after Tafamidis

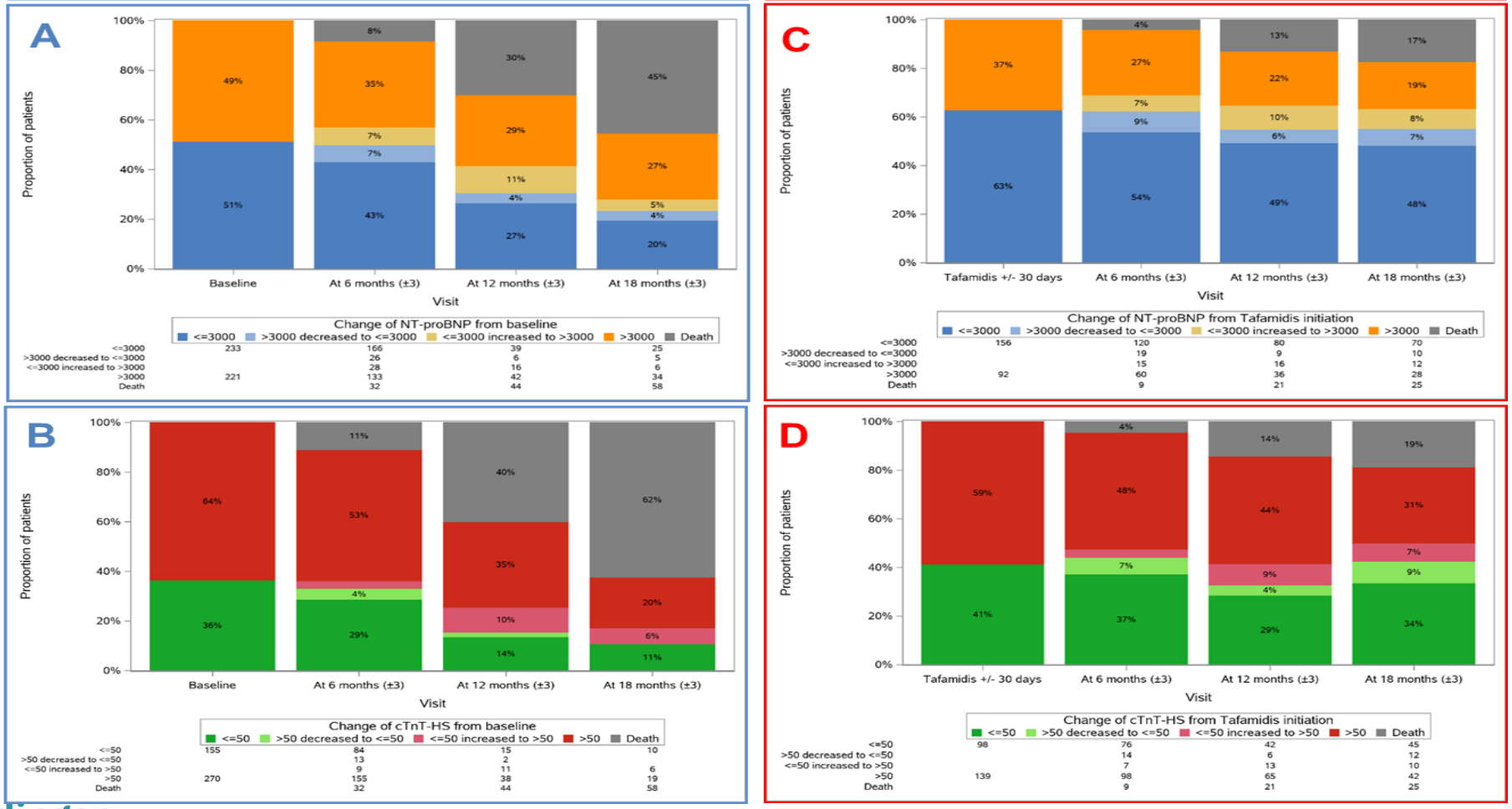
Réseau Amylose

Cohort A, Before Tafamidis

Cohort B, Under Tafamidis

NT-proBNP

cTnT-HS



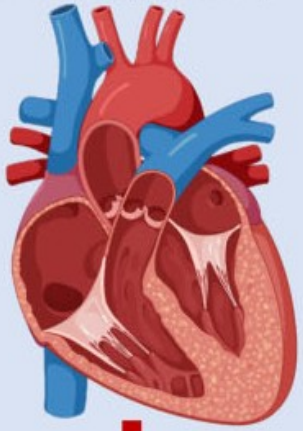
maladies rares

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

Oghina S et al, JCM 2021

Effect of tafamidis on global longitudinal strain and myocardial work in transthyretin cardiac amyloidosis

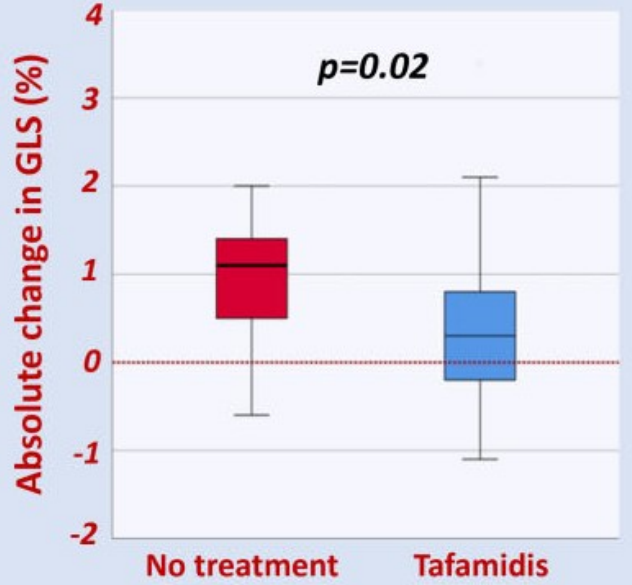
Transthyretin amyloid cardiomyopathy



23 patients treated with tafamidis

22 patients untreated

Speckle tracking echocardiography and myocardial work assessment at baseline and 1 year

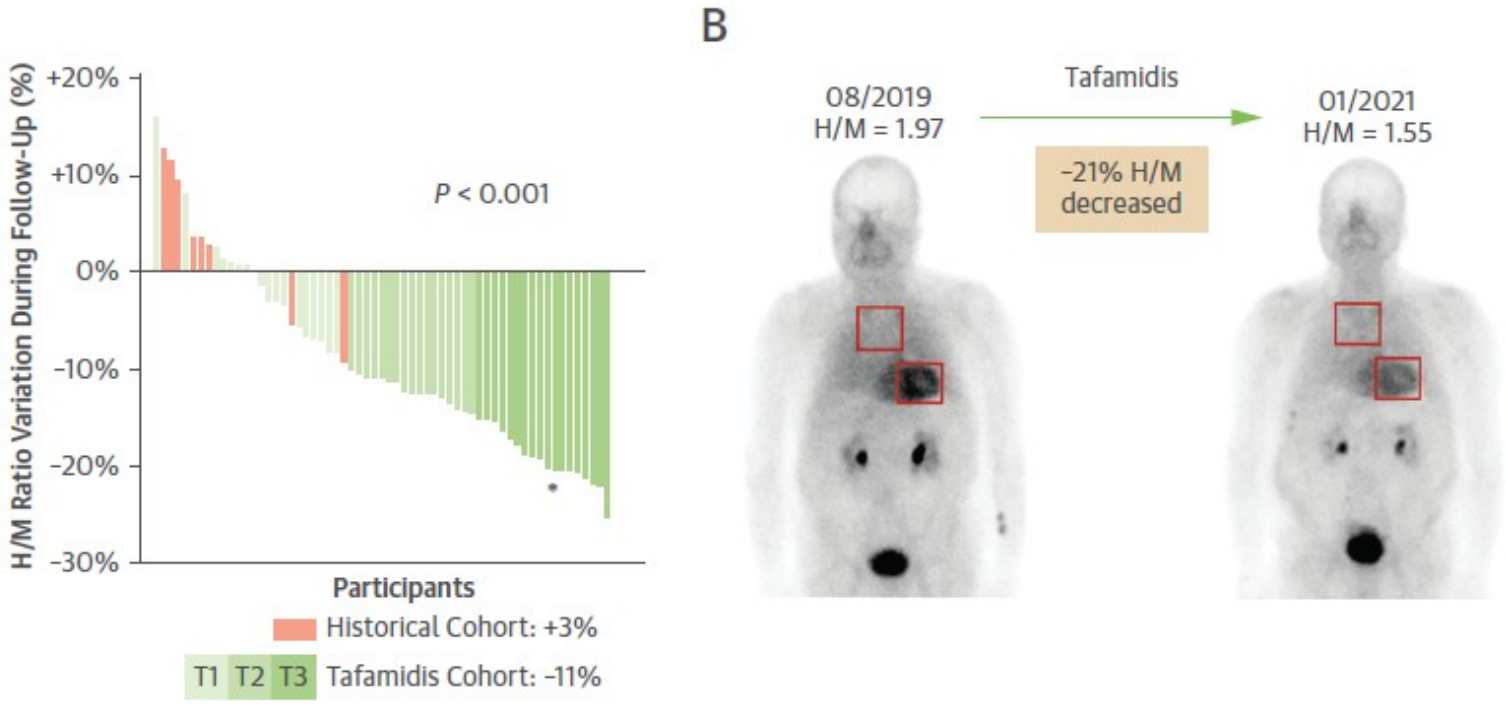


Lesser deterioration in GLS, myocardial work index and myocardial efficiency over 12 months in those treated with tafamidis

Giblin T and al European Heart Journal - Cardiovascular Imaging (2022) 23, 1029-1039

Tafamidis Decreases Cardiac Uptake of 99mTc-HMDP in ATTR Cardiac Amyloidosis

FIGURE 1 Decreased HMDP Cardiac Uptake With Tafamidis Treatment in Patients With ATTR-CM



(A) Progression of ^{99m}Tc-hydroxyl-methylenediphosphonate hydroxymethylene diphosphonate (HMDP) cardiac uptake in the historical and tafamidis cohort. Heart to mediastinum (H/M) ratio decreases in patient with transthyretin cardiac amyloidosis in the tafamidis cohort **(green)** and increases in the historical cohort **(red)**. **(B)** Two whole-body HMDP scans show reduced H/M ratio from patient (indicated with an asterisk **[*]**) following tafamidis treatment.

- Confirmed by :
- Monitoring tafamidis treatment with quantitative SPECT/CT in transthyretin amyloid cardiomyopathy
- *René Rettl et al*, Eur Heart J Cardiovasc Imaging .2023 Mar

- « ATTR-CM patients with a reduction greater than or equal to the median (n = 20) had a significant decrease in SUV retention index (P < 0.001) at follow-up, which translated into significant benefits in serum N-terminal prohormone of brain natriuretic peptide levels (P = 0.006), left atrial volume index (P = 0.038), as well as LV [LV global longitudinal strain: P = 0.028, LV ejection fraction (EF): P = 0.027, LV cardiac index (CI): P = 0.034] and right ventricular (RV) [RVEF: P = 0.025, RVCI: P = 0.048] functions compared with patients with a decrease less than the median (n = 20). »

Odouard S and al….Galat A, JACC CardioVasc Imaging 2022

maladies rares

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maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

ATTRibute-CM study design[1,2]

30-month primary endpoint[3]:
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD

Key eligibility criteria

- Subjects with diagnosed ATTR-CM (WT or variant)
- NYHA Class I-III
- ATTR-positive biopsy or 99mTc scan
- Light chain amyloidosis excluded if diagnosis by 99mTc

Screening and randomization

800 mg acoramidis HCl twice daily

N = 421

Placebo twice daily

N = 211

Efficacy assessment included 611 participants in the pre-specified mITT population (eGFR ≥30 mL/min/1.73 m²)

Tafamidis usage allowed after Month 12

800 mg acoramidis HCl twice daily

Open-label extension

6MWD = Six-minute walk distance; NYHA = New York Heart Association; 99mTc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD); mITT = Modified intent-to-treat. eGFR = Estimated glomerular filtration rate.

[1]ClinicalTrials.gov identifier: NCT03860935. [2]Gillmore JD et al. Circulation. 2019;140(1):14214. Oral poster presented at AHA. [3]Primary analysis assessed using the Finkelstein-Schoenfeld method.

Highly statistically significant result achieved on primary and selected secondary endpoints

Primary endpoint[1]	p-value
Hierarchical analysis consisting of: • All-cause mortality[2] • Cumulative frequency of CVH • Change from baseline in NT-proBNP • Change from baseline in 6MWD	p<0.0001
Win Ratio	1.8

58% of ties broken by first two components of Win Ratio analysis

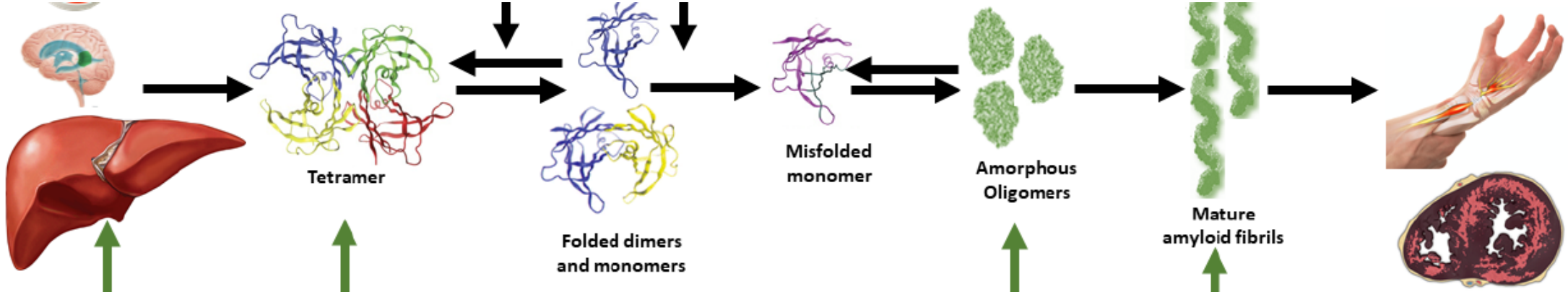
Select secondary endpoints	p-value
Cumulative frequency of CVH[3]	p<0.0001
Change from baseline in 6MWD[4]	p<0.0001
Change from baseline in KCCQ-OS[4]	p<0.0001
Change from baseline in serum TTR[4]	p<0.0001
Change from baseline in NT-proBNP[5]	p<0.0001
All-cause mortality[2,6]	p=0.057

NS on mortality

KCCQ-OS = Kansas City cardiomyopathy questionnaire overall summary score.

[1]Primary analysis assessed using the Finkelstein-Schoenfeld method. [2]Heart transplant and implantation of cardiac mechanical assistance device were treated as death for this analysis. [3]Negative binomial regression with treatment group, stratification factors and the offset term is used to analyze the cumulative frequency of adjudicated CV-related hospitalization.[4]Least squares mean difference change from baseline at 30 months. [5]Ratio of adjusted geometric mean fold change from baseline at 30 months. [6]Assessed by Cochran-Mantel-Haenszel test; p=0.15 as assessed by Cox Proportional Hazard Model.

ATTR Cardiac Amyloidosis Treatments : A new area in cardiology



Liver Transplantation

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-Tafamidis,

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-Diflunisal

Antibodies to clear Amyloidosis Deposits

-NI006

-PRX004

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

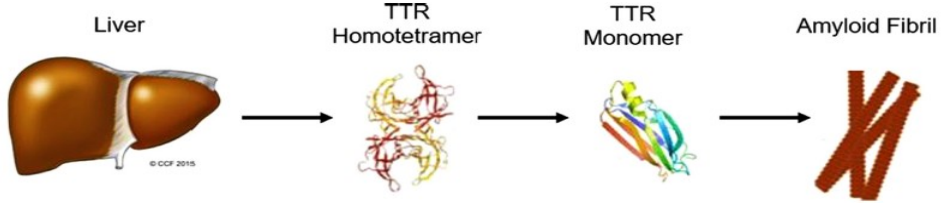
Undergoing ClinicalTrial including ATTR-WT

Drugs	Patisiran	Vutrisiran	ION-682884
Inclusion	**ATTR Cardiomyopathy**	**ATTR Cardiomyopathy**	**ATTR Cardiomyopathy**
Trial	**Phase 3 APPOLO**	**Phase 3 HELIOS B**	**Phase 3 CARDIO TTRansform**
Methodology	Phase 3 / Double blind	Phase 3 / Double blind	Phase 3 / Double blind
Administration	Intravenous	Subcutaneous	Subcutaneous
Where we are?	Inclusion started	Inclusion started	Inclusion pending

Stop
Protein production

Stop/limit
Amyloid fibrills production

Remove
Amyloid Fibrills from Organs



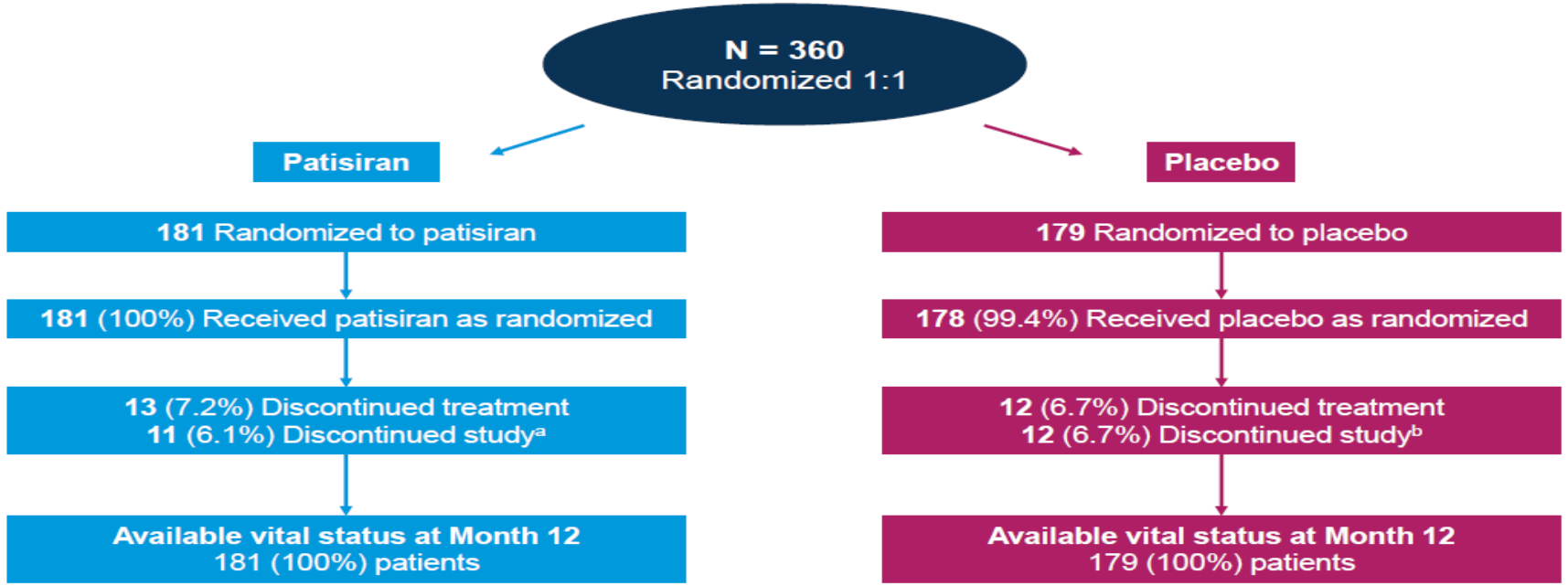
Drugs	NI006-101 –**TTR ANTIBODY**
Inclusion	**ATTR Cardiomyopathy**
Trial	**Phase 3 NI006**
Methodology	Phase ½ / Double blind
Administration	Intravenous
Where we are?	Inclusion started

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)



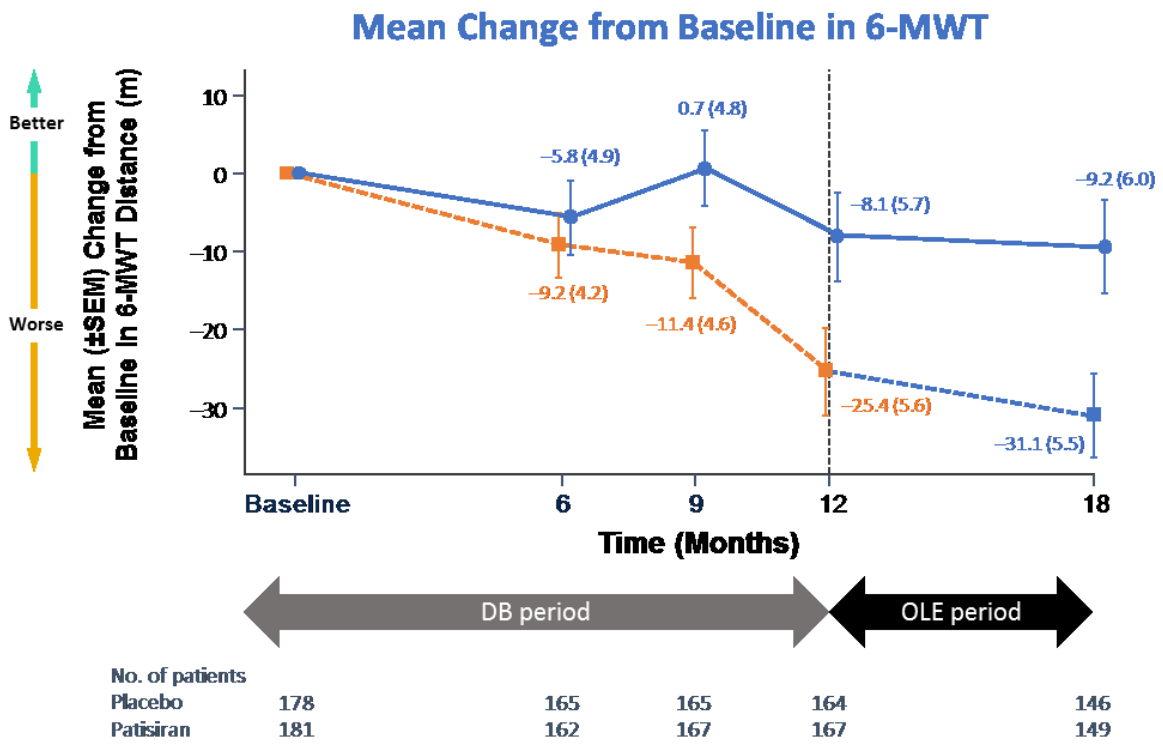
[a]Reasons for discontinuing patisiran treatment: AE (4 [2.2%]), death (3 [1.7%]), other (6 [3.3%]). [b]Reasons for discontinuing placebo treatment: AE (5 [2.8%]), death (3 [1.7%]), physician decision (1 [0.6%]), other (3 [1.7%]). Other excludes A death, lost to follow-up, physician decision, pregnancy,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

JESFC : Jeudi et Vendredi :Olivier Lairez, Vincent Algalarrondo

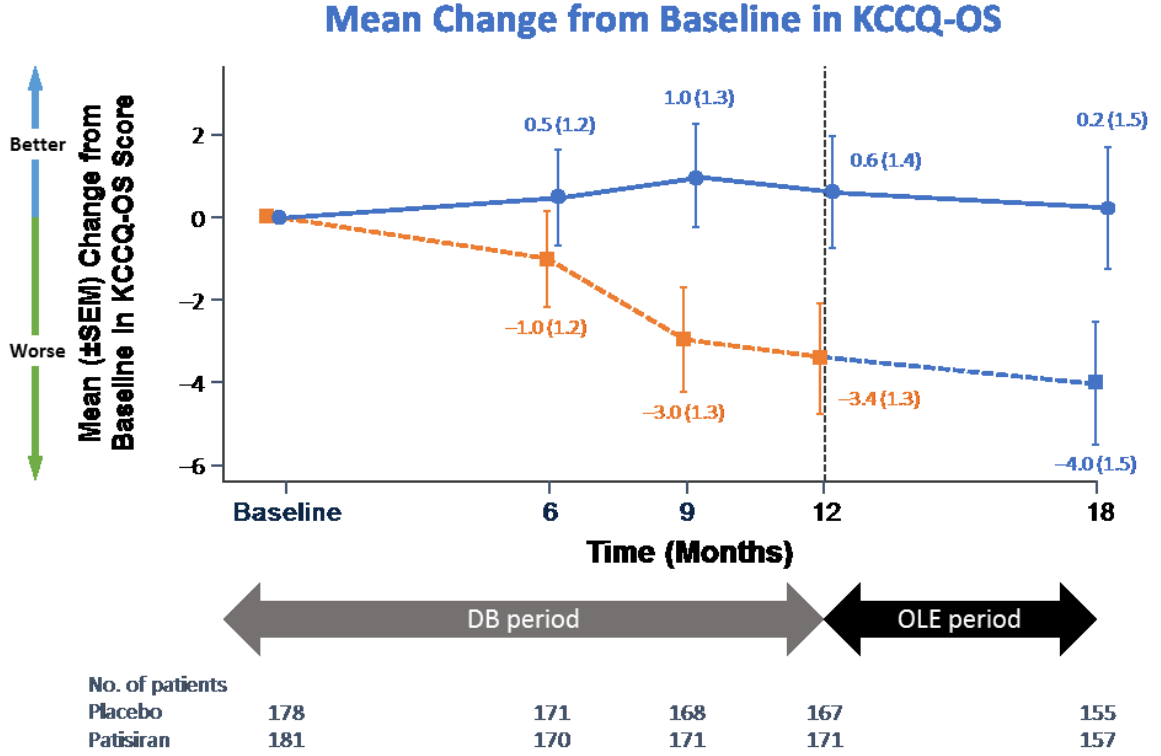
Maurer MS et al, ISA Heidelberg meeting Abstract ***: OPLB001 08_09_2022***

Appolo-B : ATTRv and ATTRwt

Primary criteria



Secondary criteria

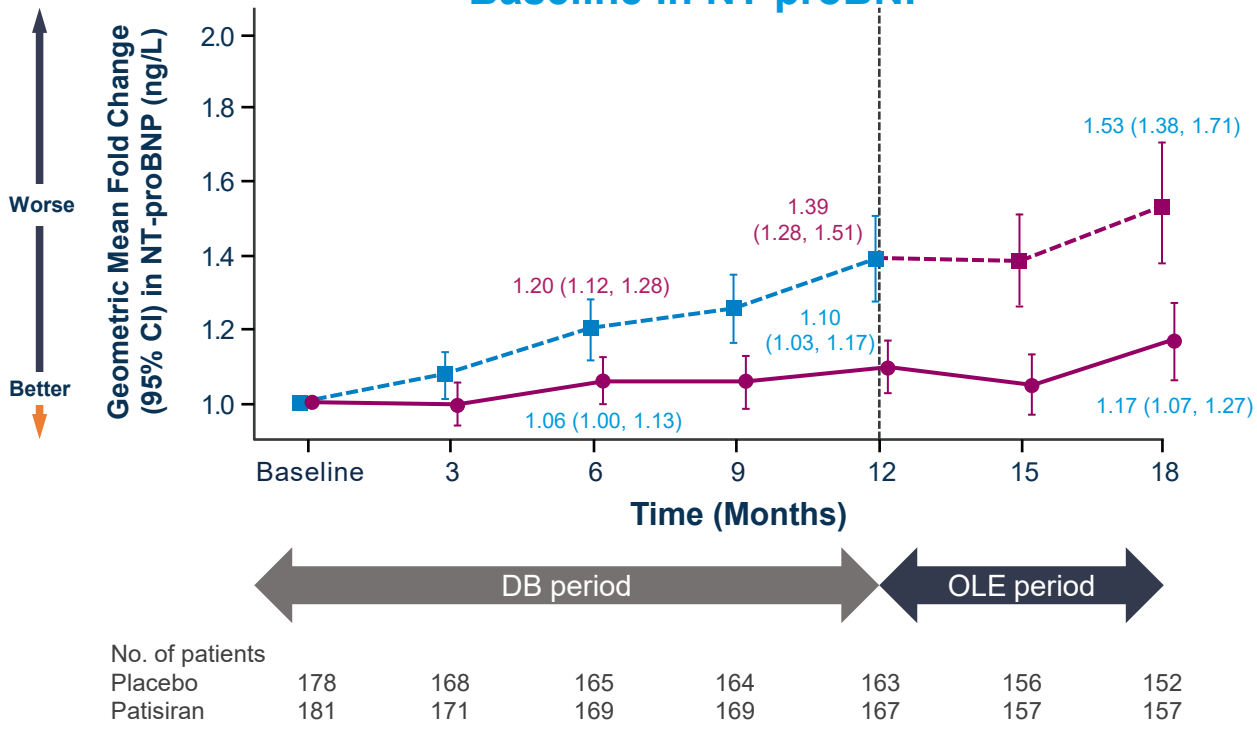


Patisiran Placebo

Maurer M, ISA 2022

Appolo B : Biomarkers change

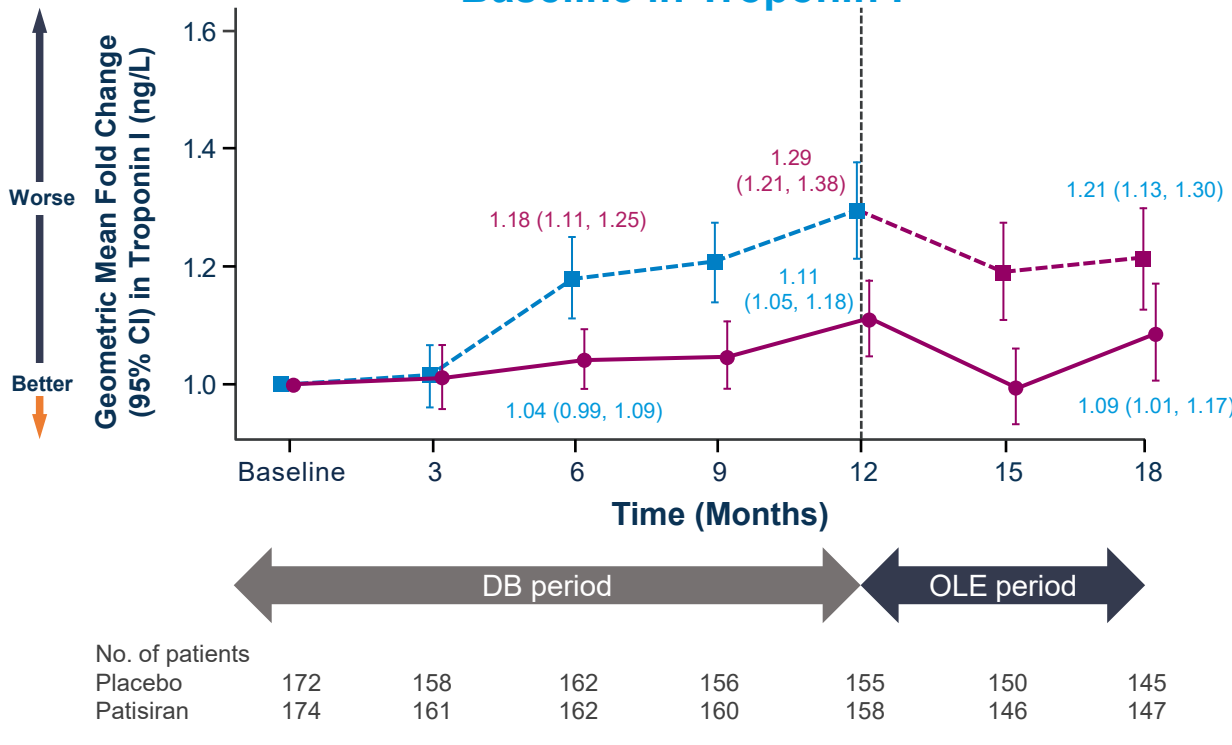
Geometric Mean Fold Change from Baseline in NT-proBNP[a]



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

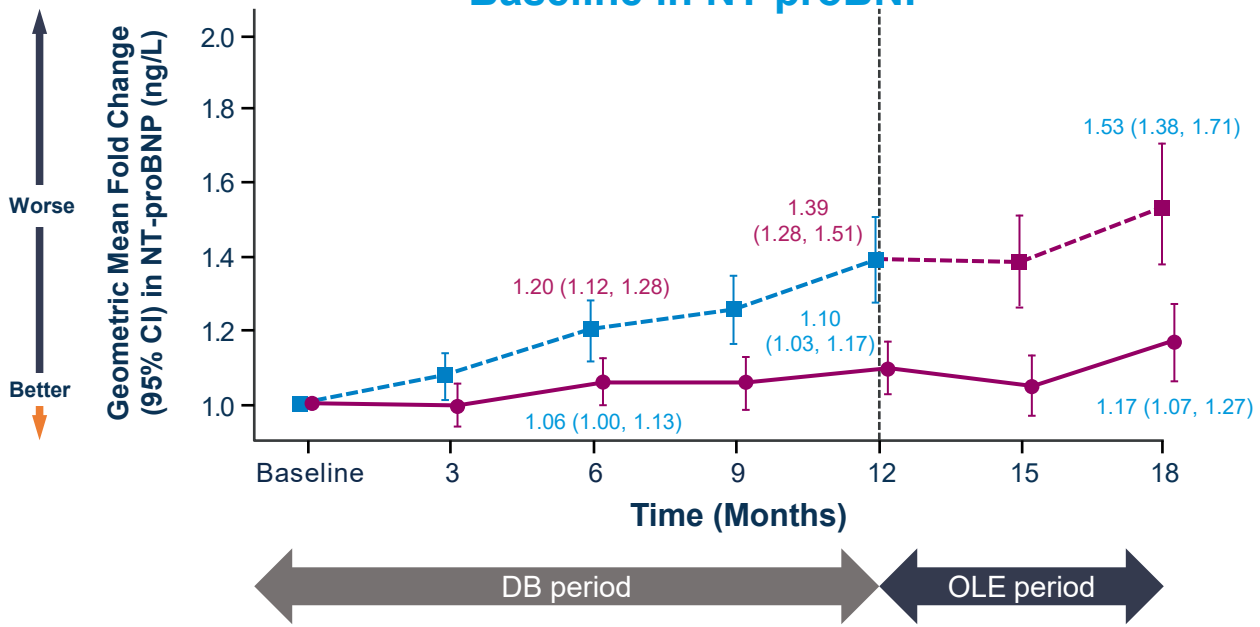
Patisiran Placebo

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.

Appolo B : Biomarkers change

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



No. of patients

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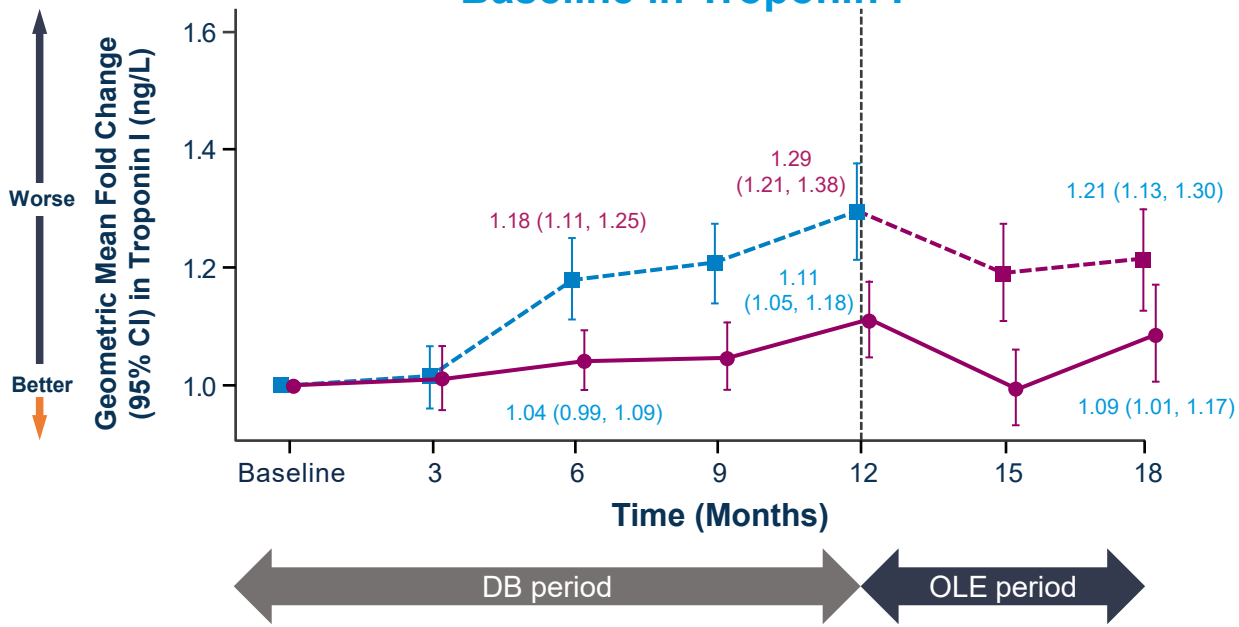
Patisiran	181	171	169	169	167	157	157

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



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Patisiran Placebo

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

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Principaux résultats d'HELIOS-B, étude de phase 3 évaluant vutrisiran chez les patients atteints d'ATTR-CM

The NEW ENGLAND JOURNAL of MEDICINE

ESC Congress 2024
London & Online

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*

M. Fontana[1] , J. L. Berk[2] , J. D. Gillmore[1] , R. Witteles[3] , M. Grogan[4] , B. Drachman[5] , T. Damy[6] , P. Garcia-Pavia[7] , S. D. Solomon[8] , N. Tahara[9] , P. Van der Meer[10] , L. Yang[11] , S. A. Eraly[11] , K. L. Boyle[11] , J. Vest[11] , M. S. Maurer [12]

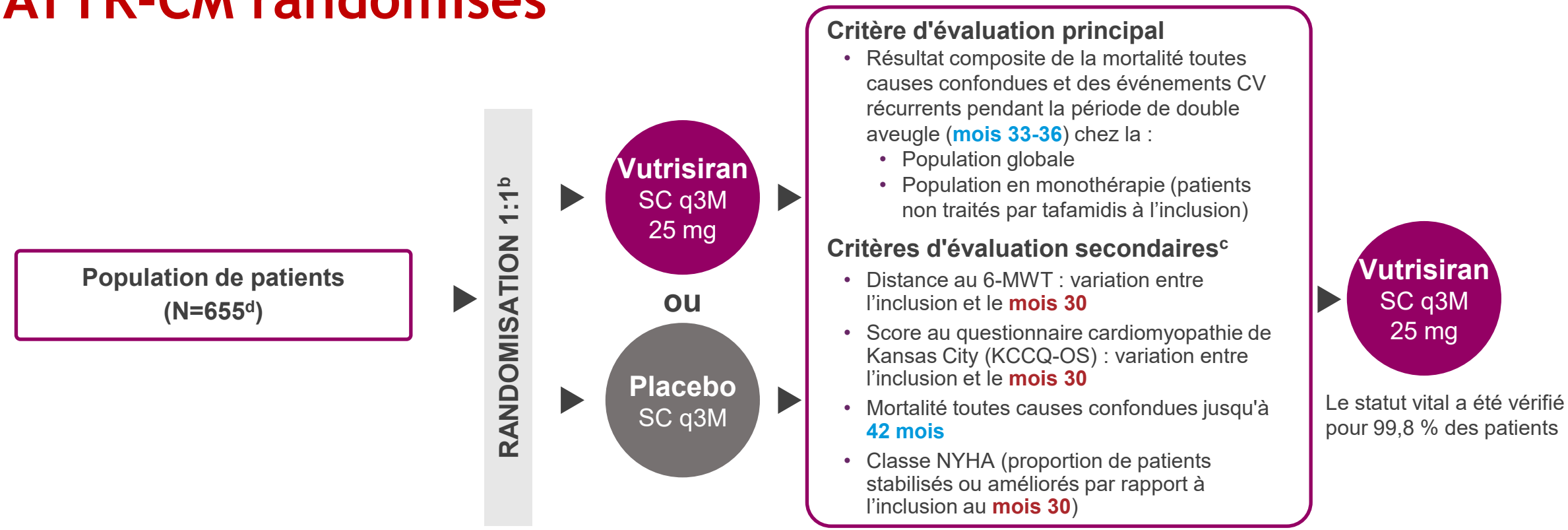
[1]Département de médecine, University College London, Royal Free Hospital, Londres, Royaume-Uni ;[2] Boston University School of Medicine, Boston, MA, USA ;[3] Département de médecine cardiovasculaire, Stanford University School of Medicine, Stanford, CA, USA ; [4]Département des maladies cardiovasculaires, Mayo Clinic College of Medicine, Rochester, MN, USA ; [5]Département de médecine cardiovasculaire, Penn Presbyterian Medical Center, Philadelphie, PA, USA ;[6] Centre de référence pour l'amylose cardiaque, Hôpital Henri Mondor, Créteil, France ; [7]Département de cardiologie, Hospital Universitario Puerta de Hierro Majadahonda, CIBERCV, Madrid, Espagne ;[8] Département cardiovasculaire, Brigham and Women's Hospital, Boston, MA, USA ;[9] Département de médecine cardiovasculaire, Départment de Medecine, Kurume University School of Medicine, Kurume, Japan ; [10]Universitair Medisch Centrum Groningen, Université de Groningen, Groningen, Pays-Bas ;[11] Alnylam Pharmaceuticals, Cambridge, MA, USA ;[12] Columbia University Medical Center, New York, NY, USA

Fontana M, et al New England Journal of Medicine 2024

Abréviations : ATTR-CM : amylose à transthyrétine avec cardiomyopathie

Référence : Identifiant Clinicaltrials.gov : NCT04153149 ; NEJM 2024 : Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

Helios B : une étude contemporaine sur 655 patients ATTR-CM randomisés



[a]Des niveaux de NT-proBNP >300 pg/mL et <8500 pg/mL (ou >600 pg/mL et <8500 pg/mL pour les patients souffrant de fibrillation auriculaire).
[b]La randomisation a été stratifiée en fonction de l'utilisation de tafamidis à l'inclusion (oui ou non), du type de maladie ATTR (ATTRv ou ATTRwt), de la classe NYHA et de l'âge au départ (classe NYHA I ou II et âge <75 ans versus tous les autres).
[c]Évalués dans la population globale et dans la population en monothérapie en tant que critères d'évaluation distincts.
[d]655 patients ont été randomisés mais 1 patient s'est retiré entre la randomisation et le dosage

Abréviations : 6-MWT, test de marche de 6 minutes ; ATTR, amylose à transthyrétine ; BL, baseline; CV, cardiovasculaire ; DB, double aveugle ; IC, insuffisance cardiaque ; NT-proBNP, prohormone *N-terminale* du peptide natriurétique de type B ; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - Overall Summary ; NYHA, New York Heart Association ; OLE, open label extension ; PND, polyneuropathy disability ; q3M, tous les 3 mois ; SC, sous-cutané ; TTR, transthyrétine.

Références : Identifiant Clinicaltrials.gov : NCT04153149

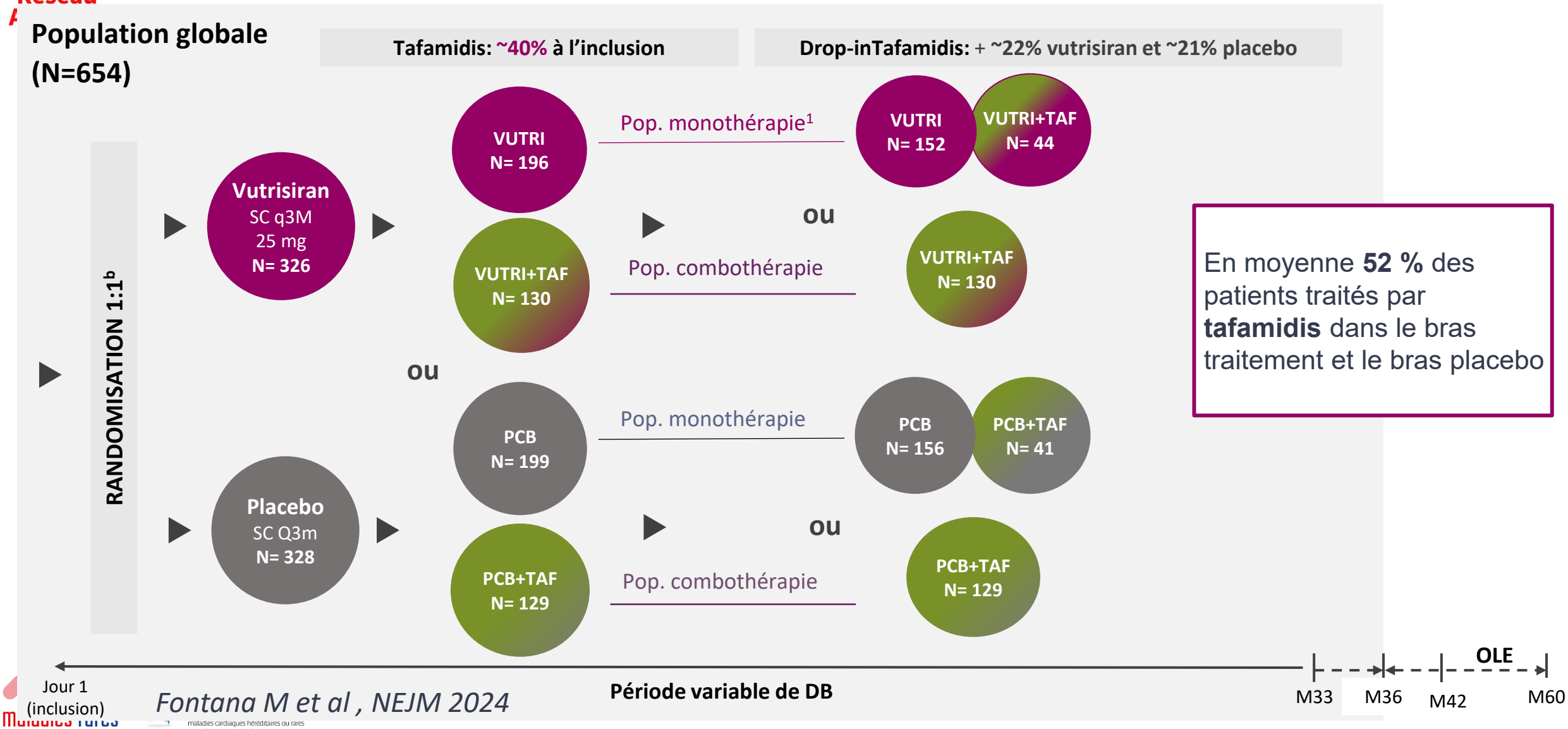
HELIOS-B inclusion and exclusion criteria

Inclusion Criteria	Main exclusion Criteria
•**Diagnosis of ATTR-CM** •**IVST >12mm** •**NTproBNP >300pg/ml** •**NTproBNP>600pg/ml if Afib** •**A clinical history of HF was required**, with at least : -One previous hospitalization for HF -Or clinical evidence of HF with signs and symptoms of volume overload or elevated intracardiac pressures warranting diuretic treatment.	•**NTProBNP <8500pg/ml** •**NYHA IV** •**NYHA III with a NAC stage of 3** (defined as an NT-proBNP level of >3000 pgMl + eGFR<45 ml /min/1.73 m^2 •**Polyneuropathy disability score of IIIa, IIIb, or IV** (indicating that a cane or stick is needed to walk or that the patient is wheelchair-bound); •**eGFR <30 ml /min/1.73 m^2**

At baseline, patients were either receiving tafamidis for ATTR-CM at the dose approved within their country or were not receiving tafamidis, with no active plan to start tafamidis during the first 12 months after randomization.

Fontana M et al , NEJM 2024
Full inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

HELIOS-B results : subgroups type depending on treatment received r placebo



En moyenne **52 %** des patients traités par **tafamidis** dans le bras traitement et le bras placebo

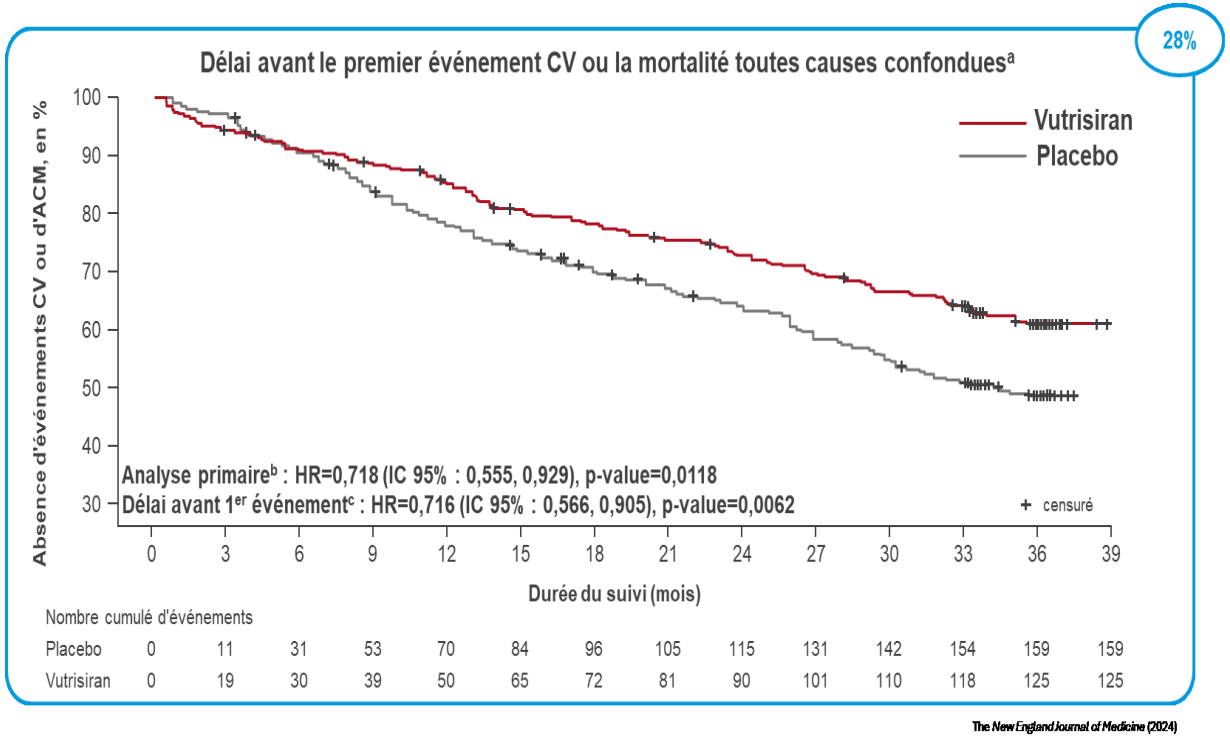
Fontana M et al , NEJM 2024

[1] Les patients qui ne recevaient pas de tafamidis à l'inclusion mais ayant reçu du tafamidis au cours de la période en double aveugle sont inclus dans la population en monothérapie.

Ainsi, à l'inclusion la population monothérapie : N = 395 **Abréviations** : pop : population ; PCB : placebo ; VUTRI : vutrisiran ; TAF : tafamidis

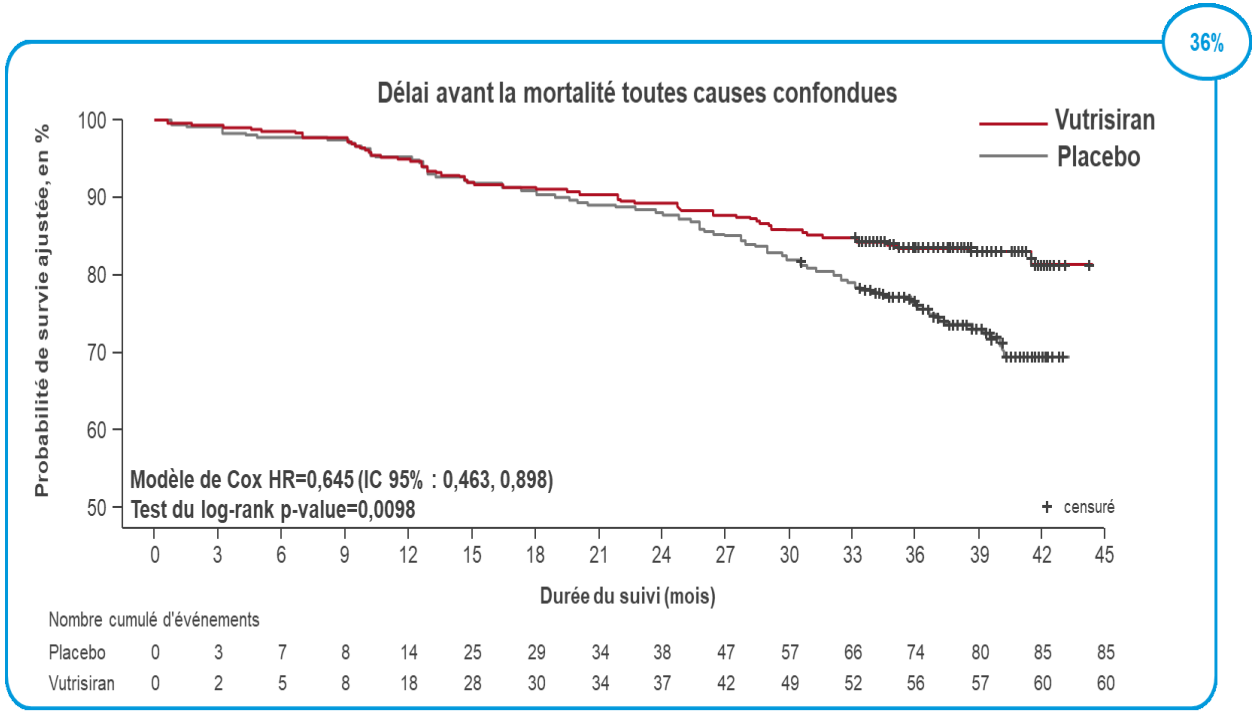
HELIOS B: Primary combined criteria and mortality

Primary combined criteria : RRR ↘28%



The New England Journal of Medicine (2024)

Mortality at 42th Month : RRR: ↘36%

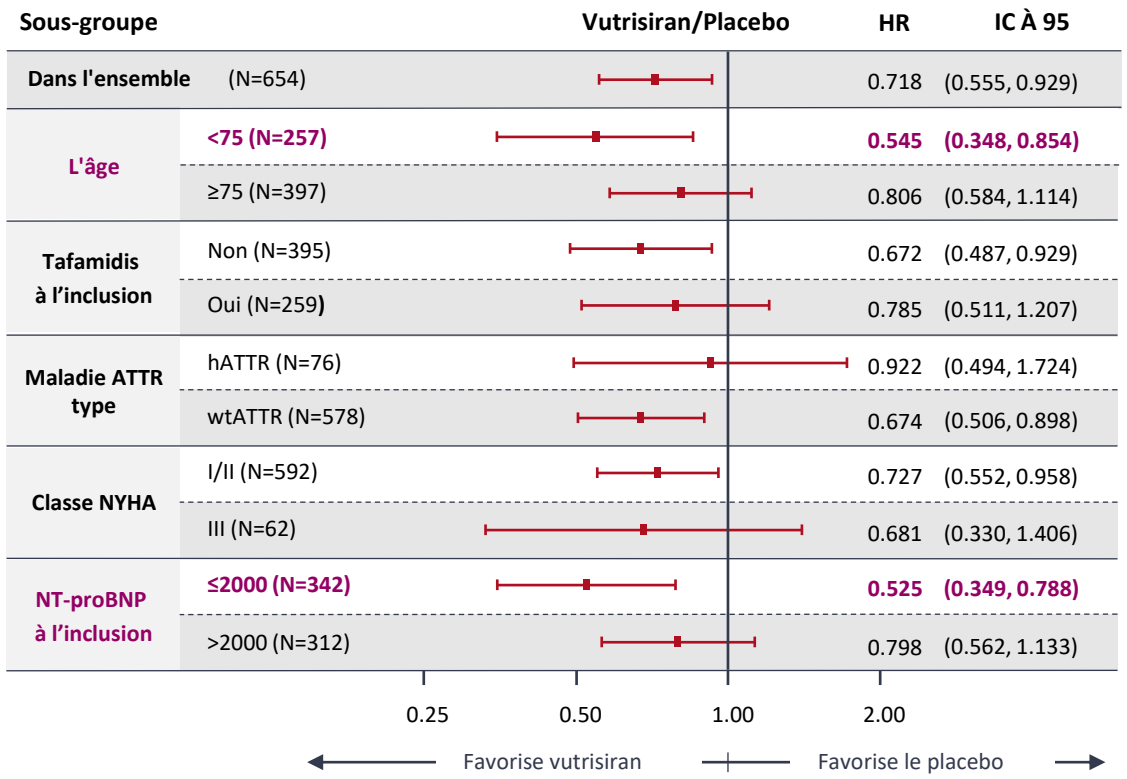


The New England Journal of Medicine (2024)

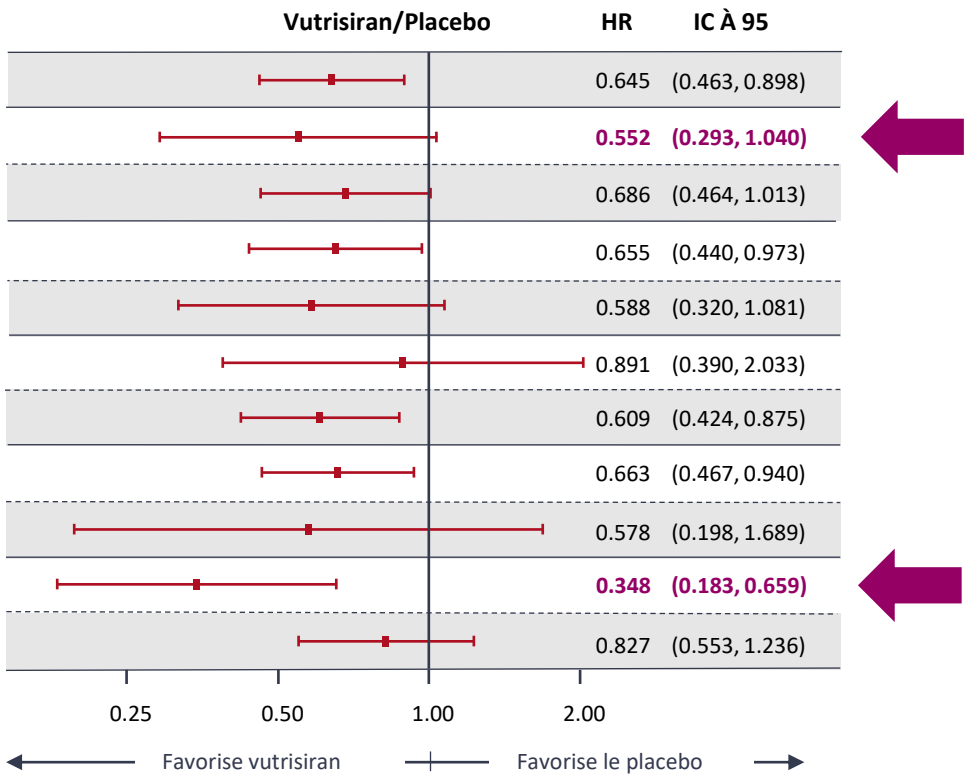
Fontana M, et al New England Journal of Medicine 2024

HELIOS B: Forest plot depending of the primary criteria or mortality

Primary combined criteria



Mortality at 42th Month

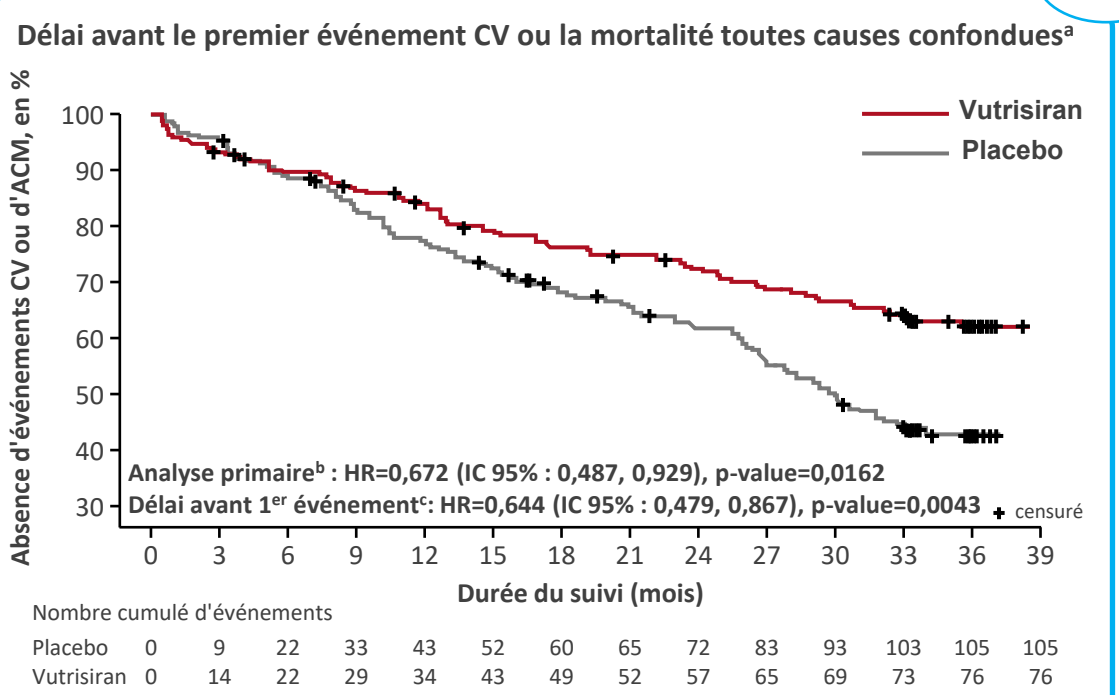


Fontana M, et al New England Journal of Medicine 2024

Primary outcome criteria and mortality in the « Monotherapy » (at baseline) subgroup.

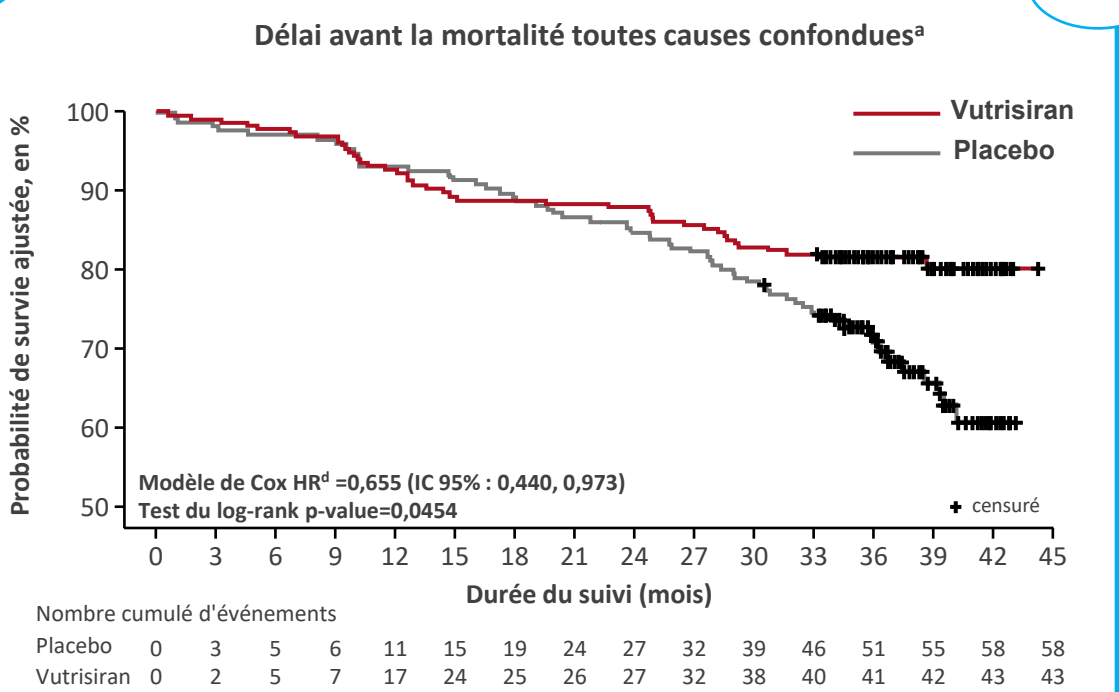
Primary combined criteria : RRR ↘33%

33%



Mortality at 42th Month : RRR: ↘35%

35%



The *New England Journal of Medicine* (2024)

La mortalité toutes causes confondues inclut la transplantation cardiaque et le placement d'un dispositif d'assistance ventriculaire gauche. [a]Basé sur les courbes de Kaplan-Meier ajustées à l'IPTW ;[b] Analyse primaire basée sur le modèle Andersen-Gill modifié, également connu sous le nom de LWYY ;[c] Temps jusqu'au premier événement HR dérivé du modèle Cox PH, valeur p dérivée du test Log-rank ;[d] Temps jusqu'à la mortalité toutes causes confondues incluant les données de la période en double aveugle et jusqu'à 6 mois dans l'OLE, les décès après la fin de l'étude sont inclus dans l'analyse, HR dérivé du modèle Cox PH.

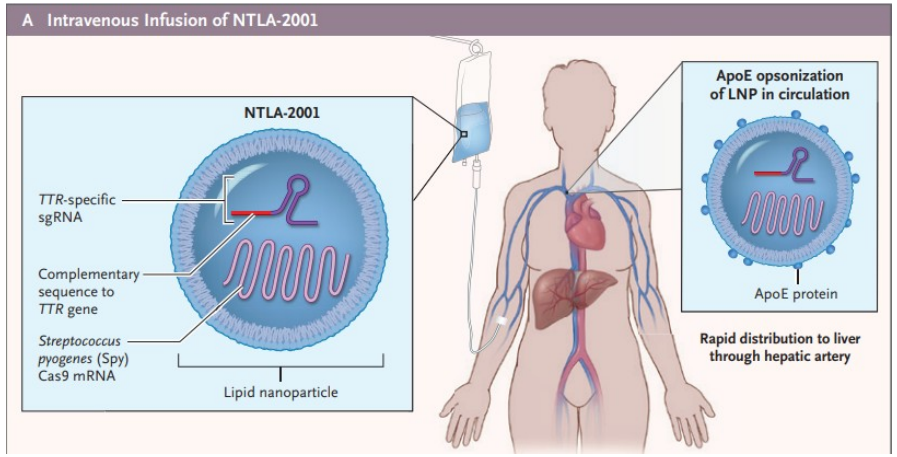
Abréviations : IC, intervalle de confiance ; CV, cardiovasculaire ; event: événements ; HR, hazard ratio ; IPTW, inverse probability of treatment weighting ; LWYY, Lin, Wei, Yang , and Ying ; PH, proportional hazard.

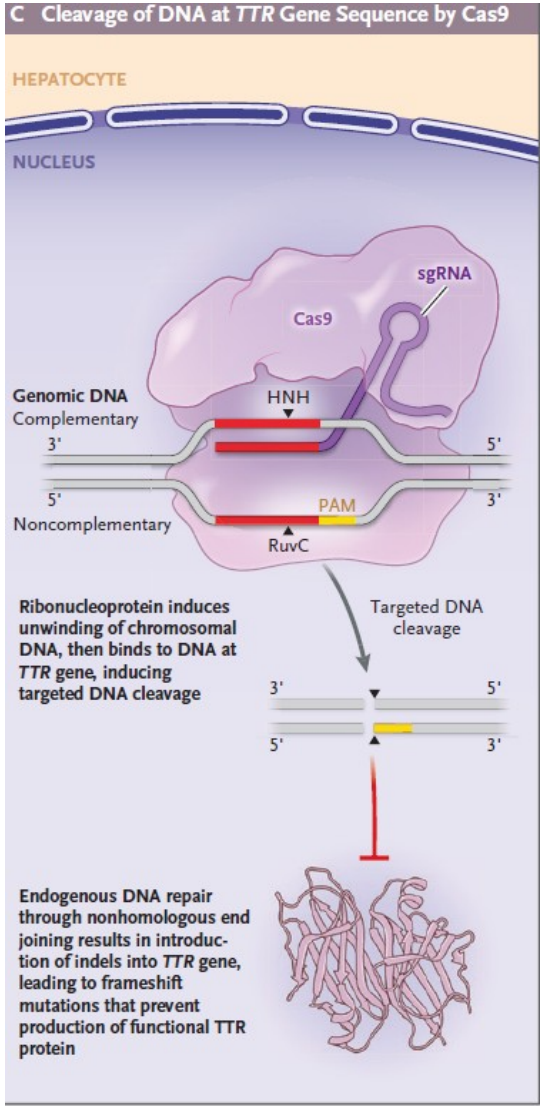
Fontana M, et al New England Journal of Medicine 2024

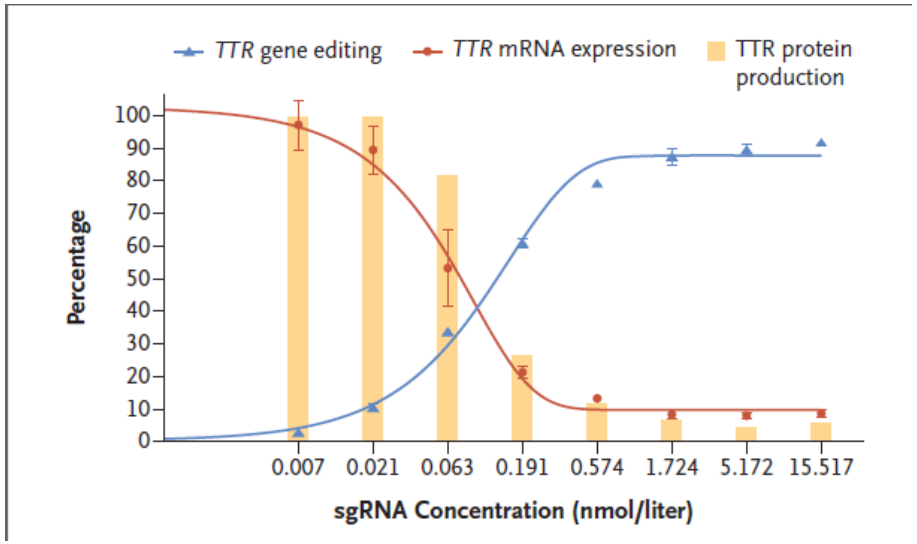
CrisprCas9: First gene therapy results for ATTR : Only one injection

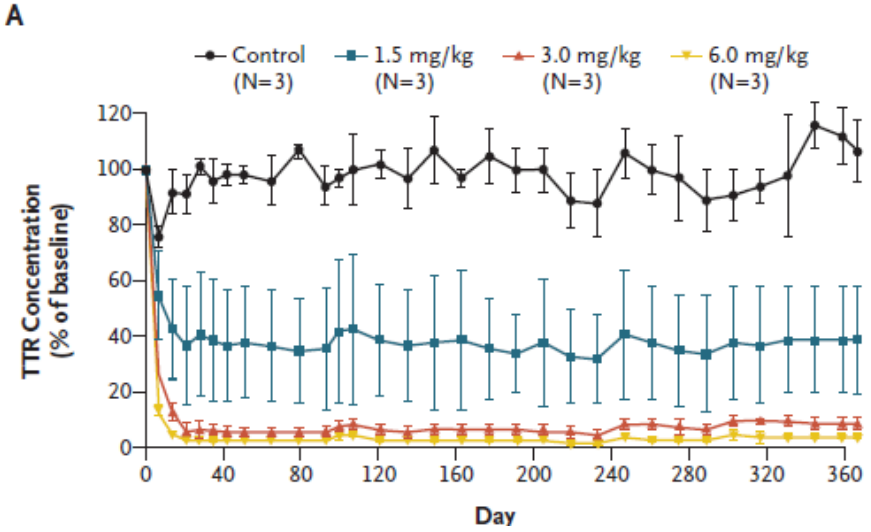
ORIGINAL ARTICLE

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis



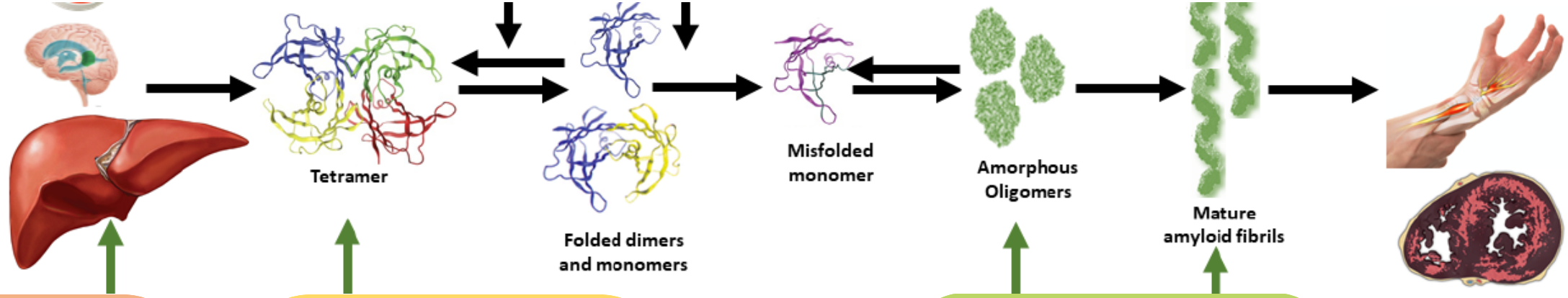






Gillmore J et al, NEJM 2021

ATTR Cardiac Amyloidosis Treatments : A new area in cardiology



Liver Transplantation

TTR Gene Silencing

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

-Crispr Cas 9

TTR Stabilizers

-Tafamidis,

-Acoramidis,

-Diflunisal

Antibodies to clear Amyloidosis Deposits

-NI006

-PRX004

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

ORIGINAL ARTICLE

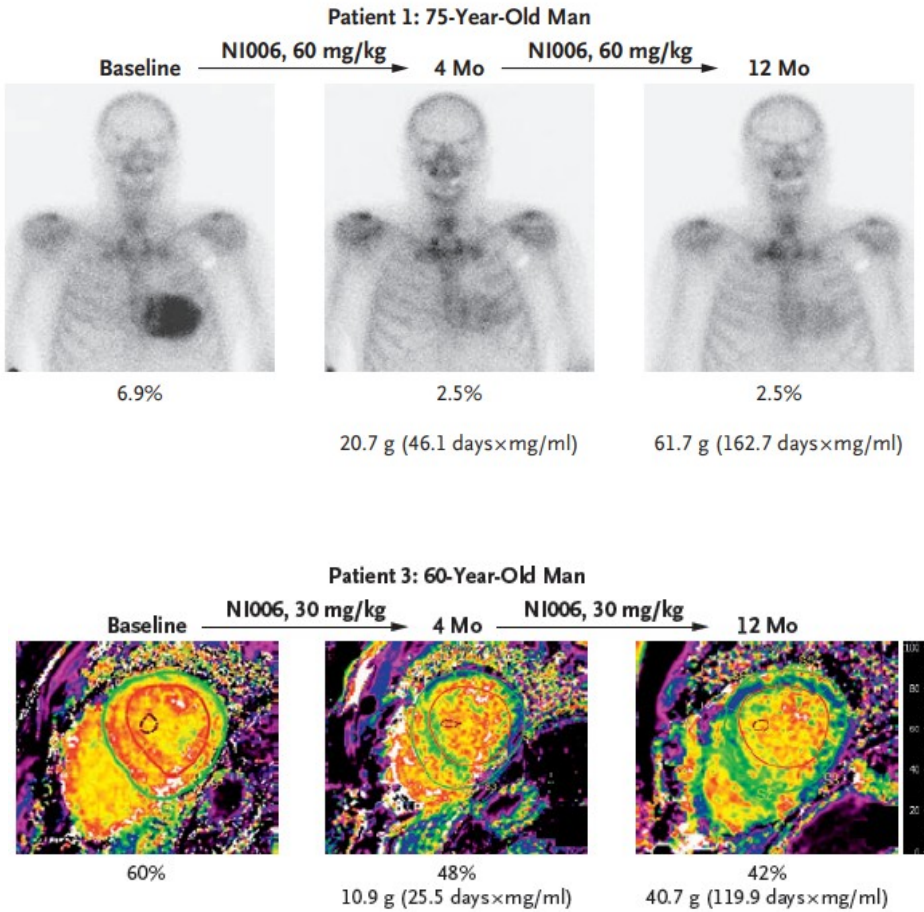
Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

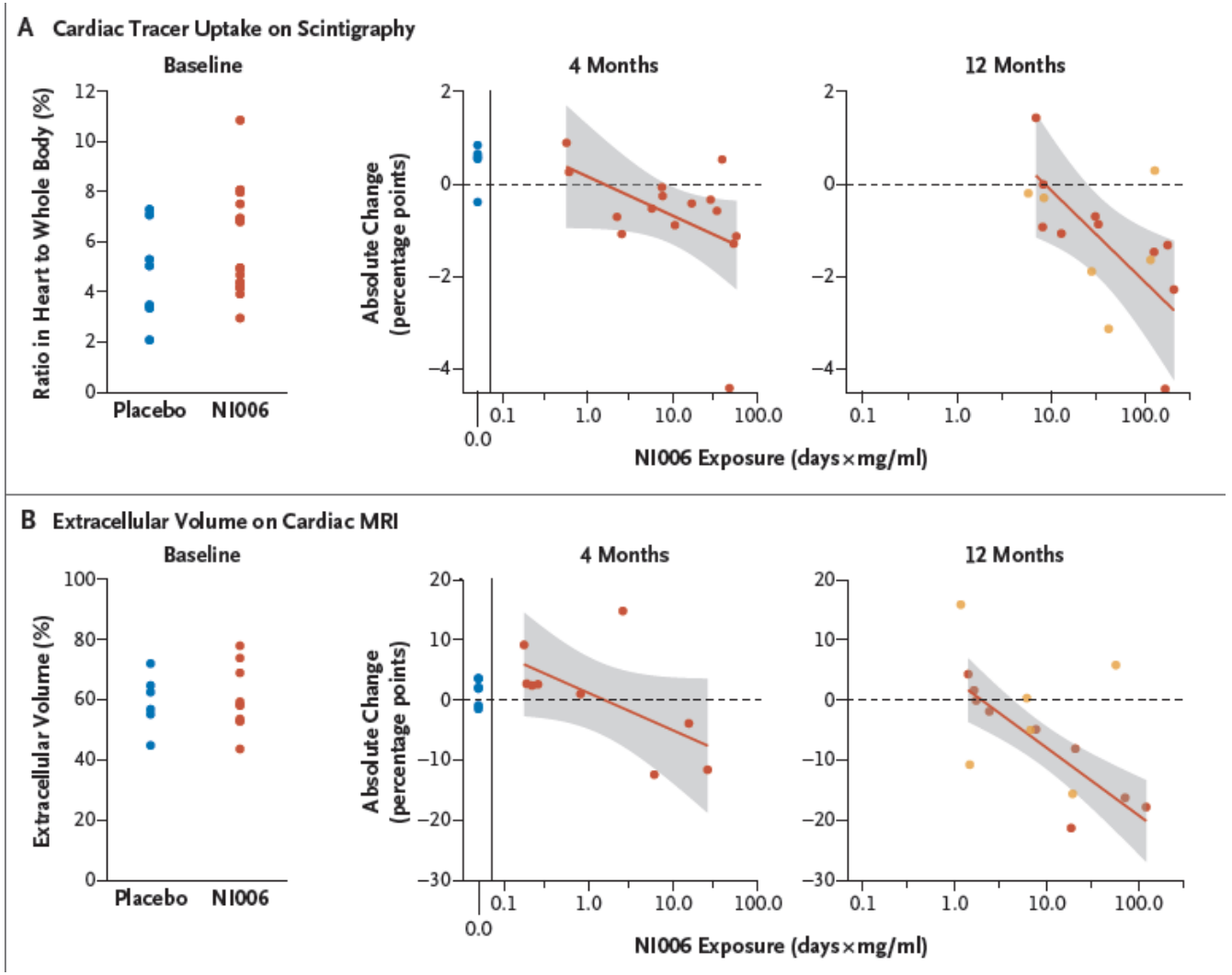
Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph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

- 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

Conclusion : Take home message

- Early diagnosis, early treatment = better outcome
- AL amyloidosis is an emergency : To refer ASAP
- Think about progressive increase in LVWT
- Think about extracardiac signs+++

- Adapt cardiac management
- Start specific treatment

- Develop dedicated network in hospital and country : Team building

  - *What I learnt : We can't face this disease alone*

Mondor Amyloidosis Organization : Team building

Cardiac Amyloidosis Referal Center – (Rare Disease Network)

Cardiologists Team

CA : T Damy, S Guendouz, L Hittinger, S Oghina, A Zaroui, S Guendouz, A Galat, S Mallet. GDS Chadha M Hentati, E Charbonneau, S Odouard, A Medioni,
Rythmologist : N Lellouche, N Elbaz, S Rouffiac

Coordination – Quality of life

Healthcare pathway: C Henrion
Referral CenterSecretariat : I Vallat
IDE amyloidosis coordination : S Maupou
Psychology: J Pompougnac

Clinical research Team / HEAR

Study Ingenior: M Kharoubi, M Bezard,
Research assistant: A Vardanian, Dylan, Wissem, Sasaf

MedicineMultidisciplinary Network

Neurology: V Planté-Bordeneuve, T Gendre
Neuro-muscular disease: J Authier, G Bassez
Nephrology: V Audard, P Rémy, K El Karoui
Haematology: F Lemmonier, K Belhadj, J Dupuis, F Le Bras, R Gounot
Internal medicin: M Michel
Hepatology: V Leroy, A Amiot
Geriatry: A Broussier, N Liu
Genetic: B Funalot, P Fannen, B Hébrard

Amyloidosis Diagnosis and MonitoringPlatforms

Bio-Haematology : O Wagner-Ballon
Electrophysiology : JP Lefaucheur
Pathology : E Poullot
Sequencing : B Funalot, P Fanen, B Hebrard, C Mekki
Immuno-biology: V Frenkel
Radiology: JF Deux
Nuclear Medecine : E Itti, M Abelisi

HF Telemonitoring

Coordination : L Alexandre, A Duchenne
Nurses : A Gauchard, M Frelat, S **Dias,** C Lecert

Surgery

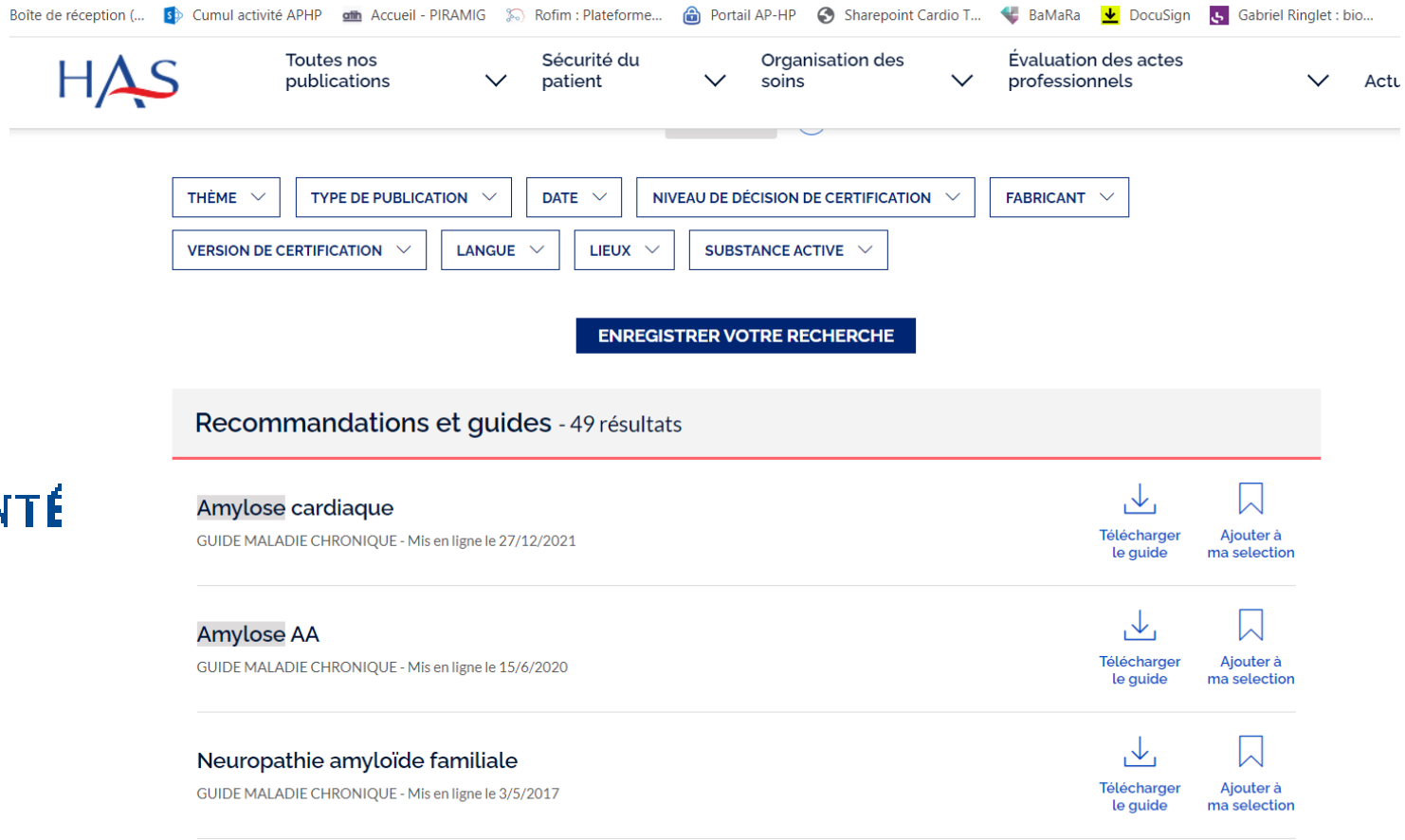
Cardiac surgery: T Folliguet, E Bergoend, C Radu,
Urology : D Vordos
Orthopedy : A Pidet

Oncopole – Toulouse : Mass spectometry : M Colombat – NGS cytogenetic: H Loiseau

Declaration of Interest

- Alexion, Alnylam, Akcea, Pfizer, Prothena, GSK, Neurimmune

Parcours Nationaux de Diagnostic et de Soins (PNDS) Amyloses Cardiaques



HAUTE AUTORITÉ DE SANTÉ

www.reseau-amylose.org

maladies rares

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

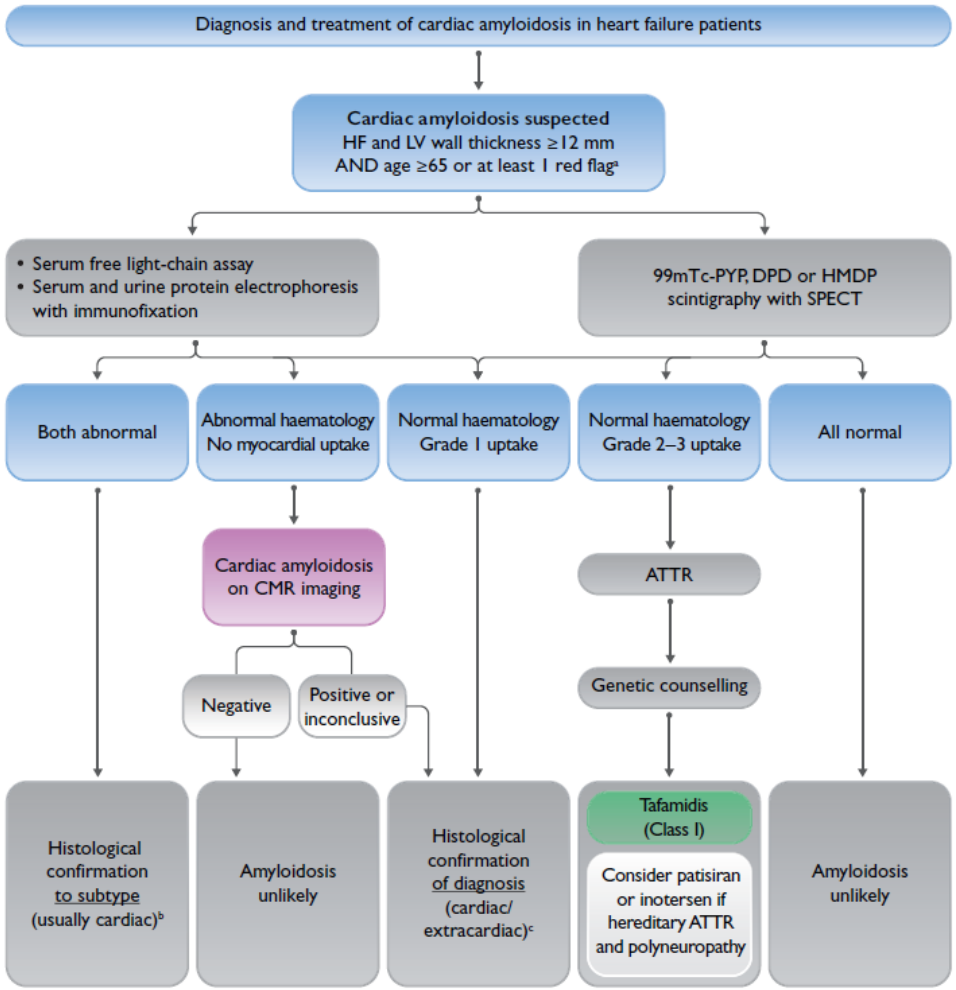
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

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, CV hospitalization and mortality.[979]	I	B
Tafamidis is recommended in patients with wtTTR-CA and NYHA class I or II symptoms to reduce symptoms, CV hospitalization and mortality.[979]	I	B



Mc Donagh T et al, EHJ 2021

Réseau Amylose

Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases

Pablo Garcia-Pavia [1,2,3]*, Claudio Rapezzi[4,5], Yehuda Adler[6], Michael Arad[7], Cristina Basso [3,8,9], Antonio Brucato [10], Ivana Burazor [11], Alida L.P. Caforio [3,12], Thibaud Damy [3,13], Urs Eriksson [14], Marianna Fontana [15], Julian D. Gillmore [15], Esther Gonzalez-Lopez[1,3], Martha Grogan[16], Stephane Heymans[17,18,19], Massimo Imazio [20], Ingrid Kindermann[21], Arnt V. Kristen [22,23], Mathew S. Maurer[24], Giampaolo Merlini [25,26], Antonis Pantazis[27], Sabine Pankuweit[28], Angelos G. Rigopoulos[29], and Ales Linhart [30]

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–15
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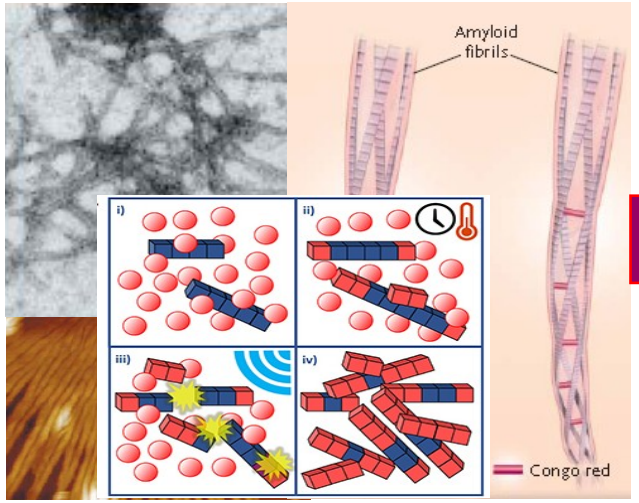
Garcia-Pavia P et al , 2021, 00, 1-15

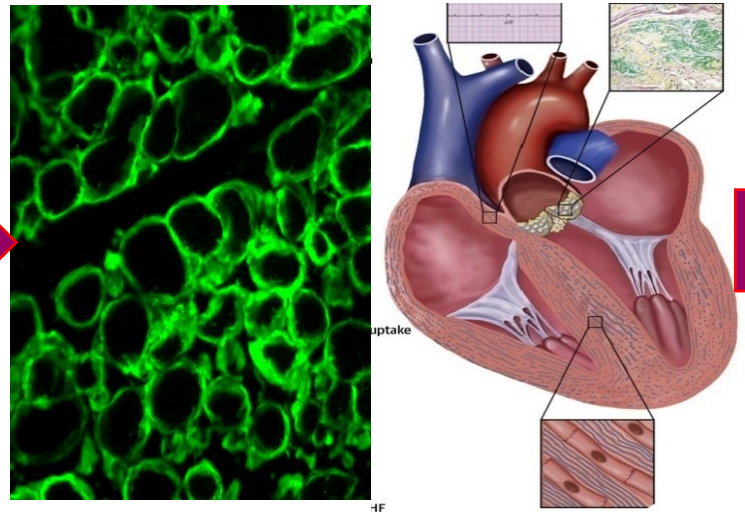
SPECIAL ARTICLE
Heart Failure and Cardiomyopathies

Amyloidosis: Definition and physiopathology

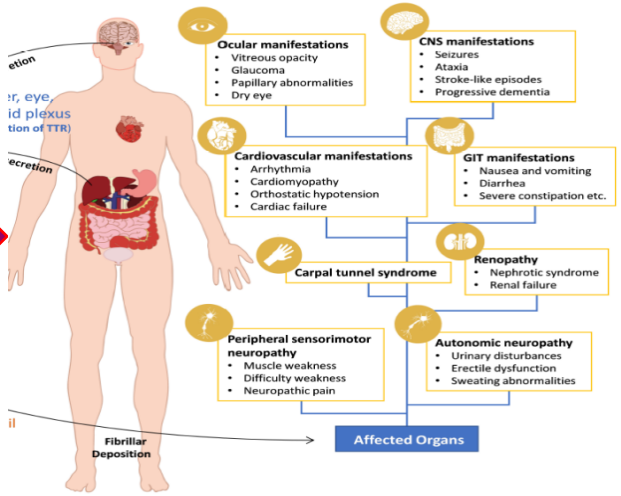
Amyloid Fibrills



Organs infiltration



Human Disease



Amyloid fibrills : >36 Proteins
Non Immunogenic++++ (most of the time!)
Associated with Aging-Process

Dynamic progress+++

Extracellular infiltration
↗ Cellular death

↗ Stiffness : CMR
↗ Thickness : LVH

↘Stroke volume
↘Cardiac Output

Extracardiac Sd

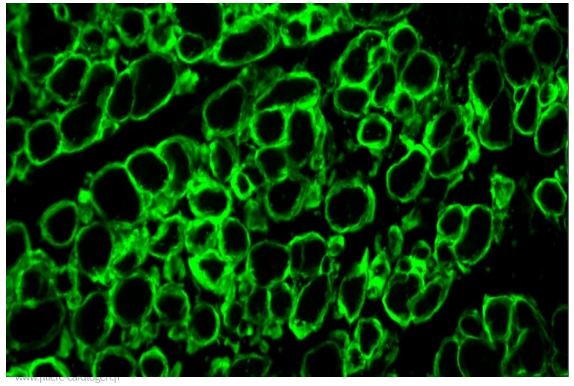
Heart Failure
Conduction D
Rhythm D
Death

Merlini, NEJM 2003
Ternacle J, JACC 2019

Consequences of Cardiac Amyloid Infiltration

Amyloid fibrils

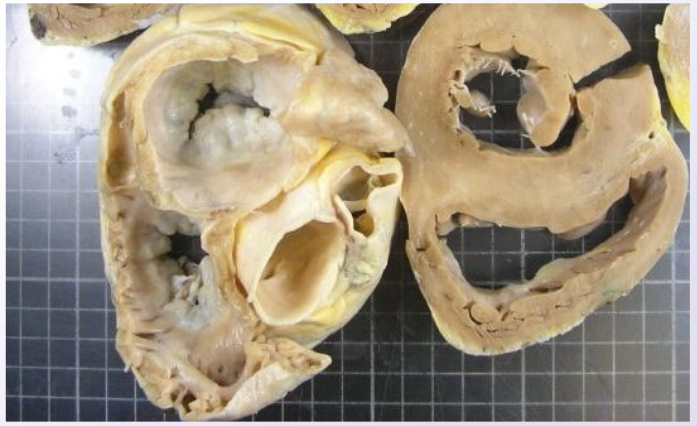
- Stable and Stiff
- Interstitial Infiltration
- Progressive and Dynamic
- Non Immunogenic++++
- Associated with Aging-Process



Cardiac Consequences…

↗ Stiffness
↗ Thickness
↗ Cellular death

↗ HF
↗ Arrhythmias
↗ Conduction D
↗ Thrombosis

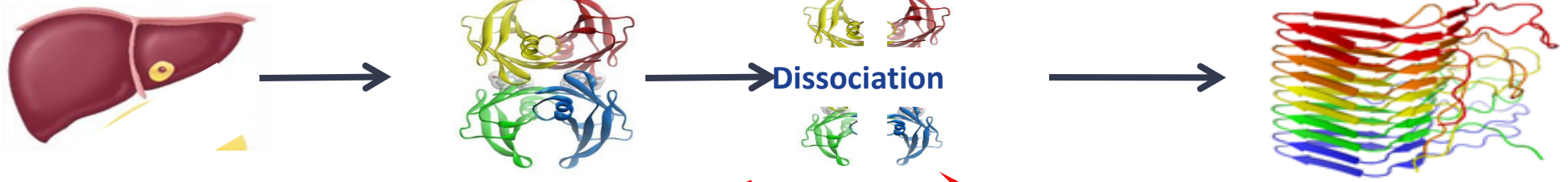


Merlini G, NEJM 2003

Amyloidosis Classification and Cardiac forms

ACQUIRED	HEREDITARY
WT-TTR Wild type Transthyretin or Senile Systemic Amyloidosis	**mTTR** **Hereditary TTR** Fibrinogen Gelsolin ApoA1 ApoA2 Lysozyme Cystatin C
AL Light Chain	
AA Maladies inflammatoires	

Transthyretin Amyloidosis (ATTR) Pathophysiology

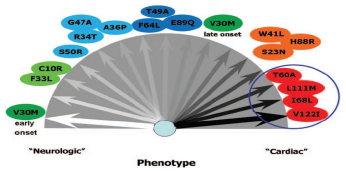


ATTRv (variant)

Autosomal dominant

120 TTR gene mutations

Heart>>> Nerve

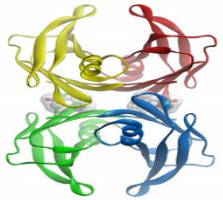


ATTRwt (wild-type)

>1/4 of men above 80 years old have ATTR deposits in the heart

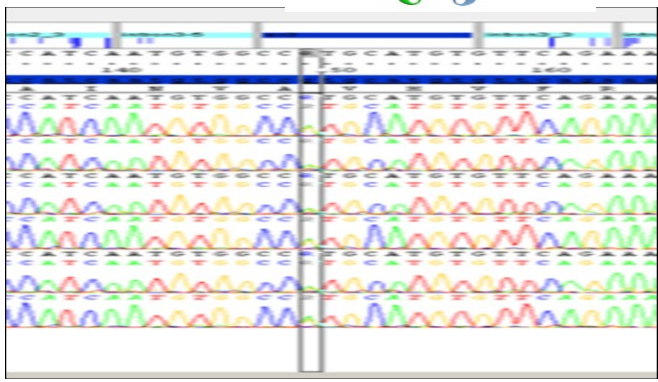
3.6% of Sub-saharian africans are carrier of the mutation ATTR Val122Ile

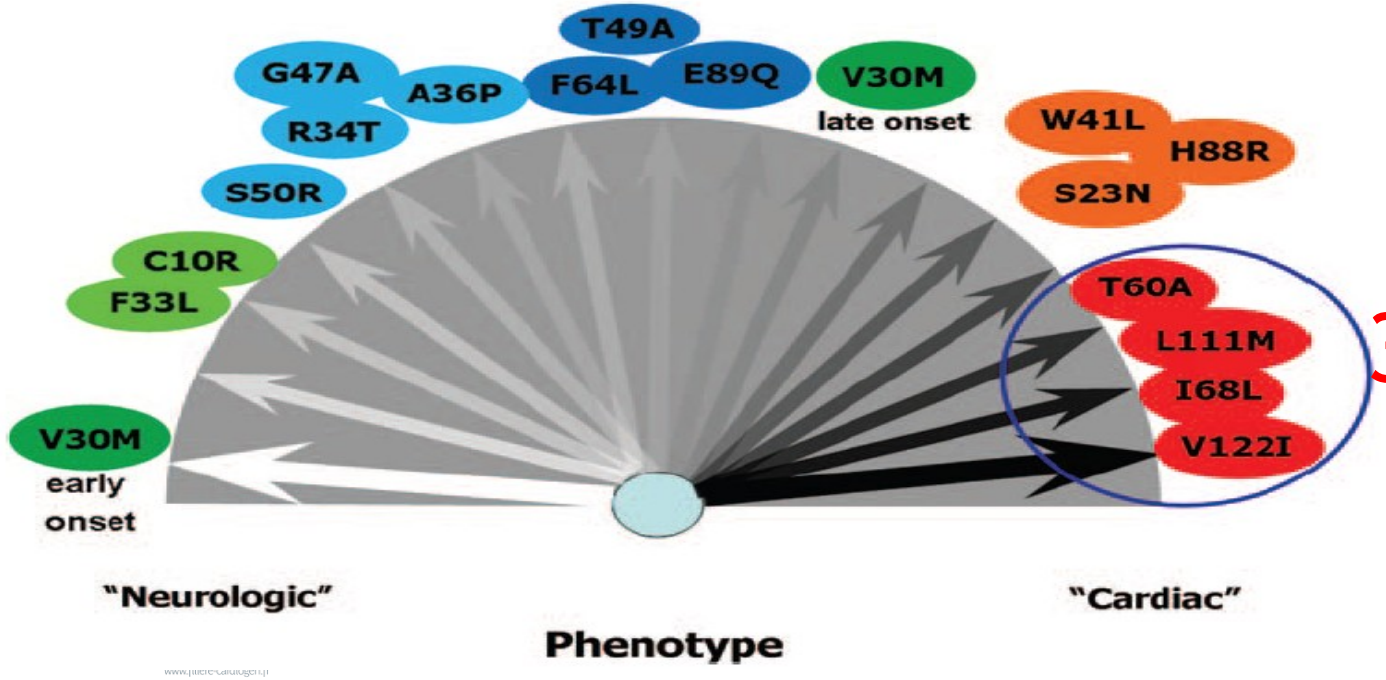
mTTR-CA: Hereditary TTR-CA



- Transthyretin gene *(Chromosome 18; 4 exons).*
- Autosomal Dominant
- >100 mutations

Genetic sequencing





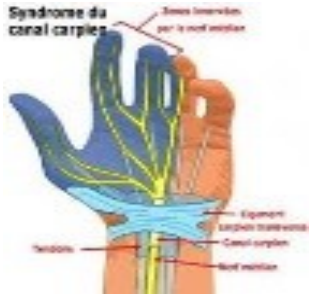
3.6% of Africans-Americans!

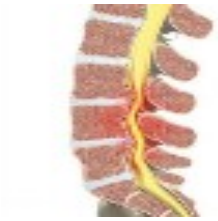
VAL122ILE

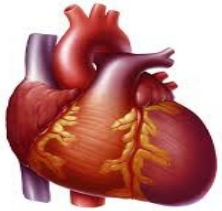
Rapezzi C et al, Eur Heart J 2013

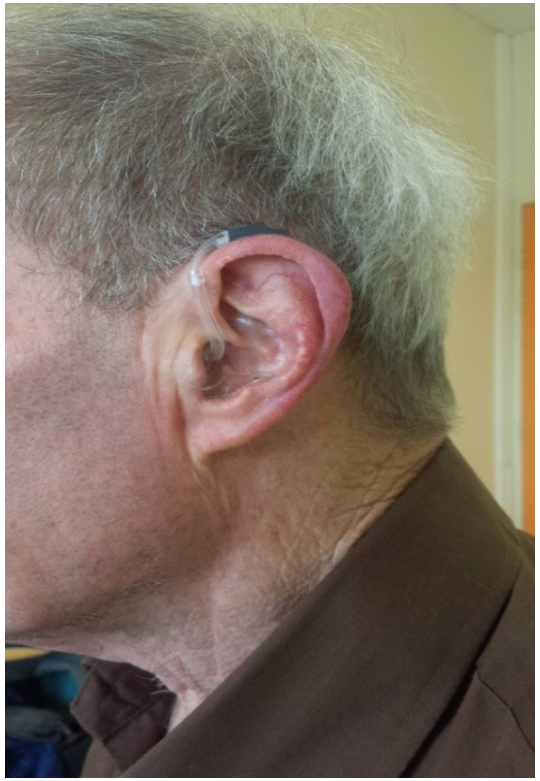
Senile Systemic Amyloidosis : WT-TTR

- Prevalence :
  - ATTR Deposits in the heart : 25% of subjects older > 80y
    WT-TTR = « Cardiac Alzeihmer disease »
  - WT-TTR CA : Prevalence underestimated in Cardiology Setting
  - Men >Women
- Physiopathology unknown : CV Risk factors or Disease?
- Diagnosis : TTR-CA with no TTR gene mutation
- History Amyloid Infiltration occurs Several Years before CA in
  - Carpal Tunnel = Syndrome and Surgery.
  - Lomber Spinal = Stenosis.
  - Deafness

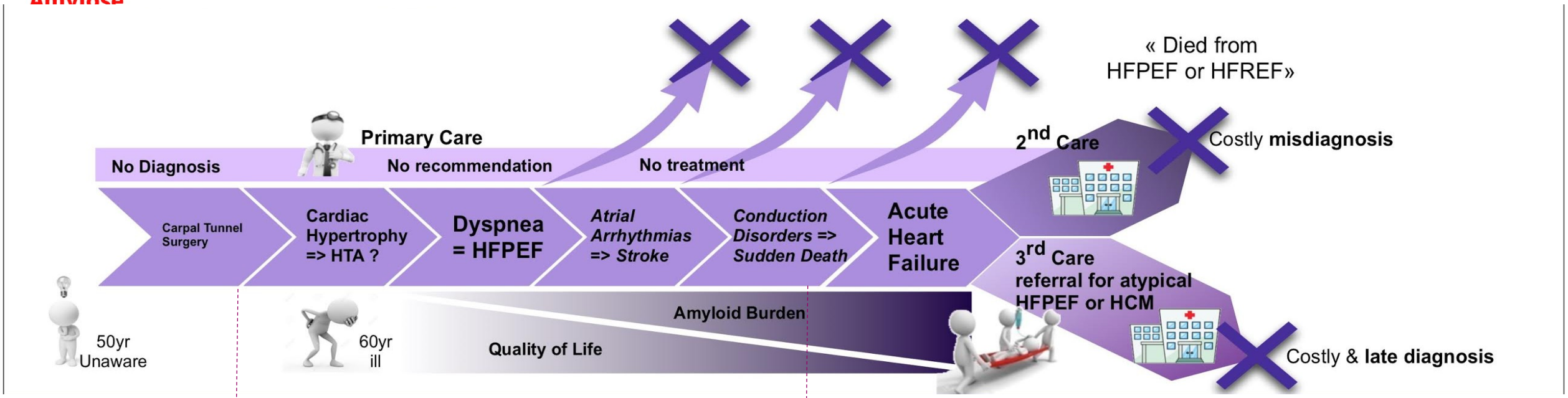








Natural History of TTR-CA



NOT DIAGNOSED

LATE OR MIS DIAGNOSIS
UNDERSTIMATED

NO CARDIAC INFILTRATION

MILD CARDIAC INFILTRATION

SEVERE CARDIAC INFILTRATION

CARDIAC SYMPTOMS AND IMAGING ABNORMALITIES

Cardiac phenotype and prognosis

Physiopathology

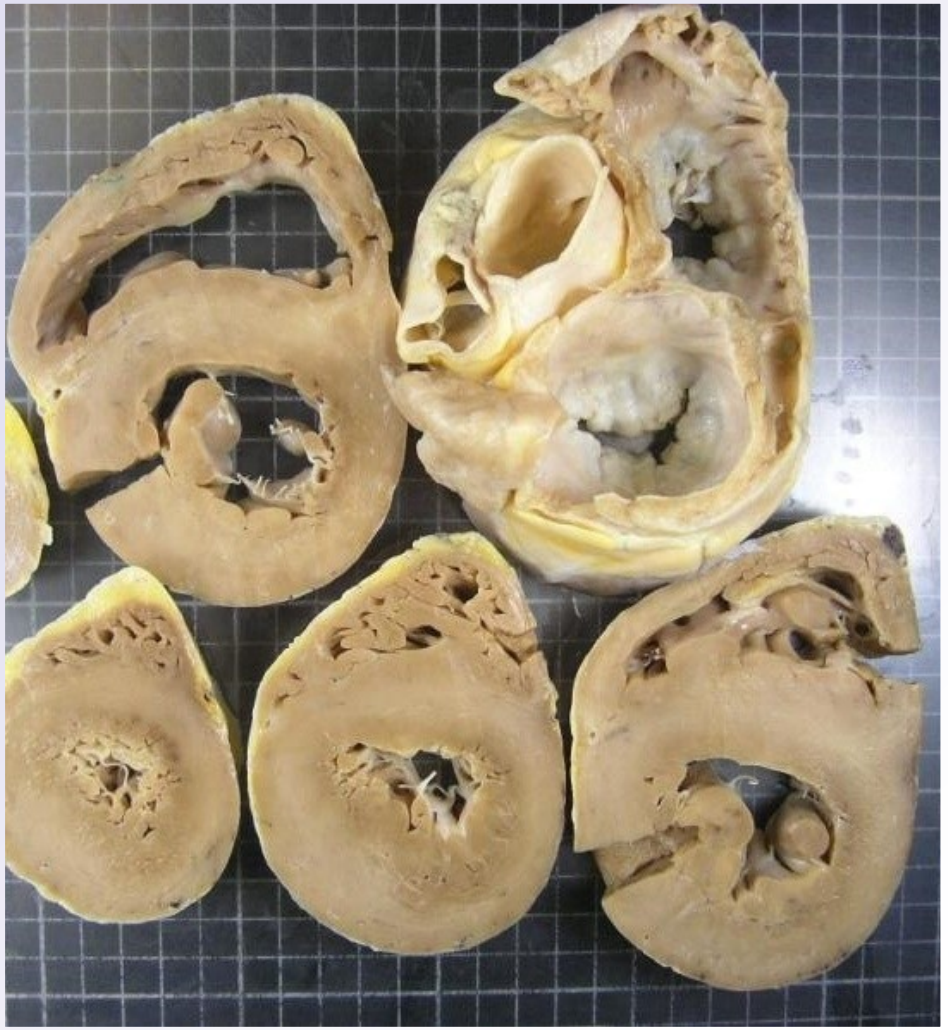
INCREASE CARDIAC STIFFNESS
+
INCREASE LV WALL THICKNESSES
+
DECREASE OF VENTRICULAR CAVITIES SIZE

Phenotype

« HYPERTROPHIC » CARDIOMYOPATHY
+
RESTRICTIVE CARDIOMYOPATHY

Consequences

SEVERE HEART FAILURE
BAD PROGNOSIS
<30-40% Alive at 3 years



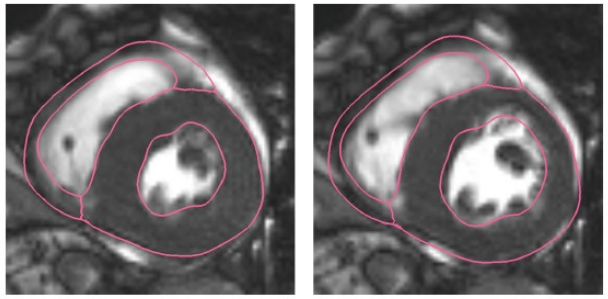
TTR-amyloidosis-Val122Ile homozygote
After Heart and liver transplant

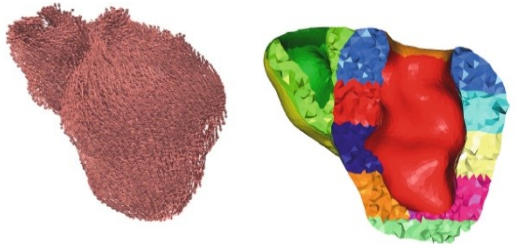
Patient - Specific Biomechanical Modeling of Cardiac Amyloidosis, A case Study

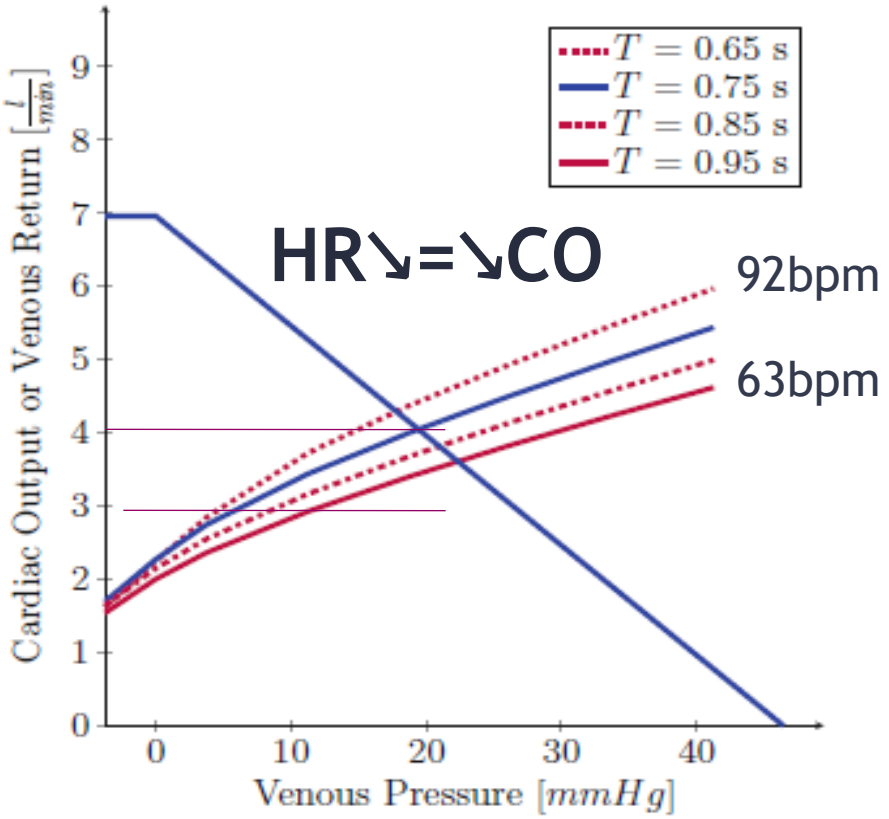
D. Chapelle, A. Felder, R; Chabiniok, A. Guellich, J-F Deux and T. Damy

- Low Stroke Volume
- No preload reserve
- HR dependency

CardiacOutput = HeartRate x SV

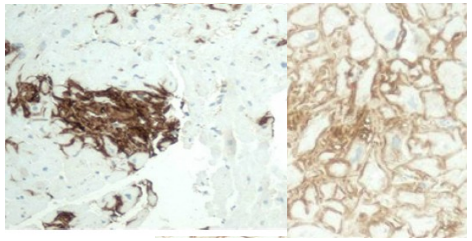






Conséquences anatomiques et physiopathologiques de l'infiltration amyloïde myocardique et du SNA

Myocarde

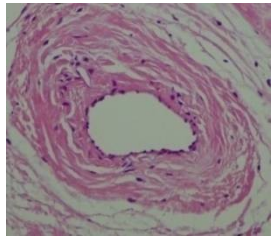


↗ Epaisseur
↗ Rigidité
Dysfonction diastolique
Dysfonction systolique
Thrombose : (EP/AVC)
Mort cellulaire : ↗ Troponine

Endocarde

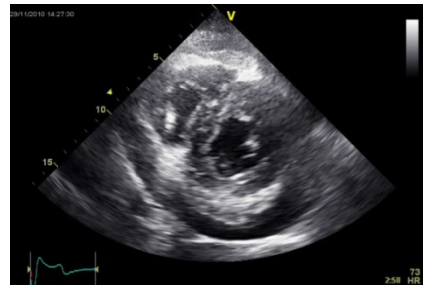
IT /IM
Rétrécissement
Aortique = 6 à 16%

Vasculaire



Ischémie
Nécrose

Pericarde



Epanchement
Péricardique
Tamponnade

Cellules "électriques"

Trouble du rythme : Arythmie, Flutter
Trouble de la conduction : BAV1-2-3

Système Nerveux Autonome

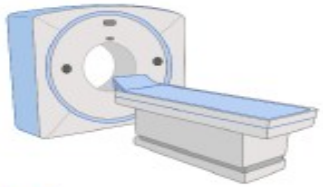
↘ Fréquence Cardiaque
Insufffisance Chronotrope à l'effort
Hypotension Orthostatique

Summary of Prevalence

	HF-PEF	AS+TAVI	HCM
Wild-type-TTR	**13%**	**6-16%**	?
Hereditary-TTR	?	?	**7.6%>65y old**
AL	?	?	?

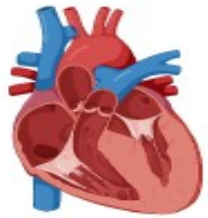
Garcia P and al, ESC position paper 2021

ATTR prevalence in cardiologic « syndromes »



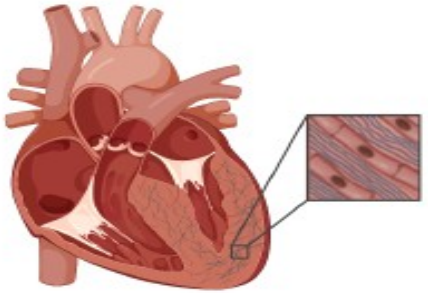
Bone scintigraphy
for non-cardiac reasons:
≥81 years: ~1.3% M, ~0.4% W

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



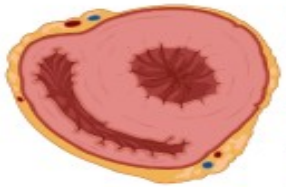
HFpEF: 12%
(95% CI 6-20%)
M 73% (39-100%)
77 years (66-86)
AL-CA 10% (0-40%)

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%

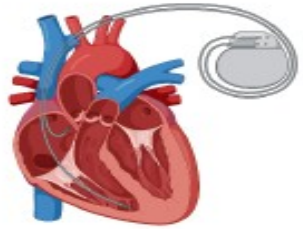
Prevalence of cardiac amyloidosis in screening studies



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

Réseau Amylose

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SPECIAL ARTICLE
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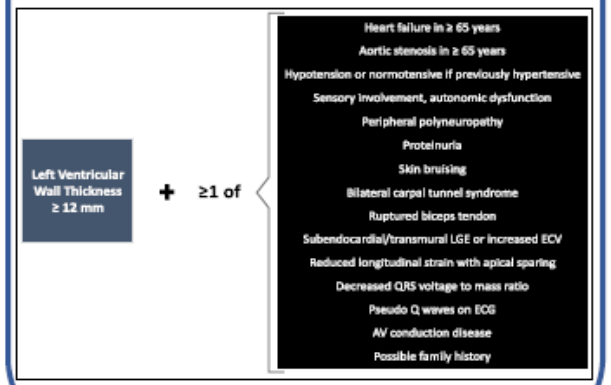
Cardiac amyloidosis

ESC Myocardial WG position paper

SUSPECT

Screen if

Left ventricle wall thickness ≥ 12 mm
&
≥ 1 Red Flag or Clinical Scenario



DIAGNOSIS

Diagnostic criteria

Invasive (all types)	Non-Invasive (only for ATTR)
Cardiac Biopsy positive for amyloid or Extracardiac Biopsy positive for amyloid + Echocardiographic/CMR criteria	Grade 2 or 3 cardiac uptake at diphosponate Scintigraphy + Negative serum free light chains & negative serum and urine immunofixation (SPIE & UPIE) + Echocardiographic/CMR criteria

Diagnostic algorithm

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

Diagnosis made or proceed to **CMR and/or biopsy** according to results

TREATMENT

Cardiac complications and comorbidities

- Heart Failure
- Thromboembolism
- Atrial fibrillation
- Conduction disorders
- Ventricular arrhythmias
- Aortic stenosis

Disease modifying treatment

- **ATTR**: genetic silencers, stabilizers and removers.
- **AL**: chemotherapy and ASCT.
- **AA**: anti-inflammatory, anti-infective and immunosuppressive drugs.

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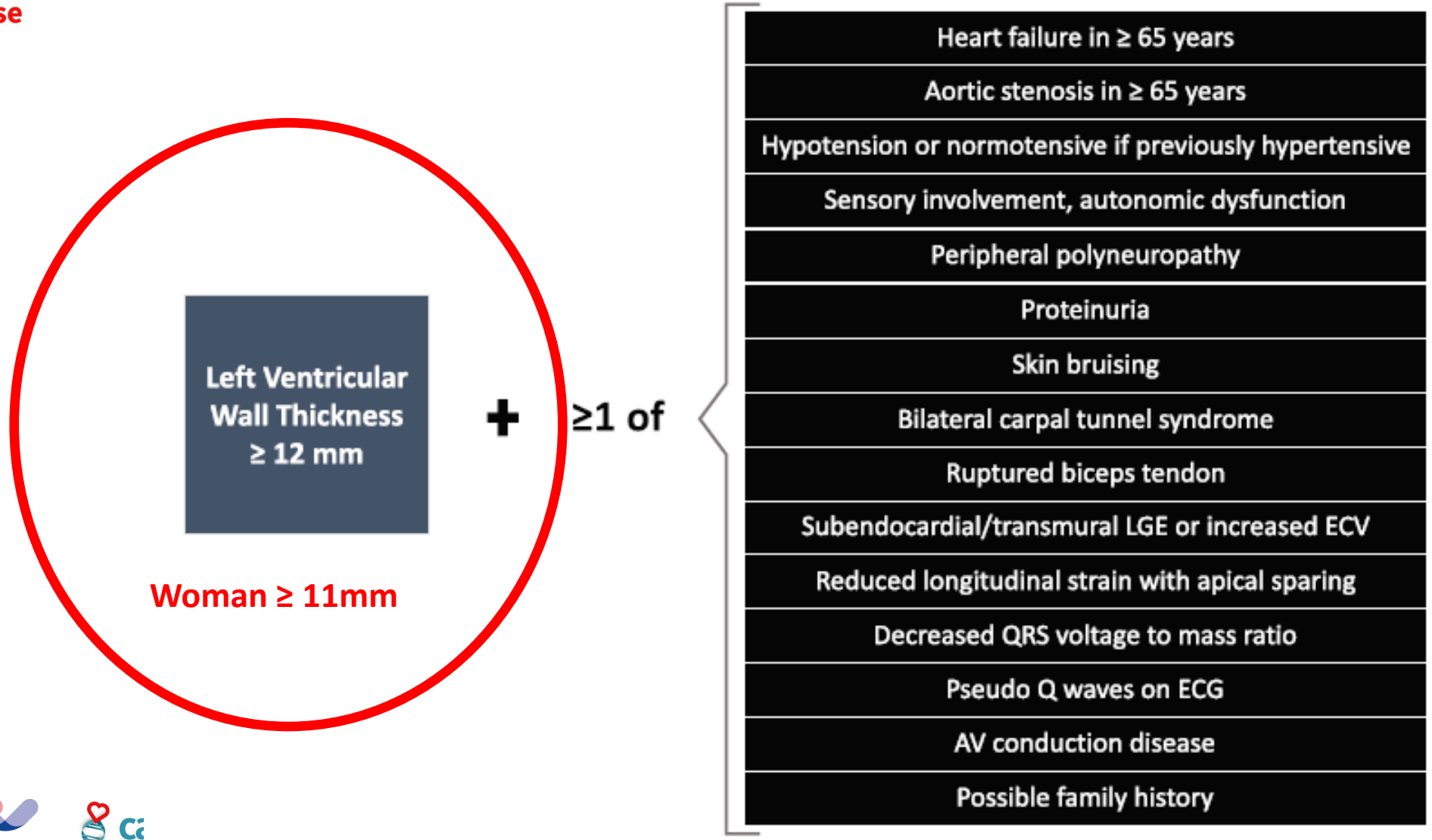
Suspicion of Cardiac Amyloidosis



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Amyloidosis subtypes

Table I Amyloidosis subtypes that affect the heart

Amyloidosis type	Protein	Hereditary	Frequency of heart involvement	Median survival from diagnosis (months)	Usual extracardiac signs
AL	Immunoglobulin light chain	No	70%	24 6 (if HF at diagnosis and not treated)	Nephropathy, proteinuria, autonomic dysfunction, polyneuropathy, macroglossia, spontaneous bruising, liver involvement
ATTRwt	Transthyretin	No	100%	57	CTS, LSS, ruptured biceps tendon
ATTRv	Transthyretin	Yes	30–100% Depending on the mutation	31 (Val142Ile) 69 (non-Val142Ile)	Polyneuropathy, orthostatic hypotension, vitreous opacities, gastrointestinal problems
AA	Serum amyloid A	No	5%	133	Renal impairment (95%), proteinuria, hepatomegaly, gastrointestinal problems
AFib	Fibrinogen α	Yes	Rare	180	Renal impairment, proteinuria
AApoAI	Apolipoprotein A-I	Yes	Rare Depending on the mutation	No data. Probably >120	Primarily renal impairment, proteinuria, hepatosplenomegaly, adrenal insufficiency, dysphonia due to laryngeal involvement
AApoAII	Apolipoprotein A-II	Yes	Rare Depending on the mutation	No data	Primarily renal impairment, proteinuria
AApoAIV	Apolipoprotein A-IV	No	Unknown	79	Primarily renal impairment
Aβ2M	β2-microglobulin	No	80%	No data	Long-term dialysis, CTS, joint problems
AGel	Gelsolin	Yes	5% Primarily conduction disease	Near normal life expectancy	Corneal lattice dystrophy, cutis laxa, drooping eyelids, paresthaesia, proteinuria (rare)

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

Biomarkers, Cardiac-Echo/MRI and Bone scintigraphy

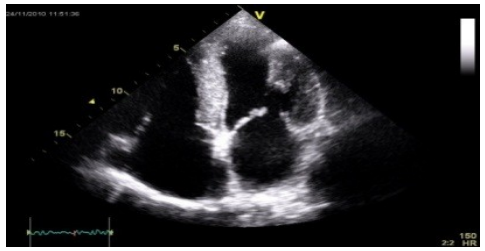
EKG

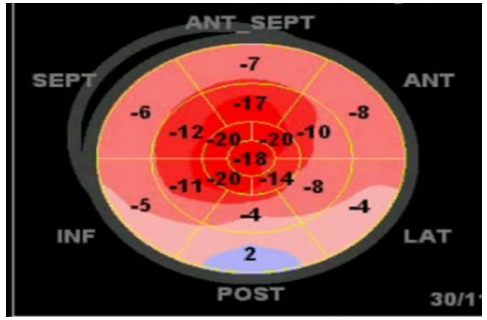
- Low voltage
- Q waves

Biomarkers

- NTproBNP
- Troponine

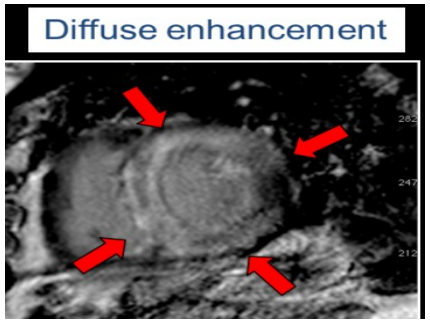
ECHO

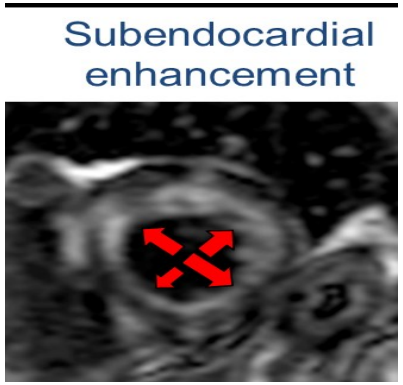




- Hypertrophie biventriculaire
- Profil restricitf
- Anomalie du Strain global
- Aspect « apical sparing »

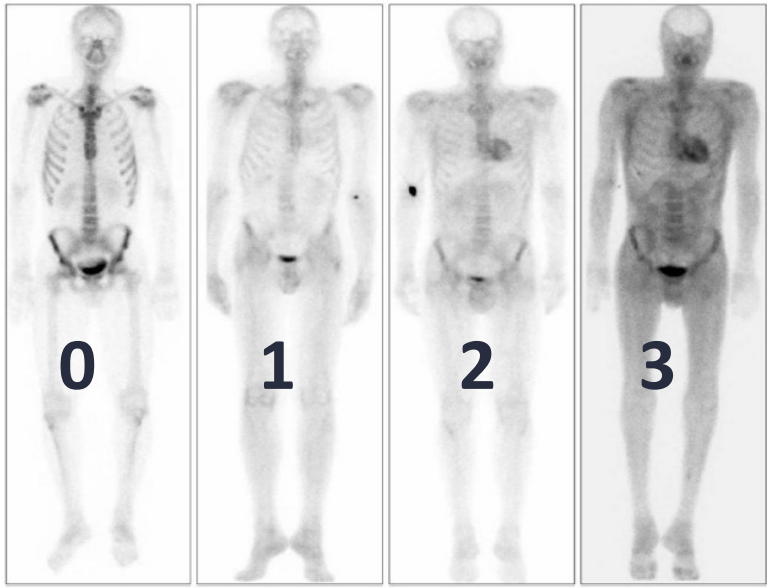
IRM





- Réhaussement Tardif diffus ou circonferenciel

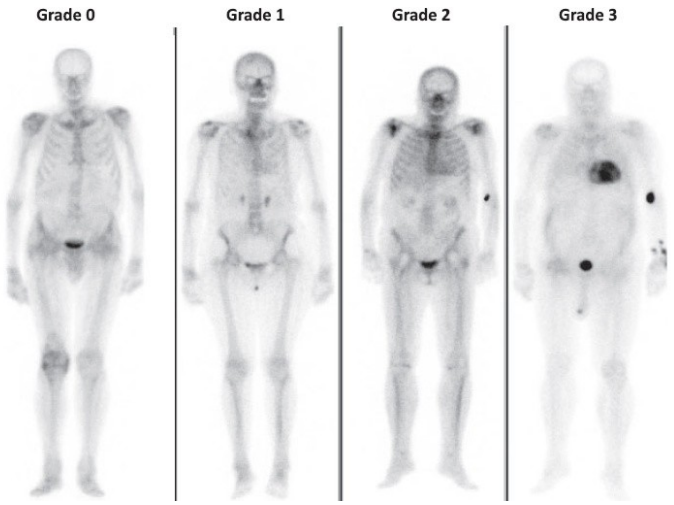
Scintigraphie



- Fixation cardiaque avec Score Visuel de Perrugini ≥ 2 = Amylose TTR
- Absence de Fixation : Ne permet pas d'éliminer une amylose AL

Brun S et al, Open Heart 2020; Maurer MS et al, Circ Heart Fail 2019

ESC Cardiac AmyloidosisDiagnosis 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

Grade 1

Histological confirmation (cardiac/extracardiac) **to diagnose**

Scintigraphy grade 0 Haematologic tests +

AL amyloidosis?

CMR negative

Amyloidosis unlikely

CMR + or inconclusive

Histological confirmation (cardiac/extracardiac) **to diagnose**

Scintigraphy grade 1-3 Haematologic tests +

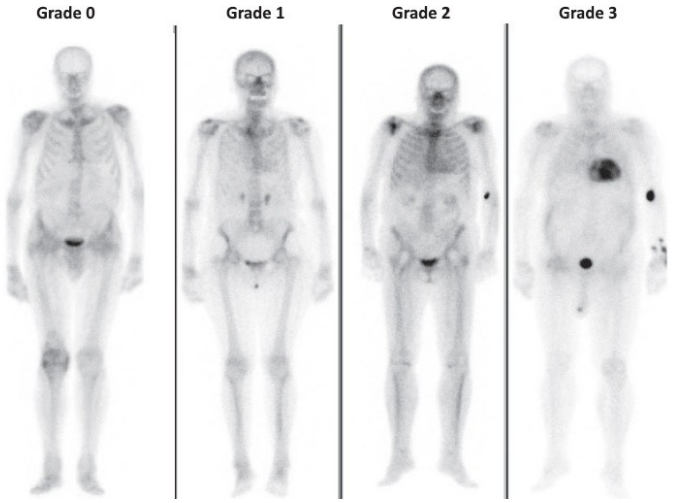
Histological confirmation (usually cardiac) **to subtype**

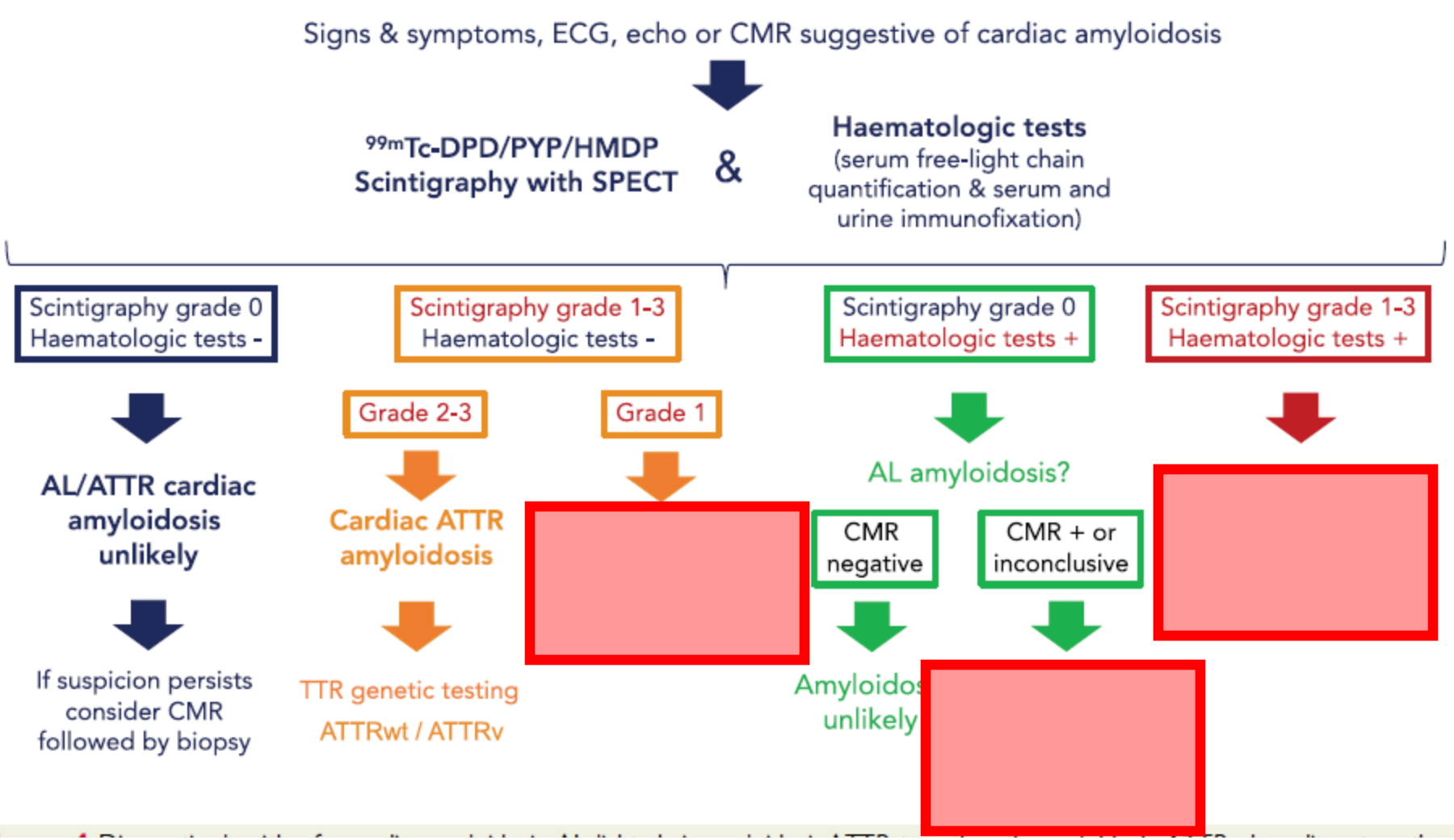
maladies rares

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

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

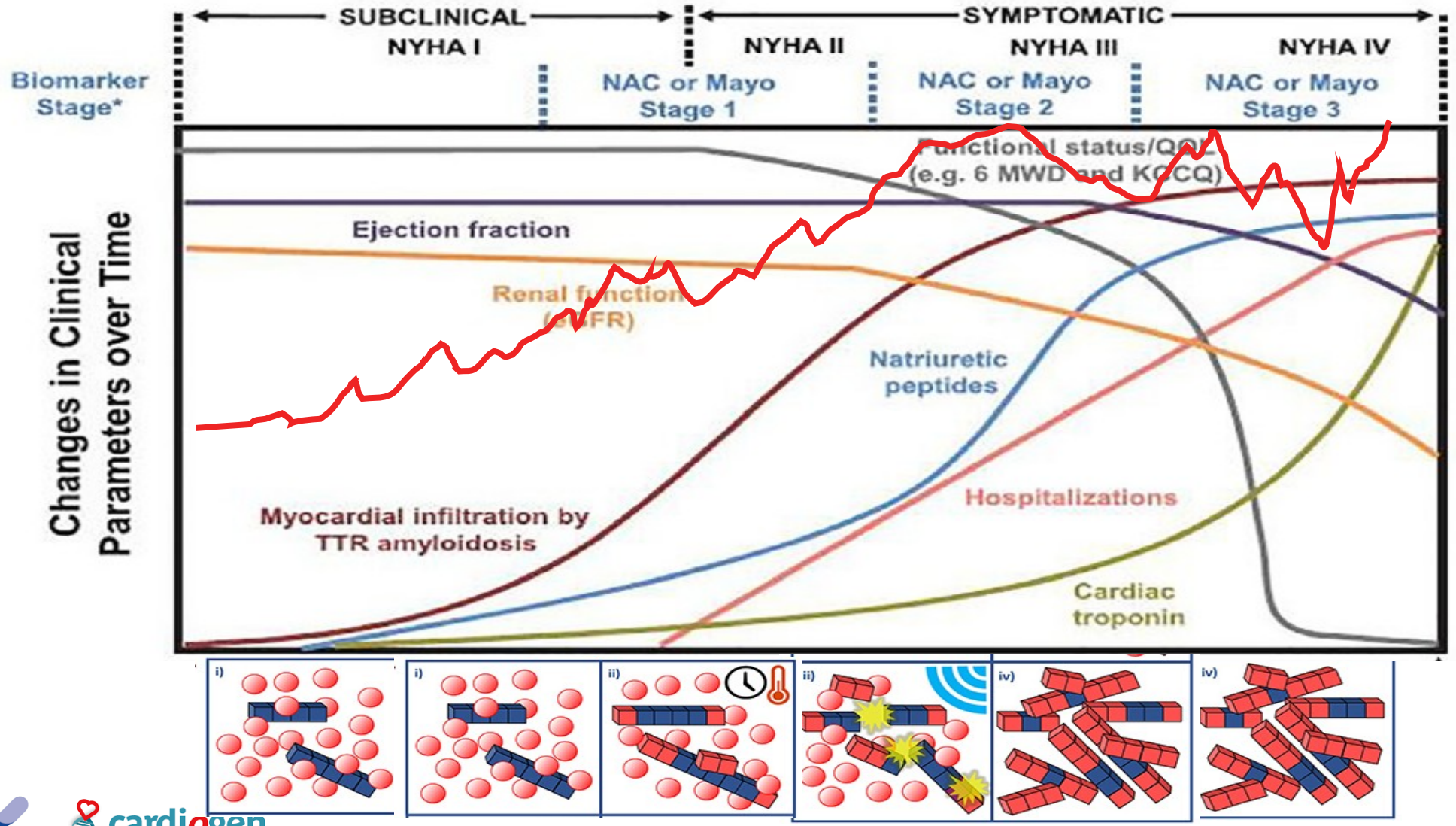
ESC Cardiac AmyloidosisDiagnosis Algorithm
Diagnostic Histological proof is needed in 3 cases





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

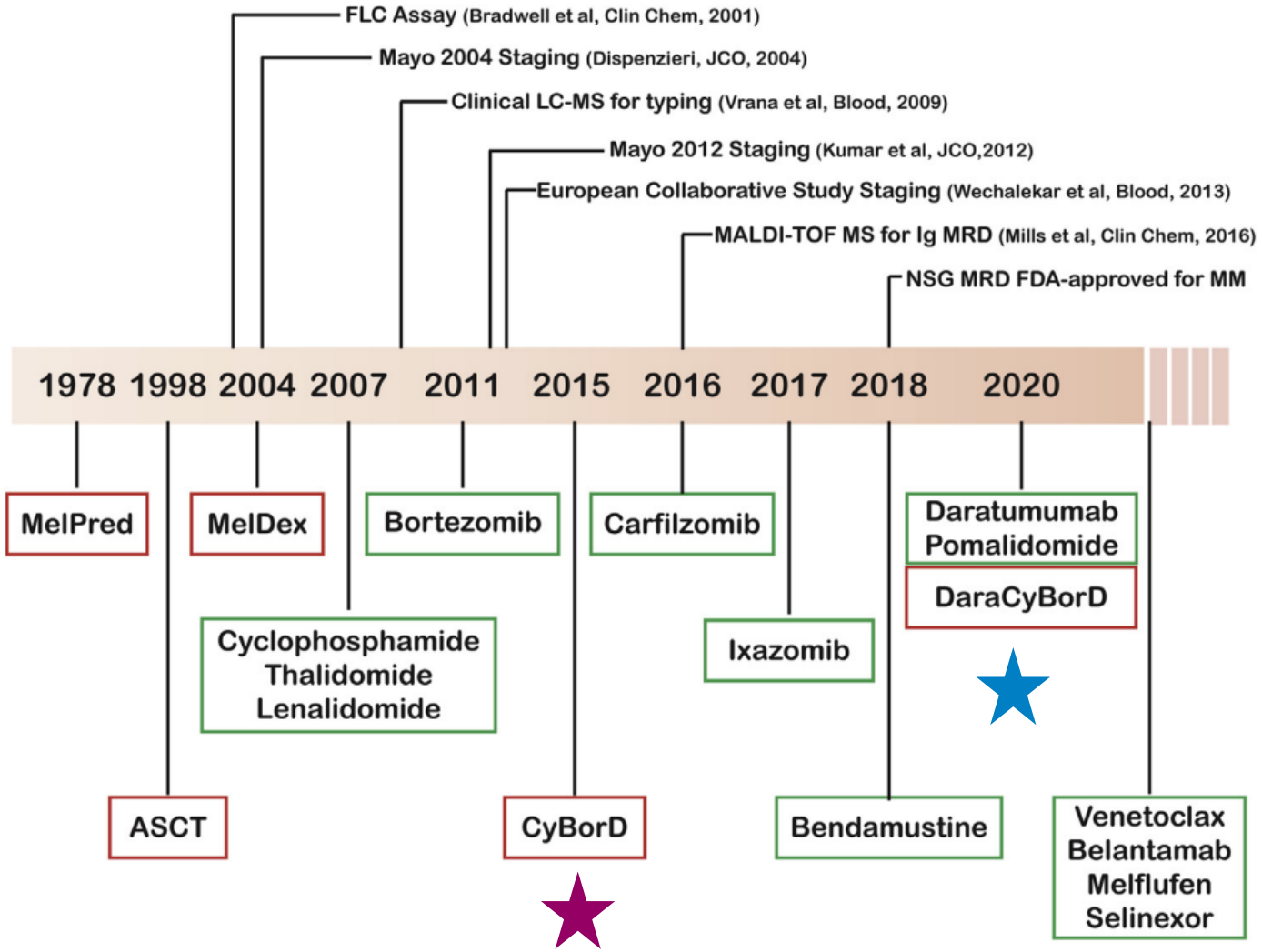
ATTR-CM Natural history of the disease before Tafamidis



Atteinte Multisystémique

Modified from Griffin JM and Maurer M, Trends in Cvar Medicine 2019

AL amyloidosis treatment: chemotherapy and immunotherapy



Giada Bianchi et al, AL Amyloidosis: Current Chemotherapy and Immune Therapy Treatment Strategies: JACC: CardioOncology State-of-the-Art Review, 2021

★ **« CyBorD »**

*Melphalan + **Cyclophosphamide***

Proteasome inhibitor: ***Bortezomid***

Dexaméthasone

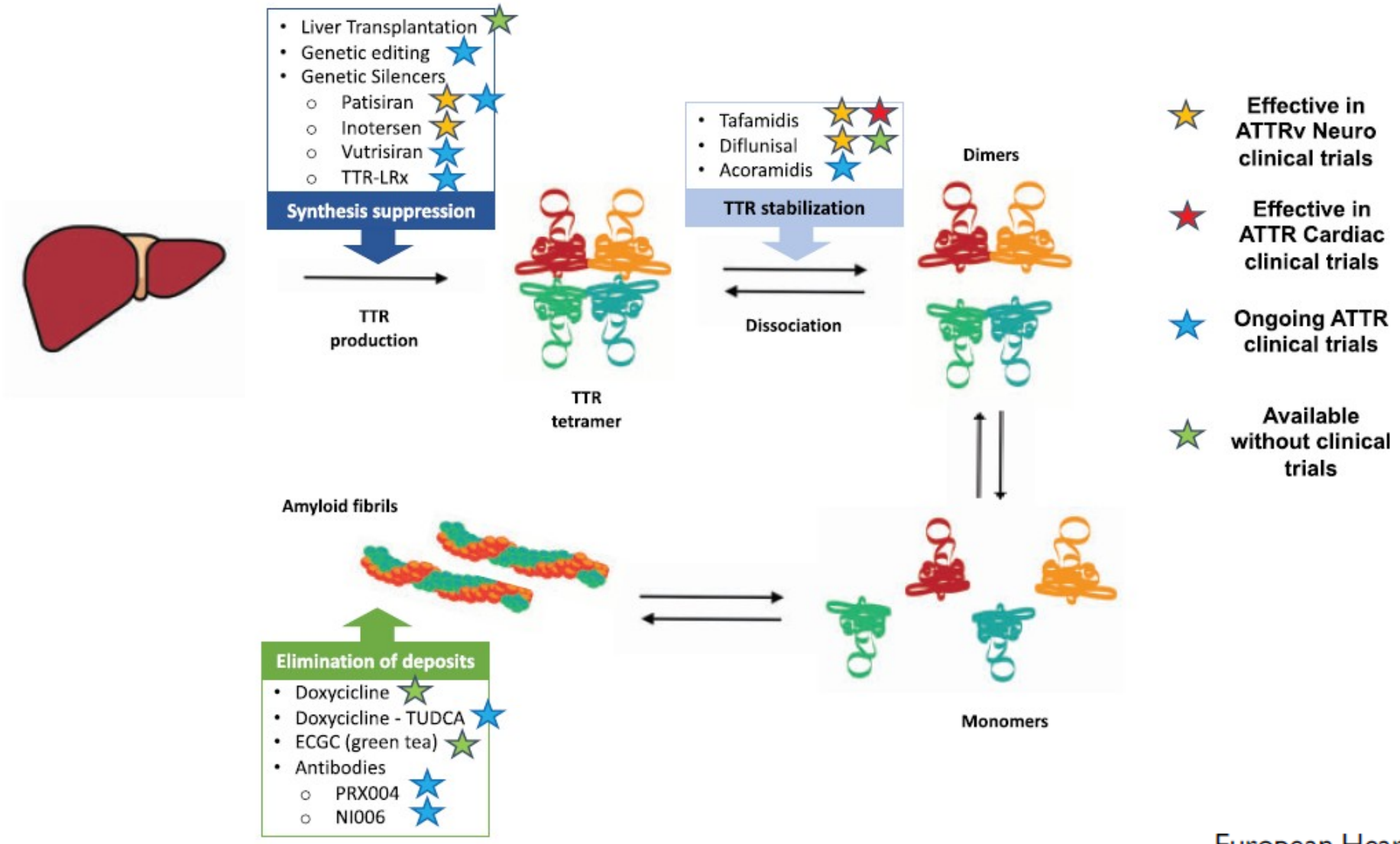
Juin 2020

★ **DaraCyBorD ou « Andromeda »**

CyBorD : *Cyclophosphamide, Bortezomib, Dexaméthasone*

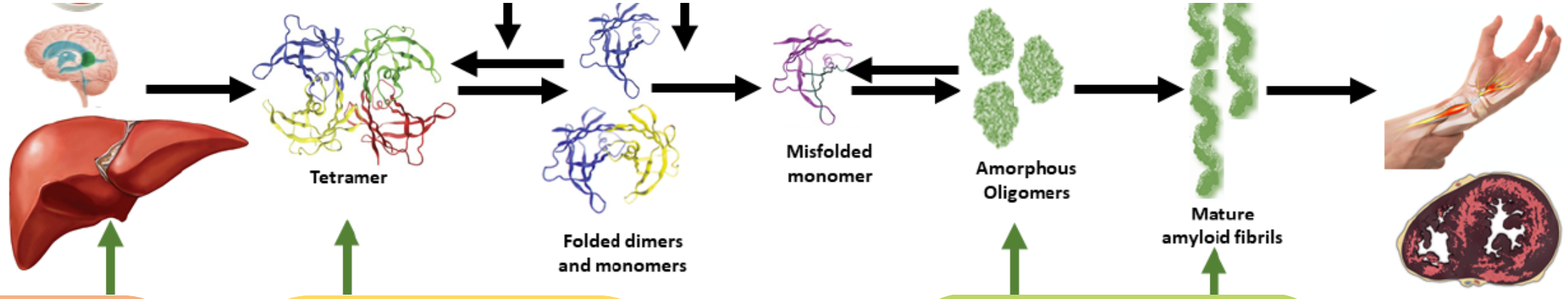
Monoclonnal anti body anti-CD 38 : **DARATUMUMAB**

Available and future disease-modifying therapies in transthyretin amyloidosis (ATTR).



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

ATTR Cardiac Amyloidosis Treatments : A new area in cardiology



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-Tafamidis,

-Acoramidis,

-Diflunisal

Antibodies to clear Amyloidosis Deposits

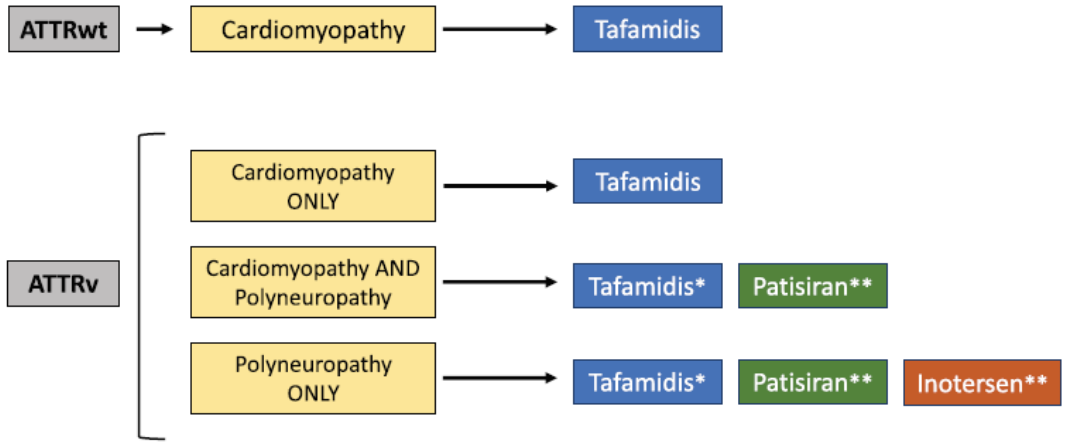
-NI006

-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

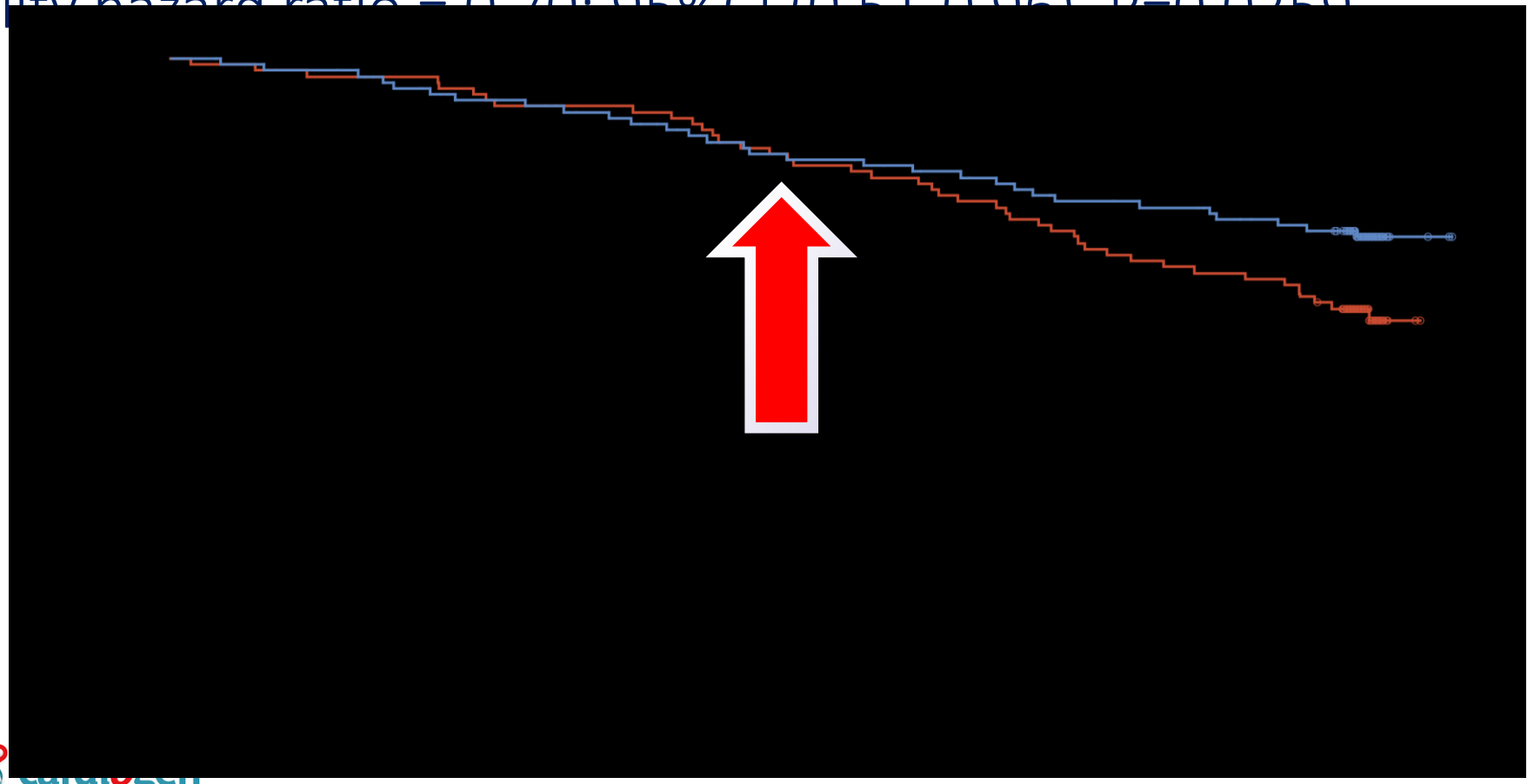
European Heart Journal (2021) **00**, 1–15

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

Tafamidis Reduces All-Cause Mortality of 30%

Tafamidis (78/264, 29.5%) vs. Placebo (76/177, 42.9%)

Mortal

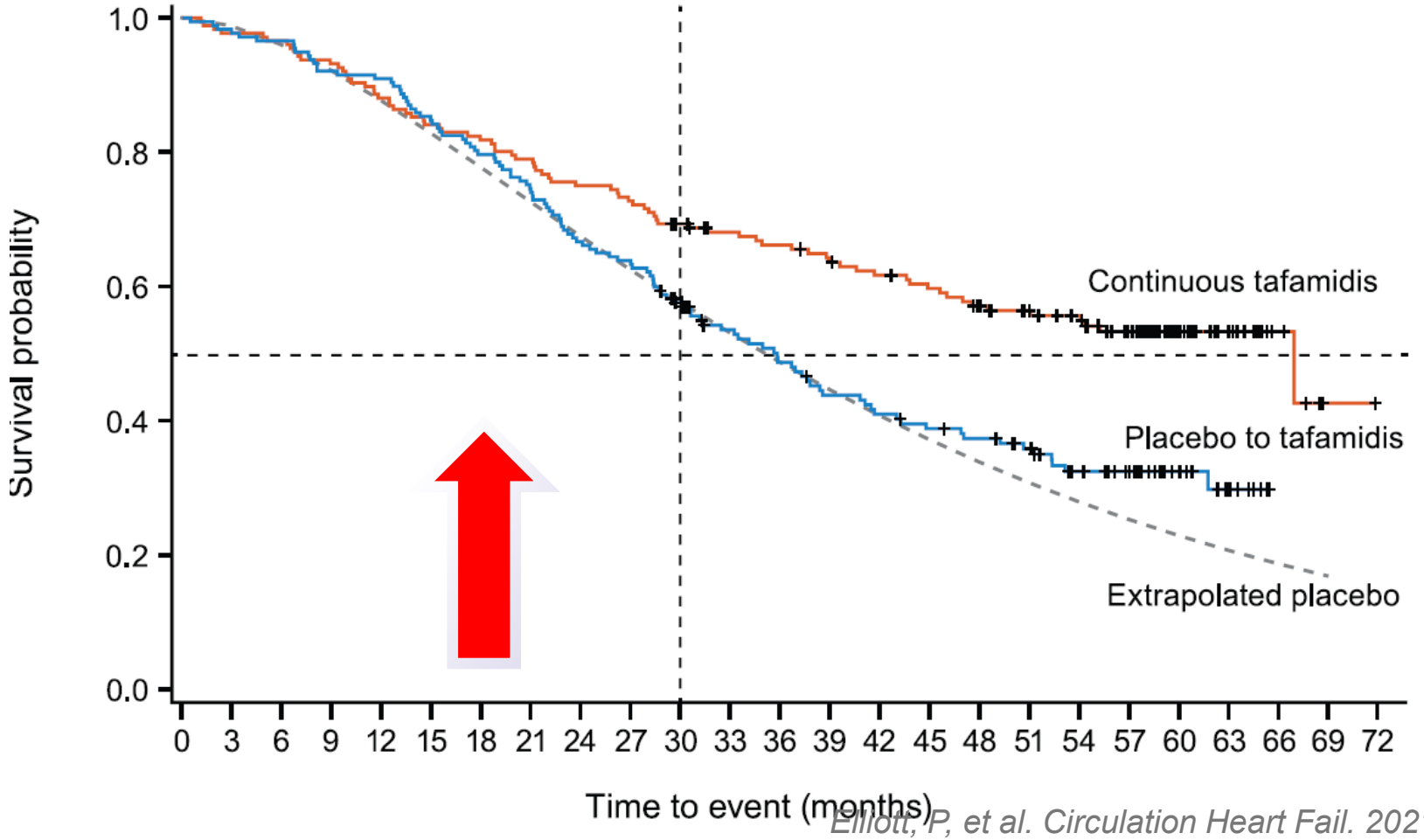


Maurer M et al , New England Journal of Medicine 2018

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

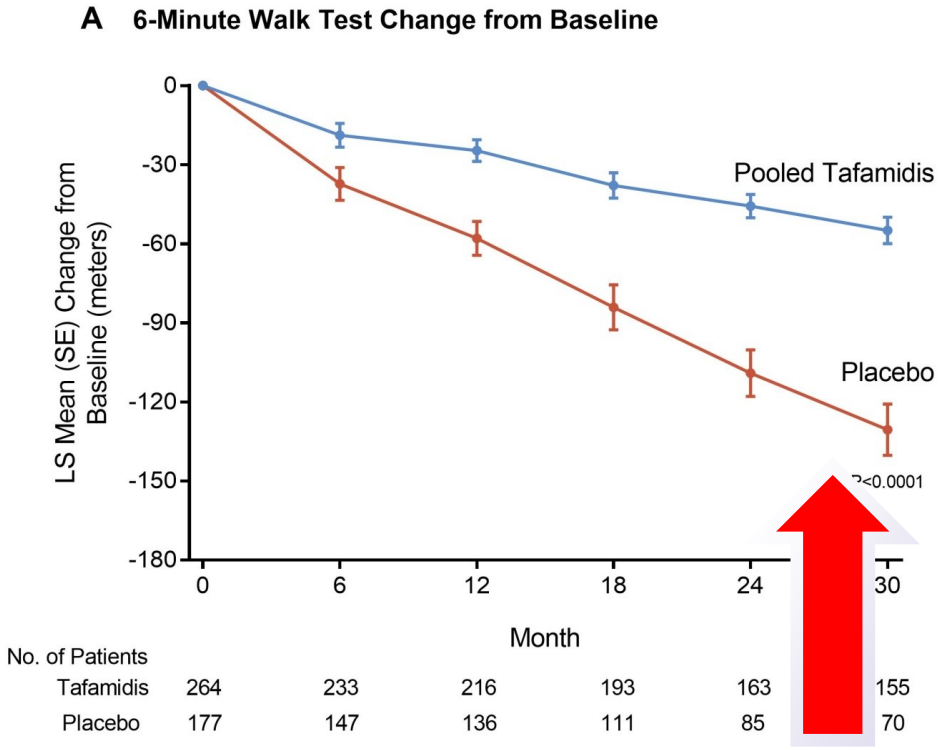
Perry Elliott, MD; Brian M. Drachman, MD; Stephen S. Gottlieb, MD; James E. Hoffman, MD; Scott L. Hummel, MD; Daniel J. Lenihan, MD; Ben Ebede, MS, MBA; Balarama Gundapaneni, MS; Benjamin Li, MS; Marla B. Sultan, MD, MBA; Sanjiv J. Shah, MD

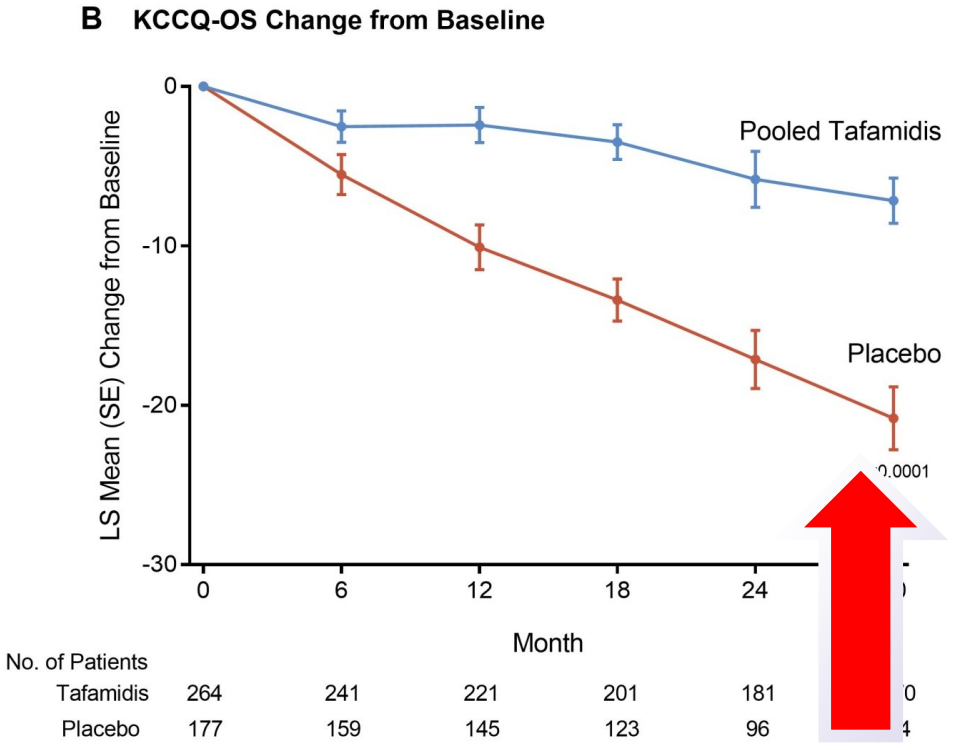
- Median follow-up was 58.5 months in the continuous tafamidis group (n=176) and 57.1 months in the placebo to tafamidis group (n=177).
- 79 (44.9%) deaths with continuous tafamidis and 111 (62.7%) with placebo to tafamidis (hazard ratio, 0.59 [95% CI, 0.44–0.79]; *P<0.001)*.



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

Tafamidis reduces the decline in the 6MWT distance and KCCQ-OS score at 30 months





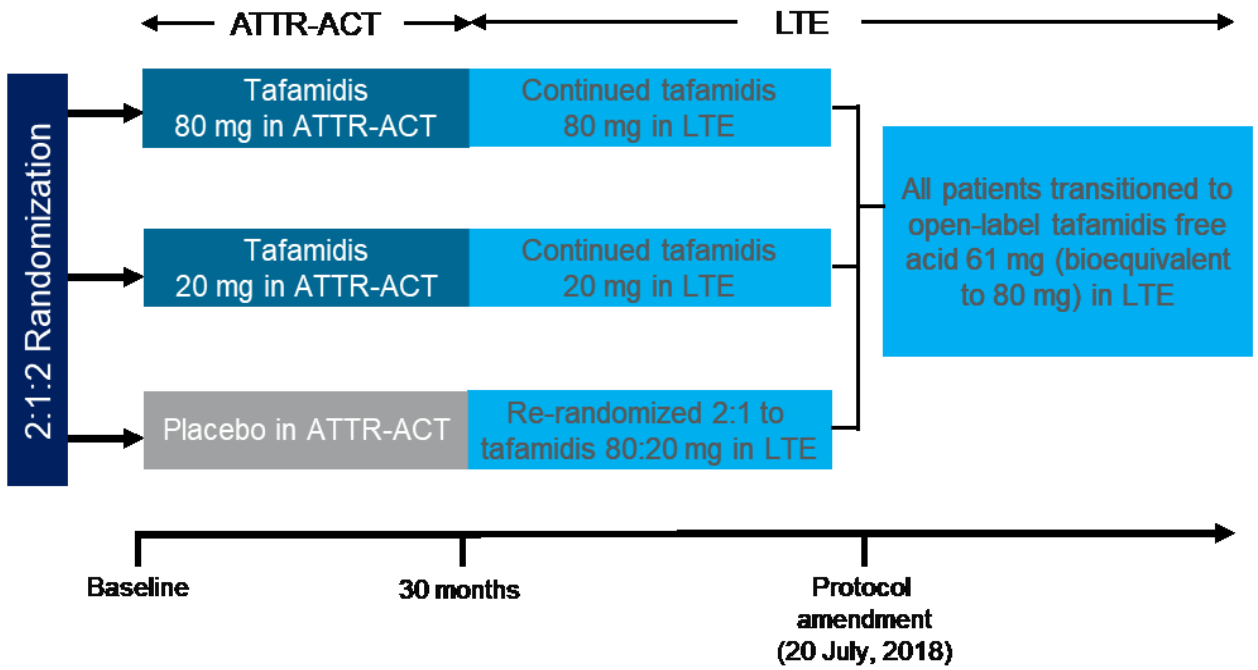
Tafamidis vs Placebo	At 12months	At 30 months
NTproBNP **Least-square mean difference**	−735.14 [95% CI, −1249.16 to −221.13]	−2180.54 [95% CI, −3326.14 to −1034.95]

Maurer M et al , New England Journal of Medicine 2018

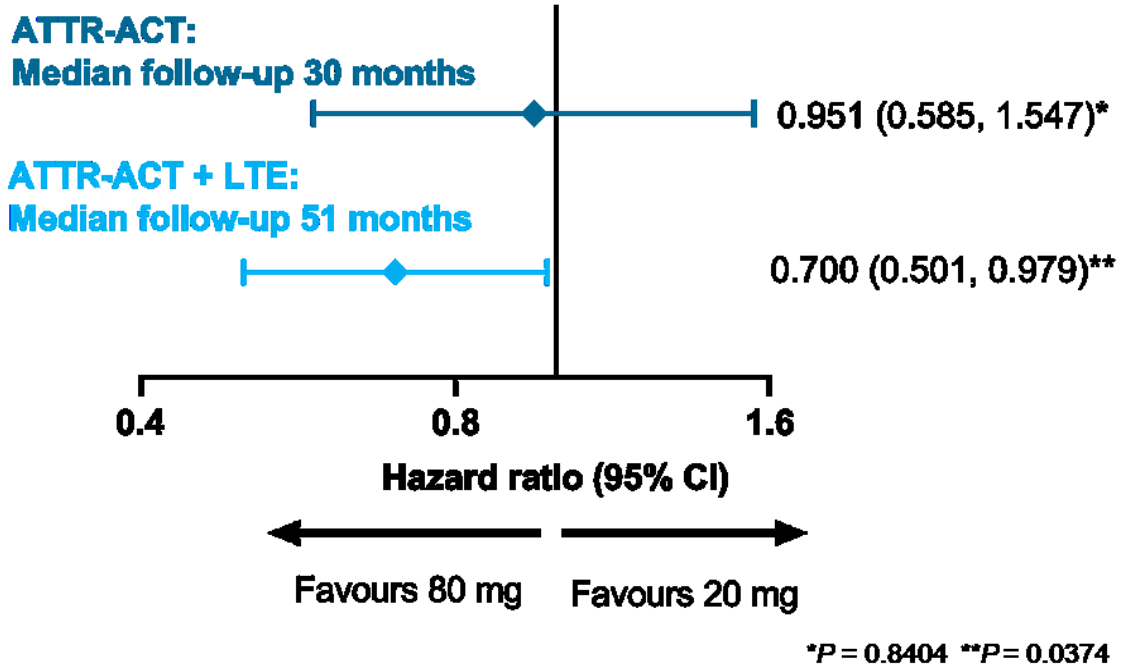
Dose efficacy of Tafamidis in ATTR-CA

Réseau Amylose

After 30 months treatment in ATTR-ACT, patients could continue in the long-term extension trial (LTE)



All-cause mortality was significantly reduced with tafamidis 80 mg / 61 mg compared with tafamidis 20 mg in ATTR-ACT combined with the LTE



*P = 0.8404 **P = 0.0374

maladies rares

cardiogen
filière nationale de santé maladies cardiaques héréditaires ou rares
www.filiere-cardiogen.fr

Damy et al, Eur J Heart Failure 2020

Comparative change of NTproBNP and HS-cTnT before and after Tafamidis

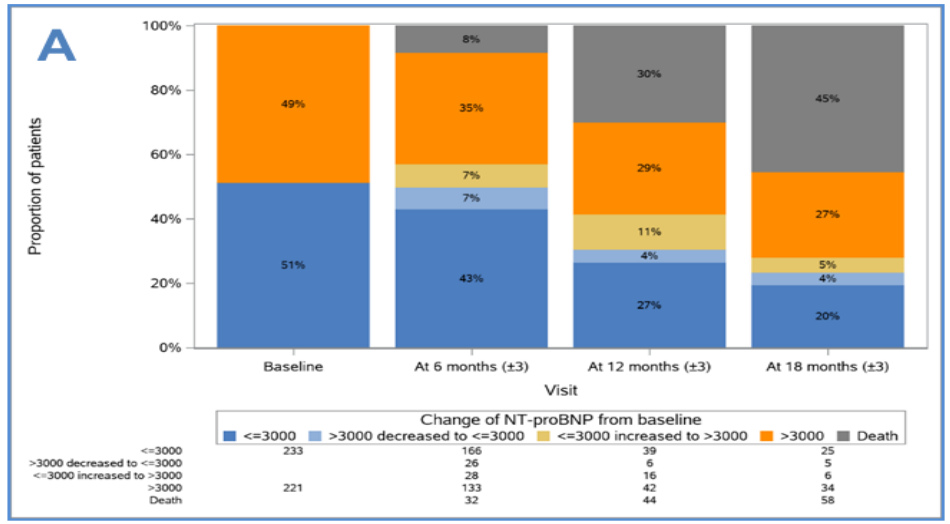
Réseau Amylose

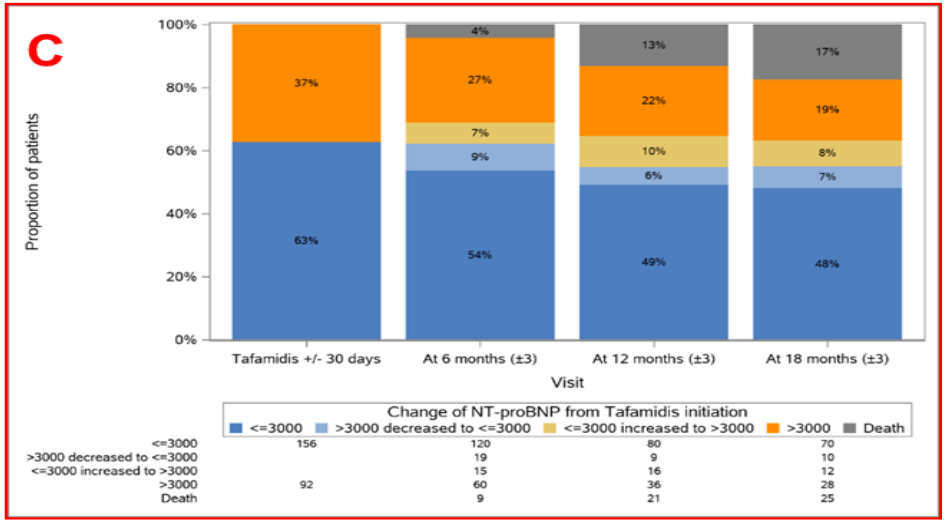
Cohort A, Before Tafamidis

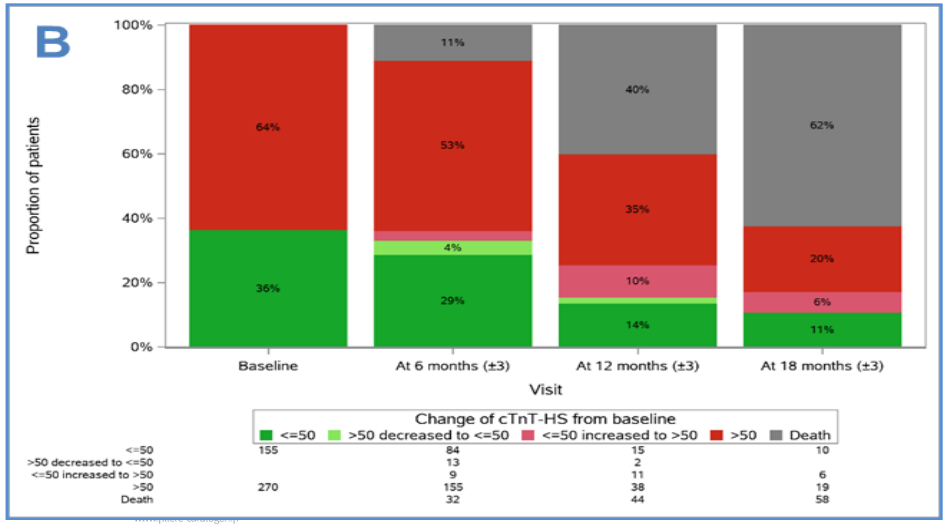
Cohort B, Under Tafamidis

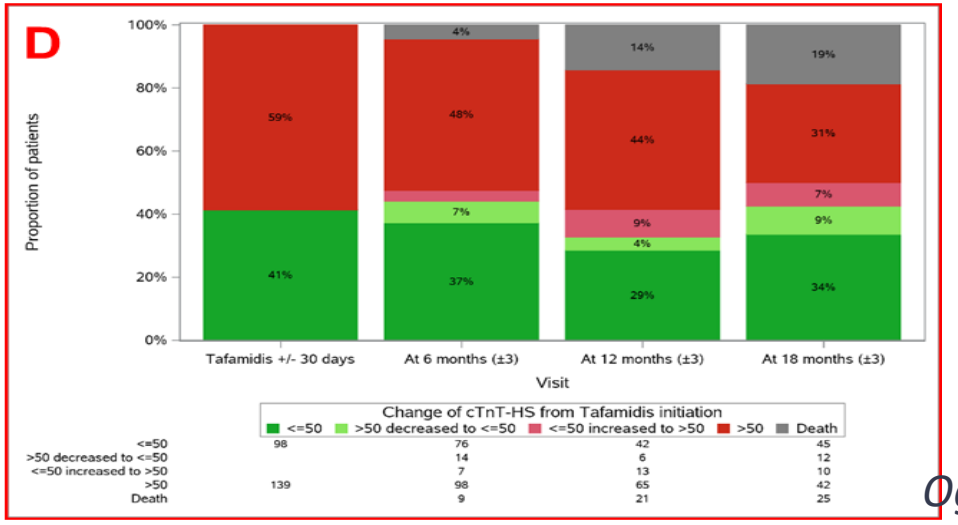
NT-proBNP

cTnT-HS



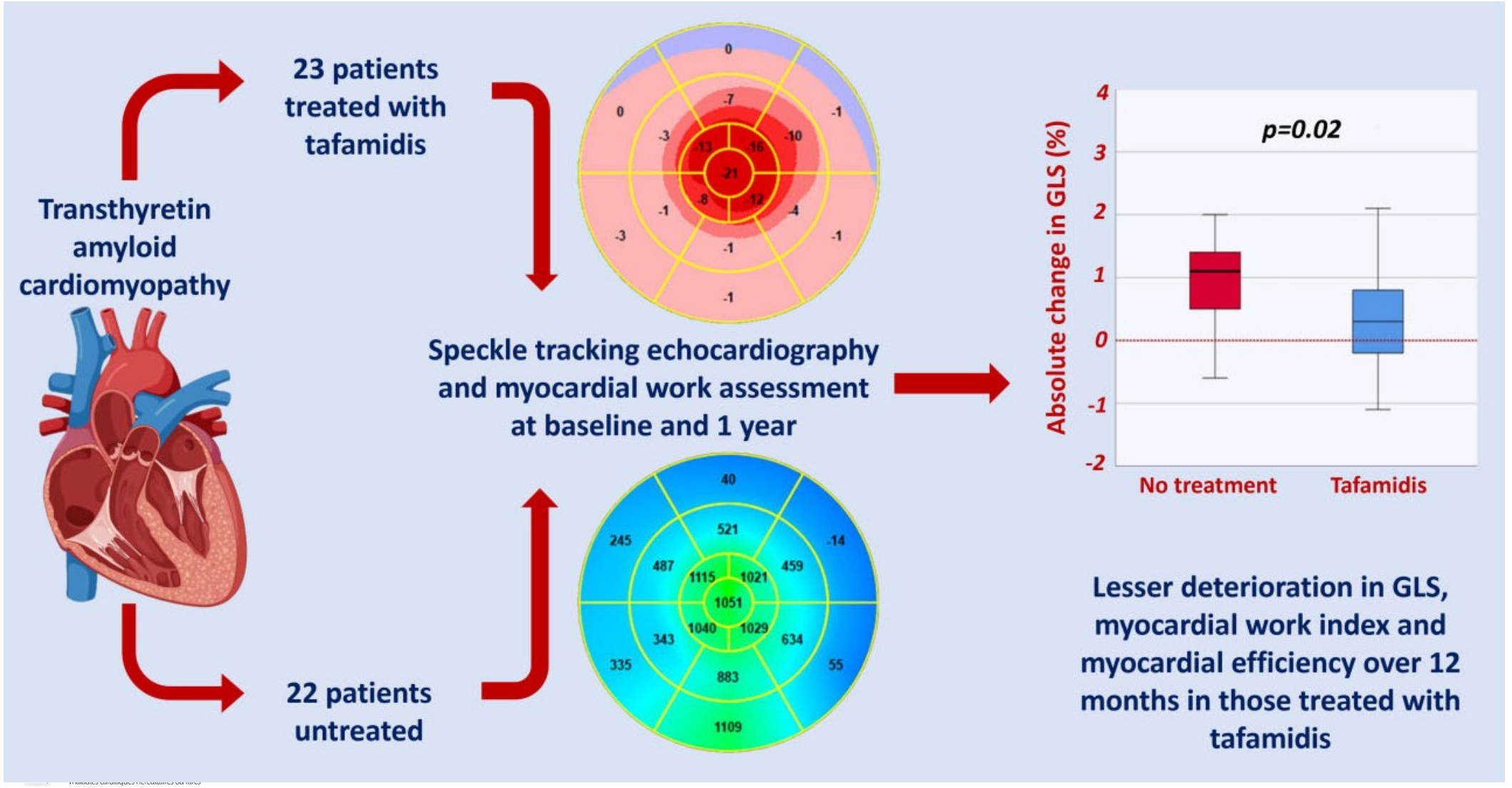






Oghina S et al, JCM 2021

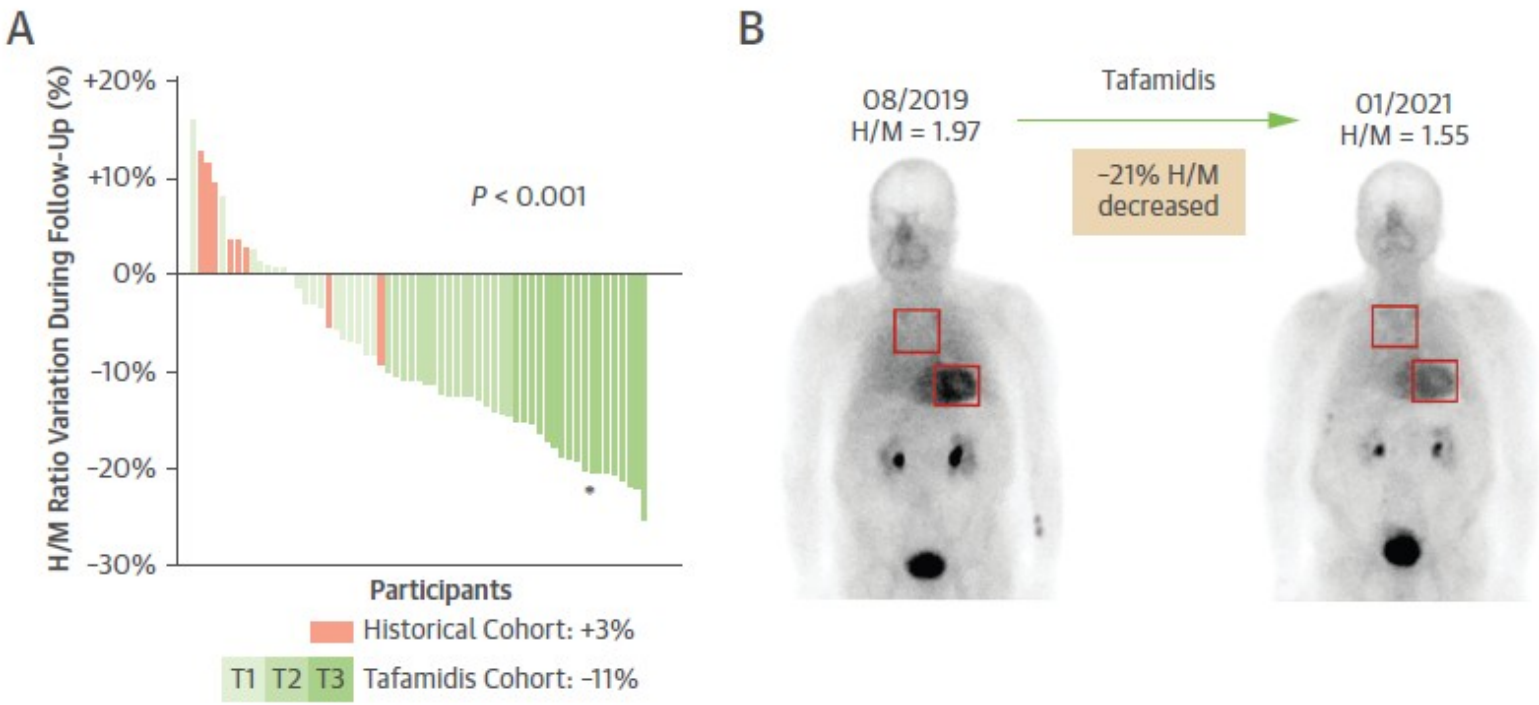
Effect of tafamidis on global longitudinal strain and myocardial work in transthyretin cardiac amyloidosis



Giblin T and al European Heart Journal - Cardiovascular Imaging (2022) 23, 1029–1039

Tafamidis Decreases Cardiac Uptake of 99mTc-HMDP in ATTR Cardiac Amyloidosis

FIGURE 1 Decreased HMDP Cardiac Uptake With Tafamidis Treatment in Patients With ATTR-CM



(A) Progression of ^{99m}Tc-hydroxyl-methylenediphosphonate hydroxymethylene diphosphonate (HMDP) cardiac uptake in the historical and tafamidis cohort. Heart to mediastinum (H/M) ratio decreases in patient with transthyretin cardiac amyloidosis in the tafamidis cohort **(green)** and increases in the historical cohort **(red)**. **(B)** Two whole-body HMDP scans show reduced H/M ratio from patient (indicated with an asterisk **[*]**) following tafamidis treatment.

- Confirmed by :
- Monitoring tafamidis treatment with quantitative SPECT/CT in transthyretin amyloid cardiomyopathy
- *René Rettl et al,* Eur Heart J Cardiovasc Imaging .2023 Mar

- « ATTR-CM patients with a reduction greater than or equal to the median (n = 20) had a significant decrease in SUV retention index (P < 0.001) at follow-up, which translated into significant benefits in serum N-terminal prohormone of brain natriuretic peptide levels (P = 0.006), left atrial volume index (P = 0.038), as well as LV [LV global longitudinal strain: P = 0.028, LV ejection fraction (EF): P = 0.027, LV cardiac index (CI): P = 0.034] and right ventricular (RV) [RVEF: P = 0.025, RVCI: P = 0.048] functions compared with patients with a decrease less than the median (n = 20). »

Odouard S and al....Galat A,
JACC CardioVasc Imaging 2022

ATTRibute-CM study design[1,2]

30-month primary endpoint[3]:
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD

Key eligibility criteria

- Subjects with diagnosed ATTR-CM (WT or variant)
- NYHA Class I-III
- ATTR-positive biopsy or 99mTc scan
- Light chain amyloidosis excluded if diagnosis by 99mTc

Screening and randomization

800 mg acoramidis HCl twice daily

N = 421

Placebo twice daily

N = 211

Efficacy assessment included 611 participants in the pre-specified mITT population (eGFR ≥30 mL/min/1.73 m²)

Tafamidis usage allowed after Month 12

800 mg acoramidis HCl twice daily

Open-label extension

6MWD = Six-minute walk distance; NYHA = New York Heart Association; 99mTc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD); mITT = Modified intent-to-treat. eGFR = Estimated glomerular filtration rate.

[1]ClinicalTrials.gov identifier: NCT03860935. [2]Gillmore JD et al. Circulation. 2019;140(1):14214. Oral poster presented at AHA. [3]Primary analysis assessed using the Finkelstein-Schoenfeld method.

Highly statistically significant result achieved on primary and selected secondary endpoints

Primary endpoint[1]	p-value
Hierarchical analysis consisting of: • All-cause mortality[2] • Cumulative frequency of CVH • Change from baseline in NT-proBNP • Change from baseline in 6MWD	p<0.0001
Win Ratio	1.8

58% of ties broken by first two components of Win Ratio analysis

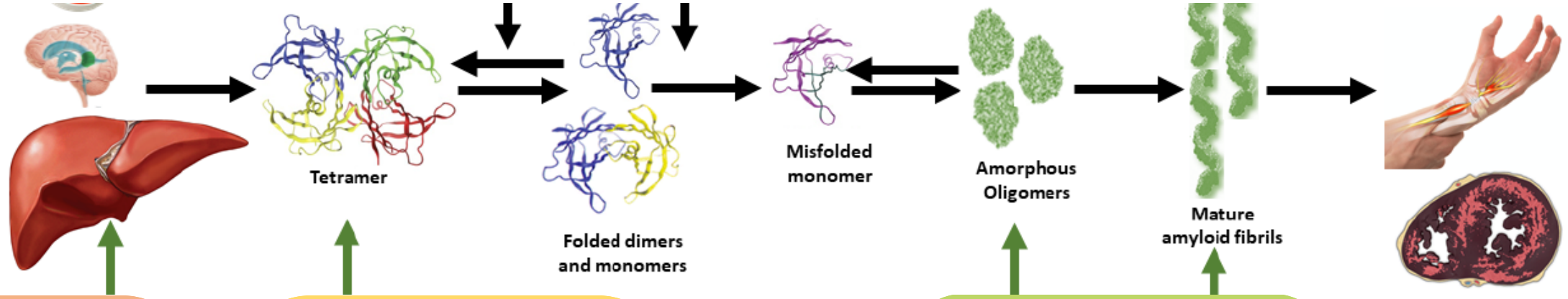
Select secondary endpoints	p-value
Cumulative frequency of CVH[3]	p<0.0001
Change from baseline in 6MWD[4]	p<0.0001
Change from baseline in KCCQ-OS[4]	p<0.0001
Change from baseline in serum TTR[4]	p<0.0001
Change from baseline in NT-proBNP[5]	p<0.0001
All-cause mortality[2,6]	p=0.057

NS on mortality

KCCQ-OS = Kansas City cardiomyopathy questionnaire overall summary score.

[1]Primary analysis assessed using the Finkelstein-Schoenfeld method. [2]Heart transplant and implantation of cardiac mechanical assistance device were treated as death for this analysis. [3]Negative binomial regression with treatment group, stratification factors and the offset term is used to analyze the cumulative frequency of adjudicated CV-related hospitalization.[4]Least squares mean difference change from baseline at 30 months. [5]Ratio of adjusted geometric mean fold change from baseline at 30 months. [6]Assessed by Cochran-Mantel-Haenszel test; p=0.15 as assessed by Cox Proportional Hazard Model.

Les mécanismes d'action des nouveaux traitements



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Antibodies to clear Amyloidosis Deposits

-NI006

-PRX004

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

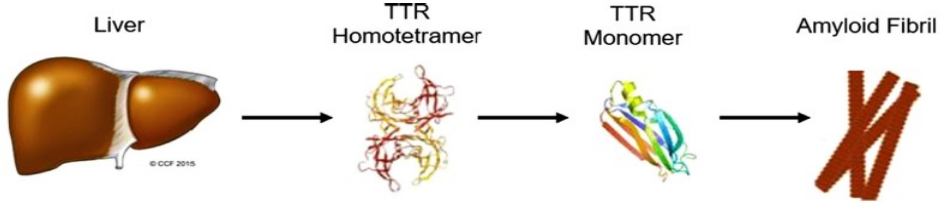
Undergoing ClinicalTrial including ATTR-WT

Drugs	Patisiran	Vutrisiran	ION-682884
Inclusion	**ATTR Cardiomyopathy**	**ATTR Cardiomyopathy**	**ATTR Cardiomyopathy**
Trial	**Phase 3 APPOLO**	**Phase 3 HELIOS B**	**Phase 3 CARDIO TTRansform**
Methodology	Phase 3 / Double blind	Phase 3 / Double blind	Phase 3 / Double blind
Administration	Intravenous	Subcutaneous	Subcutaneous
Where we are?	Inclusion started	Inclusion started	Inclusion pending

Stop
Protein production

Stop/limit
Amyloid fibrills production

Remove
Amyloid Fibrills from Organs



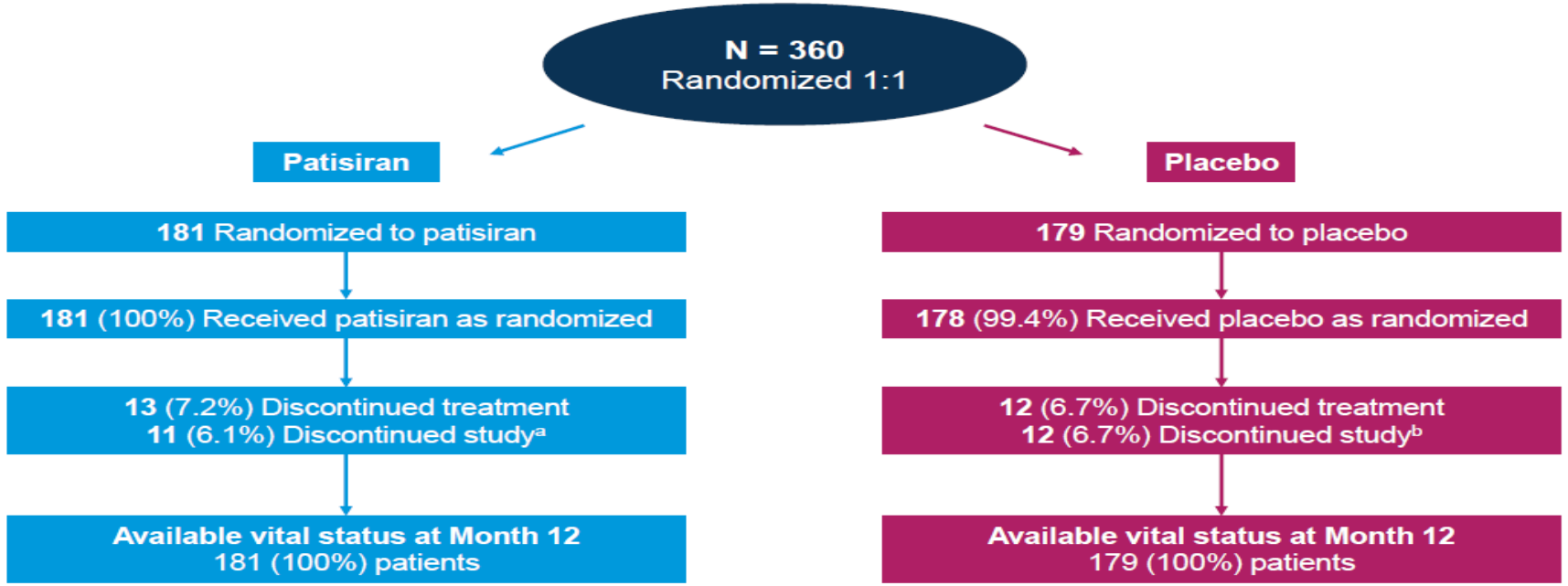
Drugs	NI006-101 –**TTR ANTIBODY**
Inclusion	**ATTR Cardiomyopathy**
Trial	**Phase 3 NI006**
Methodology	Phase ½ / Double blind
Administration	Intravenous
Where we are?	Inclusion started

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)

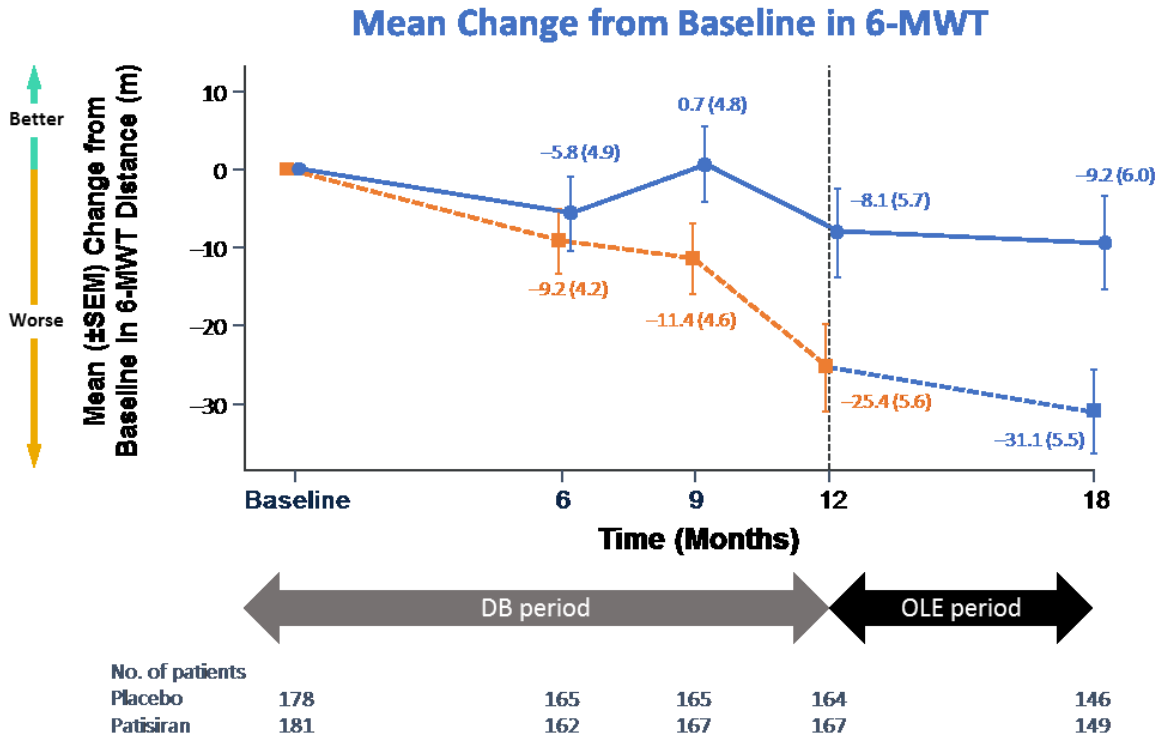


[a]Reasons for discontinuing patisiran treatment: AE (4 [2.2%]), death (3 [1.7%]), other (6 [3.3%]). [b]Reasons for discontinuing placebo treatment: AE (5 [2.8%]), death (3 [1.7%]), physician decision (1 [0.6%]), other (3 [1.7%]). Other excludes A death, lost to follow-up, physician decision, pregnancy, 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***

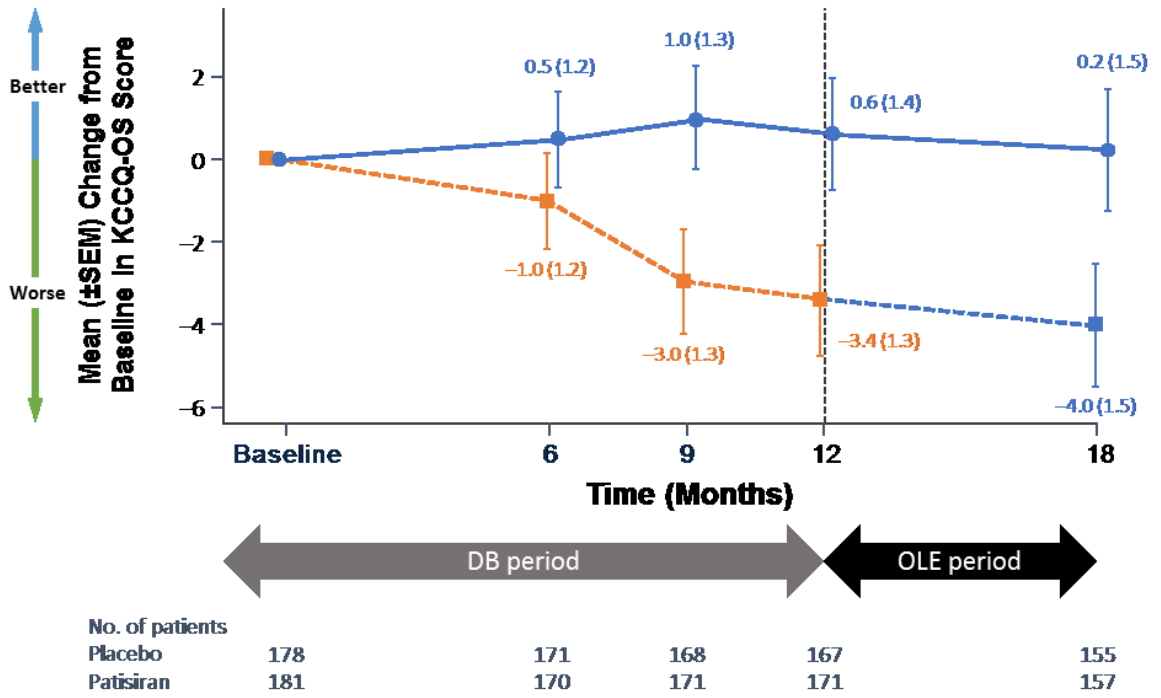
Appolo-B : ATTRv and ATTRwt

Primary criteria



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

Secondary criteria



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

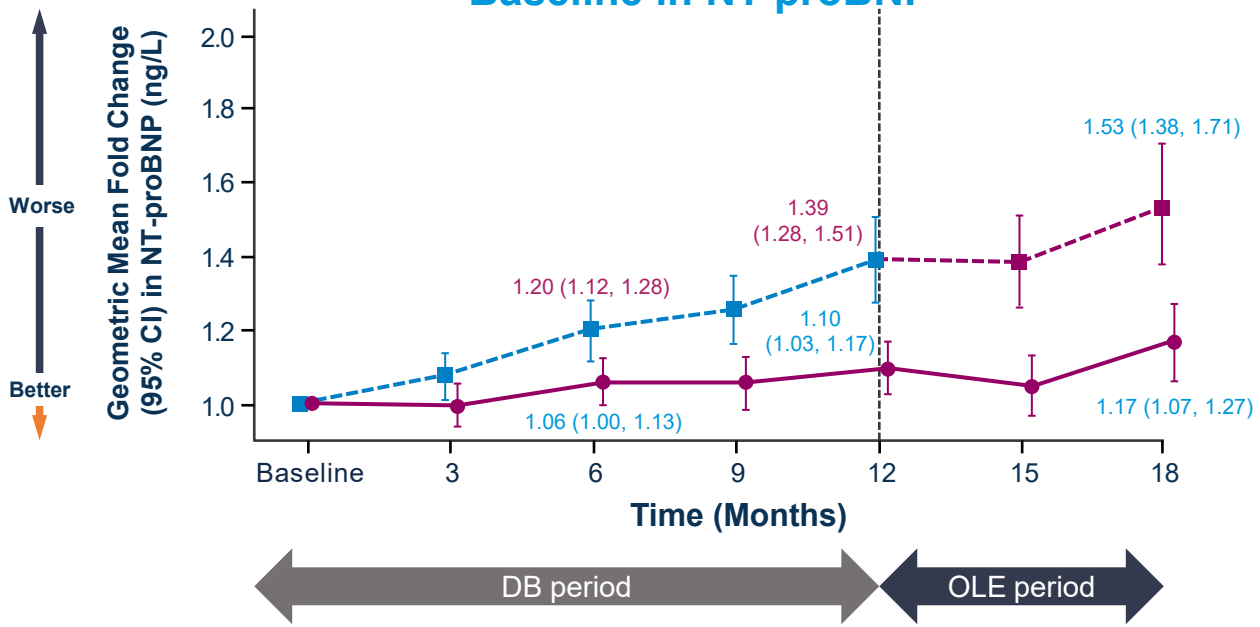
Patisiran

Placebo

Maurer M, ISA 2022

Appolo B : Biomarkers change

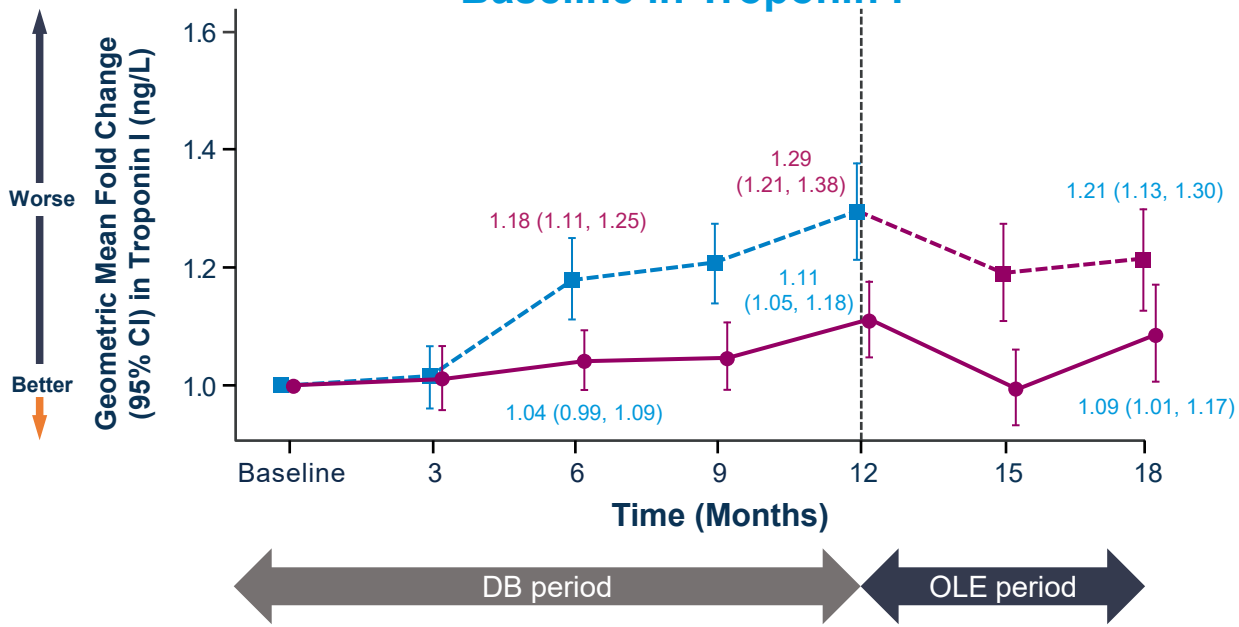
Geometric Mean Fold Change from Baseline in NT-proBNP[a]



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.

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

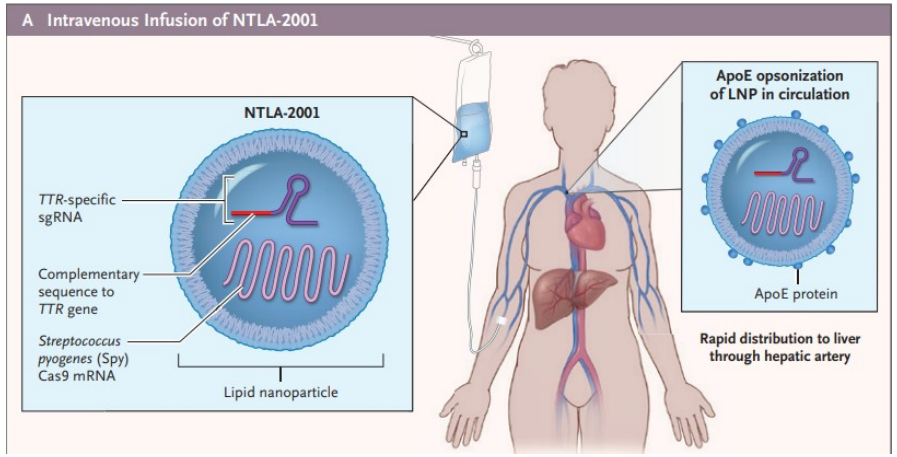
- Distance to 6-MWT
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score.
- Average wall thickness of the left ventricle (LV)
- Global longitudinal strain
- Composite endpoint of all-cause mortality and recurrent all-cause hospitalizations
- All-cause mortality
- Recurrent CV hospitalizations
-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

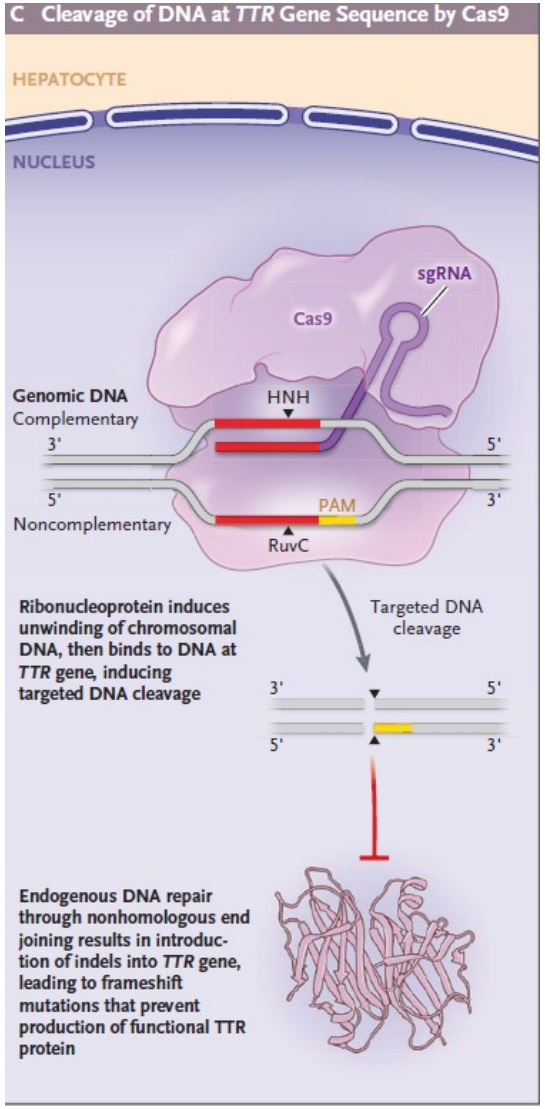
https://www.clinicaltrials.gov/ct2/show/NCT04153149

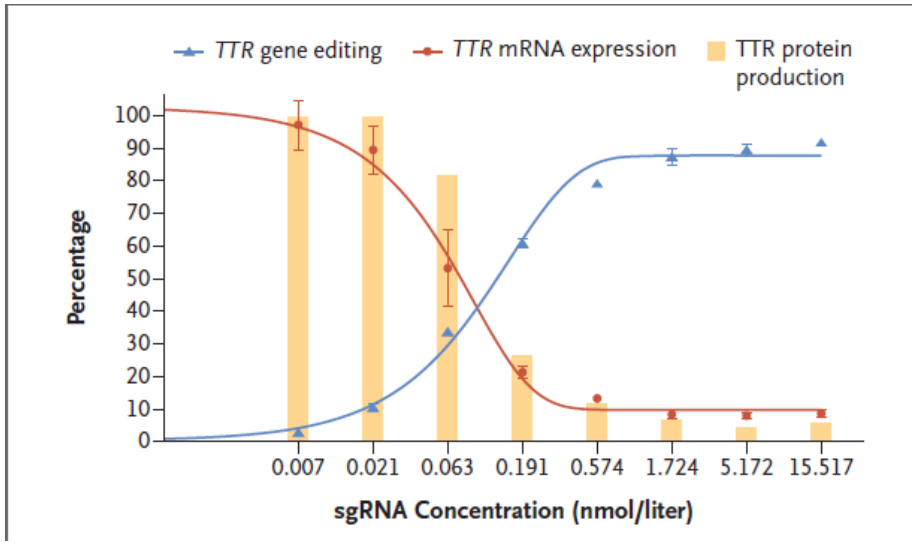
CrisprCas9: First gene therapy results for ATTR : Only one injection

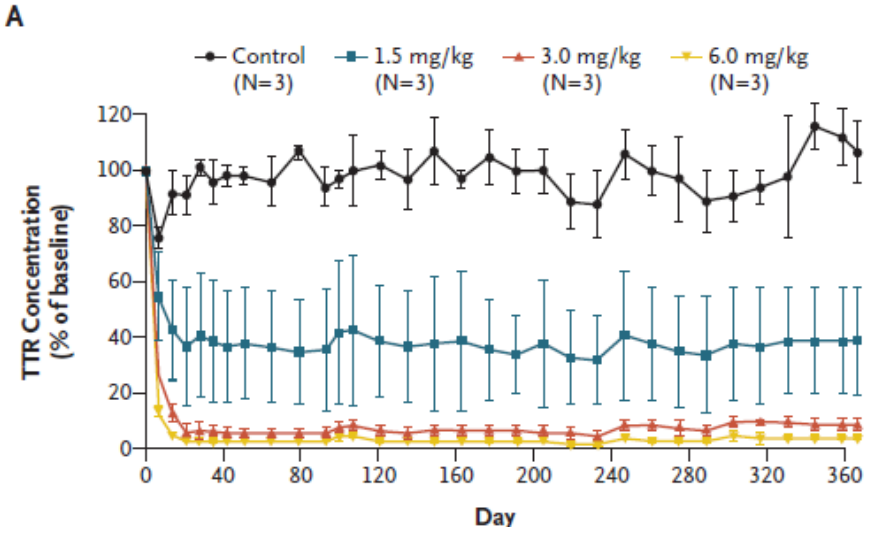
ORIGINAL ARTICLE

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis



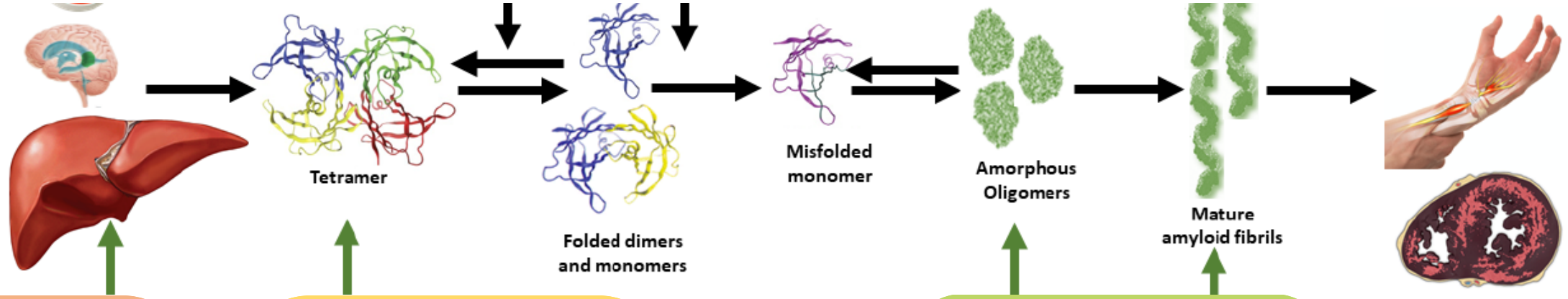






Gillmore J et al, NEJM 2021

Les mécanismes d'action des nouveaux traitements



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TTR Stabilizers

-Tafamidis,

-Acoramidis,

-Diflunisal

Antibodies to clear Amyloidosis Deposits

-NI006

-PRX004

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

ORIGINAL ARTICLE

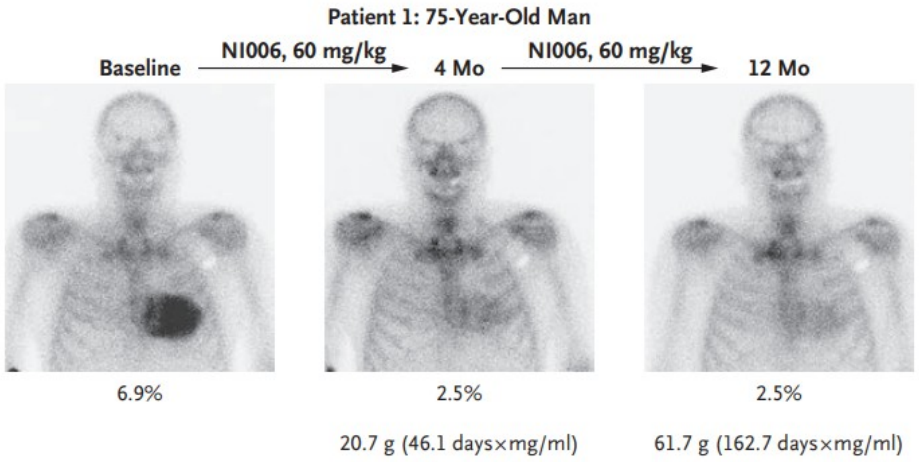
Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

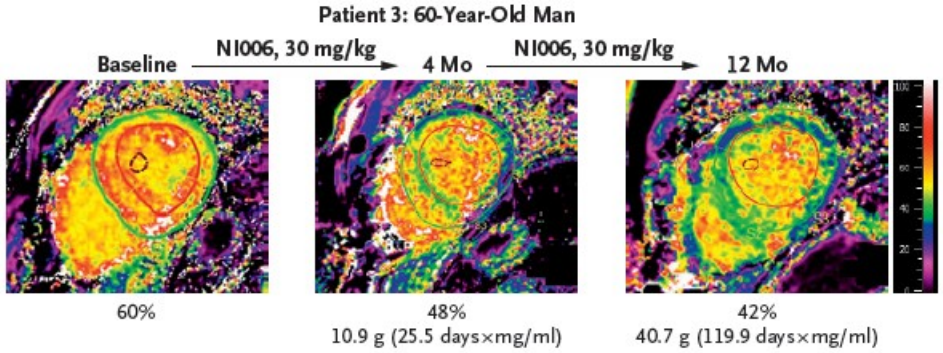
Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph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

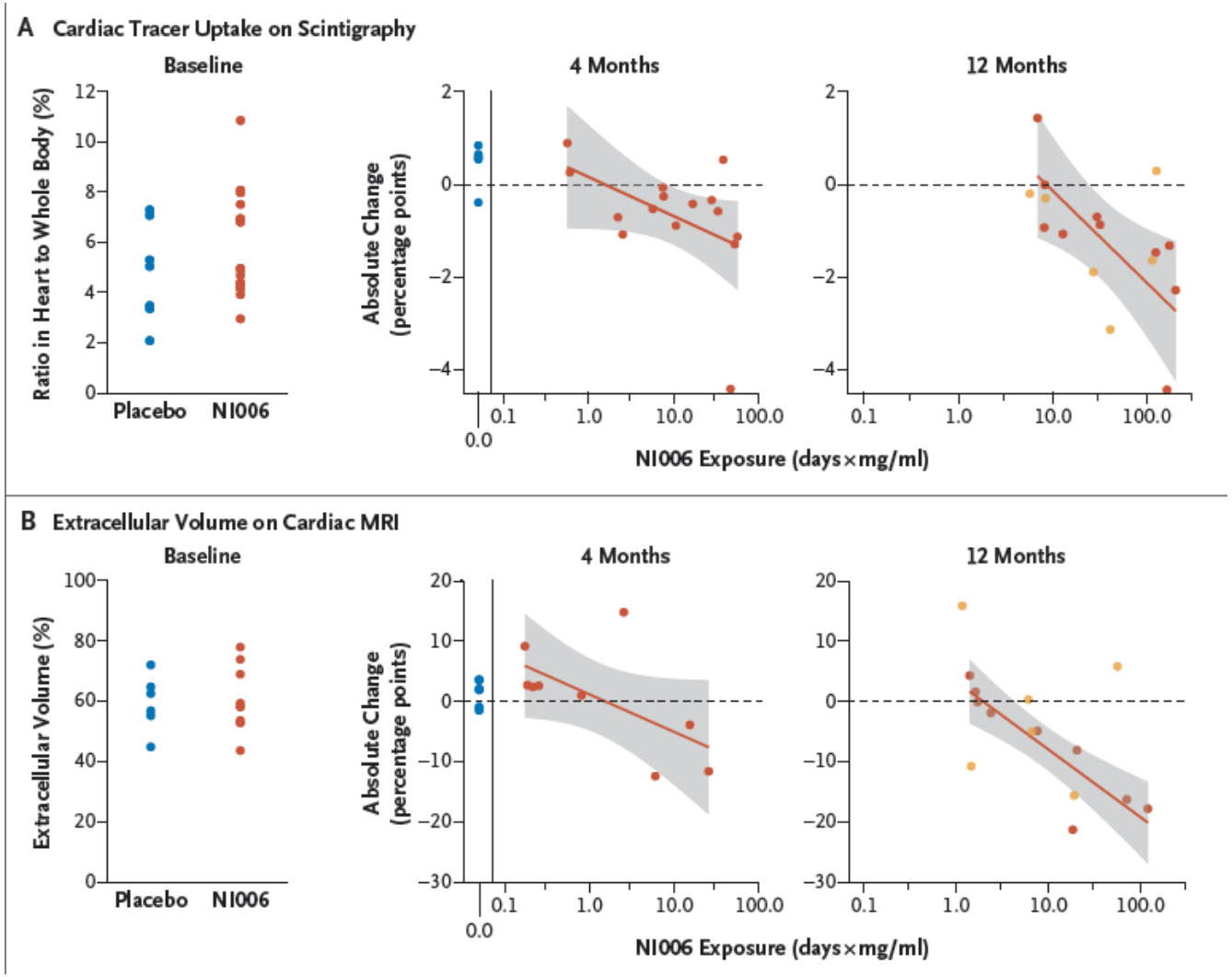
- Double-blind, placebo-controlled, international, multicenter, combined single-ascending-dose and multiple-ascending dose, randomized clinical trial with an openlabel extension phase.
- NI006 or placebo every 4 weeks for 4 months.
- The 4-month placebocontrolled, ascending-dose phase was followed by 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)

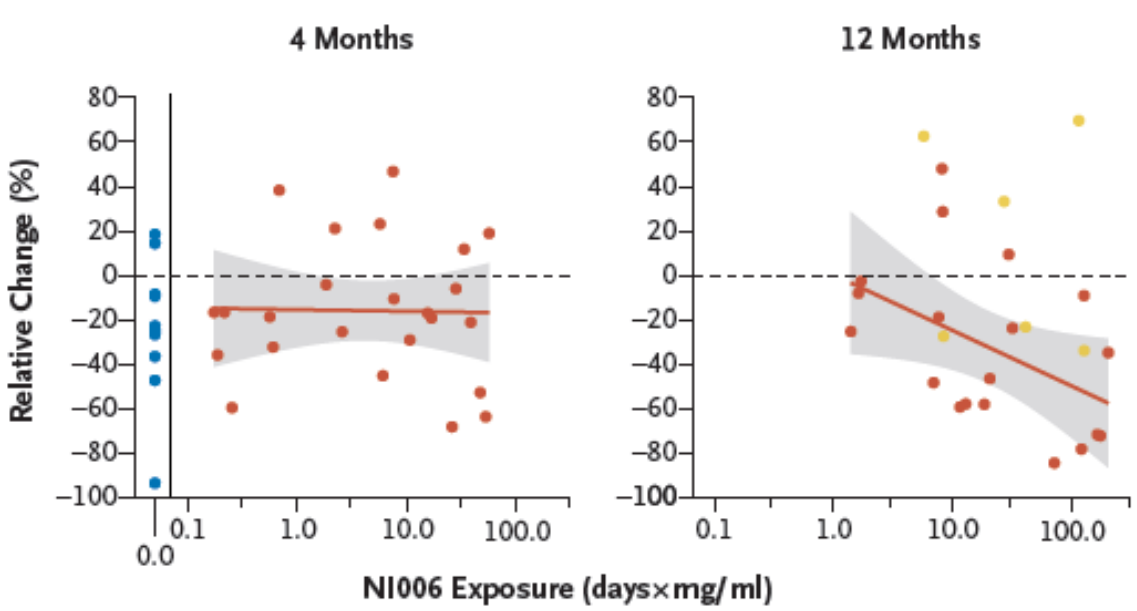


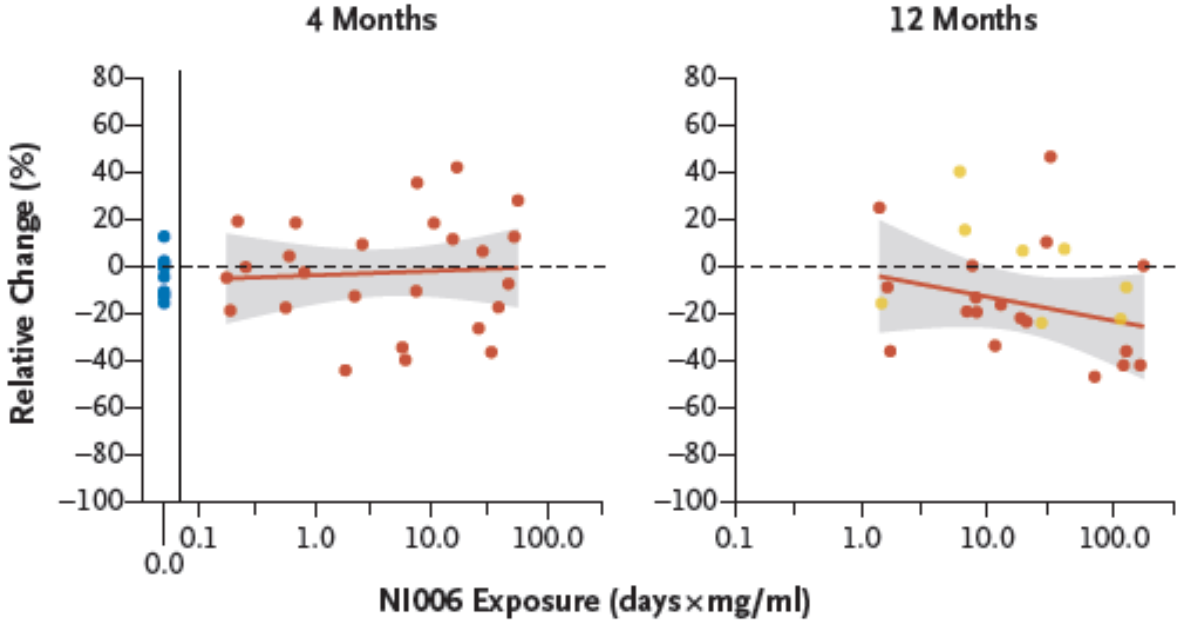




Pablo Garcia-Pavia et al, NEJM 2023, NEJM 2023

Change in NTproBNP and Troponin following NI006

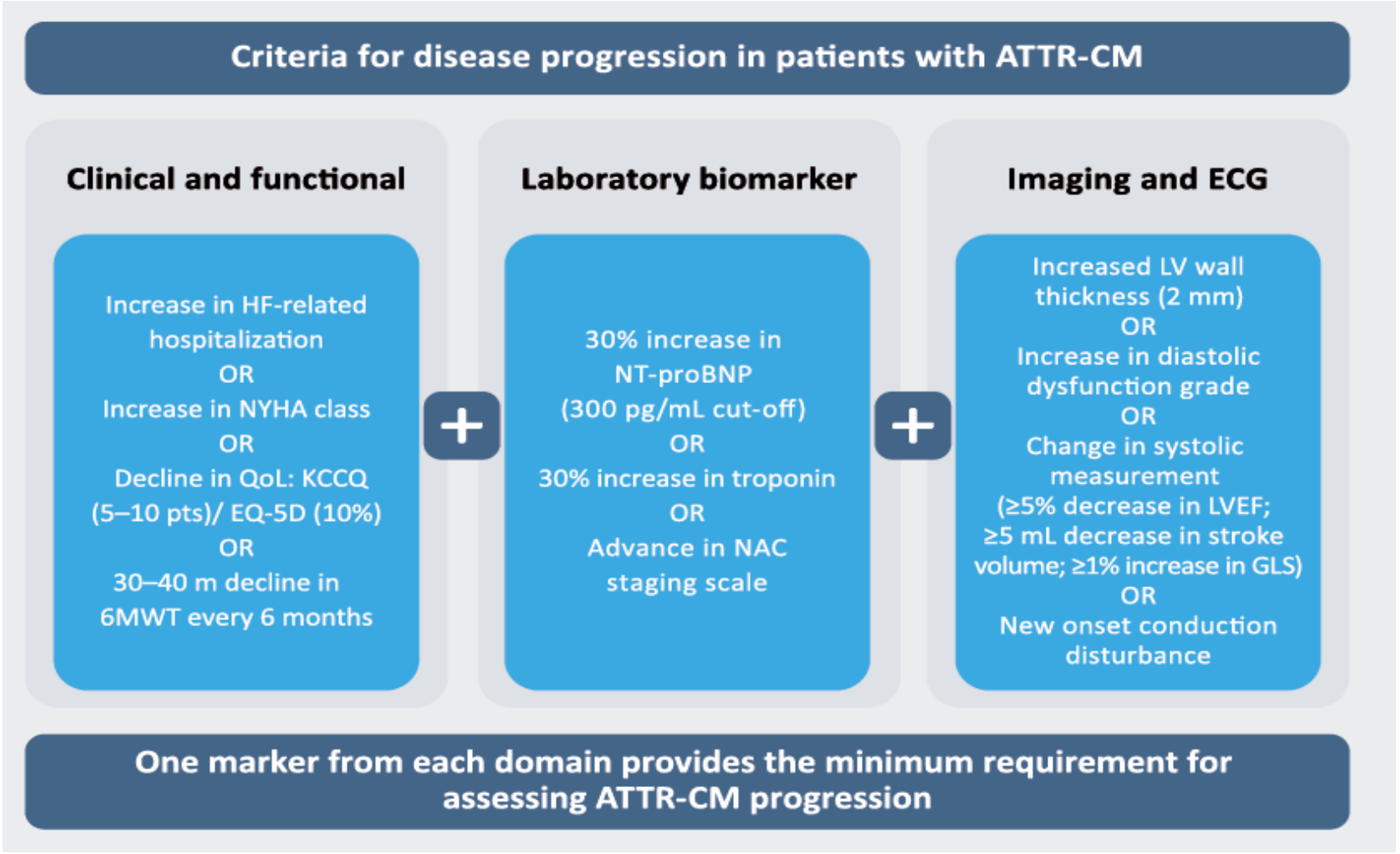




Pablo Garcia-Pavia et al, NEJM 2023, NEJM 2023

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

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

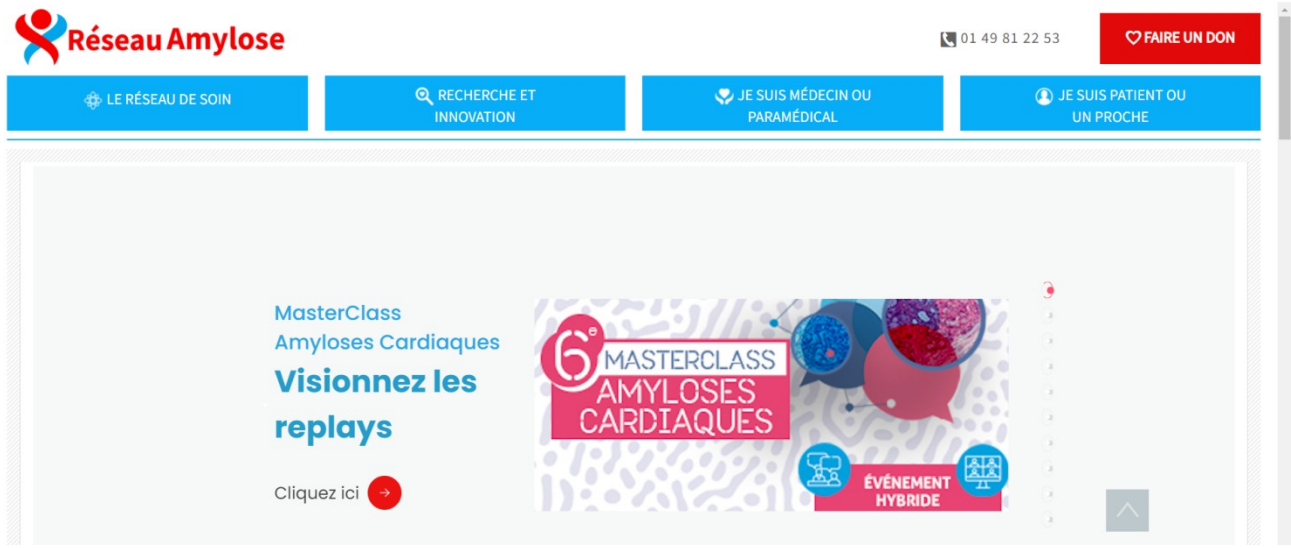
- *“The evolution of targeted treatment options, holds much promise for improving the outcomes of patients”*

Hawkins P et al , Annals of Medicine 2015

Develop websites to make the information accessible to everyone

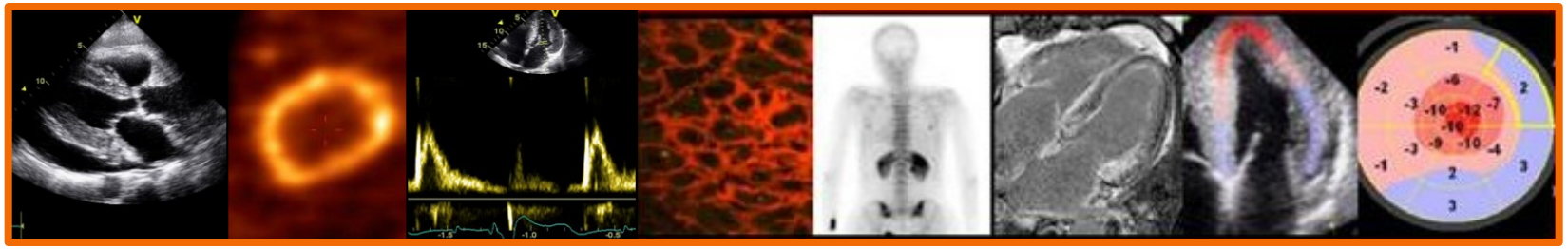
- www.reseau-amylose.org
- www.bibliose.org
- www.hearts-foundation.org

- www.congres-amylose.com
- www.masterclass-amylose.com



Réseau Amylose

RÉSEAU AMYLOSE MONDOR
CHU HENRI MONDOR



www.reseau-amylose.org

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