L'AMYLOSE,
MALADIE D ALZHEIMER DU COEUR ?

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French Referent Center for Rare Diseases
CRMR-NNERF

Disclosures

- **Michel S. Slama, MD, has disclosed the following relevant financial relationships:**
- **☒ Served as an advisor or consultant for: Alnylam Pharmaceuticals, Inc.; Pfizer Inc.**

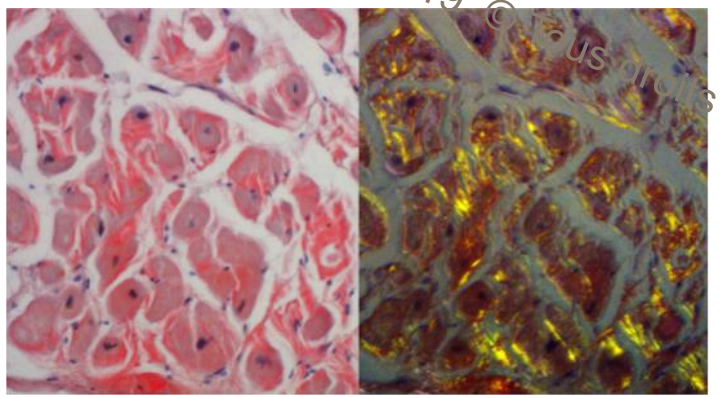
Amylose(s)

Definition:

- 1854 : Virchow 1ere description substance analogue à l'amidon
- 1859 : Friedreich et Kekulé: protéines
- Agrégats fibrillaires dépôts **extracellulaires** amorphes, acellulaires, craquelés et faiblement chromophiles, d'aspect « délavé »
- Rouge Congo : les dépôts d'amylose se colorent en rouge brique (congophilie)
- Dysfonction d'organe sans signe spécifique
- Héréditaire autosomale dominante
  - ou sénile- ou acquise
- Nomenclature: A+Suffixe de la proteine
- Maladie systémique à expression variable

R. Virchow (médecin pathologiste et homme politique allemand,1821-1902)

N. Friedreich (neurologue et neuropathologiste allemand 1825-1882)

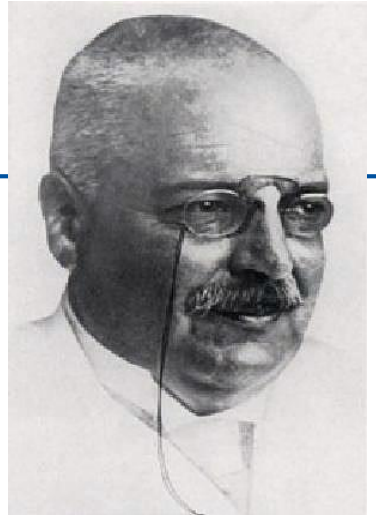


Maladie d‘Alzheimer

- **Definition:**
  - Cas d’Auguste Deter (16 mai 1850 - 8 avril 1906) admise à l'hôpital de Francfort en1901, atteinte d'une démence.
  - autopsie : plaques amyloïdes et dégénérescence neurofibrillaire.
  - Les auditeurs ne posent pas de question, apparemment plus intéressés par la lecture suivante sur la masturbation compulsive
  - Oskar Fisher = 12 cas en 1907

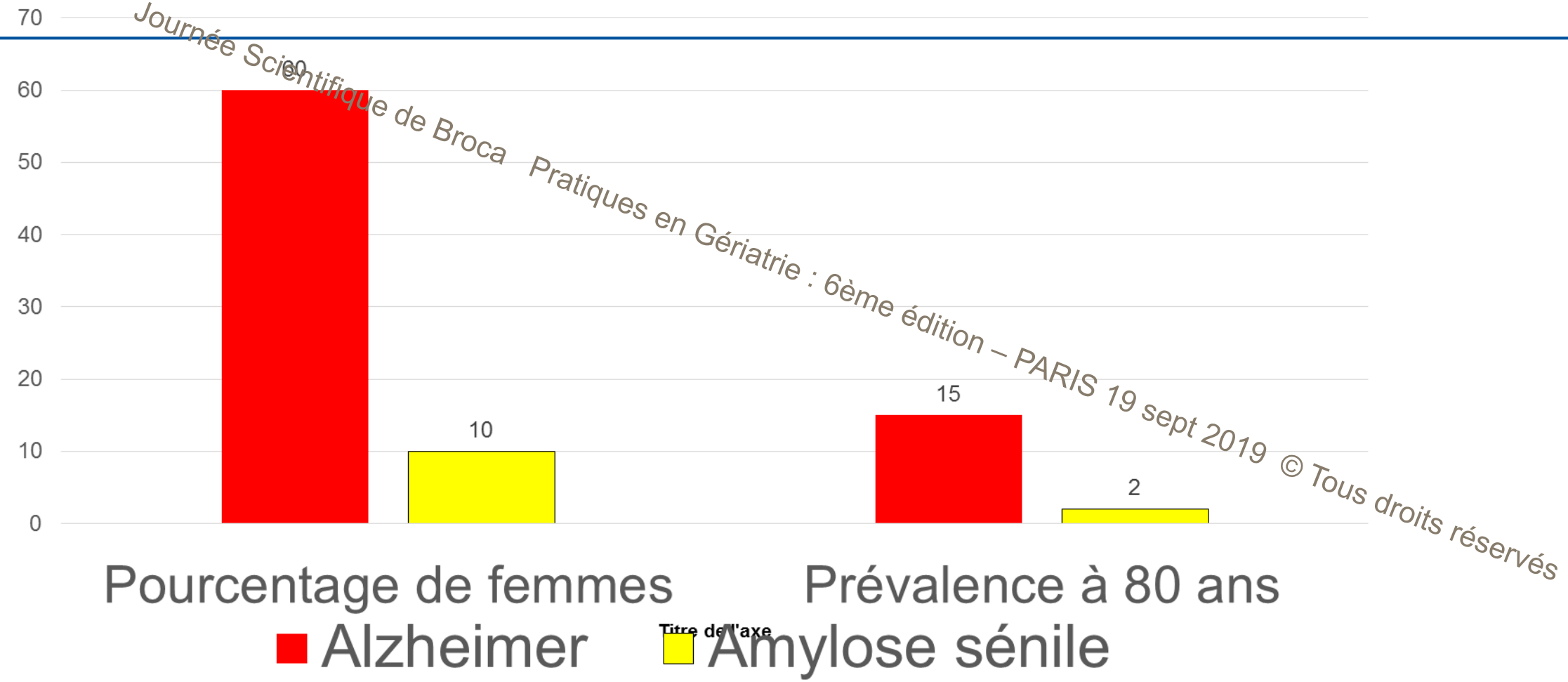
  - agrégats **intracellulaires** très proches de l’amylose ont été identifiés dans plusieurs maladies du système nerveux central (maladie de Parkinson, maladies à prion, maladie d’Alzheimer)

  - Formes héréditaires = 1,5% à 2% des cas, avant 65 ans, souvent autour de 45 ans. Dans la moitié de ces cas, des mutations rares à l’origine de la maladie ont pu être identifiées. Elles sont retrouvées au niveau de trois gènes : APP pour Amyloid Protein Precursor et protéines préséniline 1 et préséniline 2, qui interviennent dans le métabolisme de l’APP.



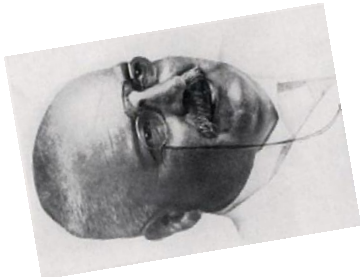
Alois Alzheimer
(psychiatre, neurologue et neuropathologiste allemand 1864-1915)

Alzheimer vs Amylose sénile



L'AMYLOSE,
MALADIE D ALZHEIMER DU COEUR ?

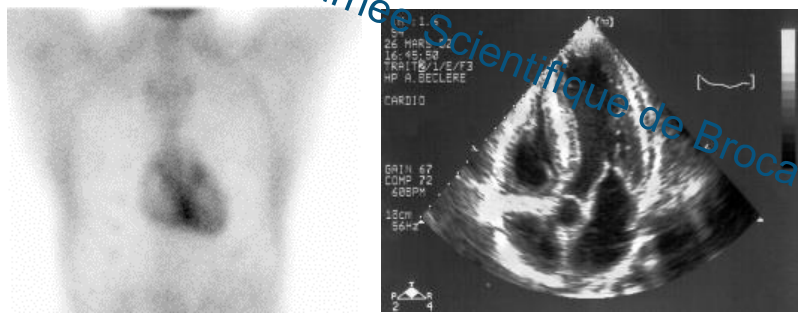
- **Amylose**
  - Pas d'atteinte centrale
  - Pas de trouble cognitif
  - Pas de proteine Tau
  - Pas de depots intra cellulaires
  - Maladie systémique
- **Maladie d'Alzheimer**
  - Pas de neuropathie périphérique
  - Pas d'atteinte cardiaque spécifique
  - Pas de dépôts extra cellulaires
  - Maladie locale



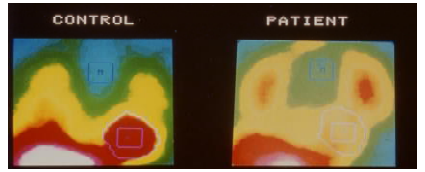
Les différents types d'amylose

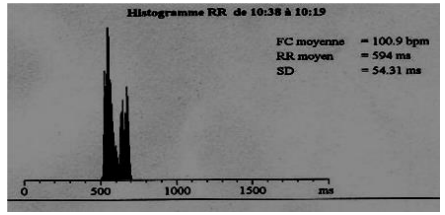
Nom	Type de protéine	Contexte	frequence	Traitement
AL« primaire »	Chaine légère Ig κ ou λ	« Myélome » 20%	4-12 10^6/an	Chimiothérapie
ATTR « mutée »	Transthyrétine	Familiale: mutation	10k ATTR-PN, 40k w ATTR-CM	Stabilisateurs inhibiteurs synthèse
ATTR « sénile »	Transthyrétine	Sénile	200k ATTRwt CM	Stabilisateurs inhibiteurs synthèse
AA inflammatoire	Protéine amyloïde A	Inflammation chronique		
Aβ2M	β-2 microglobuline	hémodialyse		

Cardiac Involvement in Amyloidosis Multidisciplinary Cardiologic Approach

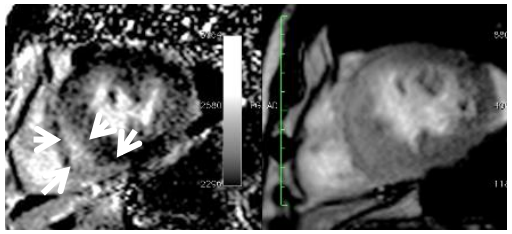


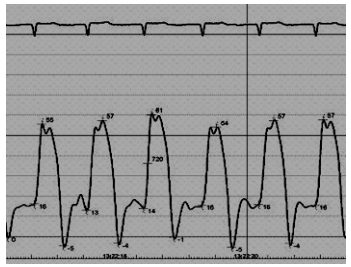
Infiltrative cardiopathy =
pseudo hypertrophy



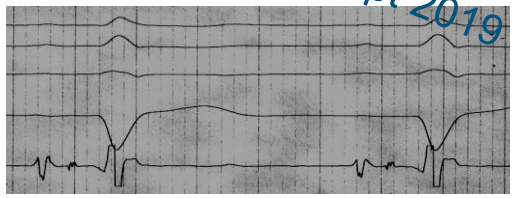


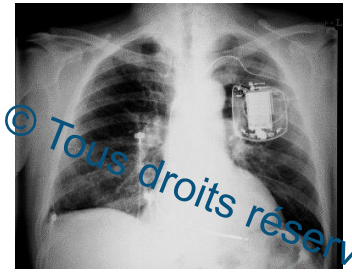
Denervation





Heart failure with PEF
Restrictive cardiomyopathy

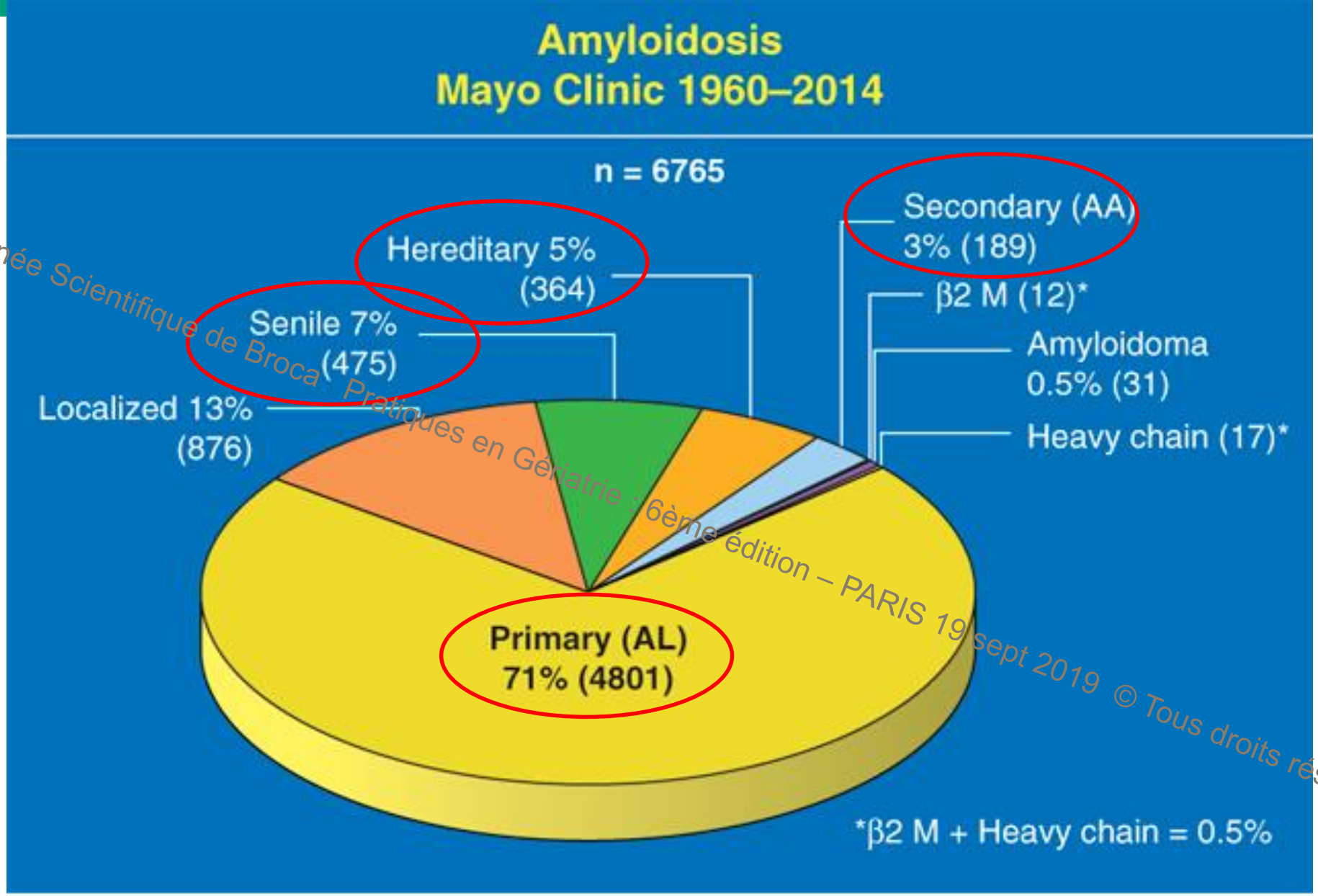




Conduction abnormalities
Possible sudden death

DELAHAYE N, ; *Eur. J. Nucl. Med*. 1999 ; 26 : 416-424; DELAHAYE N, *Circulation* 2001 ; 104 : 2911-2916 ALGALARRONDO V, *Heart Rhythm*. 2012 Jul;9(7):1069-75.
Images courtesy of MS SLAMA, MD

Amyloidosis
Mayo Clinic 1960–2014



Source: R. R. Baliga, William T. Abraham:
Color Atlas and Synopsis of Heart Failure
Copyright © McGraw-Hill Education. All rights reserved.

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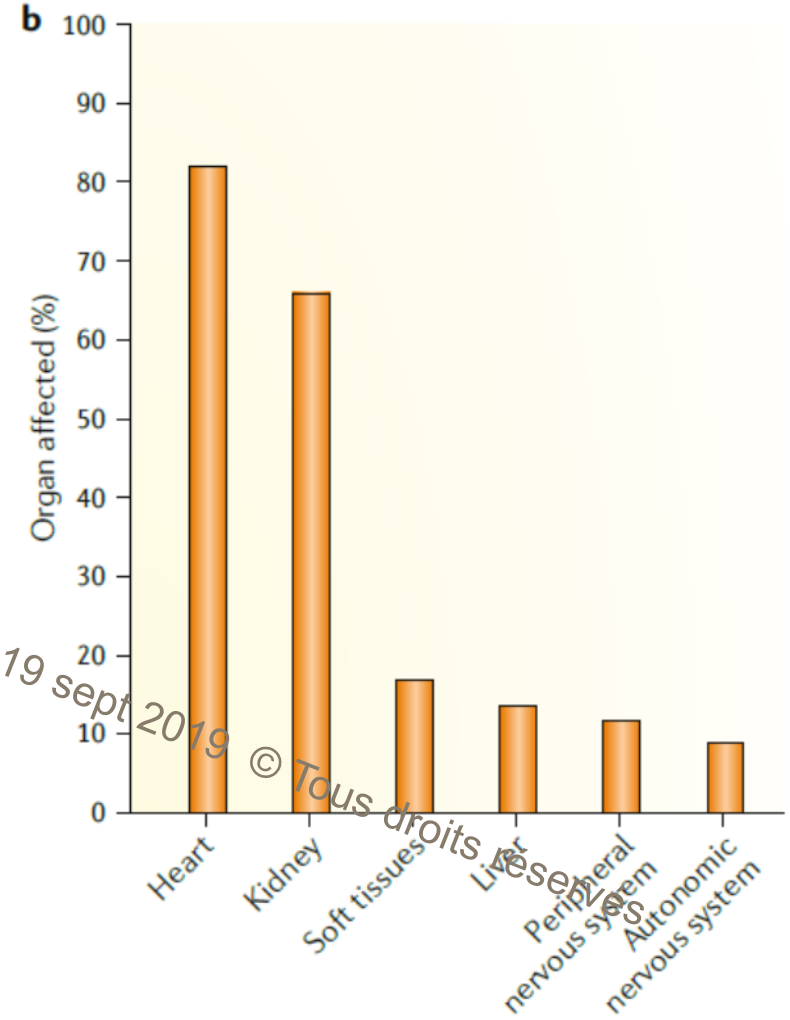
AA inflammatoire	Protéine amyloïde A	Inflammation chronique		
Aβ2M	β-2 microglobuline	hémodialyse		

AMYLOSE AL

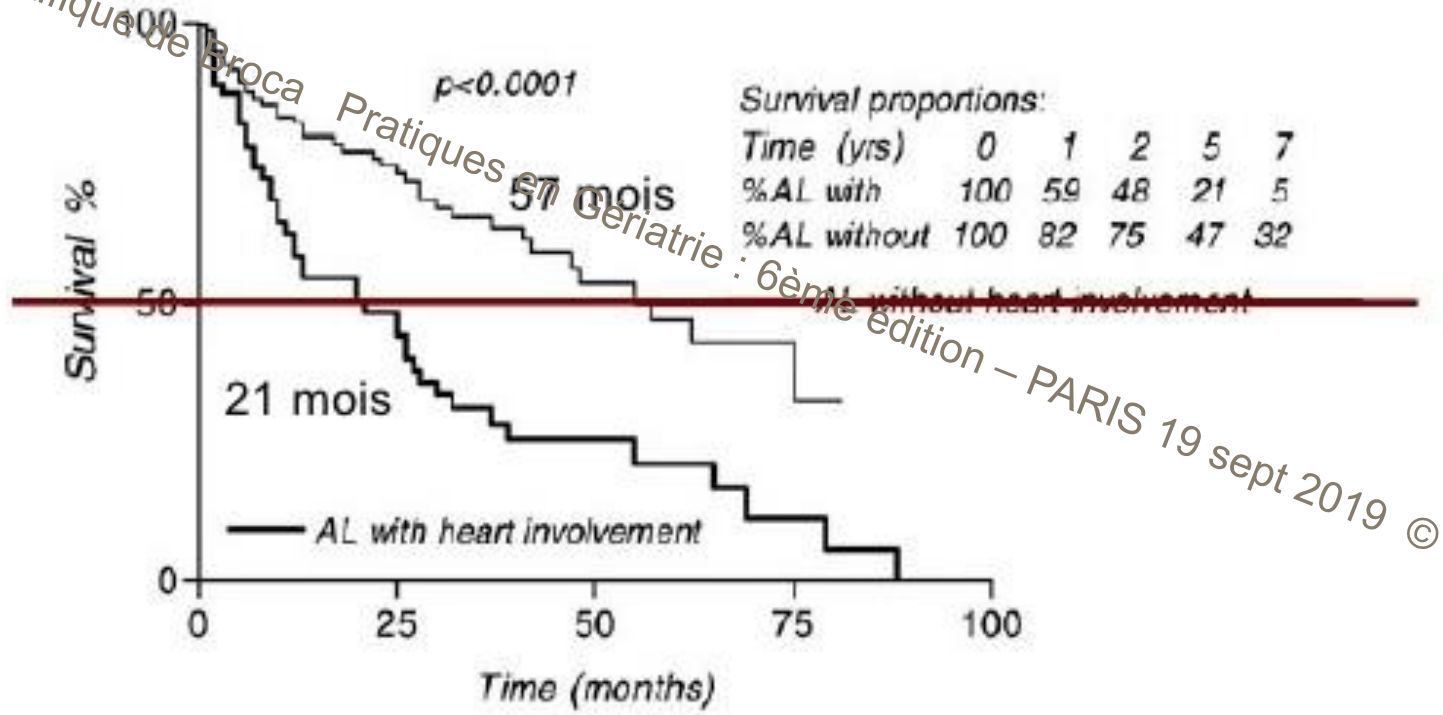
- Maladie rare 4-12 cas/10^6 / an
- Insuffisance cardiaque à Fion systolique préservée, HVG: 80% (?)
- Atteinte rénale 70% I. rénale, protéinurie, sd néphrotique
- Gammapathie monoclonale:
  - ☐ Recherche de protéinurie
  - ☐ Electrophorèse protéines sanguines et urinaires: pic:
  - ☐ Identifier la chaine légère monoclonale circulante:
    - **immunofixation des protéines sanguines**
    - **Dosage des chaines légères libres kappa et <u>lambda (85%)</u>**
  - ☐ Mettre en évidence l'amylose dans un tissu: biopsie
    - **PBR**
    - **Biopsie cardiaque**

- ***Attention: fréquence des MGUS chez sujet âgé: rechercher les d'amylose : test génétique***



Merlini G, et al, Nat Rev Dis Primers. 2018 Oct 25;4(1):38.

L’atteinte cardiaque détermine le pronostic de l’amylose AL



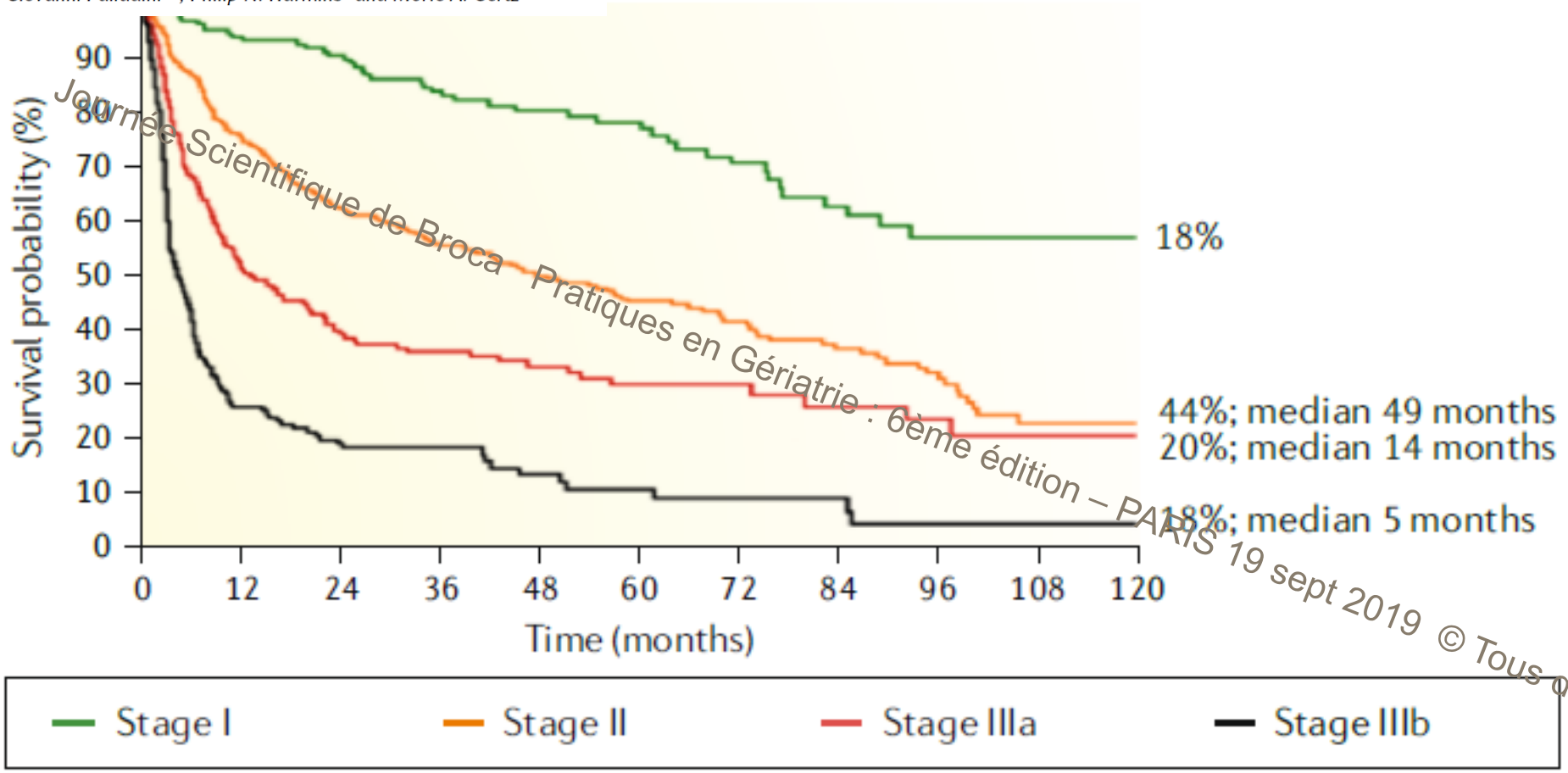
Staging

Staging system	Markers and thresholds	Stages	Outcomes*
Cardiac[54,55]	NT-proBNP >332 ng/L cTnT >0.035 ng/mL (or cTnI > 0.01 ng/mL)	I. no markers above the cutoff II. one marker above the cutoff IIIa. both markers above the cutoff and NT-proBNP <8500 ng/L IIIb. both markers above the cutoff and NT-proBNP ≥8500 ng/L	I. median survival not reached, 60% surviving 10 years II. median survival 49 months IIIa. median survival 14 months IIIb. median survival 5 months
Revised Mayo Clinic [139]	NT-proBNP >1800 ng/L cTnT >0.025 ng/mL dFLC >180 mg/L	I. 0 markers above the cutoff II. 1 marker above the cutoff III. 2 markers above the cutoff IV. 3 markers above the cutoff	I. median survival not reached, 55% surviving 10 years II. median survival 57 months III. median survival 18 months IV. median survival 6 months
Renal[60]	eGFR <50 mL/min per 1.73 m^2 proteinuria >5 g/24h	I. both eGFR above and proteinuria below the cutoffs II. either eGFR below or proteinuria above the cutoffs III. both eGFR below and proteinuria above the cutoffs	I. 1% risk of dialysis at 2 years II. 12% risk of dialysis at 2 years III. 48% risk of dialysis at 2 years

cTn, cardiac troponin; dFLC, difference between involved (amyloidogenic) and uninvolved circulating free light chain; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-natriuretic peptide type-B. *Observed in 1065 patients with AL amyloidosis newly diagnosed at the Pavia Amyloidosis Research and treatment center.

Systemic immunoglobulin light chain amyloidosis

Giampaolo Merlini[1,2], Angela Dispenzieri[3], Vaishali Sanchorawala[4], Stefan O. Schönland[5], Giovanni Palladini[1,2], Philip N. Hawkins[6] and Morie A. Gertz[3]*

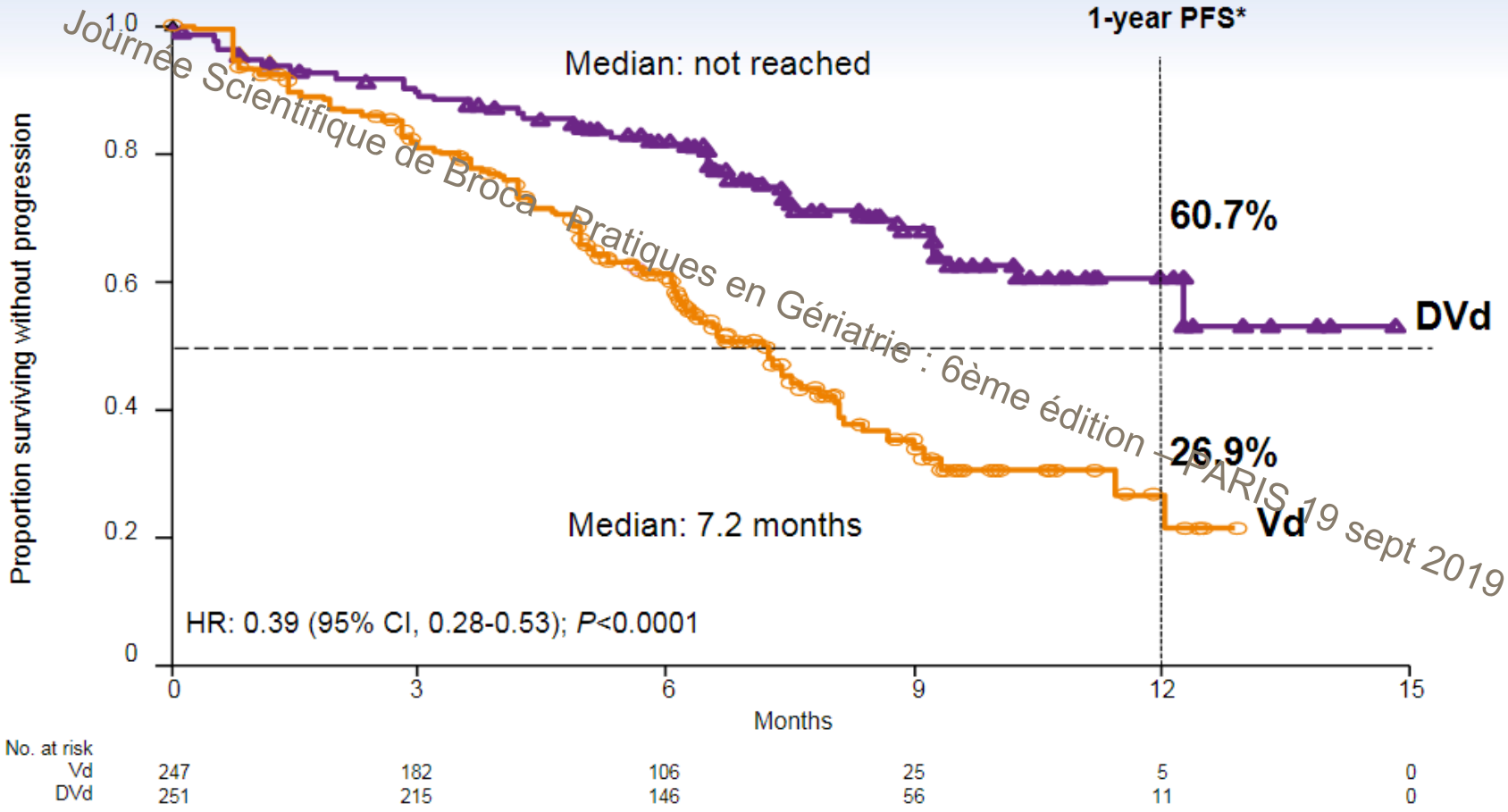


Merlini G, et al, Nat Rev Dis Primers. 2018 Oct 25;4(1):38.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma



(n = 251)
Daratumumab (16 mg/kg IV)
Vel: 1.3 mg/m2SC,
dex: 20 mg

Vd (n = 247)
Vel: 1.3 mg/m2SC
dex: 20 mg PO-IV,

61% reduction in the risk of disease progression or death for DVd vs Vd

Palumbo A et al, N Engl J Med 2016;375:754-66.

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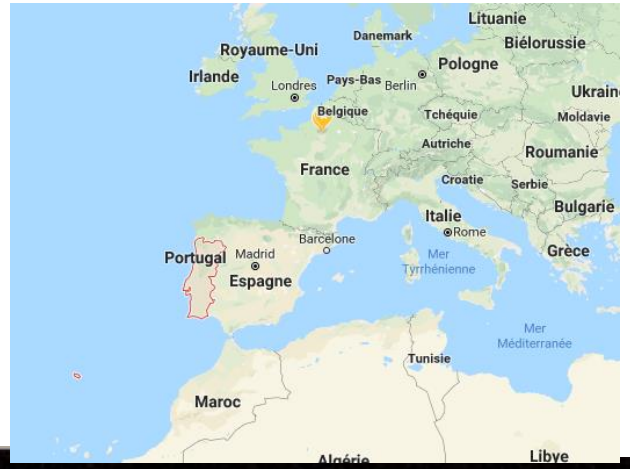
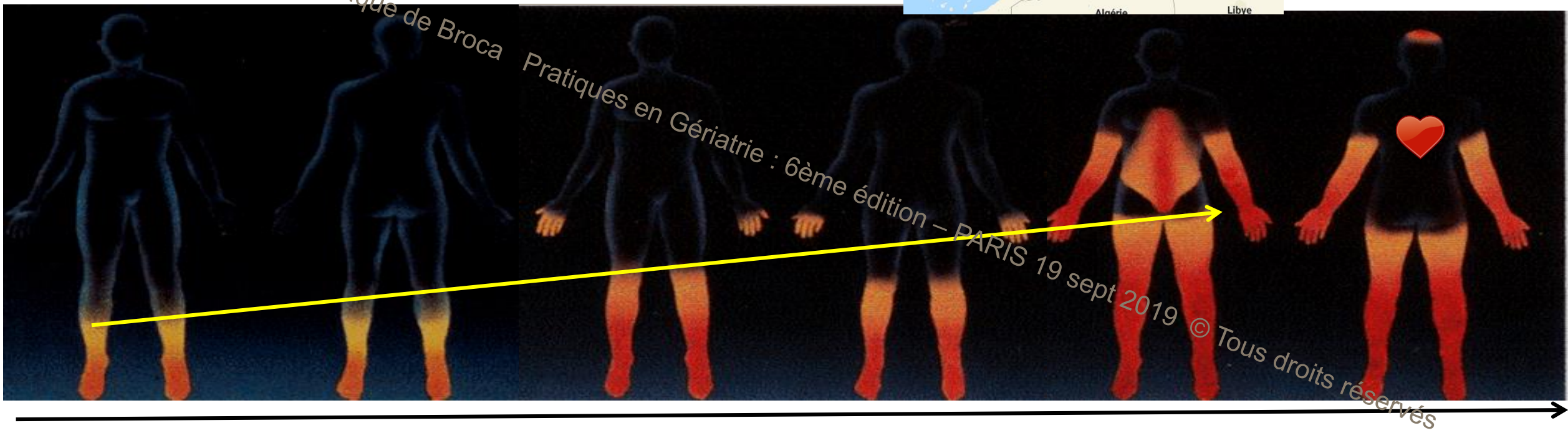
AA inflammatoire	Protéine amyloïde A	Inflammation chronique		
Aβ2M	β-2 microglobuline	hémodialyse		

NAH : histoire naturelle
une neuropathie progressive



ANDRADE 1952
Val30Met



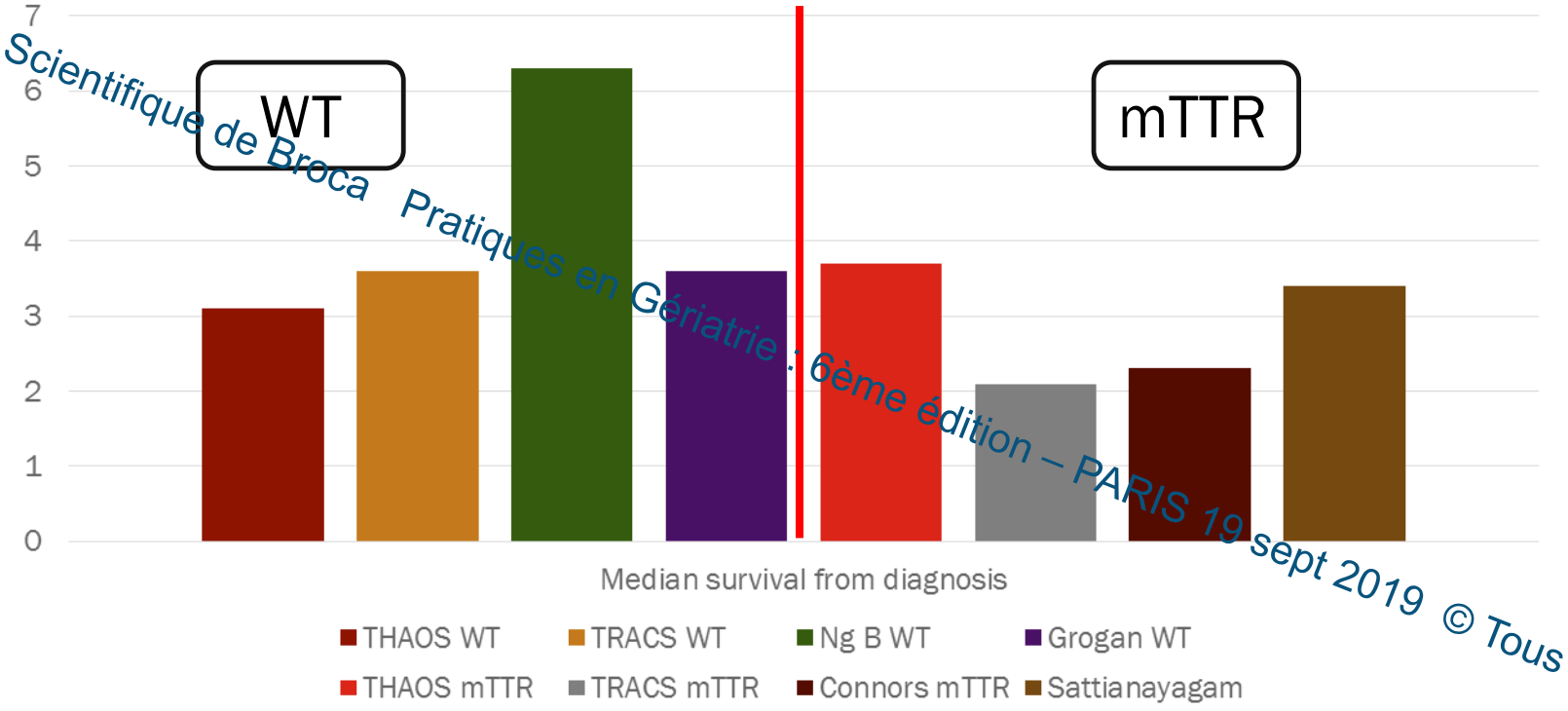
Polyneuropathie Axonale Ascendante Progressive
Perte de sensibilité température douleur

LES AMYLOSES A TRANSTHYRETINE

- **Amyloses héréditaires**
  - **Transthyrétine** anormale, instable
  - Parité H=F
  - Autosomal dominant
  - Systémique
  - Formes précoces <30 ans neuropathies
  - Atteintes cardiaques >50 ans
- **Amyloses séniles**
  - **Transthyrétine** normale
  - 90% hommes
  - Non héréditaire
  - Atteintes cardiaques “pures”; 5-10% neuropathies
  - Après 80 ans
  - Tableau d’HFpEF
  - 5% des CMH
  - 15% des TAVI

AMYLOSE ATTR
Median Survival From Diagnosis

80 ANS +



50 ANS +

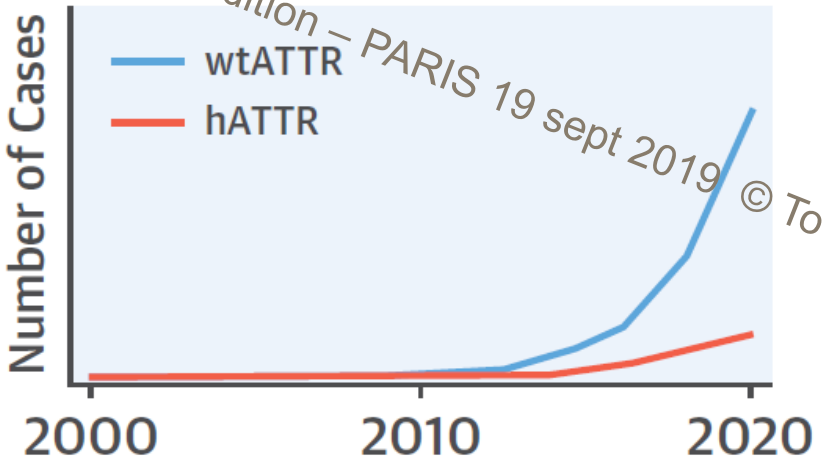
THAOS : Transthyretin Amyloidosis Outcomes Survey https://www.thaos.net/THAOS/aboutThaos.cfm
TRACS : Ruberg FL J. 2012;164(2):222–228
Ng, B., et al. Arch Intern Med: 2005 165(12): 1425-1429.
Grogan, M., et al. 2016; J Am Coll Cardiol 68(10): 1014-1020.
Connors, L. H., et al. (2009). Am Heart J 158(4): 607-614.
Sattianayagam, P. T., et al. (2012). Eur Heart J 33(9): 1120-1127.

LES AMYLOSES CARDIAQUES A TRANSTHYRETINE

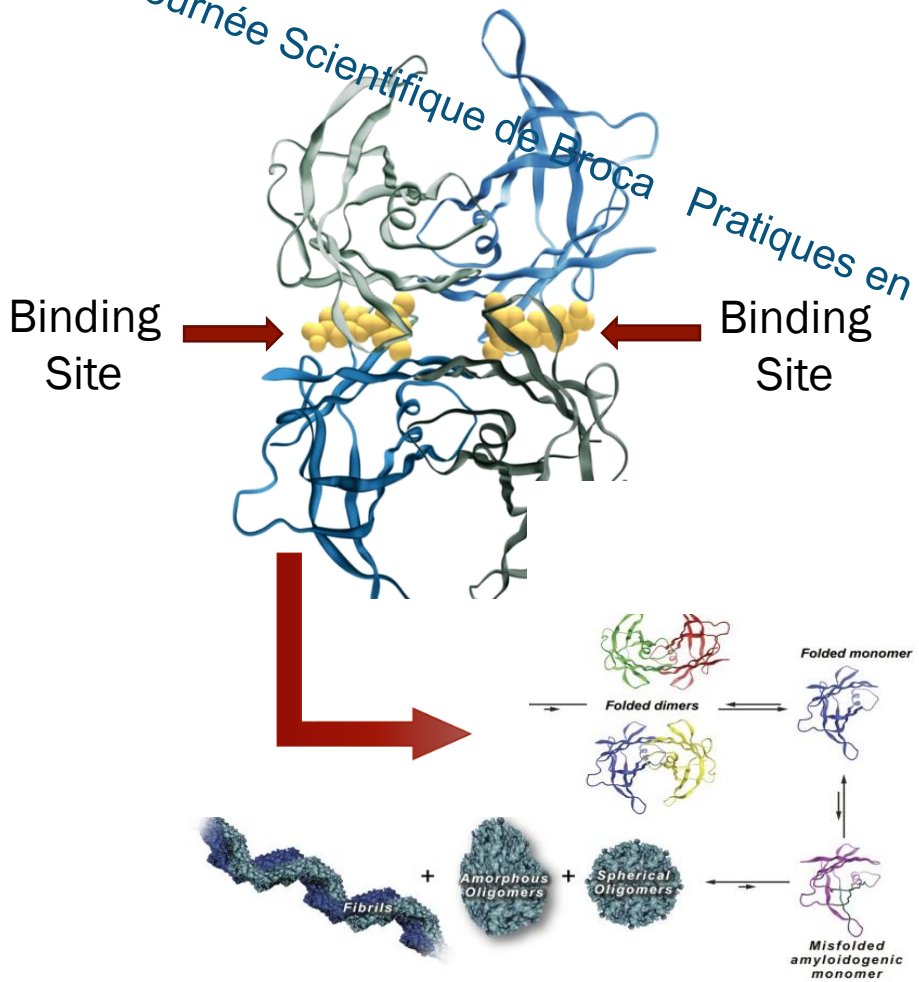
Present/Future

Recognition of ATTR-CM

Epidemiology



What is Transthyretin?

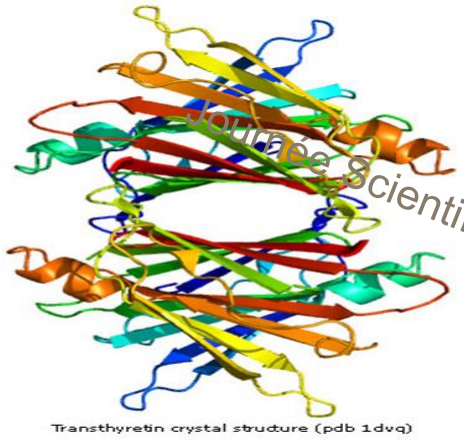


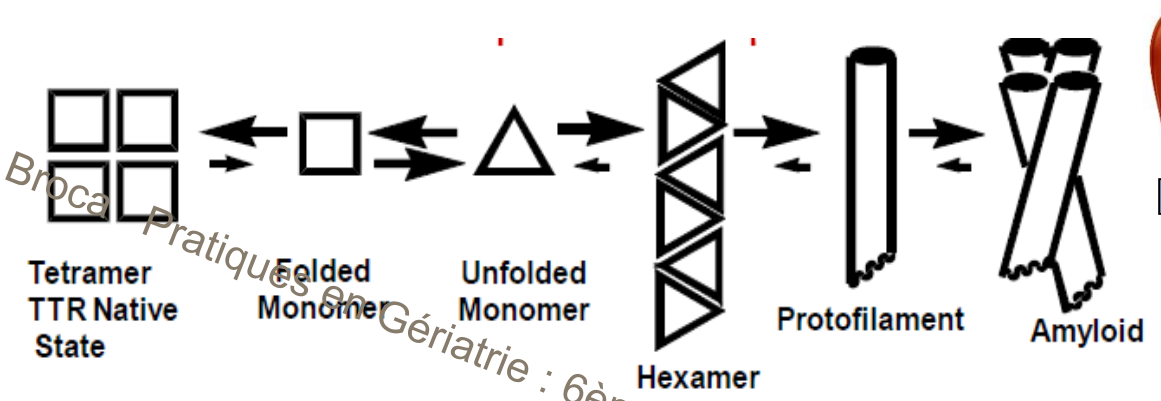
- Polypeptid of 127 amino acids
- Homotetramer
- Chromosome 18; 4 Exons, 3 Introns
- Synthesis almost exclusively in the liver
- Transport protein for thyroxin and retinol-binding protein/vitamin A
- >120 point mutations causing ATTR amyloidosis
  - Val30Met: mixed phenotype
  - Val122Ile: cardiac phenotype

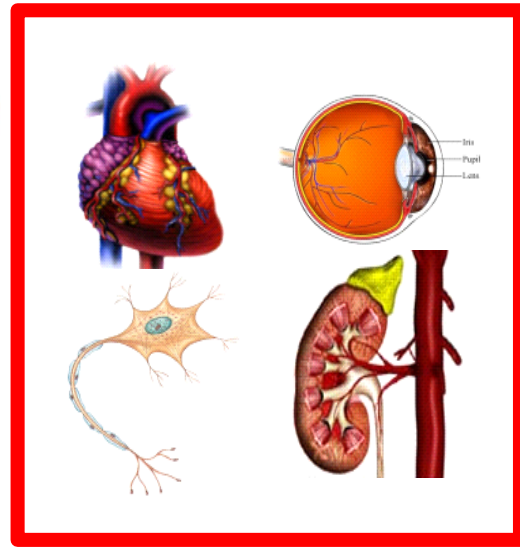
No specific treatment until 1990

Bulawa, et al, *Proc Natl Acad Sci USA.* (2012).

L’amylose héréditaire à transthyrétine





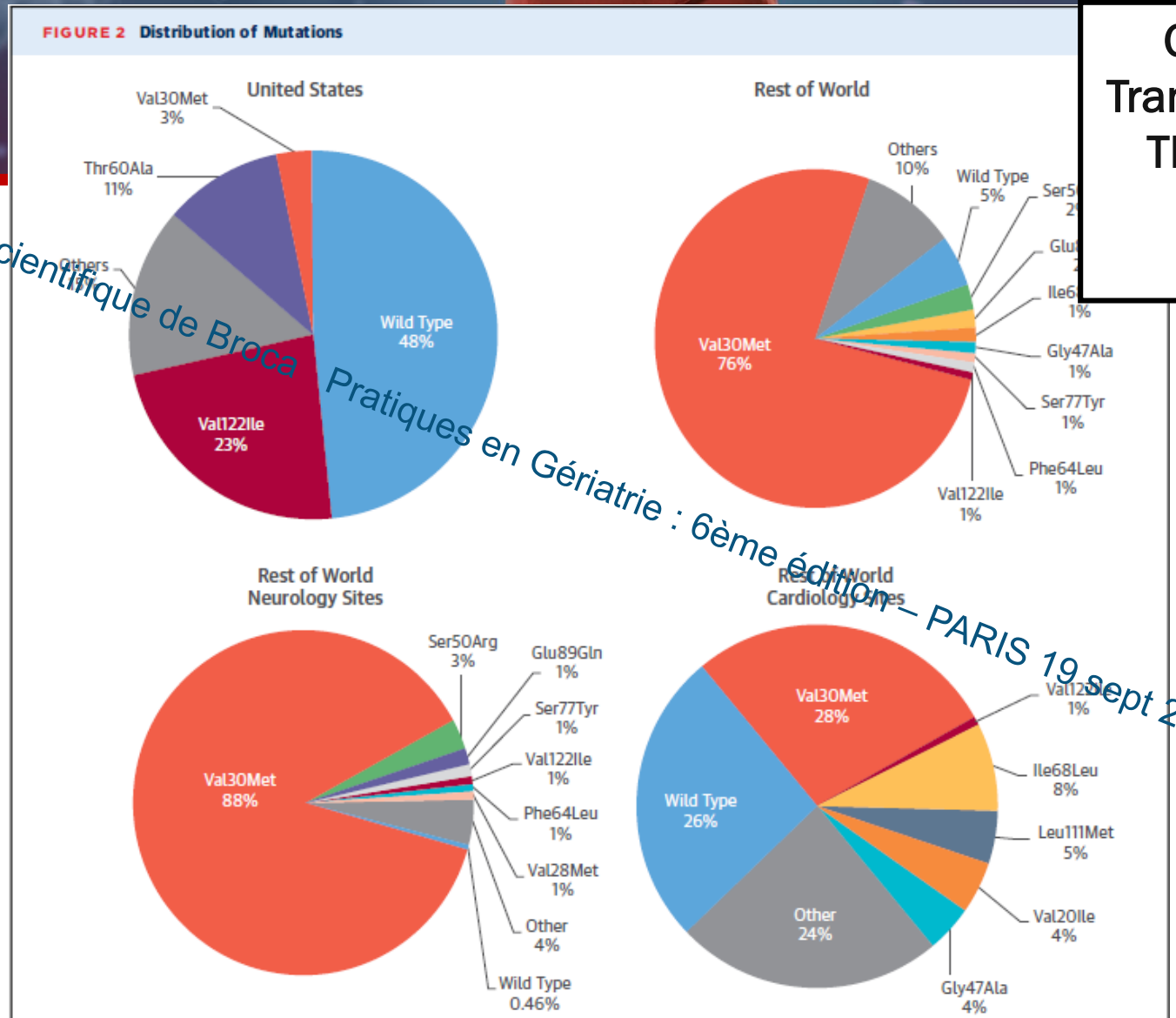


- Maladie autosomique dominante. 120 mutations
- Pénétrance variable
- Transthyrétine
  - ***Trans*** porteur
  - Hormones ***Thyr***oidiennes
  - ***Retin***ol
- Protéine mutée instable
- Atteinte multisystémique. Cibles variables selon la mutation

- Production hépatique (>90%)
- Traitement :
  - transplantation hépatique
  - Stabiliser la TTR
  - Supprimer la production de TTR (SiRNA)
- Pas de modèle animal

What do Clinicians See in Their Clinical Practice?

Genotype and Phenotype of Transthyretin Cardiac Amyloidosis THAOS (Transthyretin Amyloid Outcome Survey)



US = WT and VAL 122

Rest of world = Val30Met + 5%WT

Neuro sites = Val30Met And other mutations

Cardio sites = Val30Met and WT

Maurer M, et al. *J Am Coll Cardiol*. 2016;68:161–72.

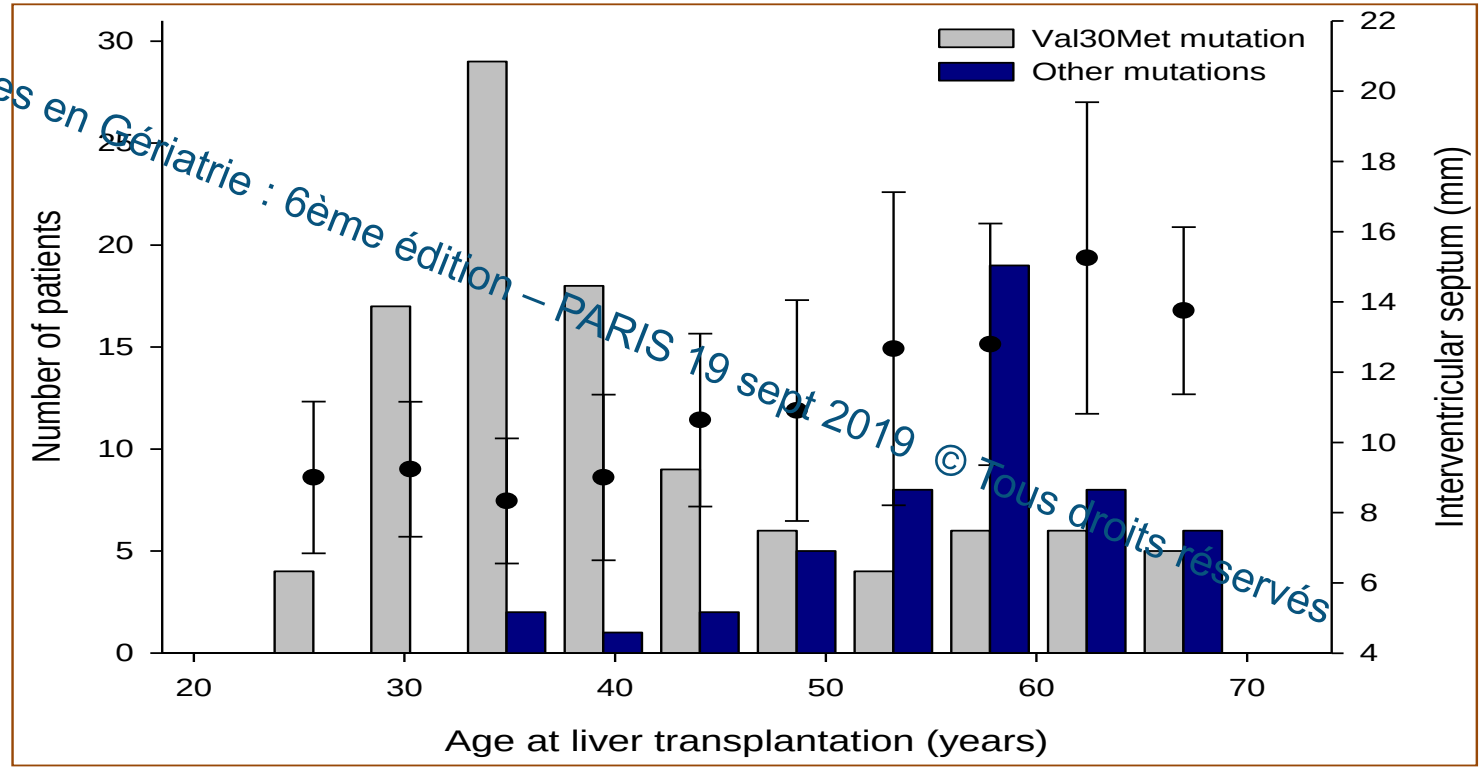
It is a question of point of view

EXPERIENCE CRMR - NNERF

Sur les patients du centres de référence:

- 50% de Met 30 précoces
- Le reste : met 30 tardifs (15%) et autres mutations

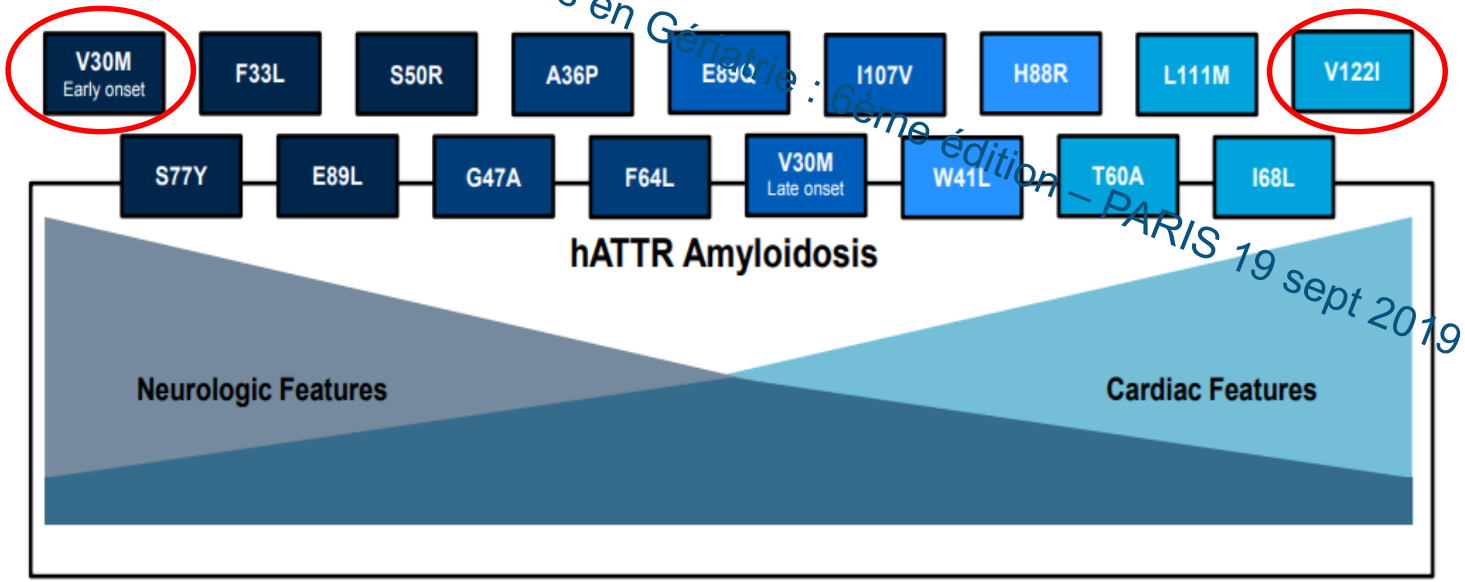
Pas de différence claire d'atteinte cardiaque **qd l'âge est pris en compte**



hATTR Amyloidosis Presents With a Heterogeneous Phenotype

- >120 amino acid substitutions have been reported in patients with hATTR amyloidosis1
- Presentation can vary by TTR mutation, but mixed phenotype is often reported

Type B deposits,
intact TTR monomers form the fibrils, common in early onset V30M polyneuropathy subjects,.

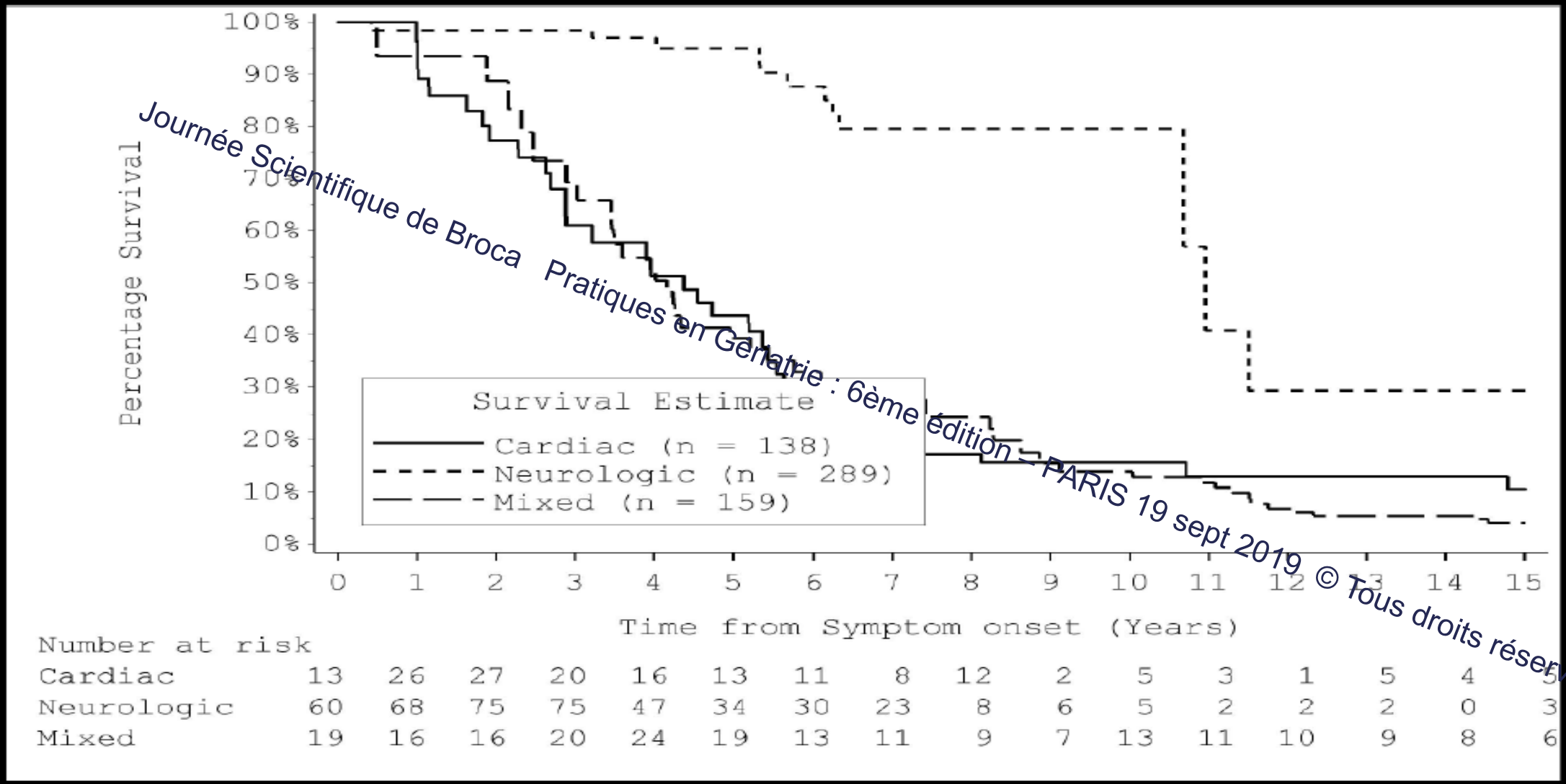


Type A deposits
aggregates of intact monomers and monomer fragments present in most cardiomyopathic mutations and ATTRwt associated cardiomyopathy.

Definition of Cardiac?

Rowcenzio, et al. *Hum Mutat* 2014;35:E2403–122; ; Rapezzi, et al. *Eur Heart J*. 2013;34:520–8; Buxbaum JN. *Amyloid*. 2019. PMID: 30907141

THAOS Registry, preliminary survival data, March 2014

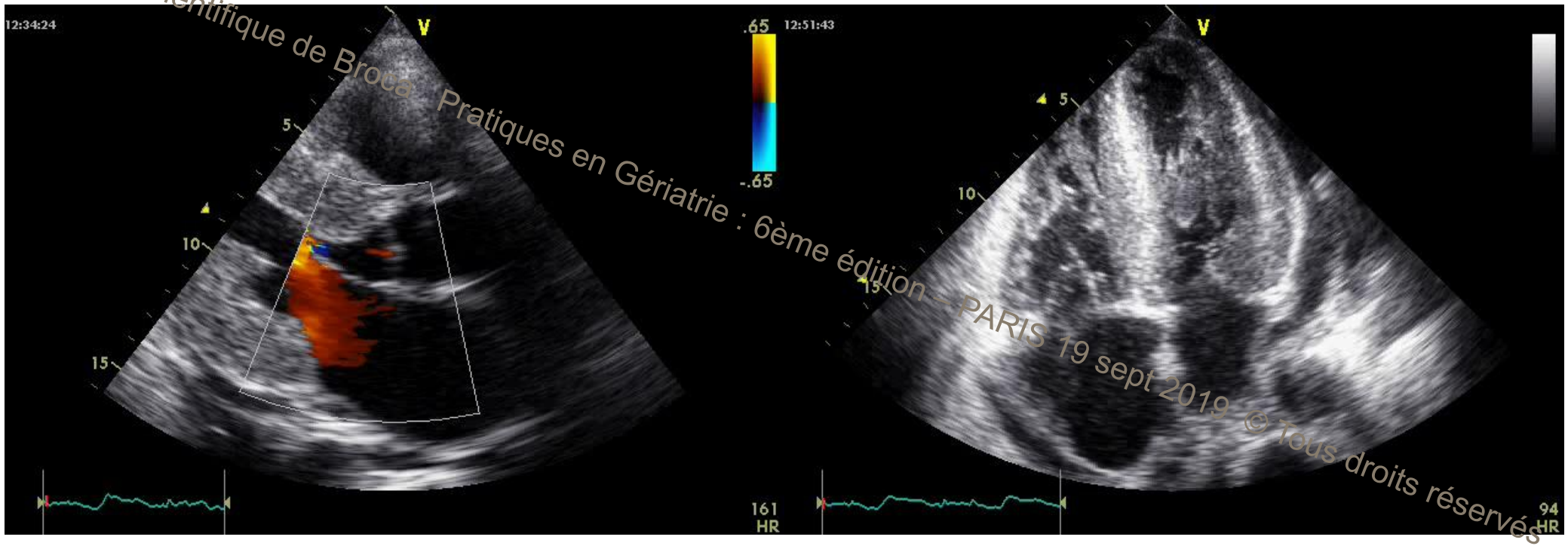


Number at risk															
Cardiac	13	26	27	20	16	13	11	8	12	2	5	3	1	5	4	5
Neurologic	60	68	75	75	47	34	30	23	8	6	5	2	2	2	0	3
Mixed	19	16	16	20	24	19	13	11	9	7	13	11	10	9	8	6

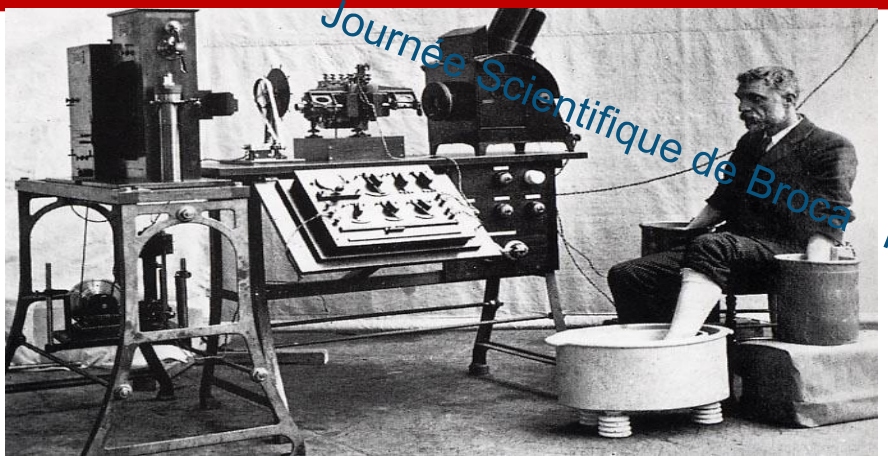
L’atteinte cardiaque est

- variable selon les mutations
- débute après 50 ans
- fréquente, sous diagnostiquée
- grave, espérance de vie ≤ 5 ans après premiers signes
- irréversible (?)

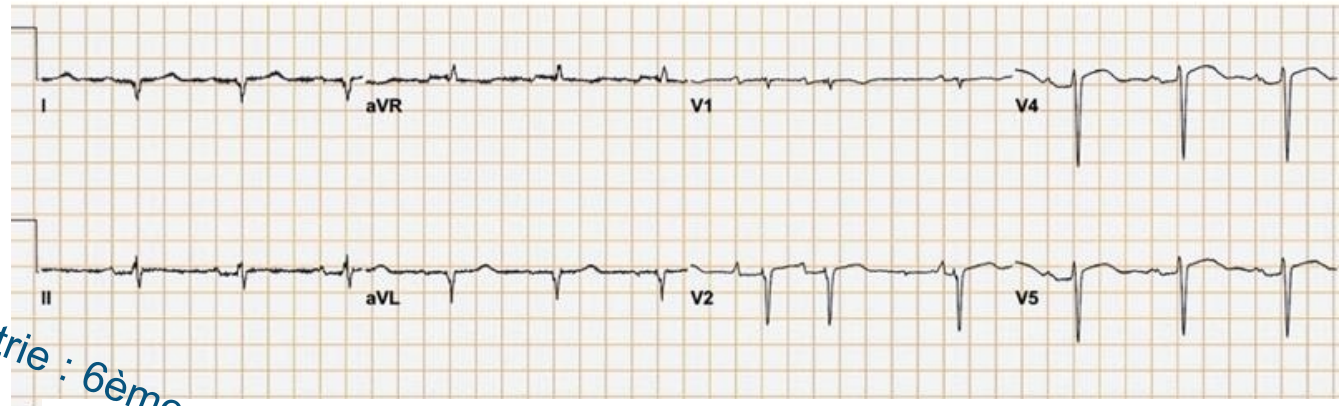
Insuffisance cardiaque à fonction systolique préservée



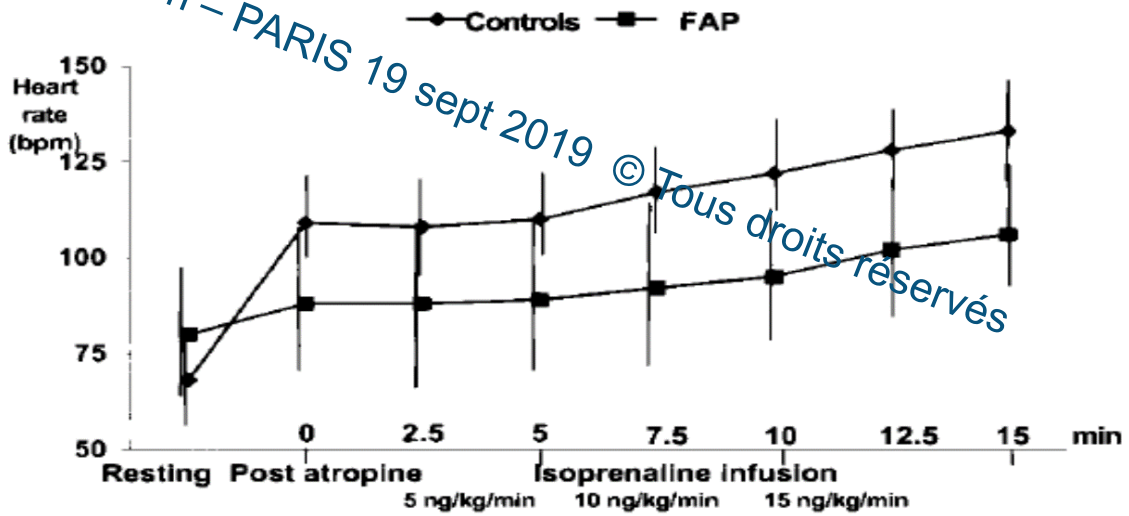
ECG



Einthoven W. *Arch f d Ges Physiol.* 1895;60:101–123



- Microvoltage VS CMH/echo
- Bloc de branche, BAV
- Fibrillation atriale
- Incompétence chronotrope, bradycardie
- Diminution de la réponse à l'atropine

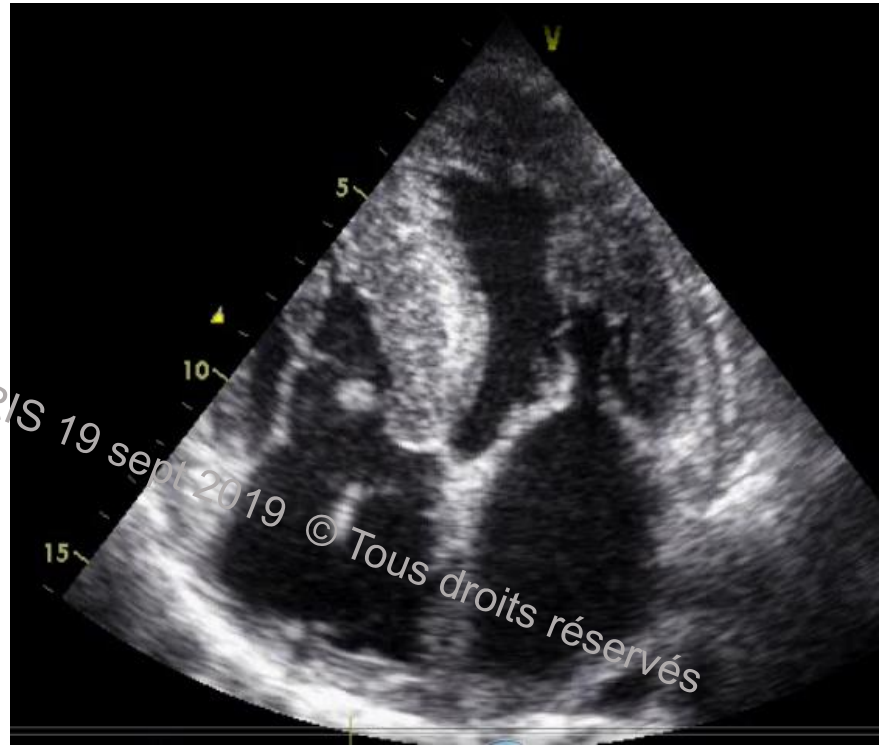


Falk RH *Cardiac Amyloidosis Circulation* 2011: 1079-1085

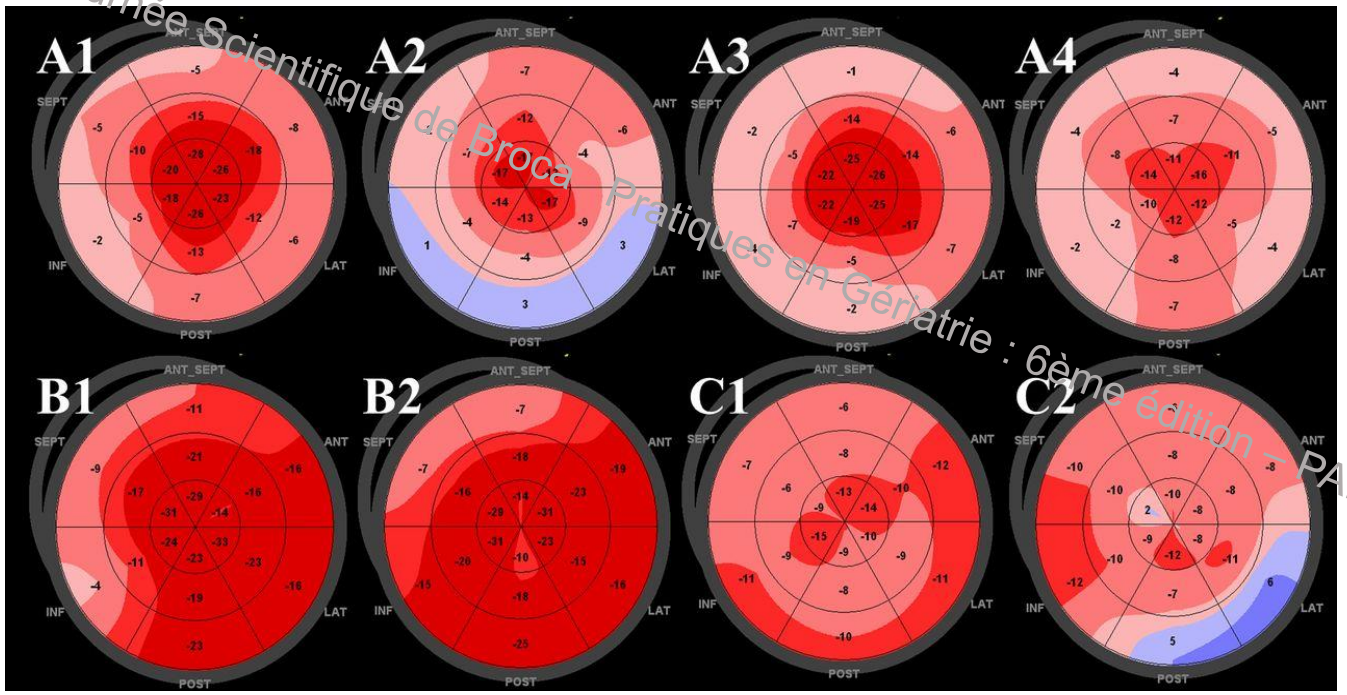
Delahaye et al, Circulation. 2001; 104:2911-2916

Echocardiographie

- « trop facile », image brillante
- Hypertrophie concentrique
- FE préservée
- SIV > 12 mm= critere dg, valeur seuil mais il existe une “zone grise”.
- Epaississement du VD
- Flux mitral restrictif
- Épaississement des feuillets mitraux et tricuspides
- Épaississement du septum inter auriculaire
- Épanchement péricardique



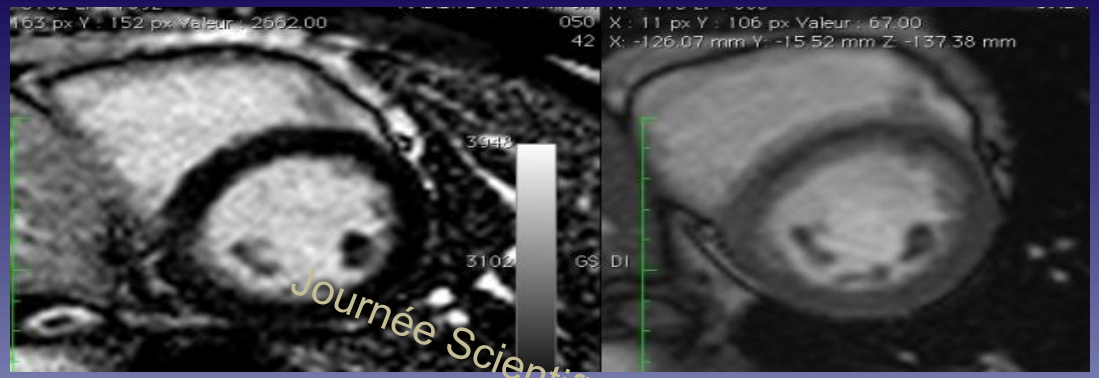
STRAIN longitudinal « préservation apicale »



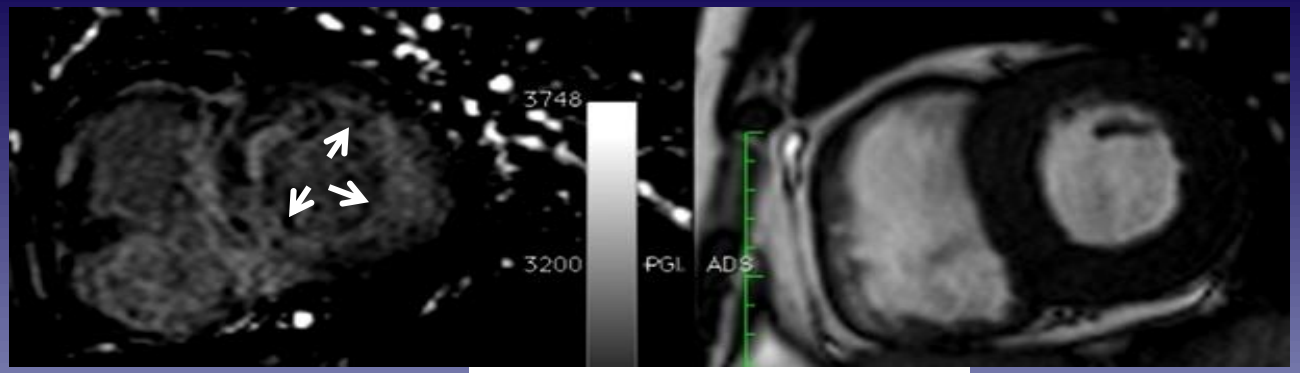
$$\text{Relative apical LS} = \frac{\text{Average apical LS}}{\text{Average basal LS} + \text{Average mid LS}}$$

If >1 = AMYLOIDOSIS
Sen 93%; Spe 82%

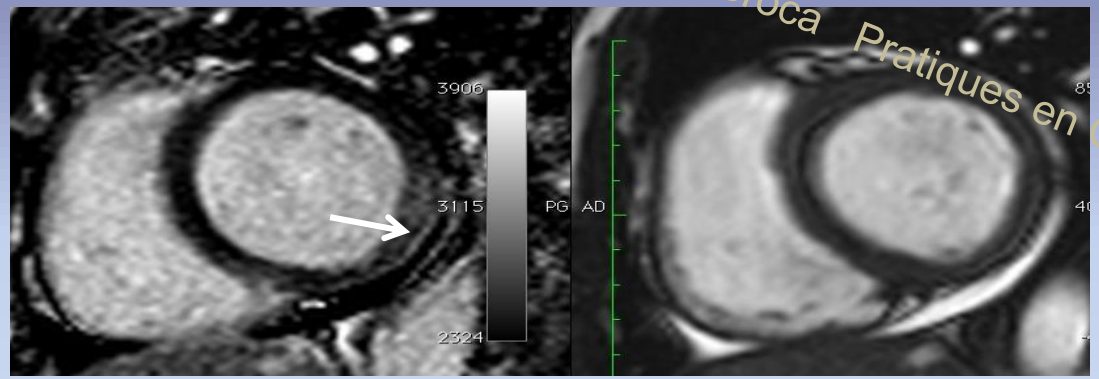
Relative apical sparing of longitudinal strain using two-dimentionnel speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis, Phelan and al, Heart, 2012



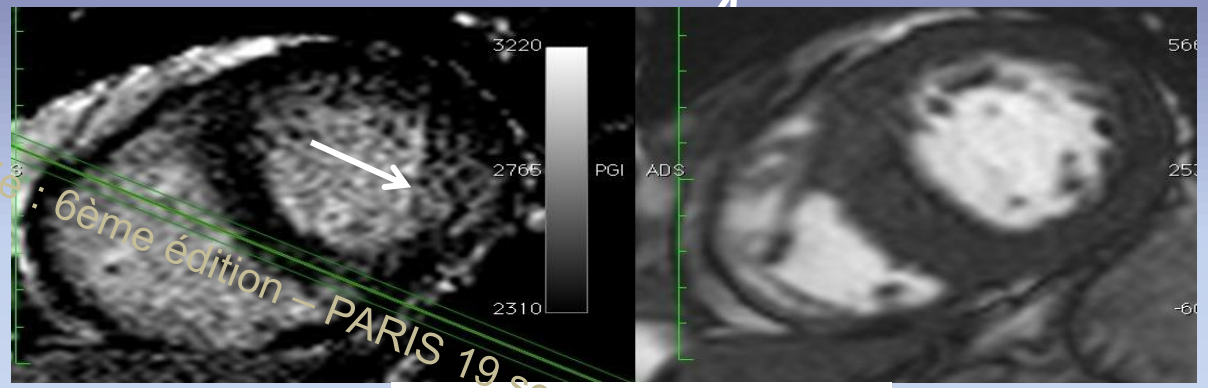
NORMAL (21%)



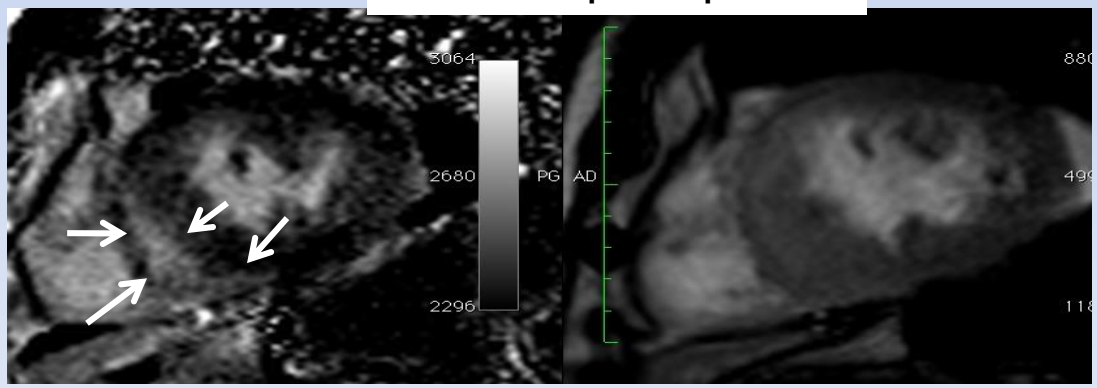
TYPE 1 (22%): sous-endocardique



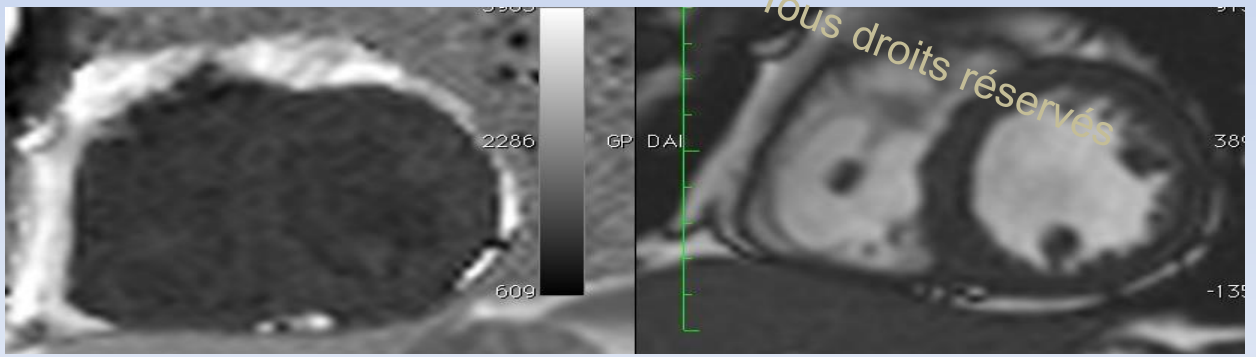
TYPE 2 (25%): sous-épicardique



TYPE 3 (44%): transmural



TYPE 4 (8%): nodulaire



ININTERPRETABLE (8%)

Noncontrast T1 Mapping for the Diagnosis of Cardiac Amyloidosis

Theodoros D. Karamitsos, MD, PhD,* Stefan K. Piechnik, PhD, MScEE,*

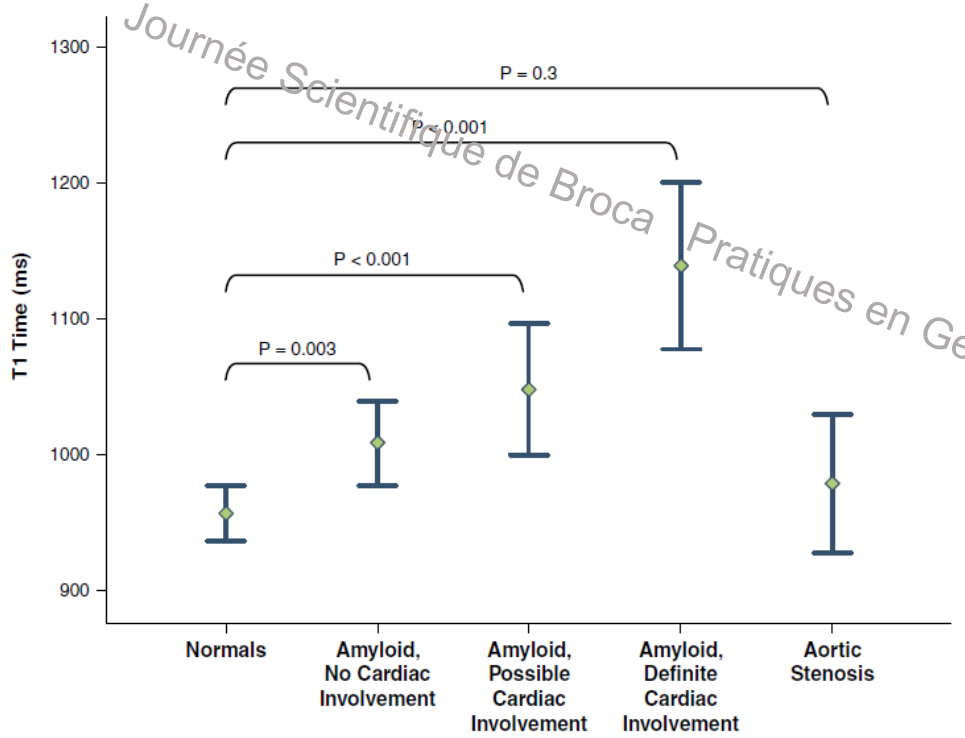


Figure 1. Myocardial T1 in Normal, Amyloid, and Aortic Stenosis

Mean noncontrast shortened modified look-locker inversion recovery (ShMOLLI) T1 values in 5 groups of patients. Error bars indicate ± 1 SD. Other between-groups comparisons: amyloid without cardiac involvement versus possible cardiac amyloid, $p = 0.265$; amyloid without cardiac involvement versus definite cardiac amyloid, $p < 0.001$; amyloid without cardiac involvement versus aortic stenosis, $p = 0.606$; possible cardiac amyloid versus definite cardiac amyloid, $p < 0.001$; possible cardiac amyloid versus aortic stenosis, $p = 0.001$; and definite cardiac amyloid versus aortic stenosis, $p < 0.001$.

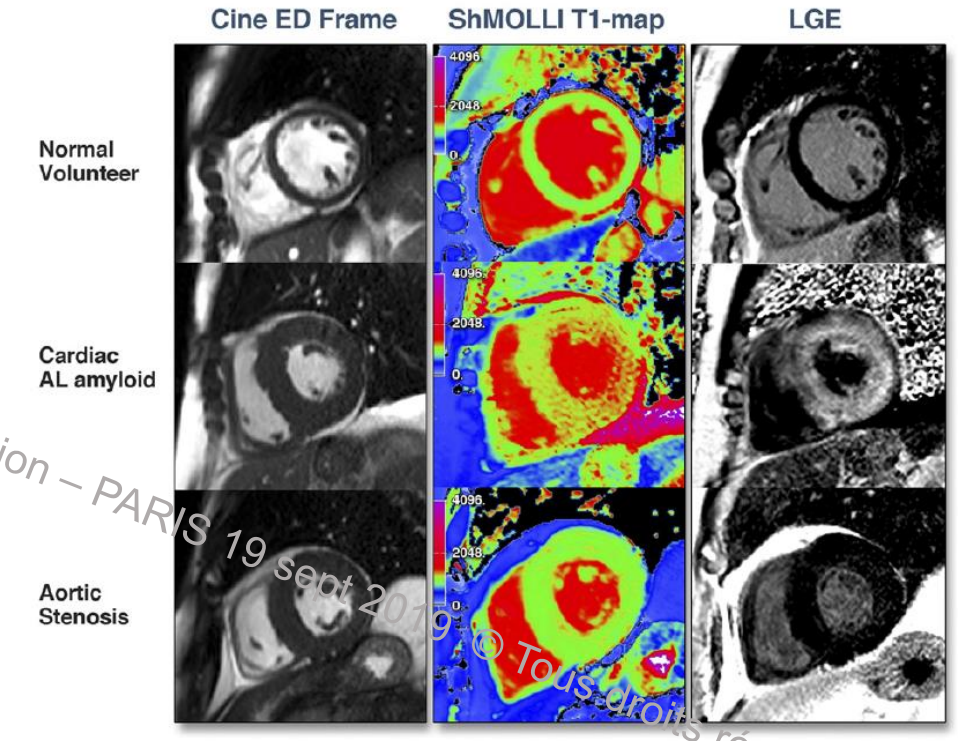


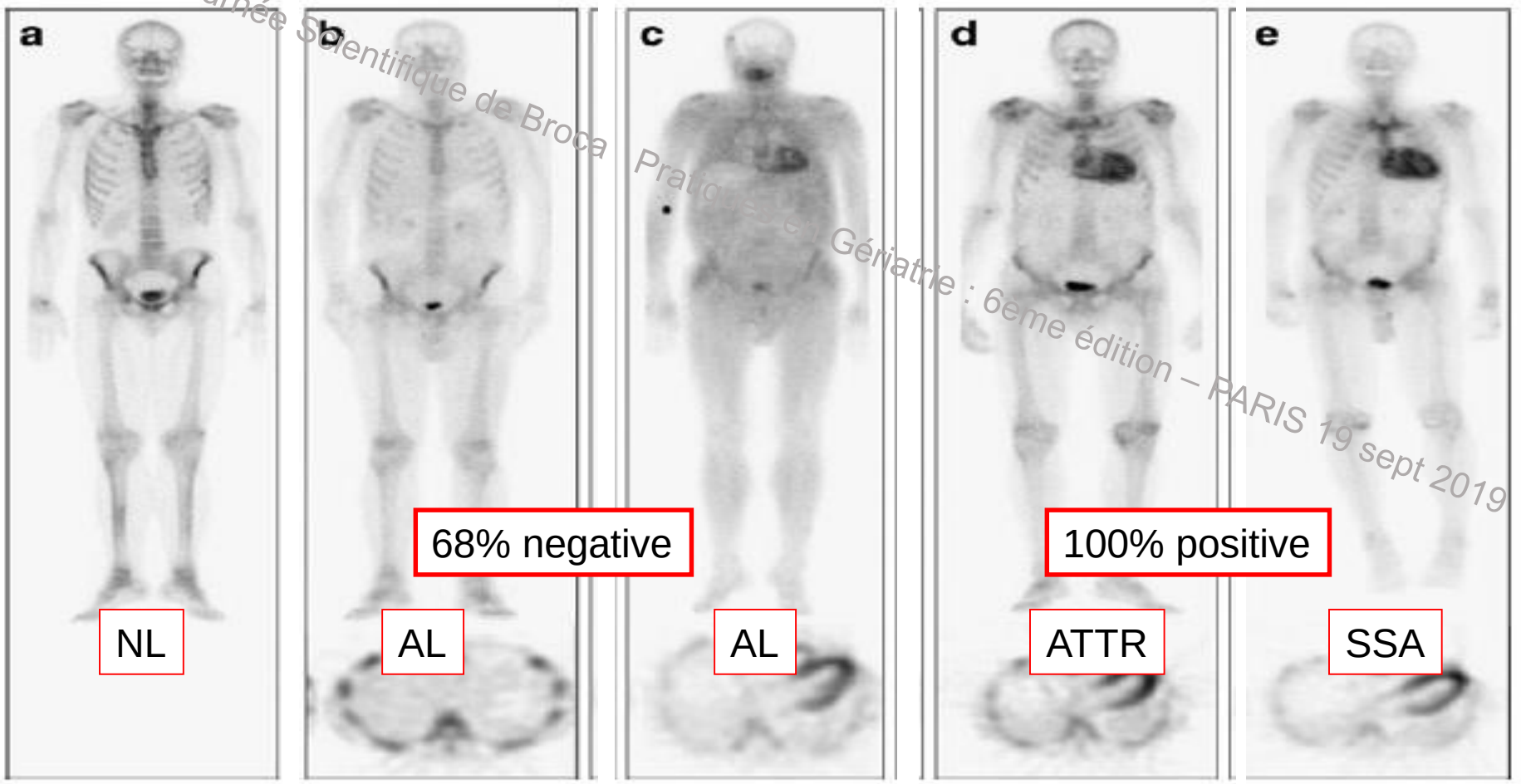
Figure 3. Characteristic Examples From CMR Scans

Cardiac magnetic resonance (CMR) end-diastolic frame from cine (**left panel**), ShMOLLI noncontrast T1 map (**middle panel**), and late gadolinium enhancement (LGE) images (**right panel**) in normal volunteer, aortic stenosis patient, and cardiac amyloid patient. Note the markedly elevated myocardial T1 time in the cardiac amyloid patient (1,170 ms, into the **red range** of the color scale) compared to the normal control (955 ms) and the patient with aortic stenosis and left ventricular hypertrophy (998 ms). ED = end diastolic; other abbreviations as in Figures 1 and 2.

J Am Coll Cardiol Img 2013;6:488–97

Usefulness and limitations of ^{99m}Tc-3,3-diphosphono-1, 2-propanodicarboxylic acid scintigraphy in the aetiological diagnosis of amyloidotic cardiomyopathy

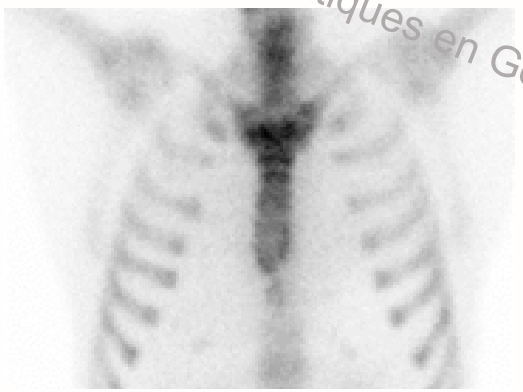
169 euros



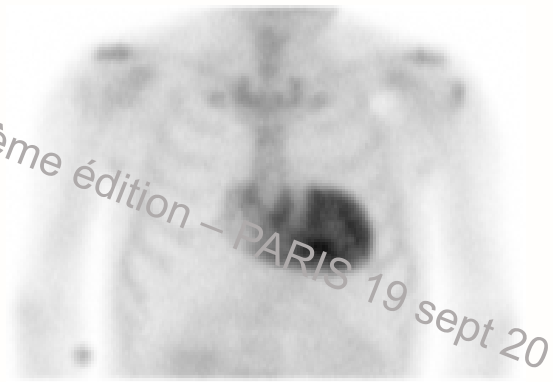
Among 45 patients with TTR-related AC, myocardial uptake of the tracer (i.e. visual score ≥1) was present in all cases, whereas among patients with AL-related AC, 23 cases (68%) did not show any myocardial tracer
uptake, and 11 cases (32%) showed a myocardial tracer uptake (mild in 5 cases, moderate in 6 cases)

Rapezzi C et al, Eur J Nucl Med Mol Imaging (2011) 38:470–478

- Planar and SPECT acquisitions performed 3 hours after tracer injection.
- Cardiac uptake was visually scored as present or absent
- Quantified by the ratio between 3D isocount volume of interest generated over the myocardium and a standard volume in lung (H/L).

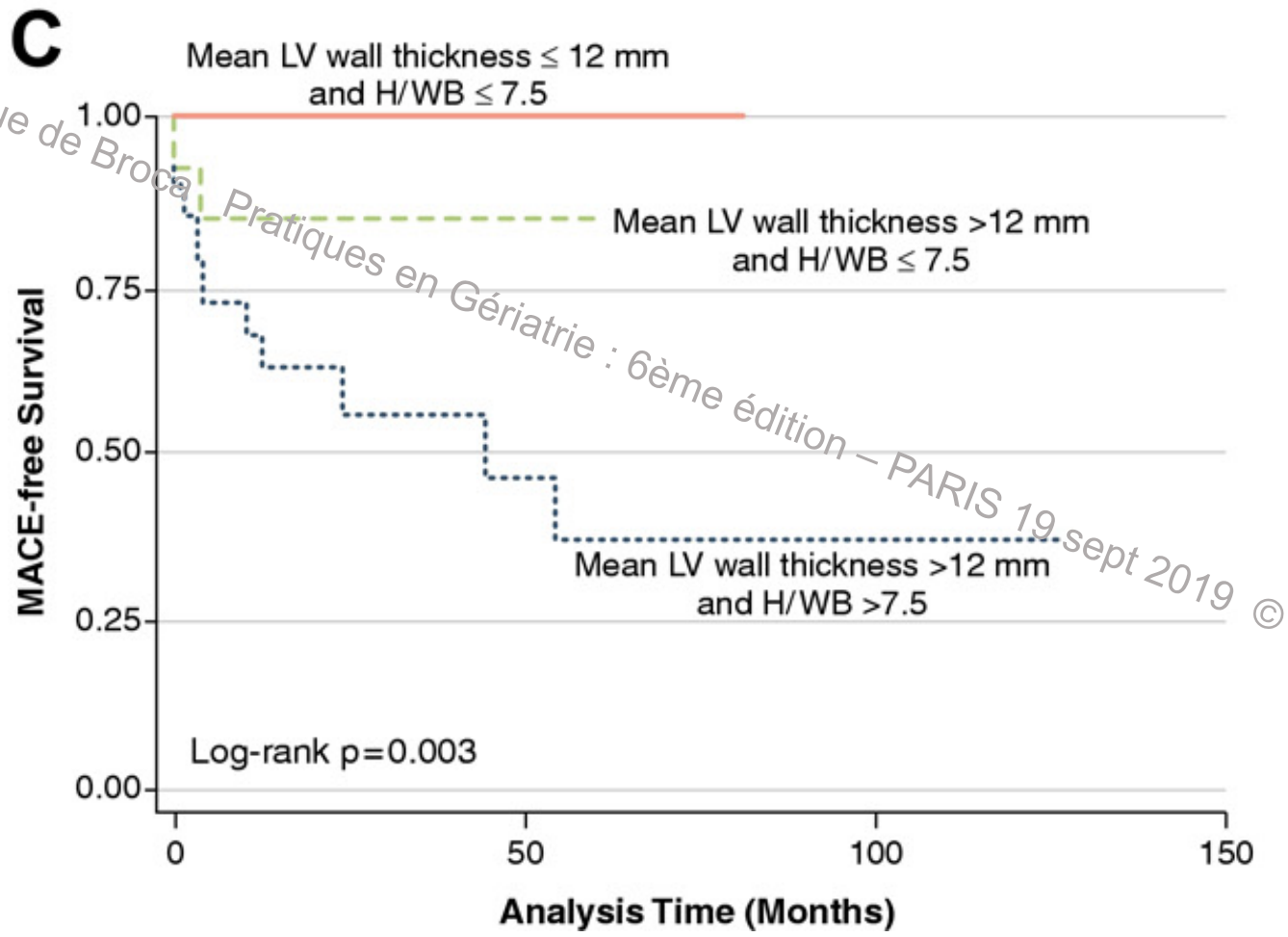


Absent (score 0)



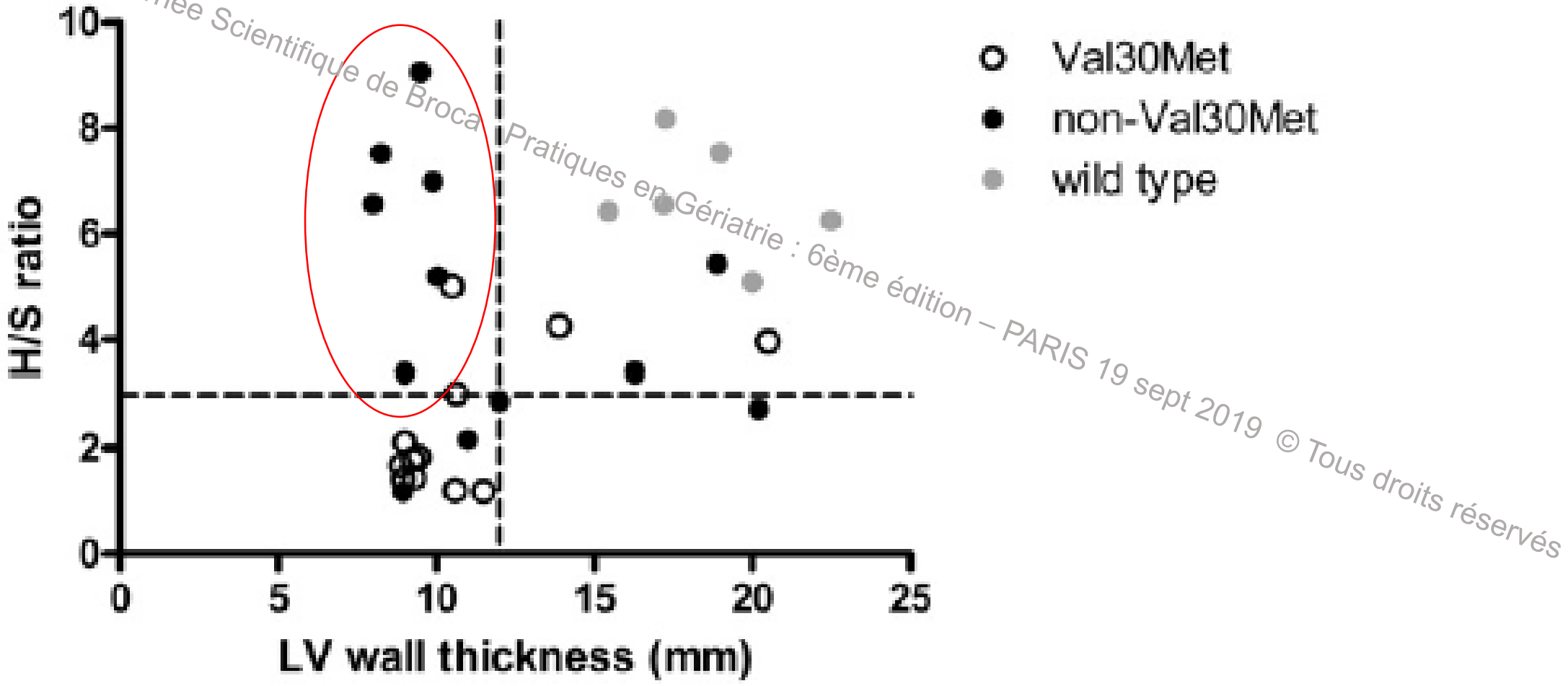
Present (score ≥1)

Role of 99mTc DPD scintigraphy in Diagnosis and Prognosis of TTR Cardiac Amyloidosis



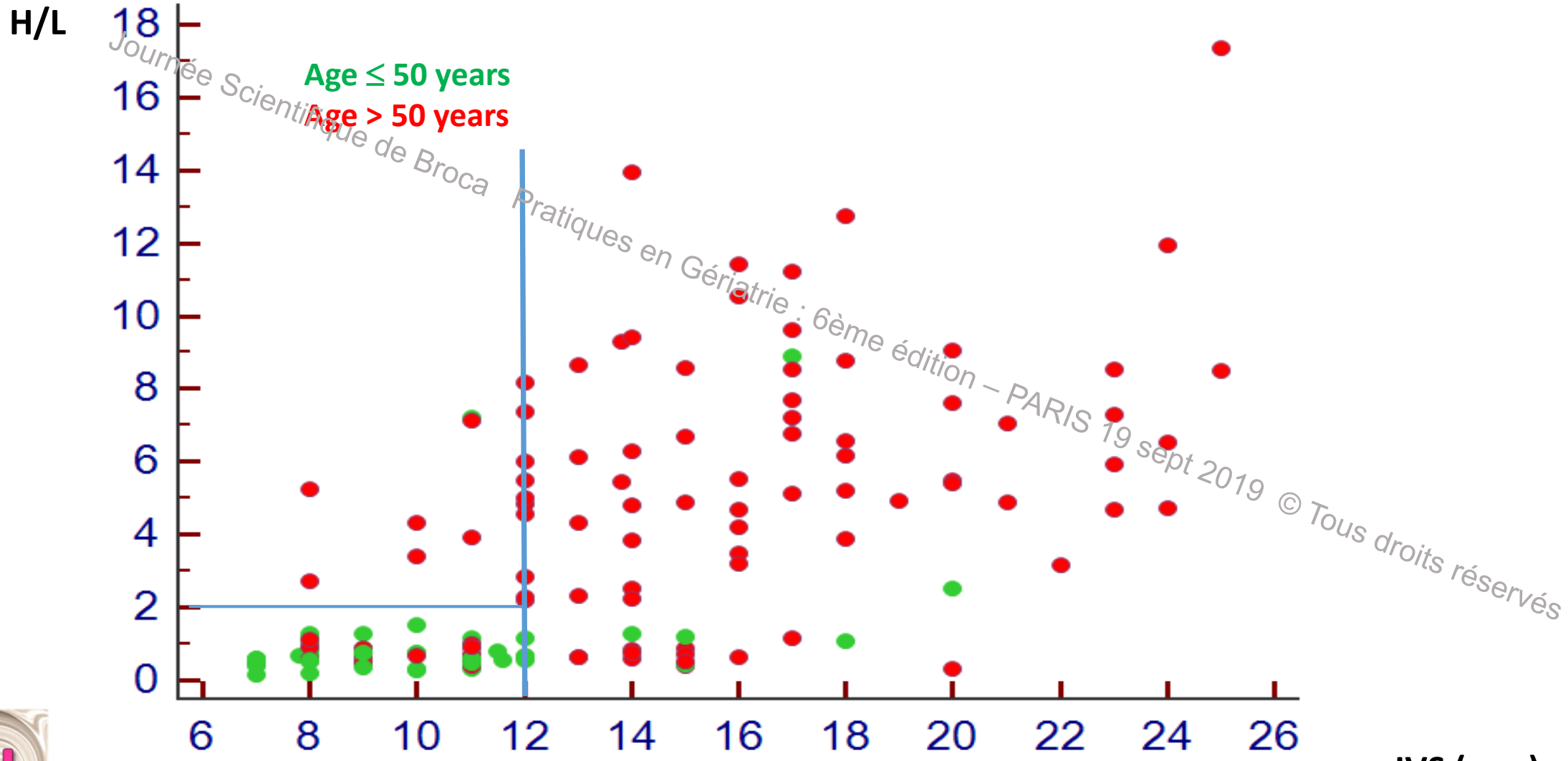
Rapezzi et al., JACC Cardiovasc Imaging. 2011 Jun;4(6):659-70.

Bone scintigraphy with ^{99m}technetium-hydroxymethylene diphosphonate allows early diagnosis of cardiac involvement in patients with transthyretin-derived systemic amyloidosis



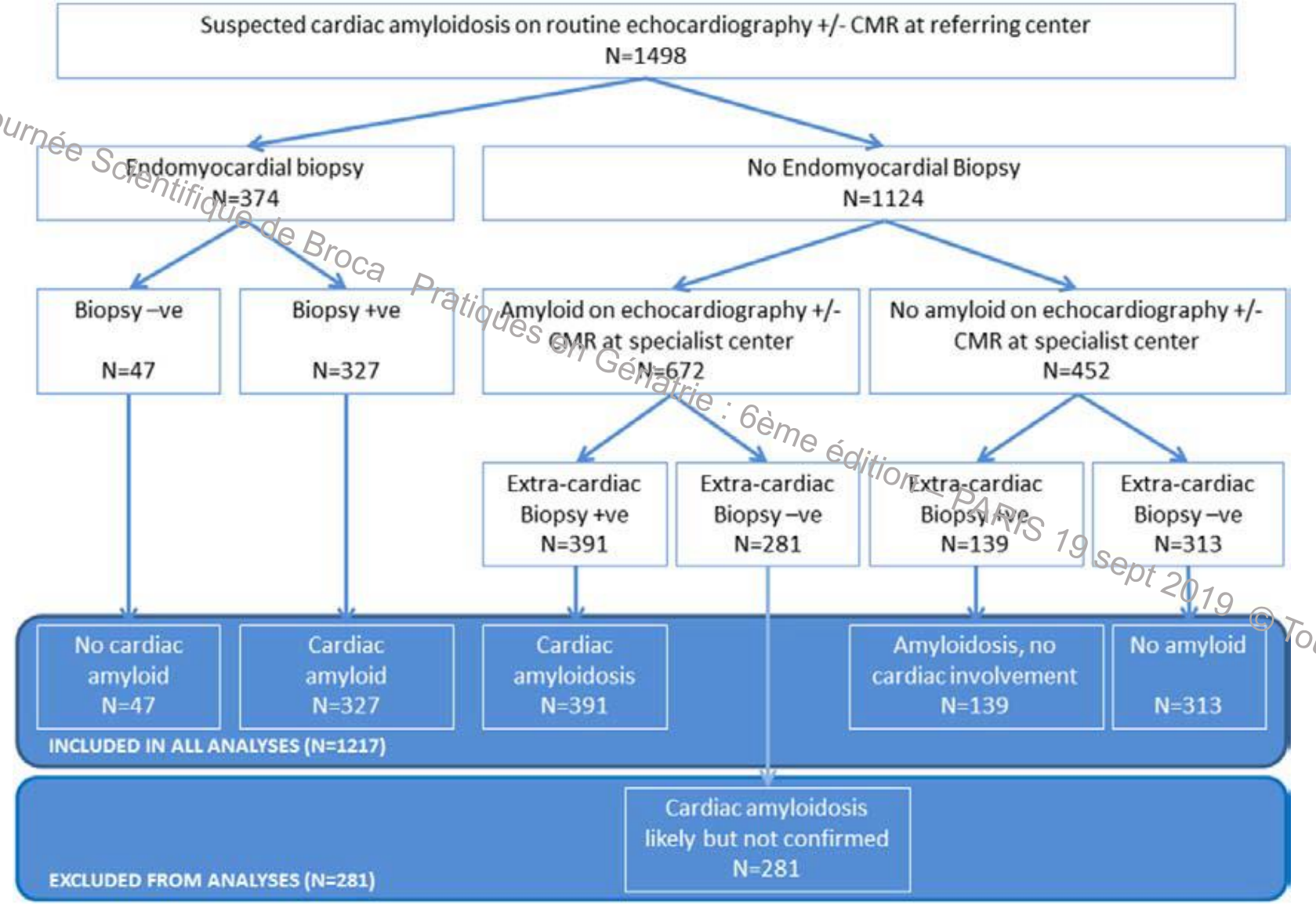
Glaudemans et al, Amyloid, 2014; 21(1): 35–44

Uptake according to IVS and age



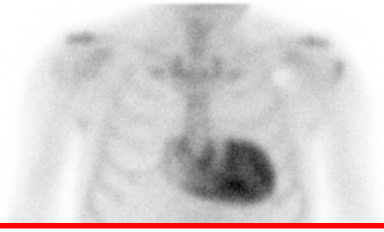
ROUZET F et al EANM 2016

Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis



Gillmore J et al, *Circulation*. 2016;133:2404-2412.

Identification of TTR-Related Subclinical Amyloidosis With ^{99m}Tc-DPD Scintigraphy



1 in 7 patients currently undergoing TAVR have occult cardiac "wild type" amyloidosis

- 12.521 pts/scintigraphy,
- 121 with suspected cardiac amyloidosis:excluded.
- oncologic (95%) or rheumatologic (5%) indications to scintigraphy (37% men; mean age 74 years; range 65 to 82 years).
- Myocardial uptake in 45 subjects (**0.36%;** 62%,men; **median age 81 years**; range 77 to 84 years
- 14 pts evaluated (11 men) :
  - LV wall thickness, 14 mm; range: 13 to 15 mm), and LV ejection fraction 58% (54% to 67%).
- If all patients with myocardial 99mTc-DPD uptake to be affected by TTRrelated cardiomyopathy (mainly SSA), the prevalence of the disease would reach 1.4% among men in the ninth decade

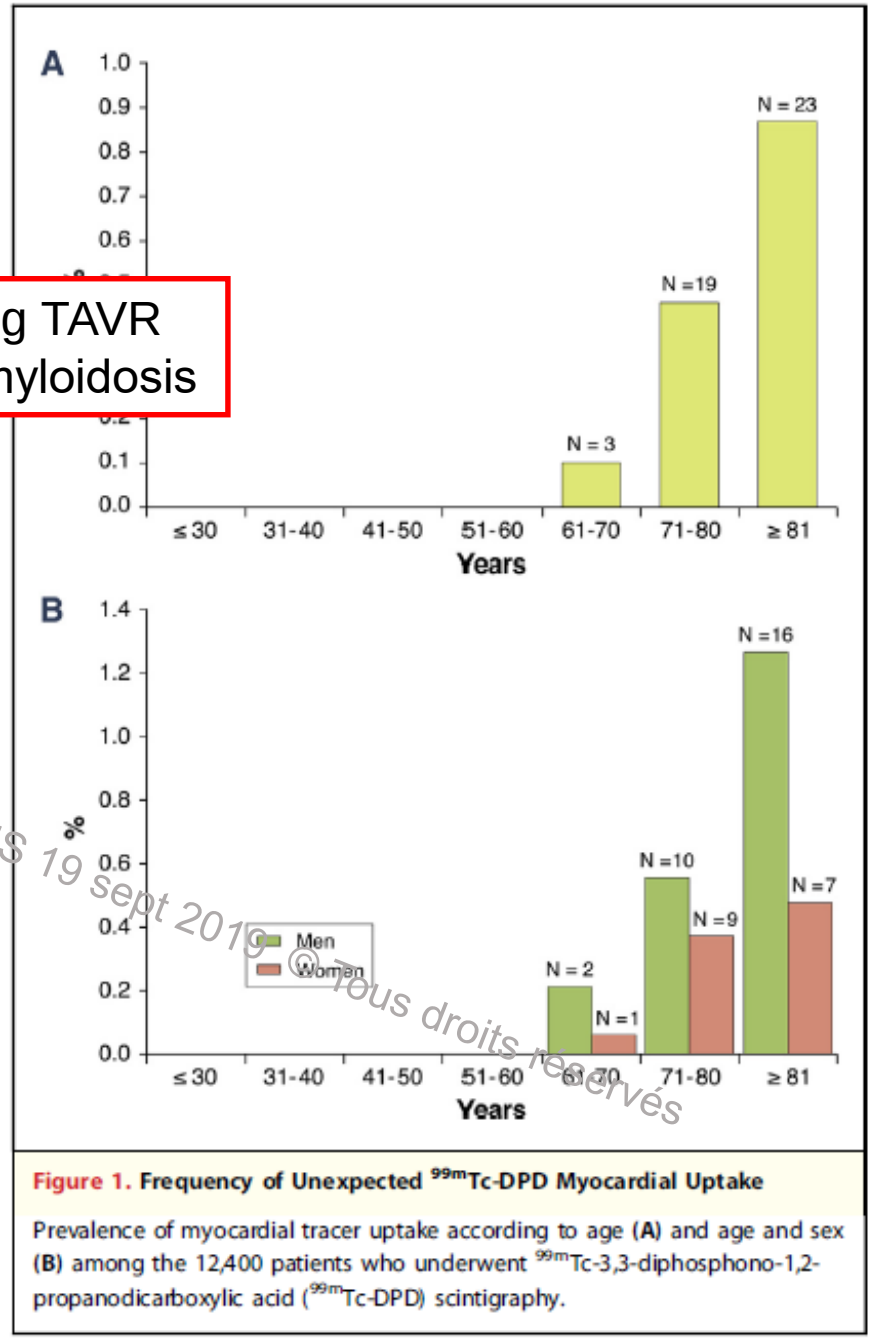


Figure 1. Frequency of Unexpected ^{99m}Tc-DPD Myocardial Uptake

Prevalence of myocardial tracer uptake according to age (**A**) and age and sex (**B**) among the 12,400 patients who underwent ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy.

Longhi S et al, J A C C : C A R D I O V A S C U L A R IMA G I N G , 7 :5 , 2 0 1 4 : 5 31– 3 2

Donc

- L’imagerie fait le DIAGNOSTIC POSITIF D’AMYLOSE
- Mais NE PERMET PAS TOUJOURS DE DISCRIMINER ENTRE LES DIFFERENTS TYPES

Comment différencier les différents types d'amylose

- **SIGNES DE MYELOME: 20% (et 20% de +80 ans ont une MGUS) -------→ AL**
- **Histoire familiale de mutation de la TTR ou de neuropathie, age <60 ans, canal carpien bilatéral -----→ATTR mutée**
- **Age >80 ans, homme----→ATTR sénile**

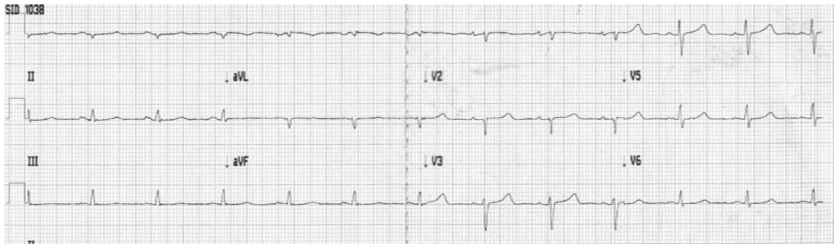
- **En fait : RIEN NE PERMET DE DIFFERENCIER A CE STADE**

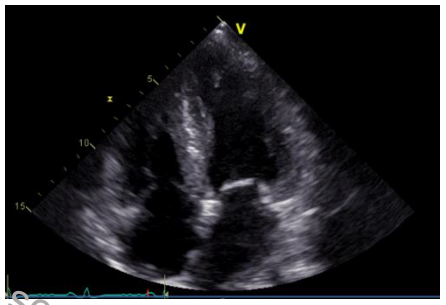
Looks like Amyloid Cardiomyopathy
Tools for an Early Diagnosis

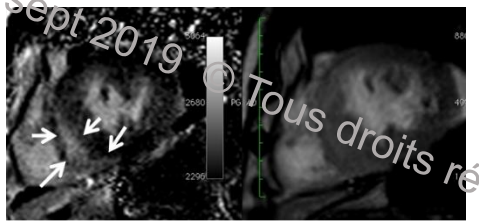
Clinical presentation
HFPEF
Family history, age
ECG
Echo
MRI

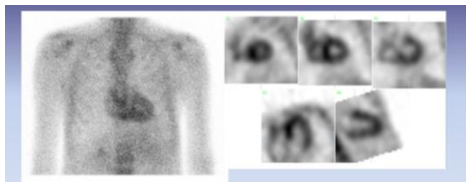
AL,
or mutated TTR,
or « wild type/senile » TTR

Light chains
« Bone » scintigraphy
Genetic testing



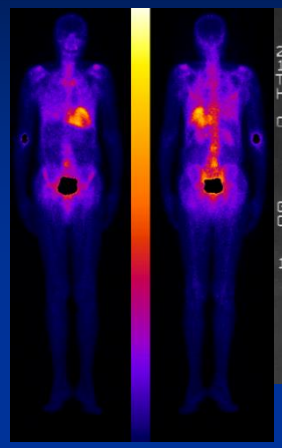


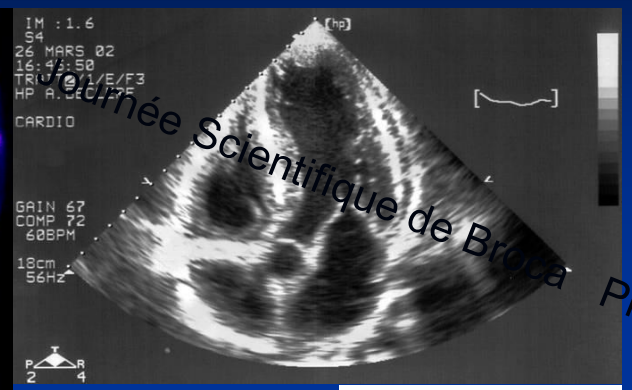




The goal is to reach an early diagnosis of hATTR amyloidosis and provide accurate trearment

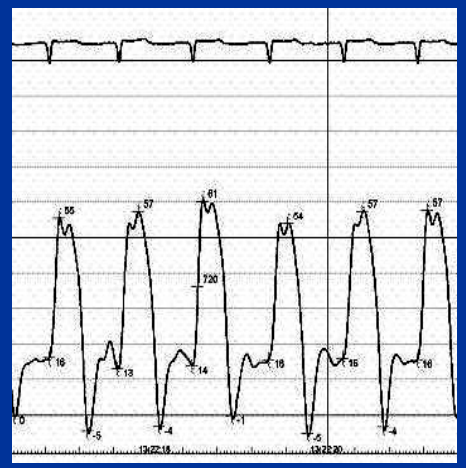
Infiltration de l'ensemble des structures cardiaques





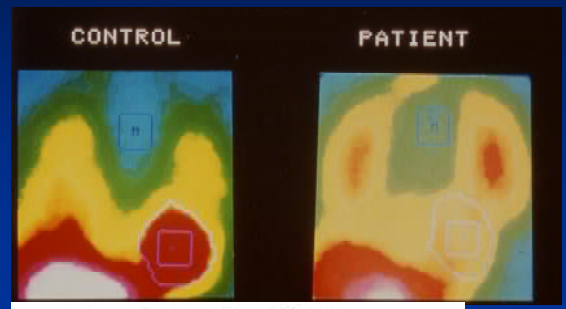
25-65%

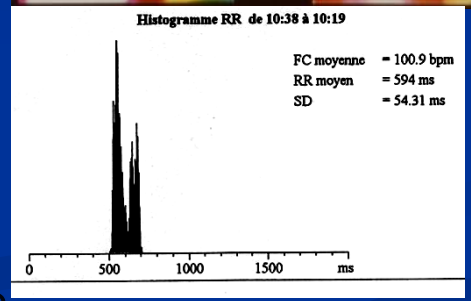
~~Hypertrophy~~
infiltration



Restrictive Cardiopathy

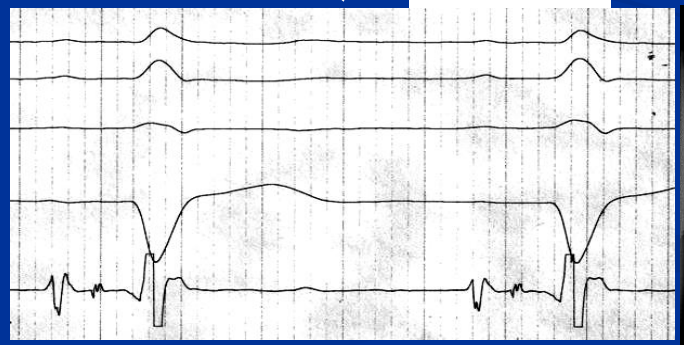
85%

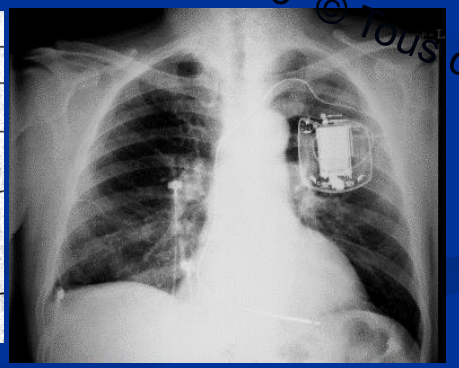




Cardiac denervation

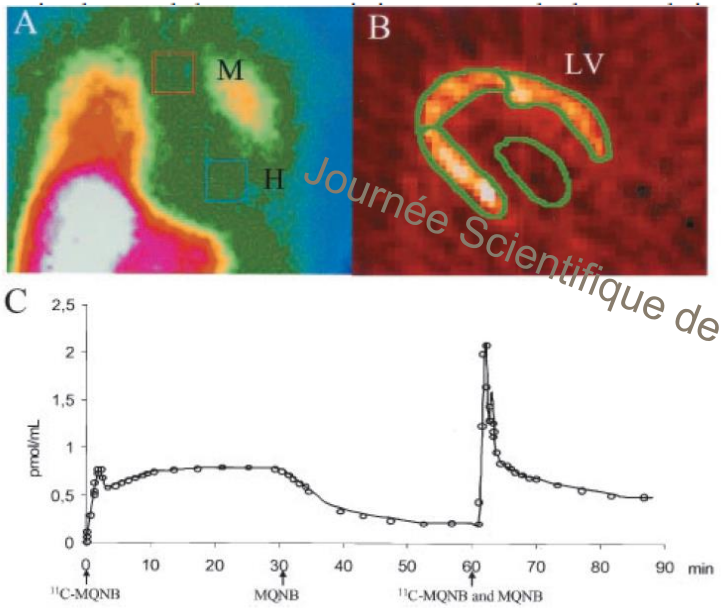
35%

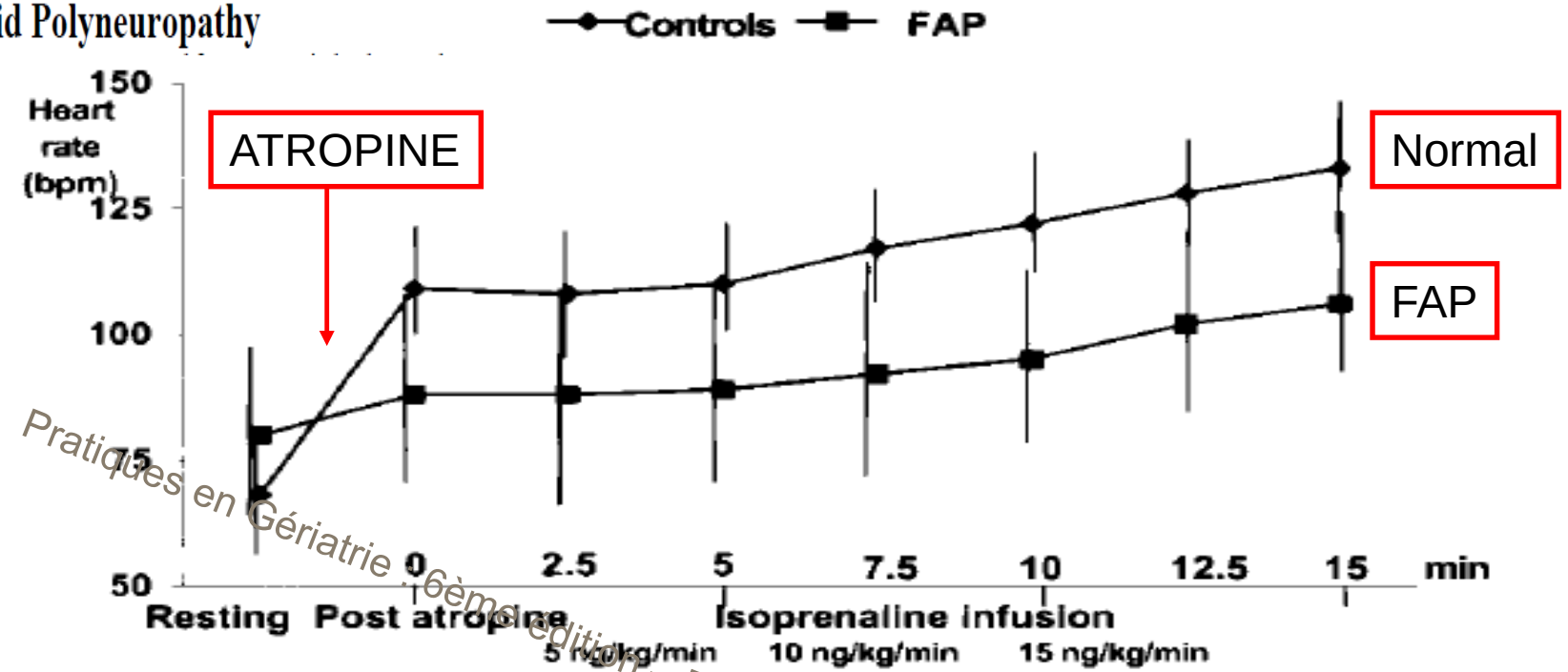




Conduction abnormalities
Sudden death ?

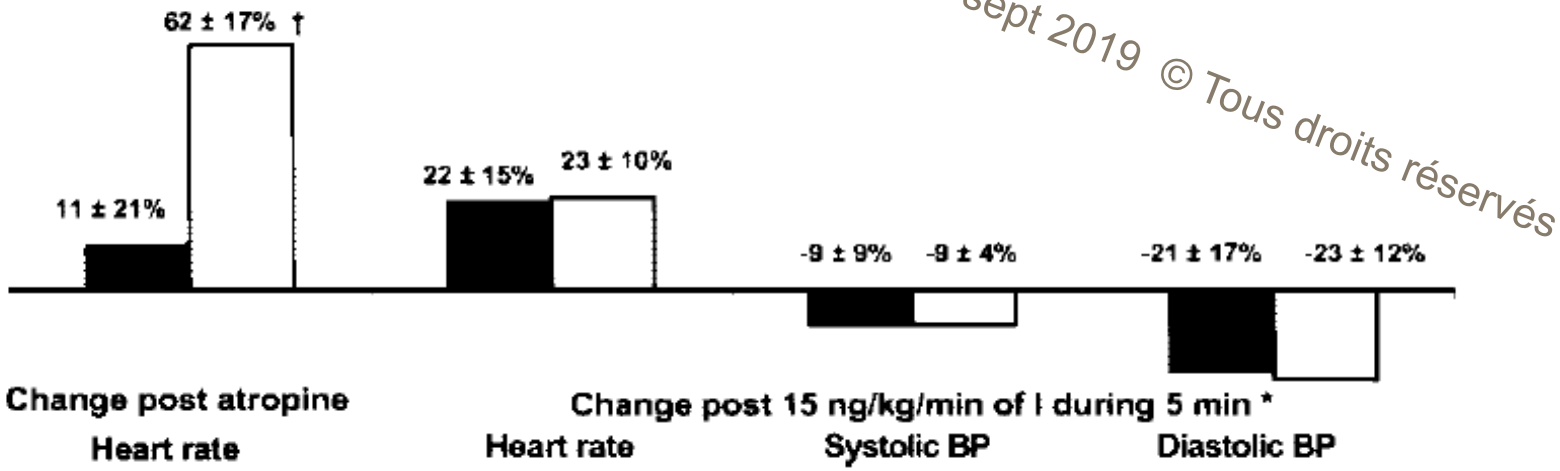
Myocardial Muscarinic Receptor Upregulation and Normal Response to Isoproterenol in Denervated Hearts by Familial Amyloid Polyneuropathy





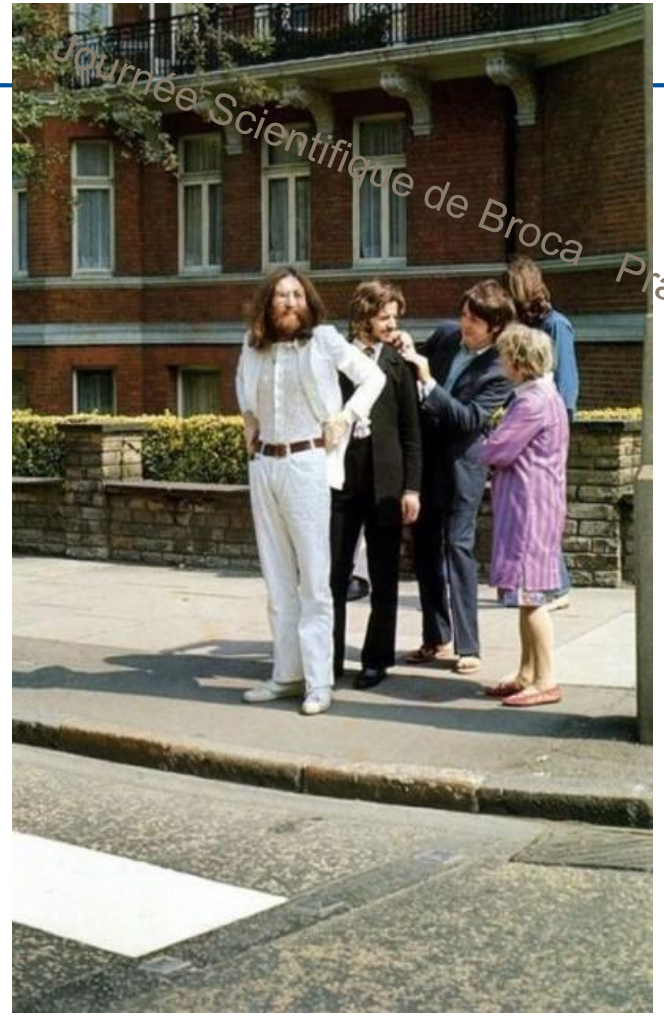
- **upregulation of myocardial muscarinic receptors** in response to the **PΣ presynaptic denervation**

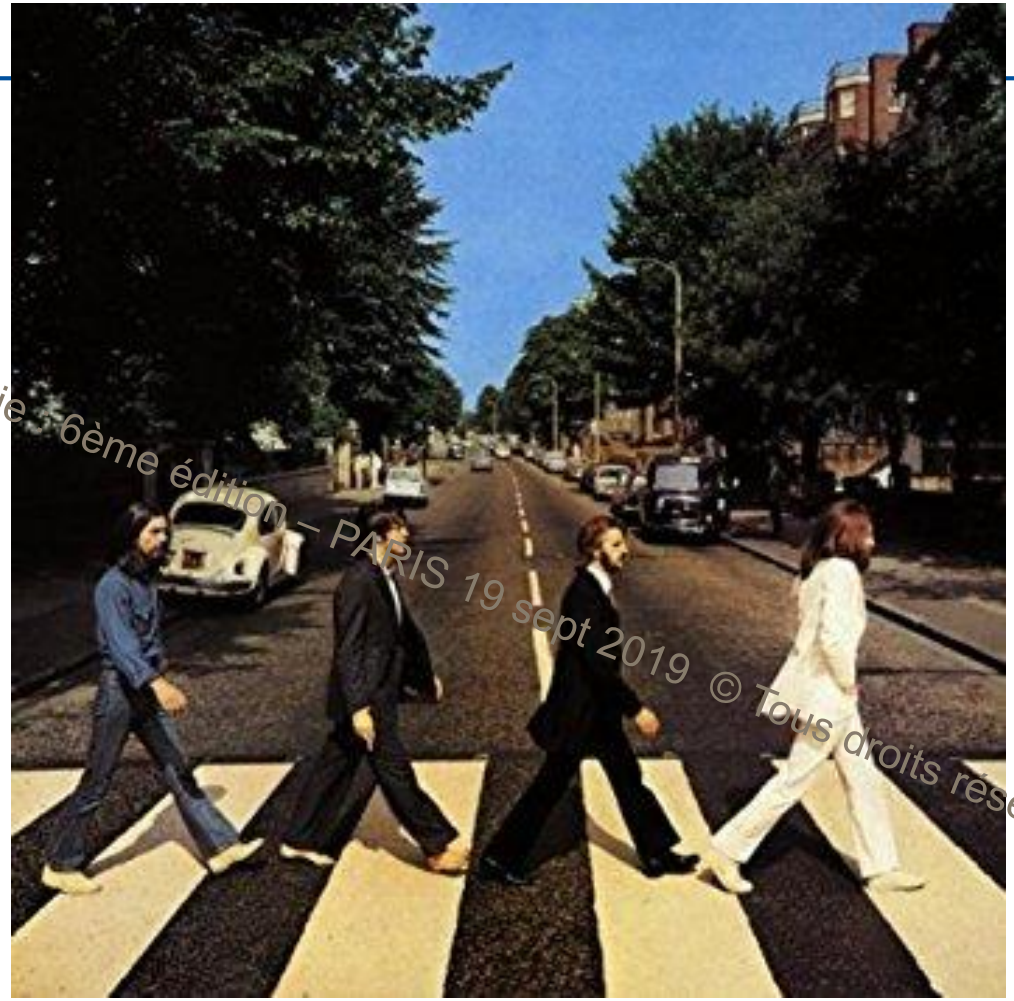
- without change in cardiac β-receptor responsiveness to catecholamines



Delahaye et al, Circulation. 2001; 104:2911-2916

Imagerie multimodalité





Summary

Pensez y ,,,,
Pensez y
Pensez y !!!!!!!

- **<u>Il faut penser à l'amylose cardiaque devant:</u>**
  - Insuffisance cardiaque à FE préservée
  - Augmentation inexpliquée de l'épaisseur cardiaque ≥12 mm
  - Diminution du strain longitudinal avec préservation apicale
  - Discordance entre épaisseur écho et voltage/ECG (mais l'absence de microvoltage n'écarte pas le diagnostic)
  - Rétrécissement aortique avec bas debit, bas gradient et HVG
  - Association à neuropathie périphérique, canal carpien bilatéral

Adapted from Maurer et al. *Circulation* 2017;135:1357–77

En résumé

- **Suspicion clinique, imagerie multimodalité**
  Scintigraphie osseuse +++
- **+**
- **Test génétique quelque soit l'âge: diagnostic pour le patient, la fratrie et les descendants**
- **+**
- **Chaines légères (immunofixation, Bence Jones)**
- **+/-**
- **Biopsie (glandes salivaires accessoires, peau, graisse abdominale)**

Think about it…
think about it…
think about it!!

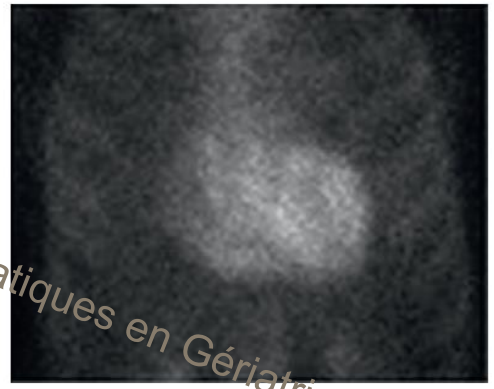
Les grandes règles du traitement symptomatique

- **FAC asymptomatique:**
  - ☐ épaississement à l'échographie/IRM/scintigraphie +/-, dénervation+/-: surveillance
  - ☐ trbles conductifs: PM ?

- **Les recommandations habituelles ne s'appliquent pas en cas d'amylose cardiaque symptomatique:**
  - Bradycardie/béta bloquants délétères sur cardiopathie restrictive
  - Accélérer la FC via stimulateur quand IC très sévère
  - IEC/ARA2 mal tolérés du fait de la vasoplégie-hypoTA orthostatique
  - En pratique: diurétiques Lasilix +/- anti aldostérones
  - Attention FA
  - IC réfractaire: transplantation cardiaque ?

Les AMYLOSES A TRANSTHYRETINE

Diagnosis



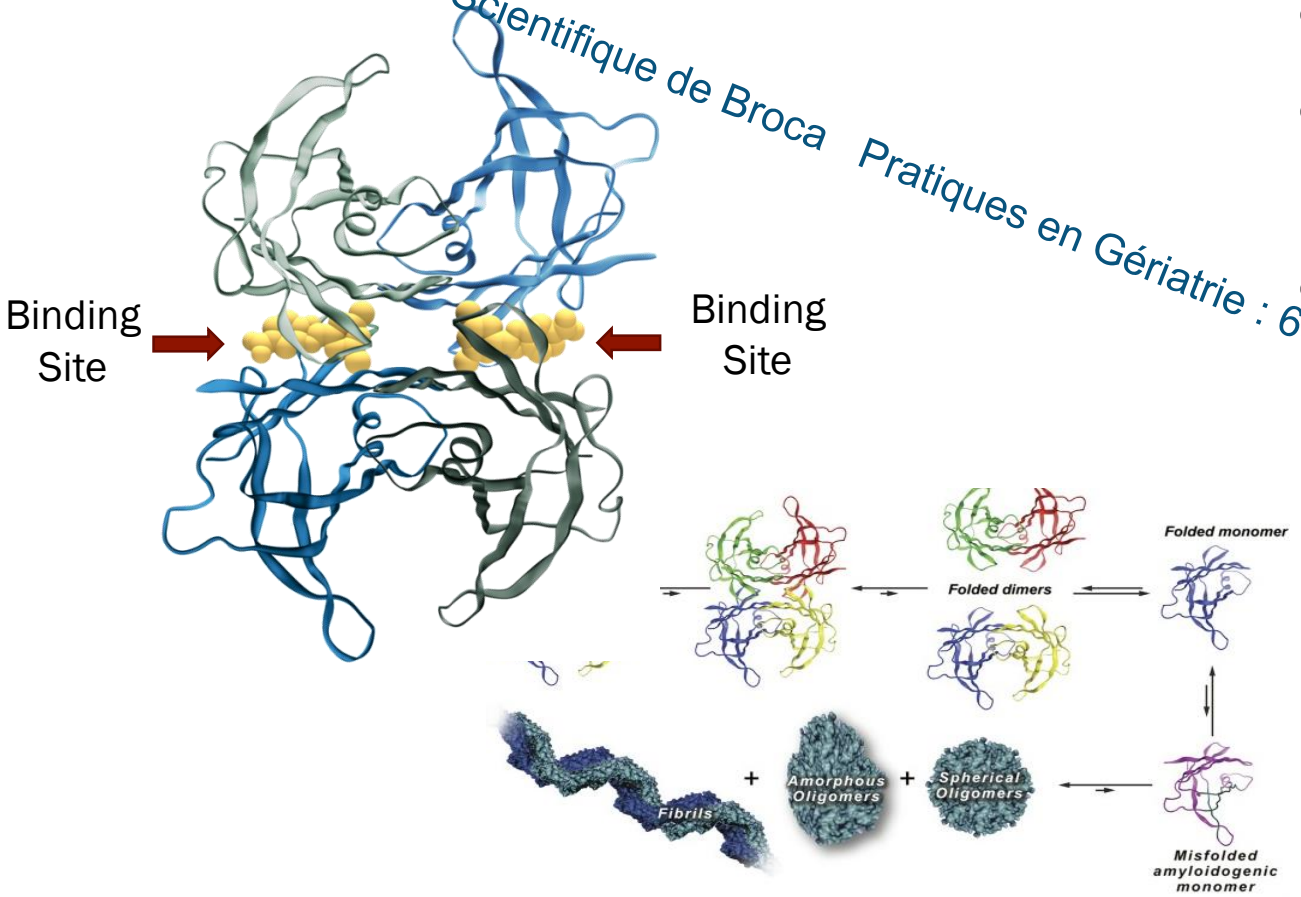
Treatment

Emerging Treatment Options

wtATTR-CM	hATTR		
	Cardiomyopathy ONLY	*Cardiomyopathy AND Neuropathy*	*Neuropathy ONLY*
TAFAMIDIS Under review by FDA	TAFAMIDIS Under review by FDA	TAFAMIDIS Under review by FDA	PATISIRAN
DIFLUNISAL Off-label usage	DIFLUNISAL Off-label usage	PATISIRAN	INOTERSEN
		INOTERSEN	DIFLUNISAL Off-label usage
		DIFLUNISAL Off-label usage	

Ruberg, F.L. et al. J Am Coll Cardiol. 2019;73(22):2872-91.

Vyndaqel® (Tafamidis)



- Selective transthyretin stabilizer
- Avoids the rate-limiting step of tetramer dissociation
- Since 2011 approved for treatment of hereditary ATTR polyneuropathy stage I by EMA, but not by the FDA

Bulawa, et al. *Proc Natl Acad Sci USA*. (2012).

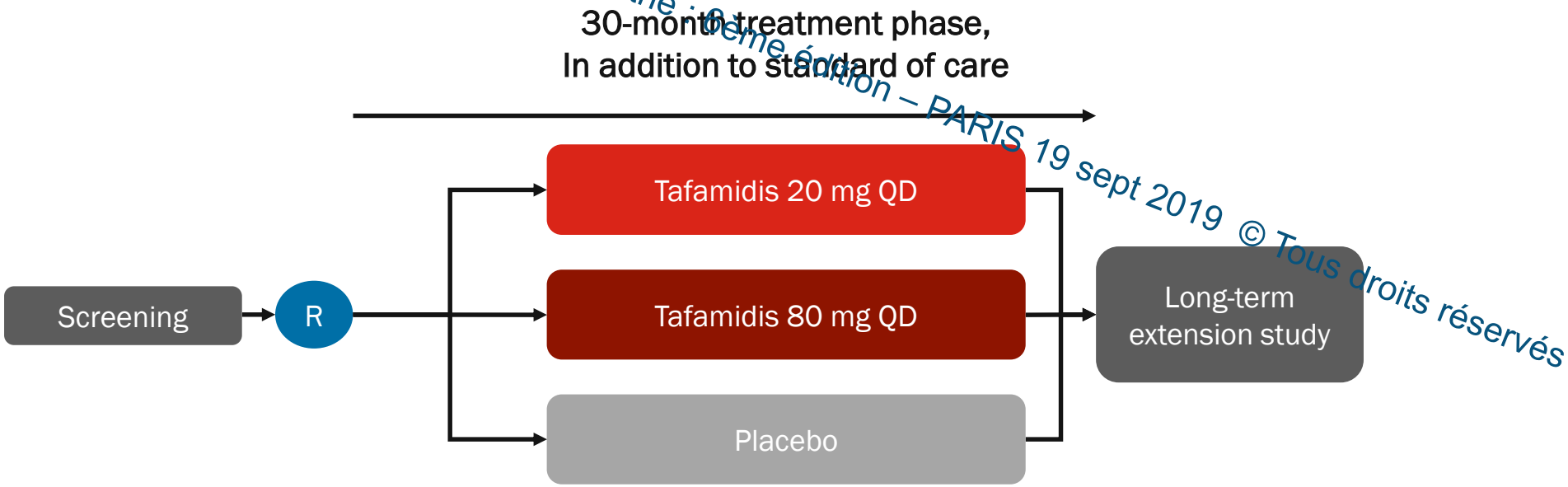
ATTR-ACT
Transthyretin Amyloid Cardiomyopathy Tafamidis Study

- Phase 3 trial. Controlled and Randomized
- Placebo/20mg/80mg Tafamidis : 30 months
- Primary endpoint : All cause of Death and Recurrency of Hospitalisation
- Secondary endpoint : 6MWT, KCCQ-OS
- Inclusion criteria
  - NYHA I to III (NYHA IV excluded)
  - End-diastolic interventricular septal wall thickness exceeding 12 mm;
  - A history of heart failure, with at least one prior hospitalization for heart failure OR clinical evidence of heart failure (without hospitalization) manifestedin signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with a diuretic for improvement
  - N-terminal pro-B-type natriuretic peptide ≥ 600 pg/ml
  - 6-minute walk-test distance>100 m
  - Tissular TTR amyloid deposit.

Maurer M, et al. *N Engl J Med*. 2018;379:1007-1016.

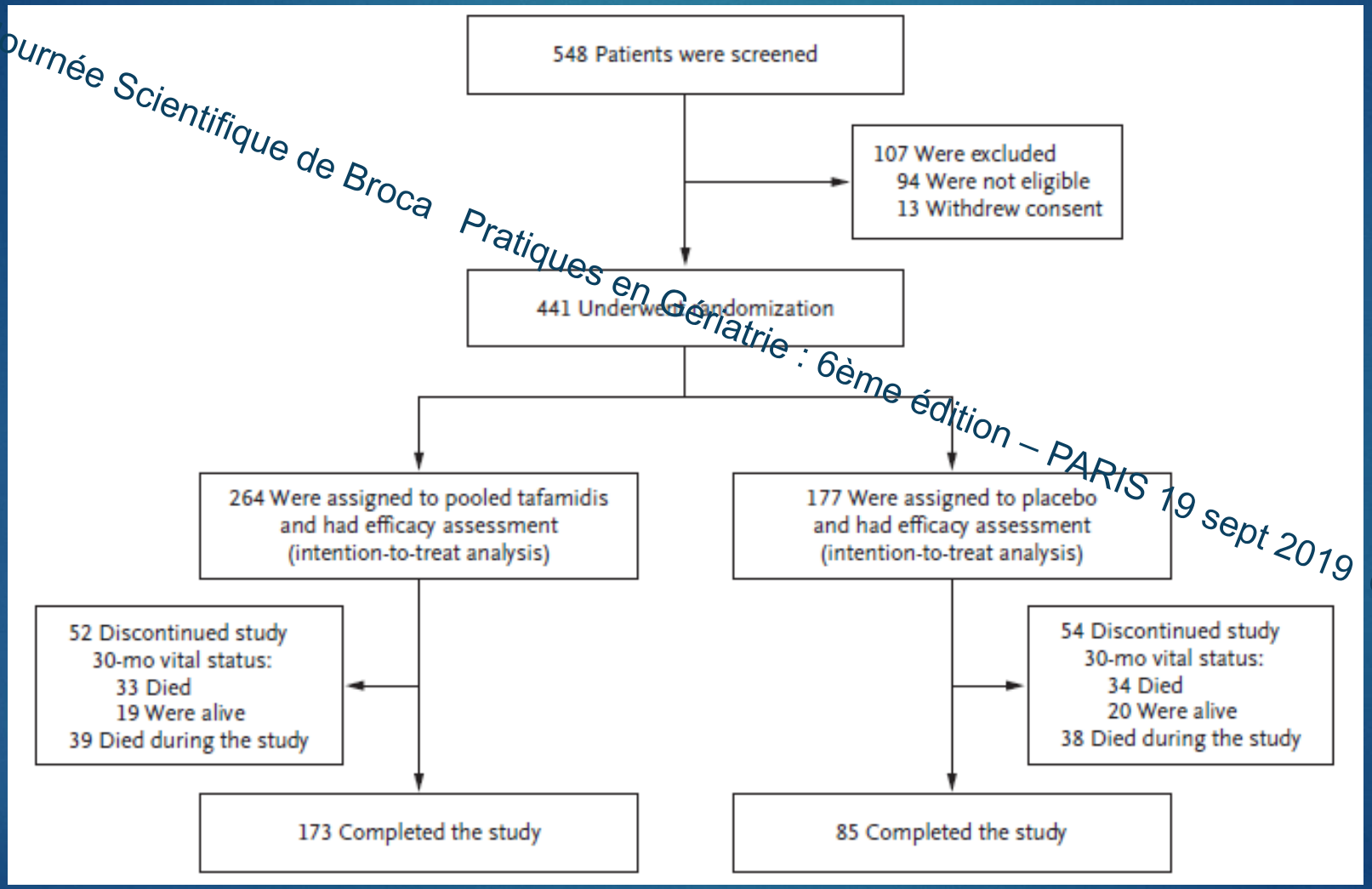
ATTR-ACT: Study design

- Patients randomized 2:1:2 to tafamidis 80 mg, tafamidis 20 mg, and placebo
- Stratification for genotype (wild-type or variant) and disease severity (NYHA class)
- A sample size of 400 pts was estimated to give 90% power to detect either a 30% reduction in mortality, or a reduction in the frequency of CV-related hospitalizations from 2.5 to 1.5, or both



Maurer MS, et al. *NEJM*. 2018.

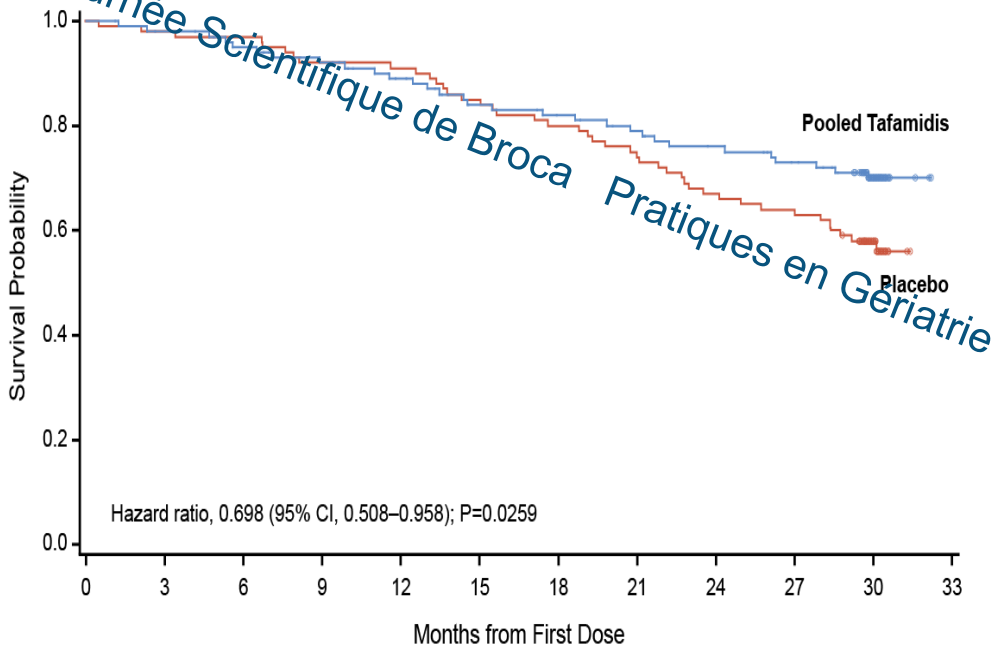
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy



N=441
75% wild type
25% mutés

Maurer MS et al, N Engl J Med. 2018 Sep 13;379(11):1007-1016

ATTR-ACT: Primary Endpoints



No. at Risk
Patients Remaining at Risk
(Cumulative Events)

Tafamidis	264	259	252	244	235	222	216	209	200	193	99	0
	0	5	12	20	29	42	48	55	64	71	78	78
Placebo	177	173	171	163	161	150	141	131	118	113	51	0
	0	4	6	14	16	27	36	46	59	64	75	76

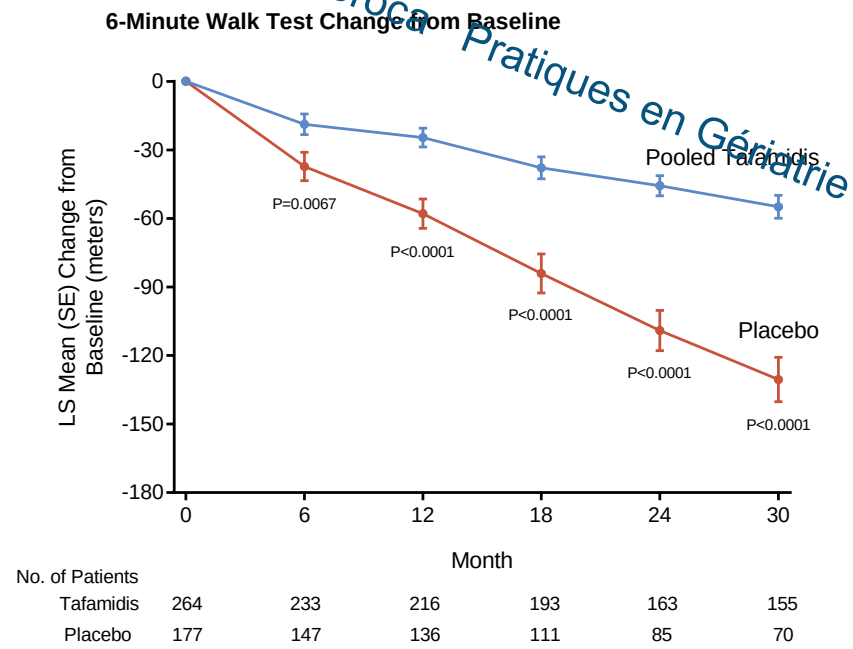
30% relative reduction of all-cause mortality 30% by FS-method

32% relative reduction of cardiovascular-related hospitalizations
(pooled Tafamidis vs. Placebo)

Maurer MS, et al. *NEJM*. 2018.

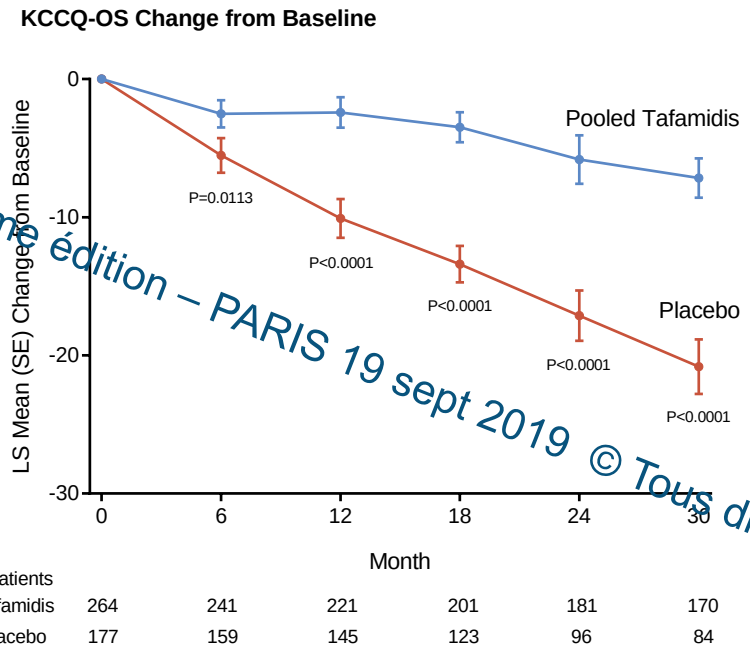
ATTR-ACT: Secondary Endpoints

6-minute-walk-test



No. of Patients						
Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70

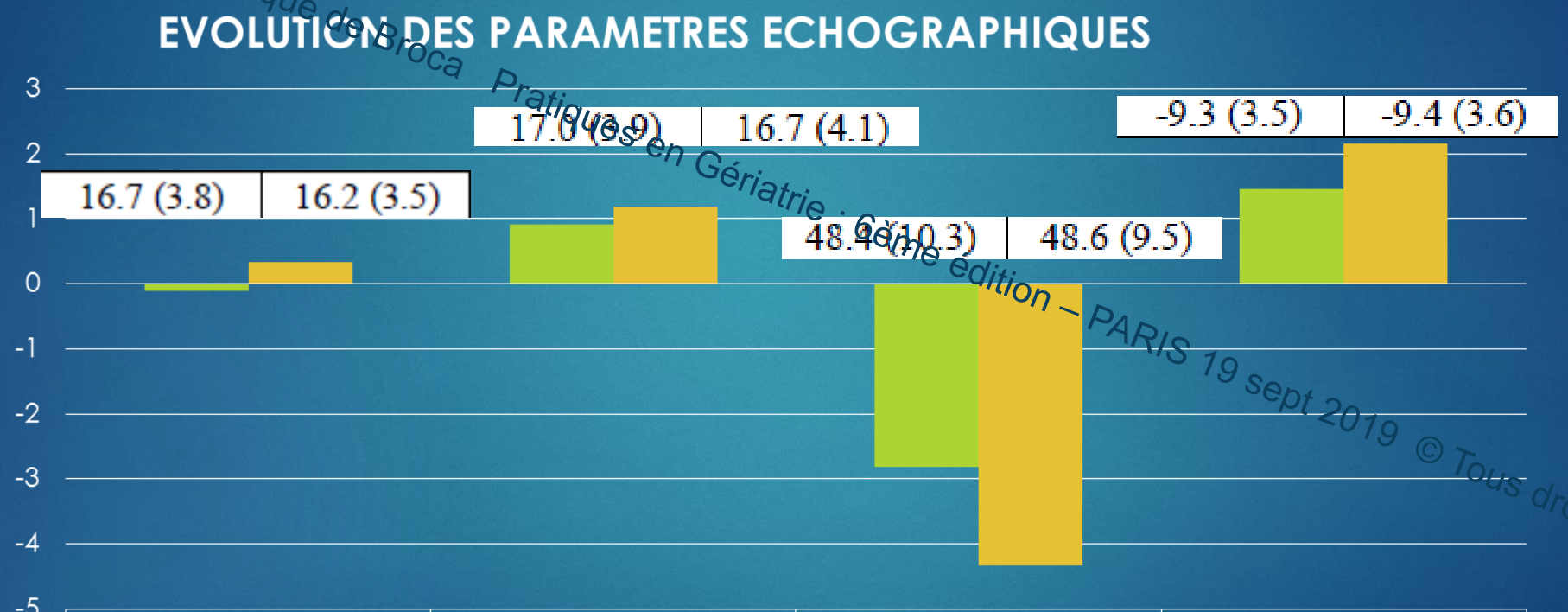
Quality of Life



No. of Patients						
Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

Maurer MS, et al. *NEJM*. 2018.

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy



	IVS	PW	EF	GLS
TAFAMIDIS n=264	-0,11	0,92	-2,82	1,46
PLACEBO n=177	0,33	1,19	-4,34	2,16

Maurer MS et al, N Engl J Med. 2018 Sep 13;379(11):1007-1016

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

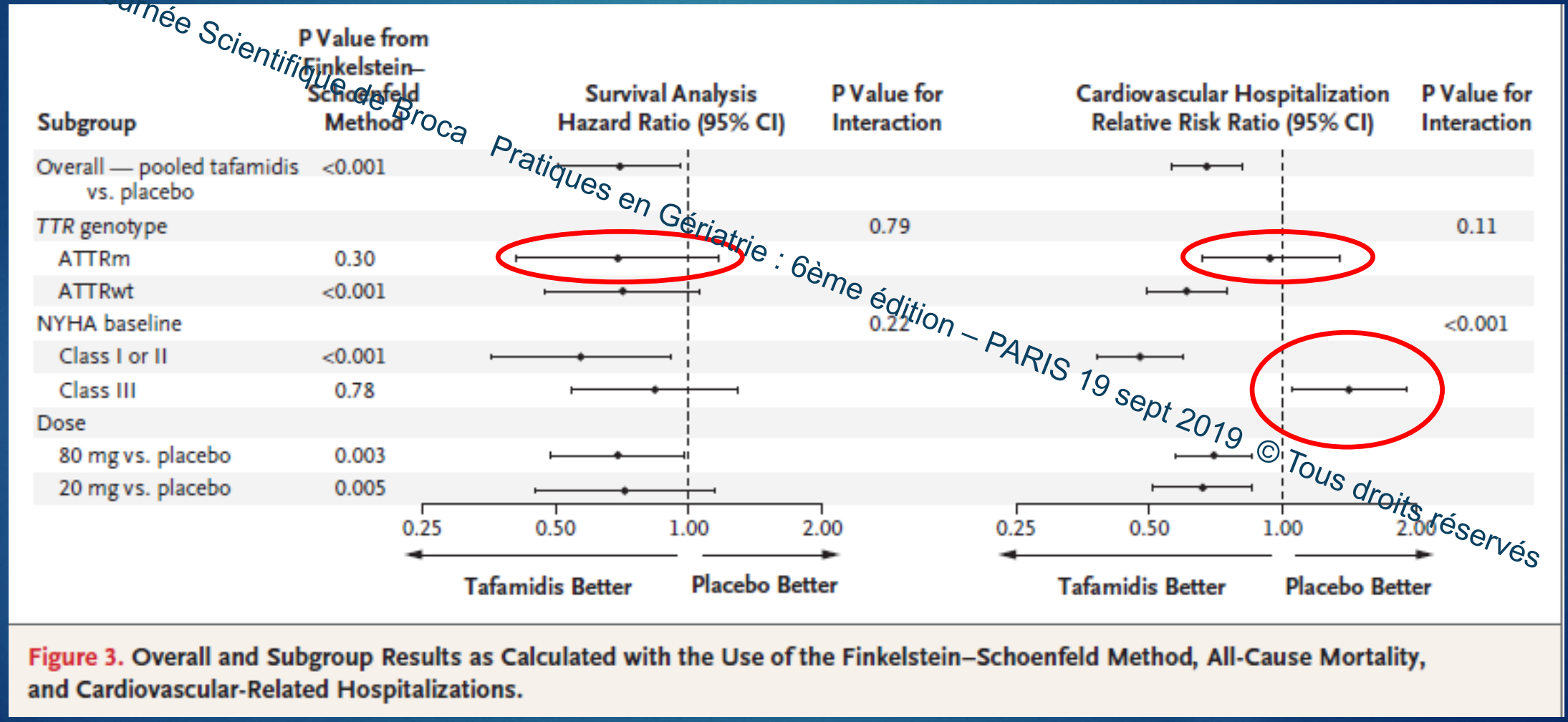
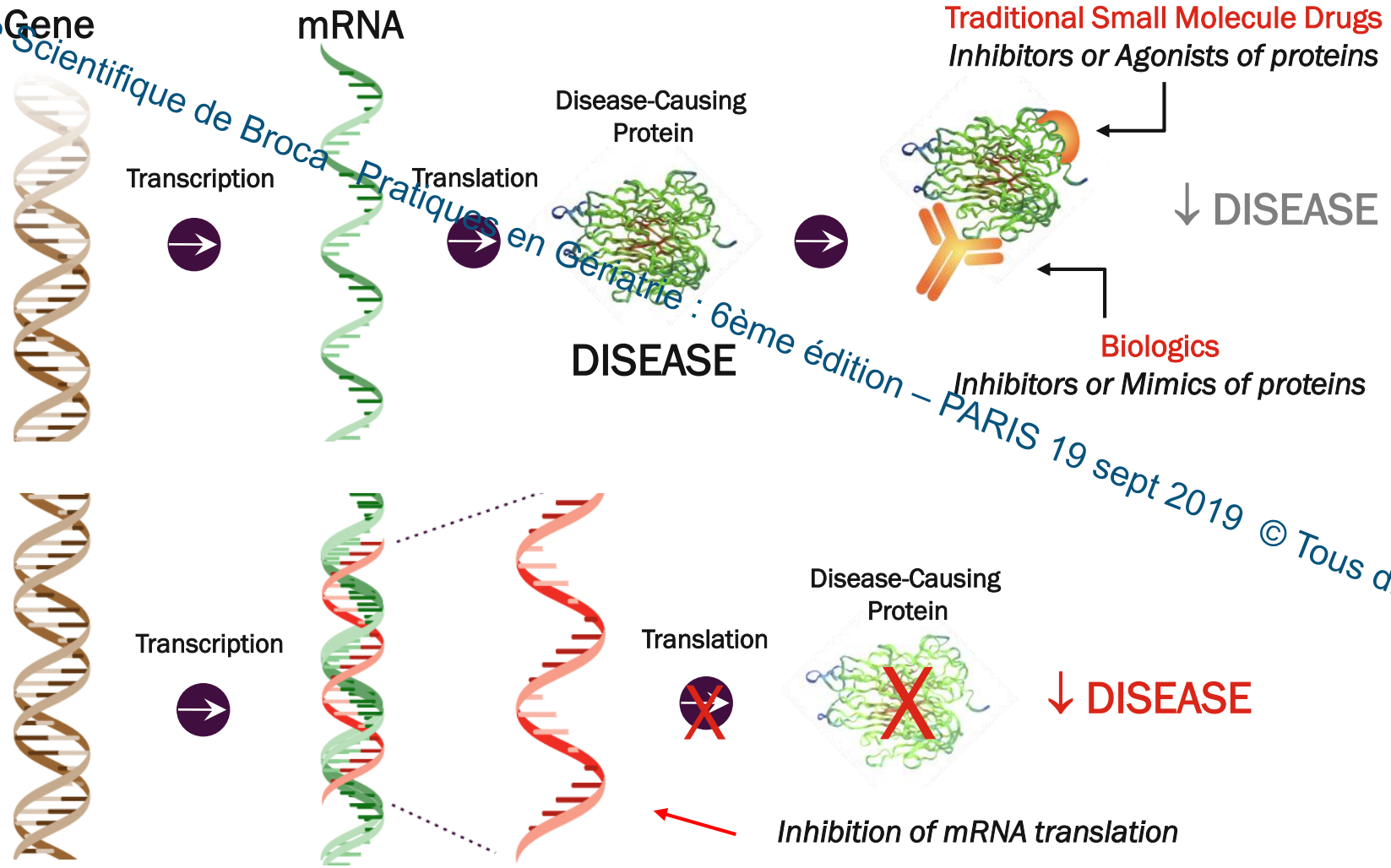


Figure 3. Overall and Subgroup Results as Calculated with the Use of the Finkelstein–Schoenfeld Method, All-Cause Mortality, and Cardiovascular-Related Hospitalizations.

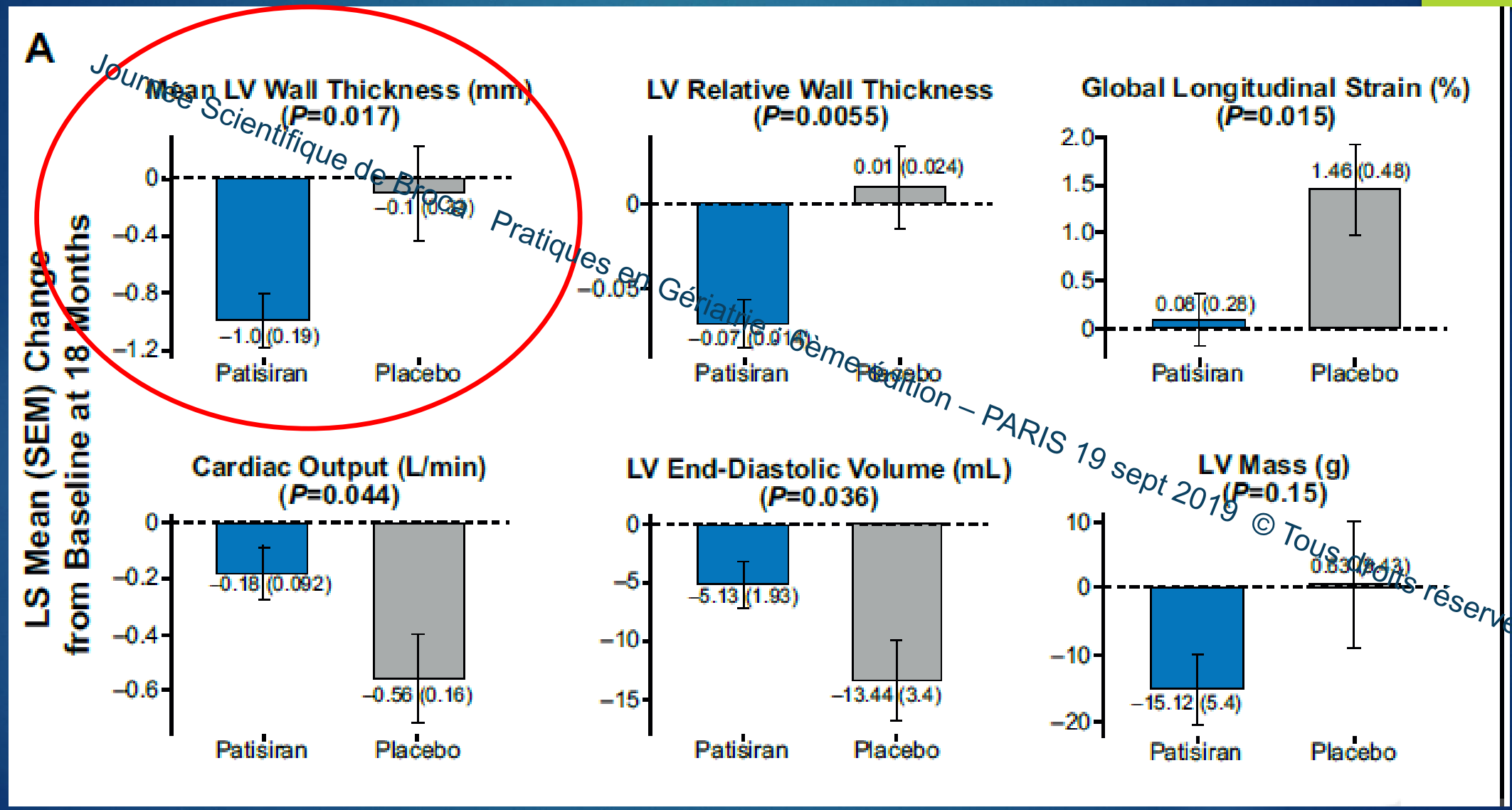
Maurer MS et al, N Engl J Med. 2018 Sep 13;379(

Next Generation Treatment: Regulation of Protein Expression by Gene Silencing



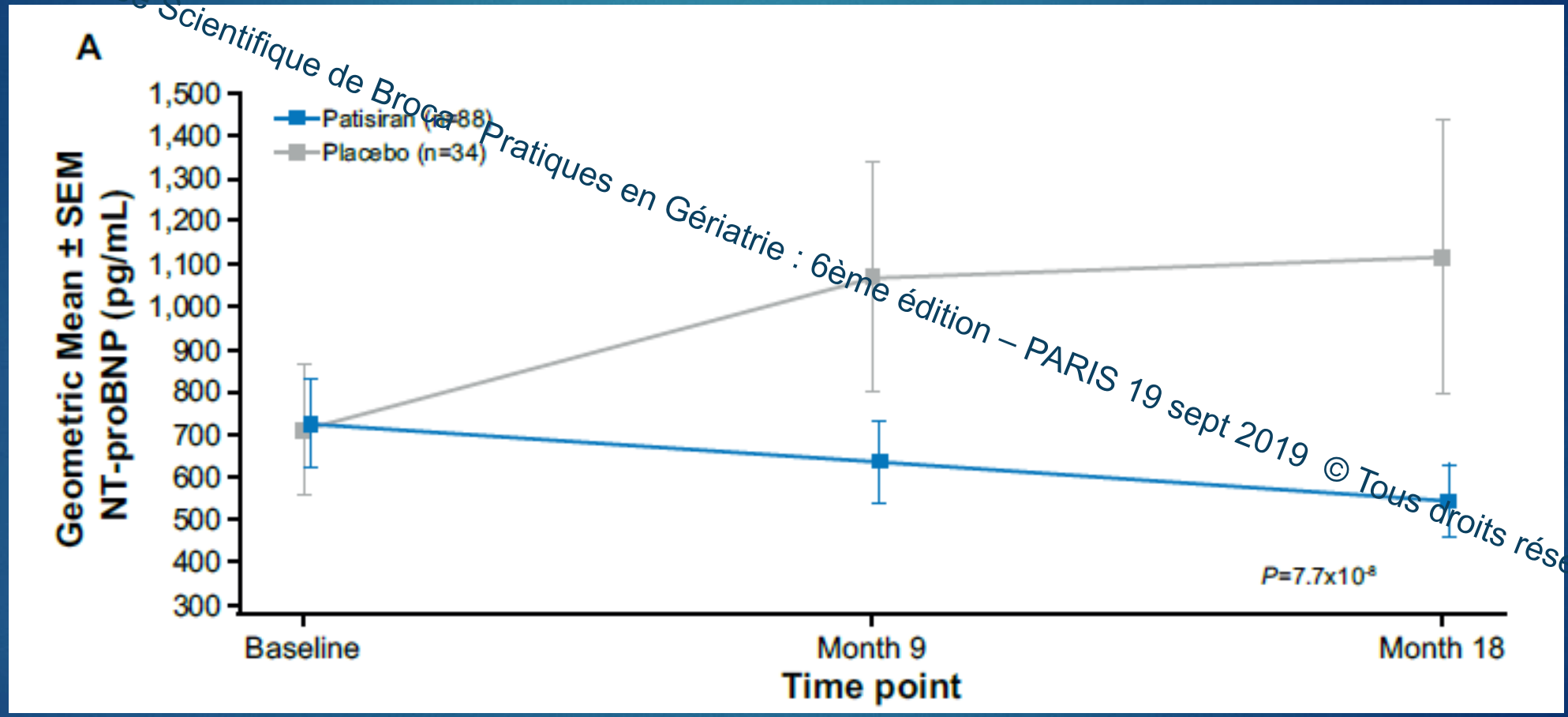
Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients with Hereditary Transthyretin-Mediated Amyloidosis: An Analysis of the APOLLO Study

cardiac subpopulation
(n=126; 56% of total population



SOLOMON SD et al, CIRCULATIONAHA.118.035831

Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients with Hereditary Transthyretin-Mediated Amyloidosis: An Analysis of the APOLLO Study



SOLOMON SD et al, CIRCULATIONAHA.118.035831

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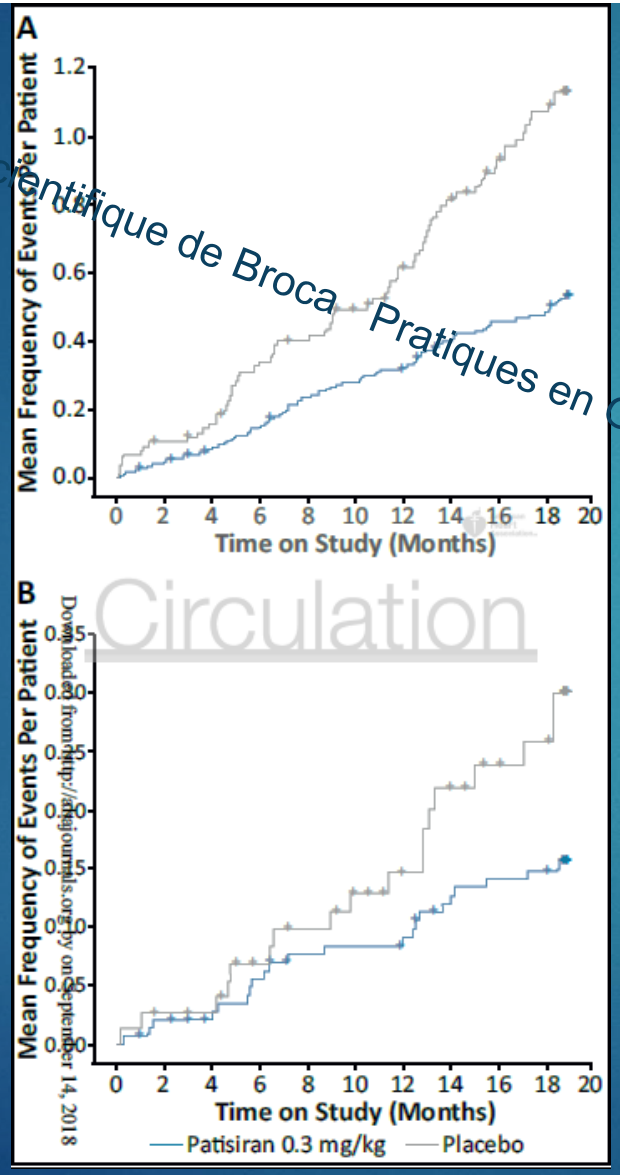

ALL CAUSE HOSPITALIZATION AND DEATH

CARDIAC HOSPITALIZATION AND DEATH

SOLOMON SD et al, CIRCULATIONAHA.118.035831

Traitement spécifique

- **Transplantation hépatique: indiquée en cas de neuropathie isolée, contre indiquée en cas d'atteite cardiaque; éventuellement transplantation combinée FOIE+COEUR**
- **Stabilisateurs de la TTR**
  - Diflunisal
  - **Tafamidis**
  - AG10
- **Inhibiteurs de synthèse de TTR**
  - **SiRNA = PATISIRAN**
  - **Oligonucleotide antisens = INOTERSEN**

Conclusion

- **Ce n'est pas vraiment « la maladie d'Alzheimer du cœur »**
- **Maladie rare, sous diagnostiquée, grave**
- **Diagnostic:**
  - Contexte familial: si porteur de mutation, surveillance et ttt dès premiers signes neuro ou cardio
  - Pas de contexte familial connu: pb du Dg etiologique d'une CMH = 5% d'amylsoe
  - Imagerie multimodalité: echo, scinti « osseuse »
- **Traitement symptomatique : ≠recommandations**
- **Traitement spécifique: Tafamidis**
- **En évaluation: Patisiran Inotersen, Ag10**