4e CONGRÈS FRANCOPHONE MULTIDISCIPLINAIRE DE L'AMYLOSE

ÉVÉNEMENT HYBRIDE

Mercredi 17 décembre 2025

Fondation Biermans-Lapôtre ■ PARIS

www.congres-amylose.com

Une vision historique de l'amylose ATTR sauvage sur 30 ans

Pr Thibaud Damy,

CRMR Amyloses Cardiaques Service de cardiologue GHU Henri Mondor, Créteil

Liens d'intêrets

- Alnylam
- Alexion
- AstraZeneca
- Bayer
- eMyoSound
- Neurimmune
- Novonordisc
- Pfizer
- Prothena

"If you want to know the future, look at the past"

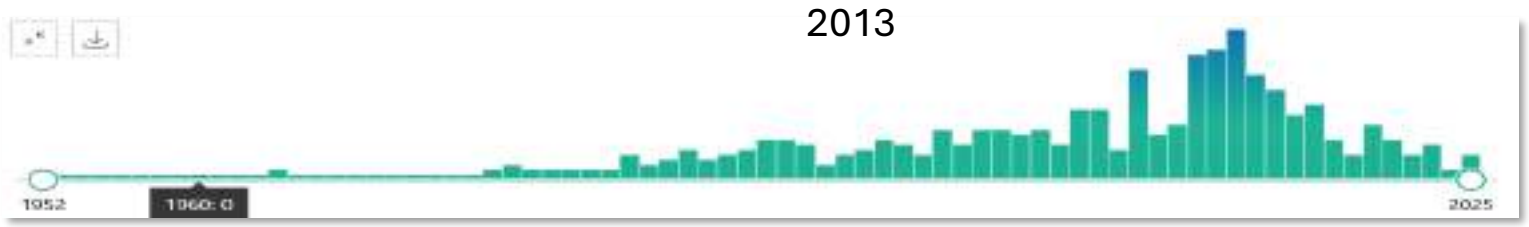
Albert Enstein

>De l'entité anatomopathologique à la cardiomyopathie infiltrative traitable

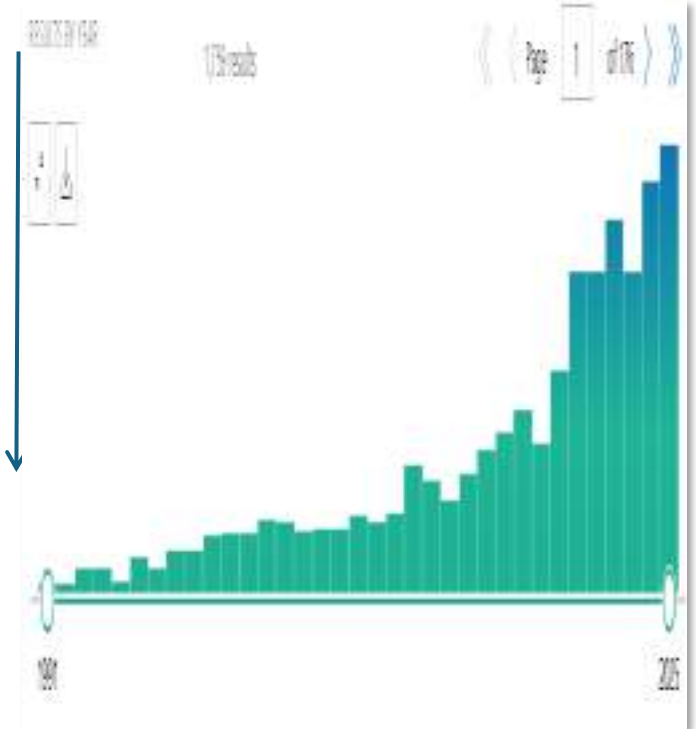
>De l'Amylose Systémique Sénile (Systemic Senile Amyloidosis-SSA) à l'Amylose à Transthyrétine Sauvage (ATTRwt)

Analyses sur le moteur de recherche pubmed (16/12/2025)

375 SSA results
"Senile Systemic Amyloidosis"



1759 ATTRwt results
"wild-type (transthyretin) amyloidosis"



https://pubmed.ncbi.nlm.nih.gov/?term=senile+systemic+amyloidosis&sort=date

https://pubmed.ncbi.nlm.nih.gov/?term=wild+type+transthyretin+amyloidosis&sort=date

https://pubmed.ncbi.nlm.nih.gov/?term=wild-type%20and%20amyloidosis&sort=date&timeline=expanded

2016

Amyloid
The Journal of Protein Folding Disorders
http://informahealthcare.com/amy
ISSN: 1350-6129 (print), 1744-2818 (electronic)
Amyloid, 2016; 23(4): 209–213
© 2016 Informa UK Limited, trading as Taylor & Francis Group. DOI: 10.1080/13506129.2016.1257986
Taylor & Francis

NOMENCLATURE ARTICLE

Amyloid fibril proteins and amyloidosis: chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines

Jean D. Sipe[1], Merrill D. Benson[2], Joel N. Buxbaum[3], Shu-ichi Ikeda[4], Giampaolo Merlini[5], Maria J. M. Saraiva[6], and Per Westermark[7]

"The designation senile systemic amyloidosis (SSA) was coined when it became clear that this is a systemic disease with a specific amyloid protein and not only a cardiac disease that occurs particularly in old age [20]. It was later shown that the fibril protein in SSA is derived from WT TTR [21] and that the disease can occur at younger age.
It is therefore the committee's recommendation to use "wild-type ATTR (ATTRwt) amyloidosis'' instead of SSA. In a transition period both SSA and ATTRwt amyloidosis can be used simultaneously in order to avoid confusion."

Sipe JD and al; ISA Nomenclature Guidelines, Amyloid Journal 2016

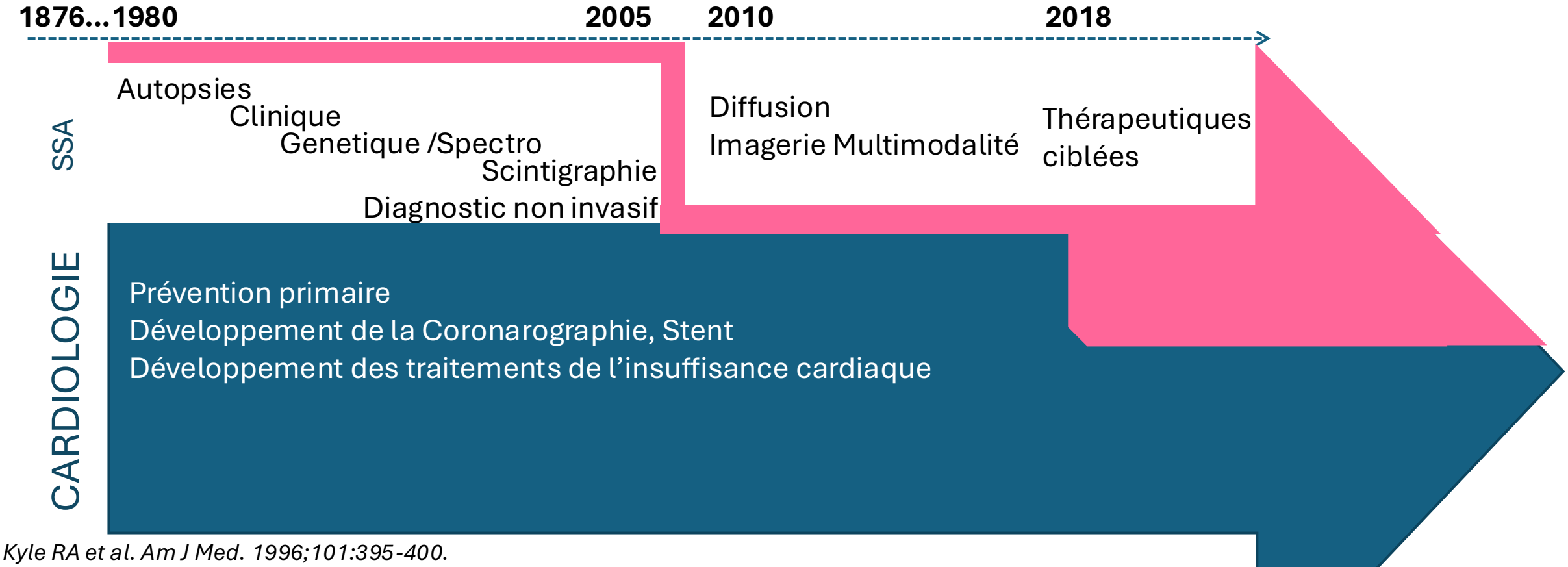
Histoire de « l'amylose à transthyrétine (ATTR) sauvage »

- L'histoire de l'amylose ATTR sauvage est emblématique de l'évolution de notre regard sur les maladies du vieillissement.
- Longtemps reléguée au rang d'épiphénomène sénile, elle est aujourd'hui reconnue comme une cardiomyopathie infiltrative fréquente, à fort impact pronostique
- Et elle est désormais accessible à des traitements modificateurs de l'histoire naturelle

Senile Systemic Amyloidosis

Senile systemic amyloidosis, an age-related disease, occurs in the aorta, heart tissue, brain, pancreas, lung, liver, kidney, and a number of other tissues.[11] Wild-type transthyretin (TTR), a transport protein synthesized in the liver and choroid plexus, forms the amyloid deposits.[12] Senile systemic amyloidosis affects men predominantly, usually after age 70 years, and affects the heart in 25% of persons older than 80 years.[13] The disease is often unrecognized; however, extensive amyloid deposition leads to clinically significant heart failure. The disease course is less aggressive than AL, with a median survival of 75 months.[14]

Histoire de l'ATTR sauvage en "Cardiologie"…2005?



Kyle RA et al. Am J Med. 1996;101:395-400.

80ans, de l'amylose "reliée à l'âge" la "SSA".

- **Premier cas rapporté**
  - **1876** : **Age-related or senile cardiac amyloidosis** : Isidor Soyka J. *Prag Med Wochenschr.* 1876;1:165-171.
  - First to describe amyloidosis affecting predominantly the heart in 2 older patients
- **Descriptions de Cas Cliniques de 1948 de "l'amylose primaire" au Concept de "SSA":**
  - **1939: Primary systemic amyloidosis: involvement of cardiac valves, joints and bones, with pathologic fracture of the femur. Koletsky. S., and Stecher, R.** M Arch. Path., 1939, 27, 267-288.
  - **1948 : Atypical amyloid disease, with observations on a new silver stain for amyloid**
  - **King LS** Am J Pathol . 1948 Sep;24(5):1095-1115 : *"With this classification, a new category, **"atypical amyloidosis associated with senility,"***
  - **1957 : The Relation between Amyloid and Ageing in Comparative Pathology** P.J. Thung *Gerontologia* (1957) 1 (4): 234–254.
  - **1960** : **Clinical Study, Senile cardiac amyloidosis**; Buerger L. Braunstein H, American Journal of Medicine Volume 28, Issue 3, March 1960, Pages 357-367
- **De la « SSA » à la Transhyrétine**
  - **1980 : Senile cardiac amyloid is related to prealbumin, L**etten, K · Westermark, P · Natvig, JB, *Scand J Immunol.* 1980; **12**:503-506
  - **1982 : Senile aortic amyloid: a third distinctive type of age-related cardiovascular amyloid** Cornwell, III, GG · Westermark, P · Murdoch, W ...*Am J Pathol.* 1982; **108**:135-139

De 1960 à 1985 L'ère anatomopathologique
SSA : une maladie longtemps peu connue des cliniciens

- Séries autopsiques décrivant l'ATTR comme liée au vieillissement
- Dépôts amyloïdes cardiaques fréquents chez le sujet âgé
- L'Interprétation dégénérative/vieillissement prédomine largement.
- Classification dans Amylose Primaire ou groupe séparé?

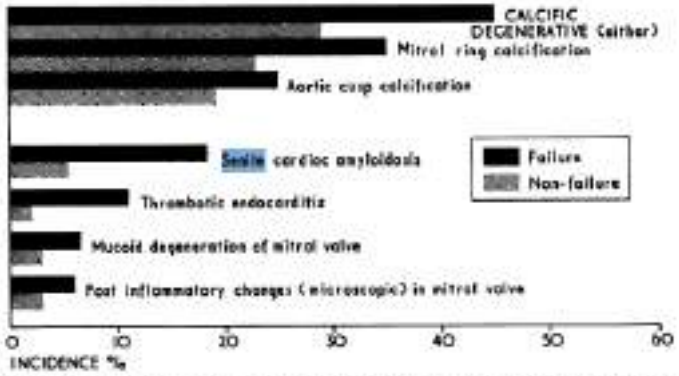


FIG. 2.—Comparative incidence of less well-recognized cardiac abnormalities in failure and non-failure cases.

Briggs, G. W. (1961). Amyloidosis. Ann. intern. Med., 55, 943.
Ariela Pomerance, Senile Cardiac Amyloidosis Brit. Heart J., 1965, 27, 711.
Arelia Pomerance "PATHOLOGY OF THE HEART WITH AND WITHOUT CARDIAC FAILURE IN THE AGED", *Brit. Heart J., 1965, 27, 697.*

Cornwell GG III, Murdoch WL, Kyle RA, Westermark P, Pitkänen P. Frequency and distribution of senile cardiovascular amyloid. American Journal of Medicine. 1983;75(4):618-623.

1985 – 1990 : Amylose Systémique Sénile : Maladie Cardiaque

1985

- D'un état perçue comme le plus souvent bénin à une maladie inéluctable
- Absence de stratégie diagnostique
- Intégré dans la physiopathologie des amyloses mais en arrière fond…

1990

- Identification de la transthyrétine sauvage : »Fibril in senile systemic amyloidosis is derived from normal transthyretin ». Westermark P, Sletten K, Johansson B, Cornwell GG III. *Proceedings of the National Academy of Sciences USA. 1990;87(7):2843-2845.*
- Distinction AL, ATTR héréditaire et ATTR sauvage

Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Seminars in Hematology. 1995;32(1):45-59.

1987 : Un diagnostic HISTOLOGIQUE : *Senile cardiac amyloidosis with myocardial dysfunction. Diagnosis by endomyocardial biopsy and immunohistochemistry?*

- L'amylose cardiaque sénile est longtemps considérée comme une découverte fortuite à l'autopsie.
- La forme systémique peut être identifiée par immunohistochimie à l'aide d'un antisérum dirigé contre la préalbumine.
- Cas de patients avec dysfonction cardiaque (50-70 ans) = SSA diagnostiquées par BIOPSIE
- « Cette distinction est essentielle car le pronostic et la prise en charge diffèrent de ceux des autres formes d'amylose cardiaque. »
- **Un marquage immunohistochimique de la préalbumine est recommandé chez les patients présentant une amylose cardiaque prouvée par biopsie en l'absence de chaîne légère monoclonale détectable.**

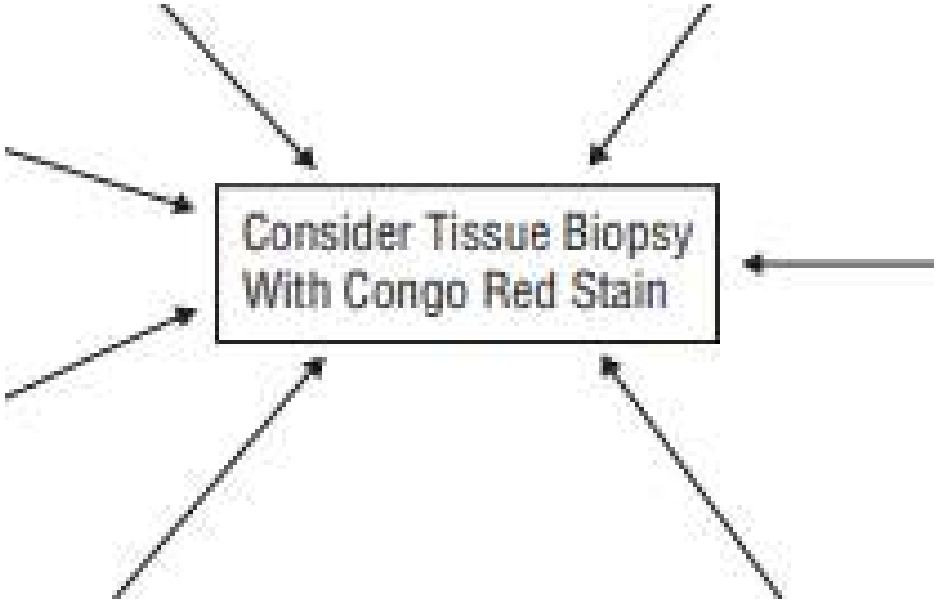
Olson LJ, Gertz MA, Edwards WD, et al. Senile cardiac amyloidosis with myocardial dysfunction. Diagnosis by endomyocardial biopsy and immunohistochemistry. *N Engl J Med. 1987;317:738-742.*

1996 : Un diagnostic HISTOLOGIQUE : *"The premortem recognition of systemic senile amyloidosis with cardiac involvement"*

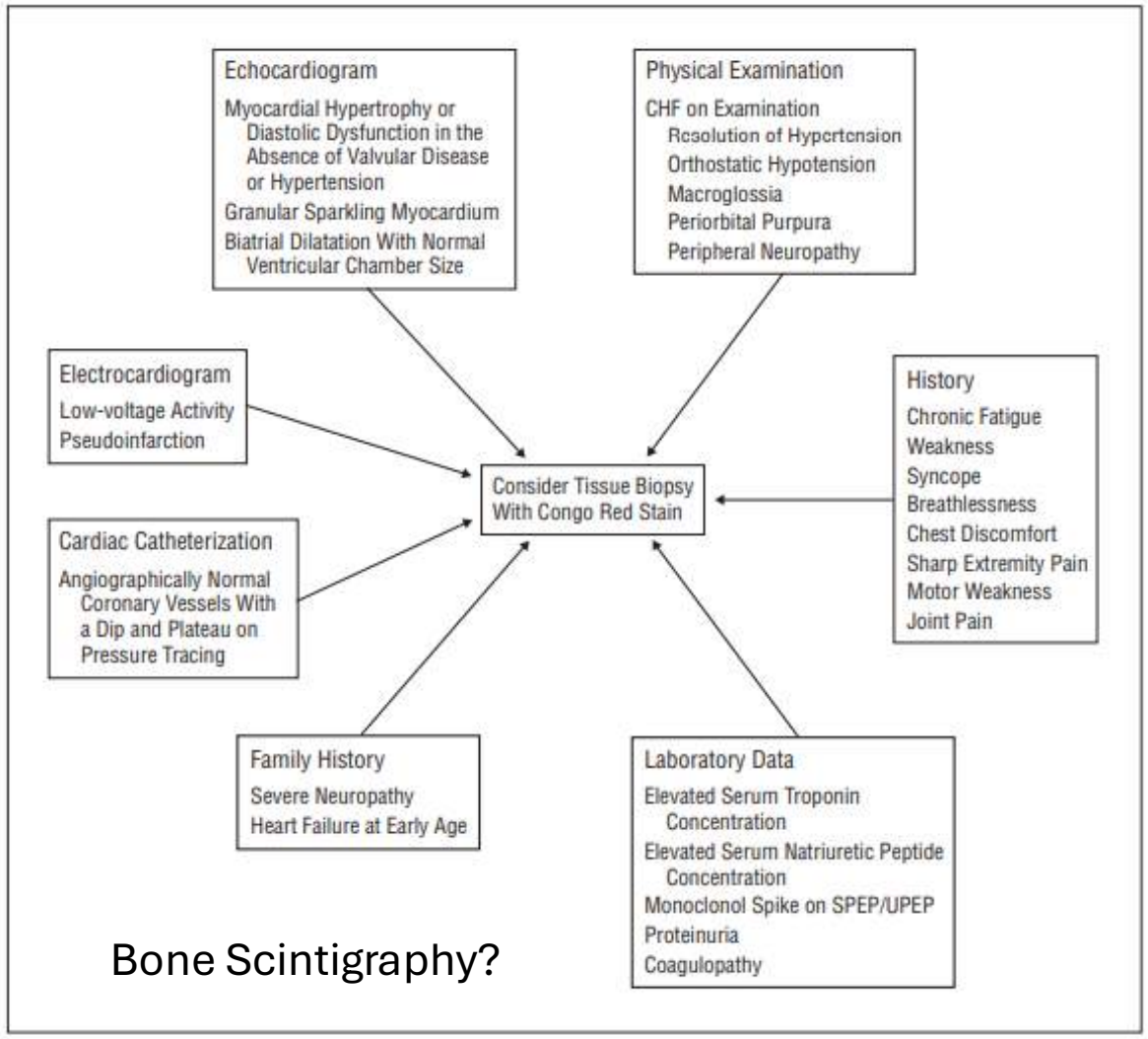
- 18 patients avec « SSA » confirmée par histologie (alcian blue, rouge Congo) et immunomarquage à la transthyrétine.
- L'atteinte cardiaque était sévère dès le diagnostic, avec IC (17/18) et FA (11).
- Pas de gammapathie, pas de mutation ATTR chez les patients testés
- Le typage immunohistochimique (chaînes légères κ/λ et transthyrétine) **est indispensable** pour différencier amylose sénile systémique, amylose familiale et amylose AL.
- Le pronostic est nettement meilleur que dans l'amylose AL, et **les agents alkylants sont contre-indiqués dans l'amylose sénile systémique**.

Kyle RA, Spittell PC, Gertz MA, Li CY, Edwards WD, Olson LJ, Therneau TM. The premortem recognition of systemic senile amyloidosis with cardiac involvement. American Journal of Medicine. 1996;101(4):395-400.

2006: Toujours un diagnostic Histologique



Amyloidosis and the Heart
A Comprehensive Review
Keyur B. Shah, MD; Yoshio Inoue, MD; Mandeep R. Mehra, MD ARCH INTERN MED/VOL 166, SEP 25, 2006



Bone Scintigraphy?

Figure 5. Constellation of symptoms and signs and objective data suggestive of cardiac amyloidosis. CHF indicates congestive heart failure; SPEP, serum protein electrophoresis; and UPEP, urine protein electrophoresis.

De 1985 à 2005 : De Émergence du "phénotype cardiaque"

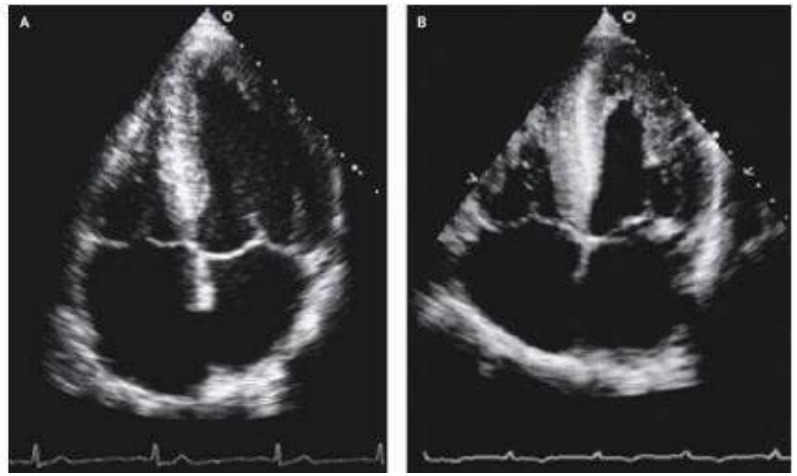
- HFpEF, hypertrophie ventriculaire gauche inexpliquée
- Dysfonction cardiaque
- Troubles conductifs et rythmologiques
- *Mais pourtant :*

CLINICAL PRACTICE

Diastolic Heart Failure

Authors: Gerard P. Aurigemma, M.D., and William H. Gaasch, M.D. Author Info & Affiliations

Published September 9, 2004 | N Engl J Med 2004;351:1097-1105 | DOI: 10.1056/NEJMcp022709
VOL. 351 NO. 11 | Copyright © 2004



Ng B, Connors LH, Davidoff R, Skinner M, Falk RH. Senile systemic amyloidosis presenting with heart failure. American Journal of Cardiology. 2005;95(4):534-536.

Quand la SSA s'entremèle avec l'Amylose Héréditaire Cardiaque (ATTRv-CM) insuffisament connue.

VARIANT-SEQUENCE TRANSTHYRETIN (ISOLEUCINE 122) IN LATE-ONSET CARDIAC AMYLOIDOSIS IN BLACK AMERICANS

DANIEL R. JACOBSON, M.D., RAYMOND D. PASTORE, M.D., ROBERT YAGHOUBIAN, M.D., IMMACULATA KANE, M.S., GLORIA GALLO, M.D., FRANCIS S. BUCK, M.D., AND JOEL N. BUXBAUM, M.D.

- This variant was discovered in 1988, in transthyretin isolated from the fibrils of a 68-year-old black man with no known family history of amyloidosis who died of massive cardiac amyloidosis.
- "In the absence of a known family history, patients with cardiac transthyretin Ile 122 amyloidosis may be given a clinical diagnosis of senile cardiac amyloidosis."

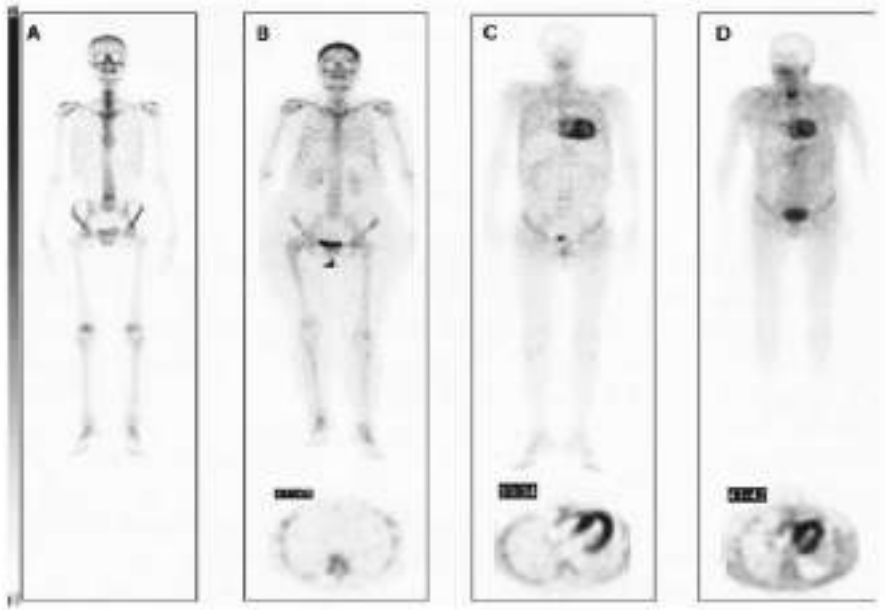
2005 : Scintigraphie osseuse : Révolution diagnostique

- Diagnostic non invasif spécifique de l'ATTR

Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis Using ^{99m}Tc-3,3-Diphosphono-1,2-Propanodicarboxylic Acid Scintigraphy

Enrica Perugini, MD,* Pier Luigi Guidalotti, MD,† Fabrizio Salvi, MD,‡ Robin
Cinzia Pettinato, MD,† Letizia Riva, MD,* Ornella Leone, MD,§ Mohsen Farsad
Paolo Ciliberti, MD,* Letizia Bacchi-Reggiani, MSc, MBIOSTAT,* Francesco Falla
Angelo Branzi, MD,* Claudio Rapezzi, MD*

Bologna, Italy



Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, Leone O, Farsad M, Ciliberti P, Bacchi-Reggiani L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-DPD scintigraphy. Journal of the American College of Cardiology. 2005;46(6):1076-1084.

2016 Diagnostic non biopsique intégré

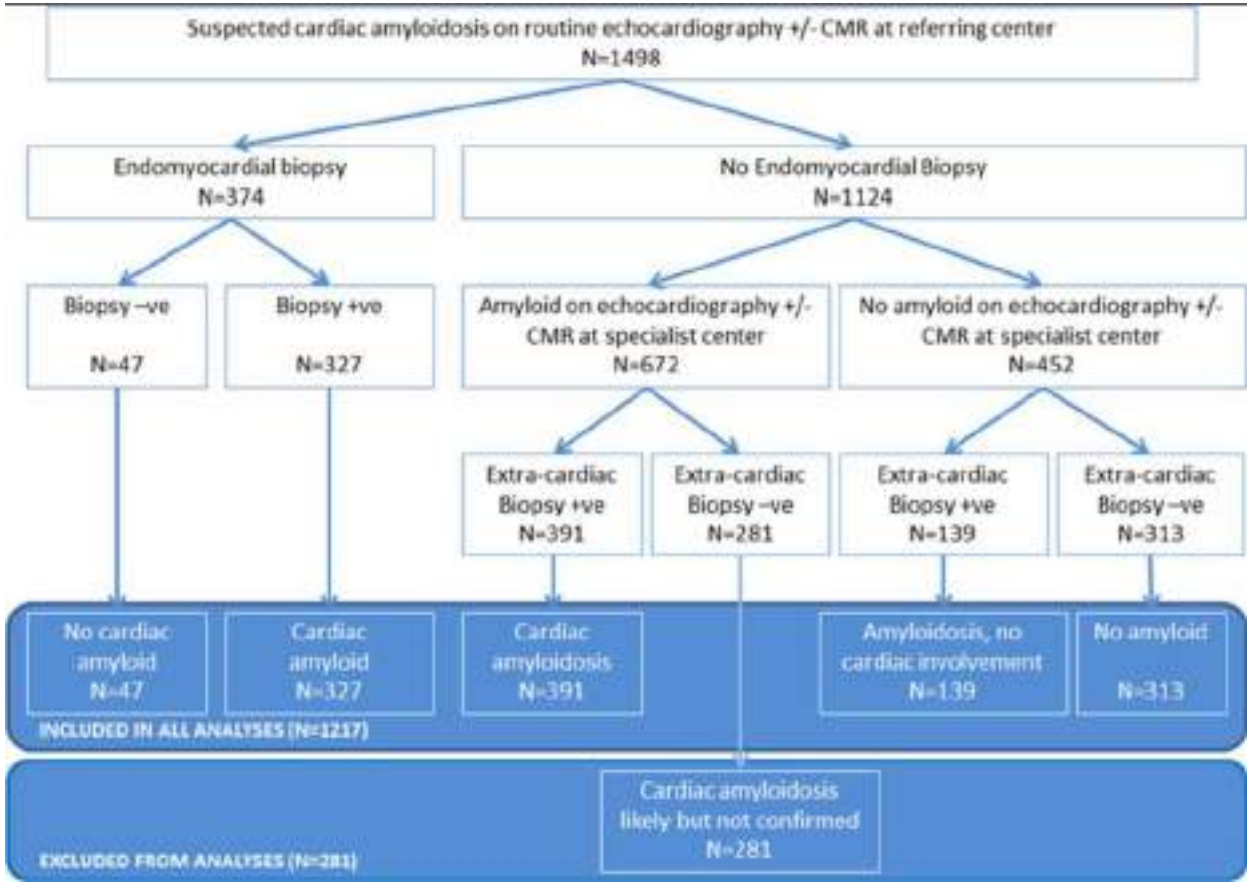
- Scintigraphie positive + exclusion amylose AL
- Standard international

Circulation
Volume 133, Issue 24, 14 June 2016, Pages 2404-2412
https://doi.org/10.1161/CIRCULATIONAHA.116.021612

HEART FAILURE

Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

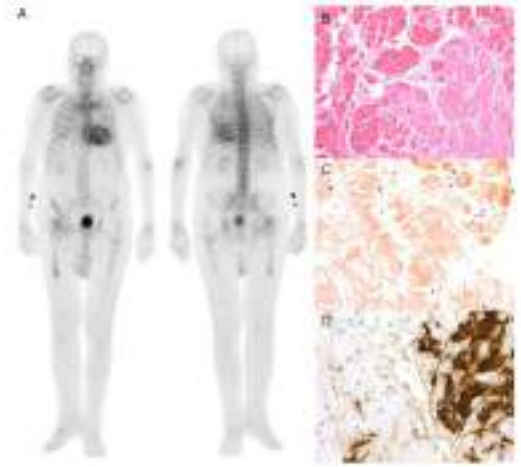
Julian D. Gillmore, MD, PhD, Mathew S. Maurer, MD, Rodney H. Falk, MD, Giampaolo Merlini, MD, Thibaud Damy, MD, Angela Dispenzieri, MD, Ashutosh D. Wechalekar, MD, DM, John L. Berk, MD, Candida C. Quarta, MD, PhD, Martha Grogan, MD, Helen J. Lachmann, MD, Sabahat Bokhari, MD, Adam Castano, MD, Sharmila Dorbala, MD, MPH, Geoff B. Johnson, MD, PhD, Andor W.J.M. Glaudemans, MD, PhD, Tamer Rezk, BSc, Marianna Fontana, MD, Giovanni Palladini, MD, PhD, Paolo Milani, MD, Pierluigi L. Guidalotti, MD, Katarina Flatman, Thirusha Lane, MSc, Frederick W. Vonberg, MBBS, Carol J. Whelan, MD, James C. Moon, MD, Frederick L. Ruberg, MD, Edward J. Miller, MD, PhD, David F. Hutt, BApSc, Bouke P. Hazenberg, MD, PhD, Claudio Rapezzi, MD, and Philip N. Hawkins, PhD, FMedSci



Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404-2412.

2015 : ATTR sauvage : Cause majeure de HFpEF

- Prévalence élevée chez le sujet âgé
- Errance diagnostique prolongée



Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction

Esther González-López[1], Maria Gallego-Delgado[1], Gonzalo Guzzo-Merello[1], F. Javier de Haro-del Moral[2], Marta Cobo-Marcos[1], Carolina Robles[1], Belén Bornstein[3,4,5], Clara Salas[6], Enrique Lara-Pezzi[7], Luis Alonso-Pulpon[1], and Pablo Garcia-Pavia[1,7]*

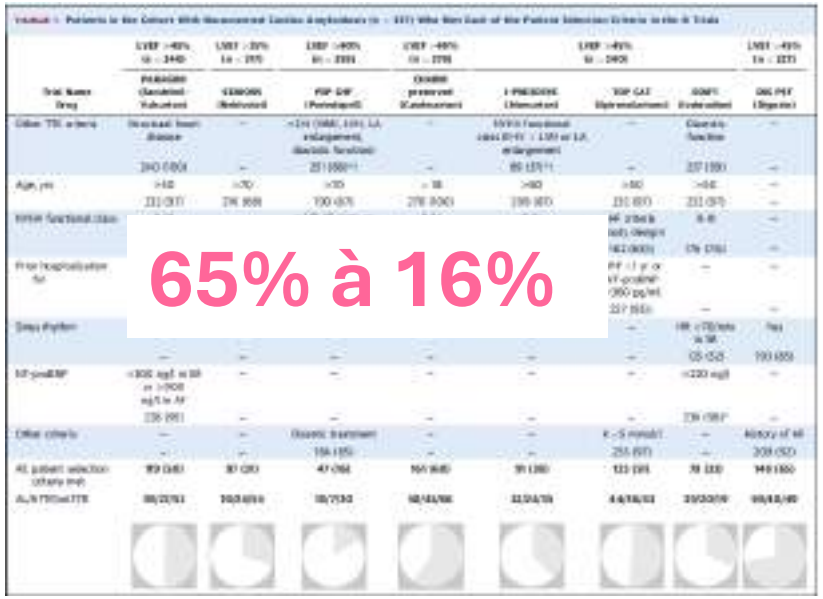
"ATTRwt is an underdiagnosed disease that accounts for a significant number (13%) of HFpEF cases. The effect of emerging TTR-modifying drugs should be evaluated in these patients"

González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. European Heart Journal. 2015;36(38):2585-2594.

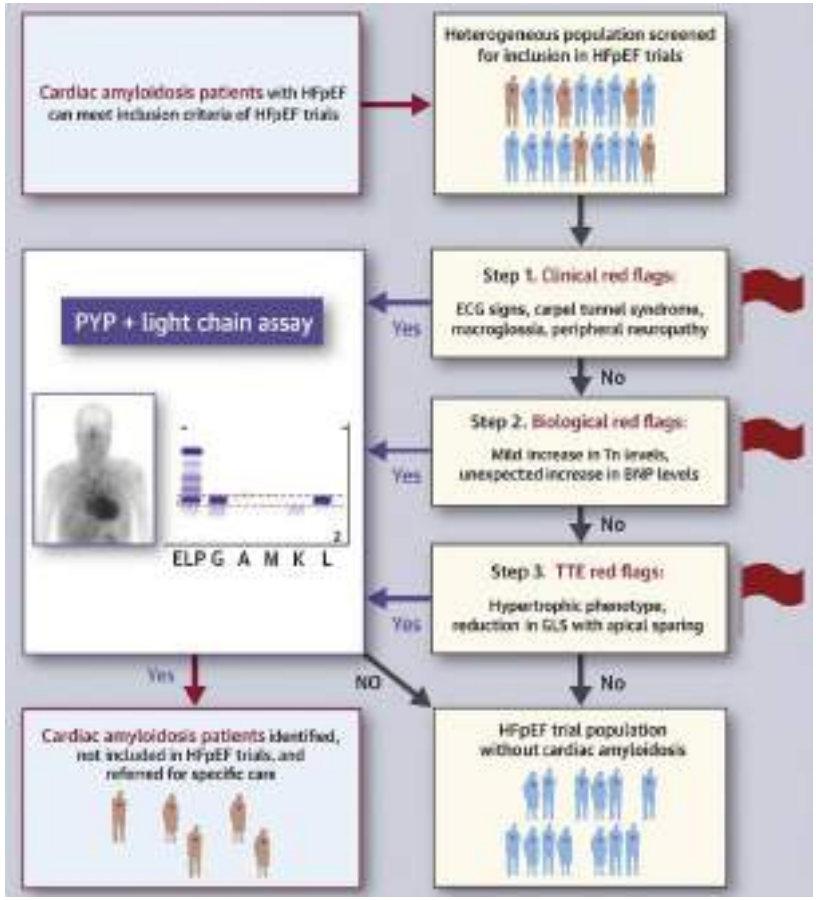
2021 : Et si les ATTR avaient été inclus dans les essais de l'IC-FEP?

The Impact of Patients With Cardiac Amyloidosis in HFpEF Trials

Silvia Oghina, MD,[a,b] Wulfran Bougouin, MD, PhD,[c,d] Mélanie Bézard, MSc,[a,b] Mounira Kharoubi, MSc,[a,b] Michel Komajda, MD, PhD,[e] Alain Cohen-Solal, MD, PhD,[f] Alexandre Mebazaa, MD, PhD,[g] Thibaud Damy, MD, PhD,[a,b,h] Diane Bodez, MD, PhD[a,b,h]



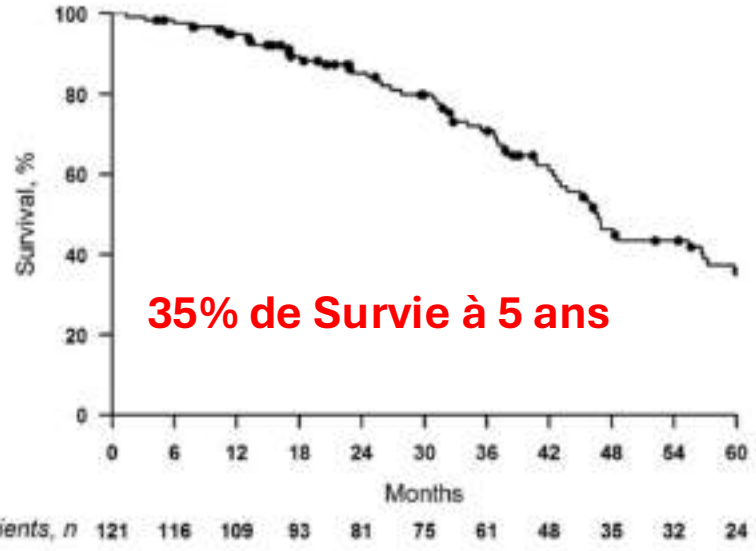
65% à 16%



Oghina S, Bougouin W, Bézard M, Kharoubi M, Komajda M, Cohen-Solal A, Mebazaa A, Damy T, Bodez D.JACC Heart Fail. 2021 Mar;9(3):169-178 The Impact of Patients With Cardiac Amyloidosis in HFpEF Trials.

2016 : Avant l'ère thérapeutique spécifique : Comment traiter les patients?

- Traitement symptomatique seul
- Pronostic défavorable



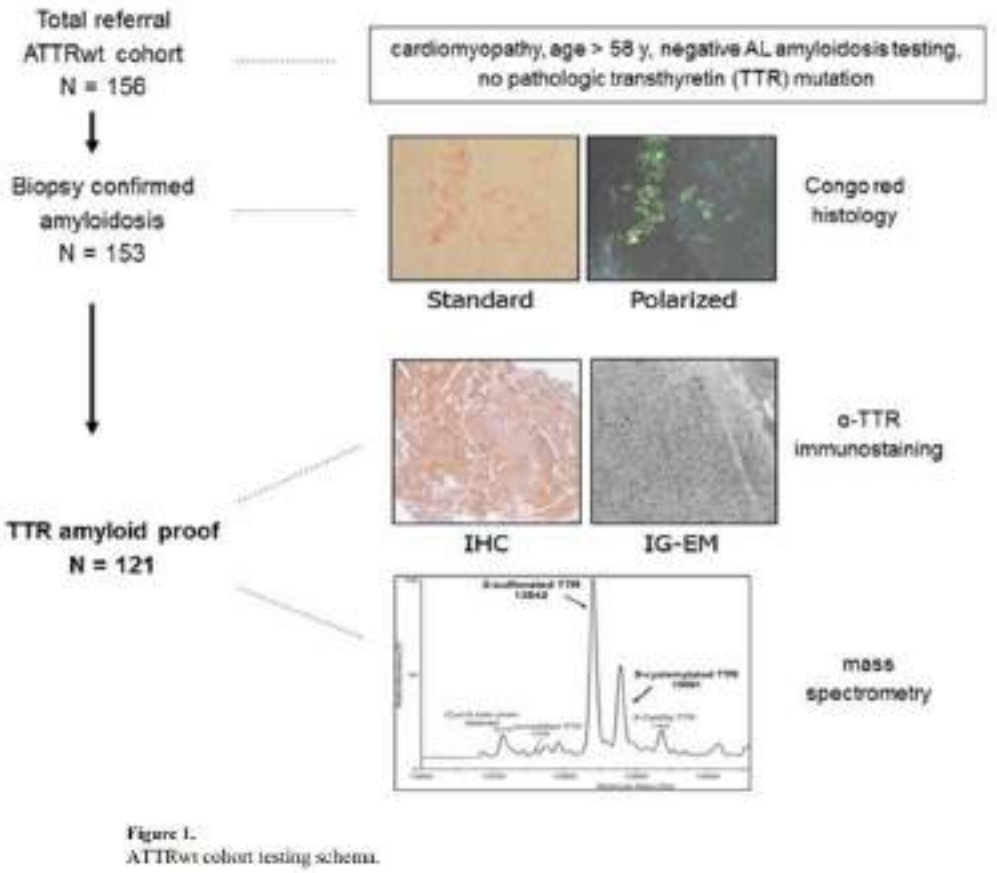


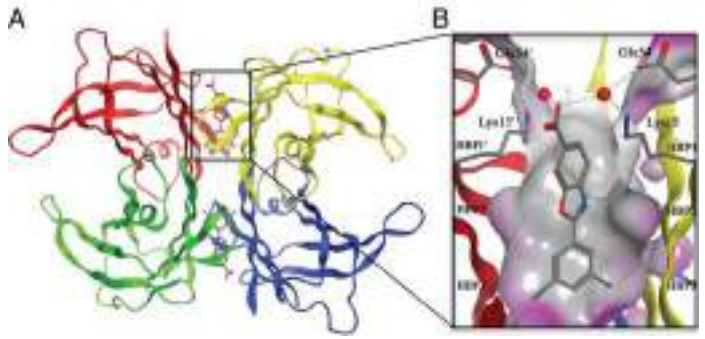
Figure 1.
ATTRwt cohort testing schema.

Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, Berk JL, Seldin DC. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin. Circulation. 2016;133(3):282-290.

2010-2018 Du rationnel mécanistique de la stabilisation de la transthyrétine à ATTR-ACT

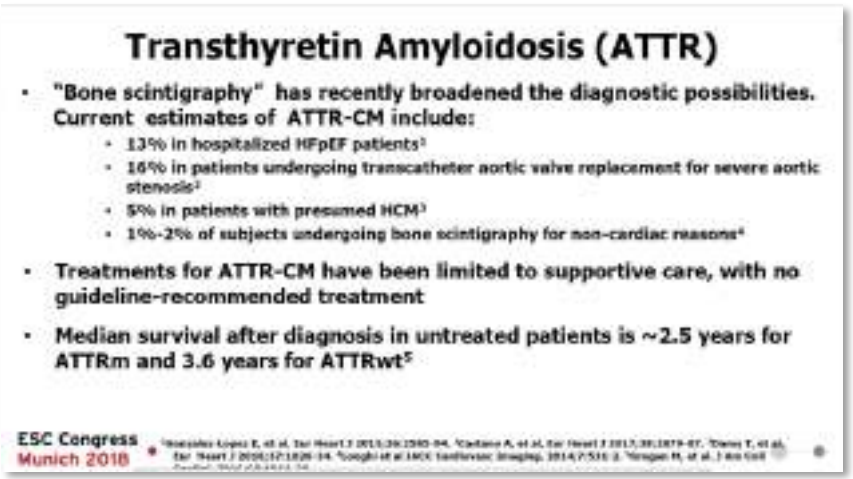
Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade

Christine E. Bulawa[a,1], Stephen Connelly[b], Michael DeVit[c], Lan Wang[d], Charlotte Weigel[a], James A. Fleming[a], Jeff Packman[c], Evan T. Powers[e,f], R. Luke Wiseman[g], Theodore R. Foss[b], Ian A. Wilson[e,f], Jeffery W. Kelly[a,f,1], and Richard Labaudinière[c]



ESC 2018 Munich

"Maestro Claudio"



Bulawa CE, Connelly S, DeVit M, Wang L, Weigel C, Fleming JA, Packman J, Prokop S, Chen Y, Barclay J, et al. Tafamidis, a potent and selective transthyretin kinetic stabilizer. Proceedings of the National Academy of Sciences USA. 2012;109(24):9629-9634.

Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, et al. Tafamidis treatment for patients with transthyretin amy cardiomyopathy. New England Journal of Medicine. 2018;379:1007-1016.

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ÉVÉNEMENT HYBRIDE

Mercredi 17 décembre 2025
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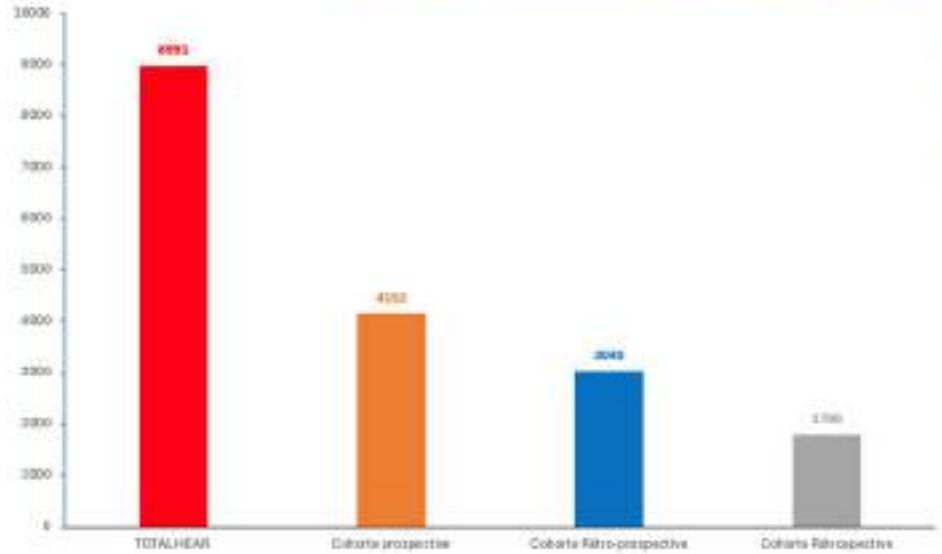
Le boom du dépistage dans le monde et en France!!

8 MASTERCLASS AMYLOSES CARDIAQUES

ÉVÉNEMENT HYBRIDE

Jeudi 18 décembre 2025
Fondation Biermans-Lapôtre ■ PARIS
www.masterclass-amylose.com

Etat d'avancement des inclusions (28.11.2025)



- → Nov 2025 : 8 991 patients
- → 4153 patients = prospective; patients adressés au centre « suspicion d'amylose »
- → 3040 patients = rétro-prospective; patients vivants avec un diagnostic d'amylose confirmé
- → 1798 patients = rétrospective → Cohorte historique, patients décédés dont le diagnostic d'amylose a été confirmé avant la mise en place du registre HEAR dans le centre.

Réseau Amylose
www.reseau-amylose.org

GRACE

FSPCF
cardiogen

Mounira Kharoubi, MAC 2025

Controverses actuelles et perspectives

- Dépistage ciblé vs systématique
- Pathologique pour tous ou Bénin pour certains?
- Coût-efficacité
- Thérapies émergentes

TIC-TAC,

*Il est temps de changer de **TAC-TIC,***

*Passons du **TACØTAC !!!***

Damrauer SM, Chaudhary K, Cho JH, Liang LW, Argulian E, Chan L, Drachman BM, Hsu S, Kittleson MM, Maurer MS, et al. Association of tafamidis with survival in transthyretin amyloid cardiomyopathy. Circulation. 2021;143(18):1833-1844.

Conclusion

- Relire l'histoire pour mieux anticiper l'avenir thérapeutique et le chemin parcouru…

« Pour ce qui est de l'avenir, il ne s'agit pas de le prévoir mais de le rendre possible »

Antoine de Saint-Exupéry, *Citadelle*, œuvre posthume, écrite entre 1941 et 1944, publiée en 1948

Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. Circulation. 2016;133(24):2404-2412.

Une intégration des Amyloses Cardiaque dans la Cardiologie

2010-18

Remerciements

Platinium sponsor

BAYER

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Alnylam PHARMACEUTICALS

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MECHANISMS OF DISEASE

Molecular Mechanisms of Amyloidosis

Giampaolo Merlini, M.D., and Vittorio Bellotti, M.D., Ph.D.

In amyloid disease, potentially pathogenic misfolded proteins can form in different ways. The protein may have an intrinsic propensity to assume a pathologic conformation, which becomes evident with aging (e.g., normal transthyretin in patients with senile systemic amyloidosis)[15] or at persistently high concentrations in serum (e.g., beta$_2$-microglobulin in patients undergoing long-term hemodialysis).[16] Another mechanism is the replacement

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Table 1. Amyloid Proteins and Their Precursors.*

Amyloid Protein	Precursor	Distribution	Type	Syndrome or Involved Tissues
Aβ	Aβ protein precursor	Localized Localized	Acquired Hereditary	Sporadic Alzheimer's disease, aging Prototypical hereditary cerebral amyloid angiopathy, Dutch type
APrP	Prion protein	Localized Localized	Acquired Hereditary	Sporadic (iatrogenic) CJD, new variant CJD (alimentary?) Familial CJD, GSSD, FFI
ABri	ABri protein precursor	Localized or systemic?	Hereditary	British familial dementia
ACys	Cystatin C	Systemic	Hereditary	Icelandic hereditary cerebral amyloid angiopathy
Aβ2M	Beta$_2$-microglobulin	Systemic	Acquired	Chronic hemodialysis
AL	Immunoglobulin light chain	Systemic or localized	Acquired	Primary amyloidosis, myeloma-associated
AA	Serum amyloid A	Systemic	Acquired	Secondary amyloidosis, reactive to chronic infection or inflammation including hereditary periodic fever (FMF, TRAPS, HIDS, FCU, and MWS)
ATTR	Transthyretin	Systemic Systemic	Hereditary Acquired	Prototypical FAP Senile heart, vessels
AApoAI	Apolipoprotein A-I	Systemic	Hereditary	Liver, kidney, heart
AApoAII	Apolipoprotein A-II	Systemic	Hereditary	Kidney, heart
AGel	Gelsolin	Systemic	Hereditary	Finnish hereditary amyloidosis
ALys	Lysozyme	Systemic	Hereditary	Kidney, liver, spleen
AFib	Fibrinogen Aα chain	Systemic	Hereditary	Kidney