REGARD CROISÉ NEUROLOGIE/CARDIOLOGIE DANS L'HATTR

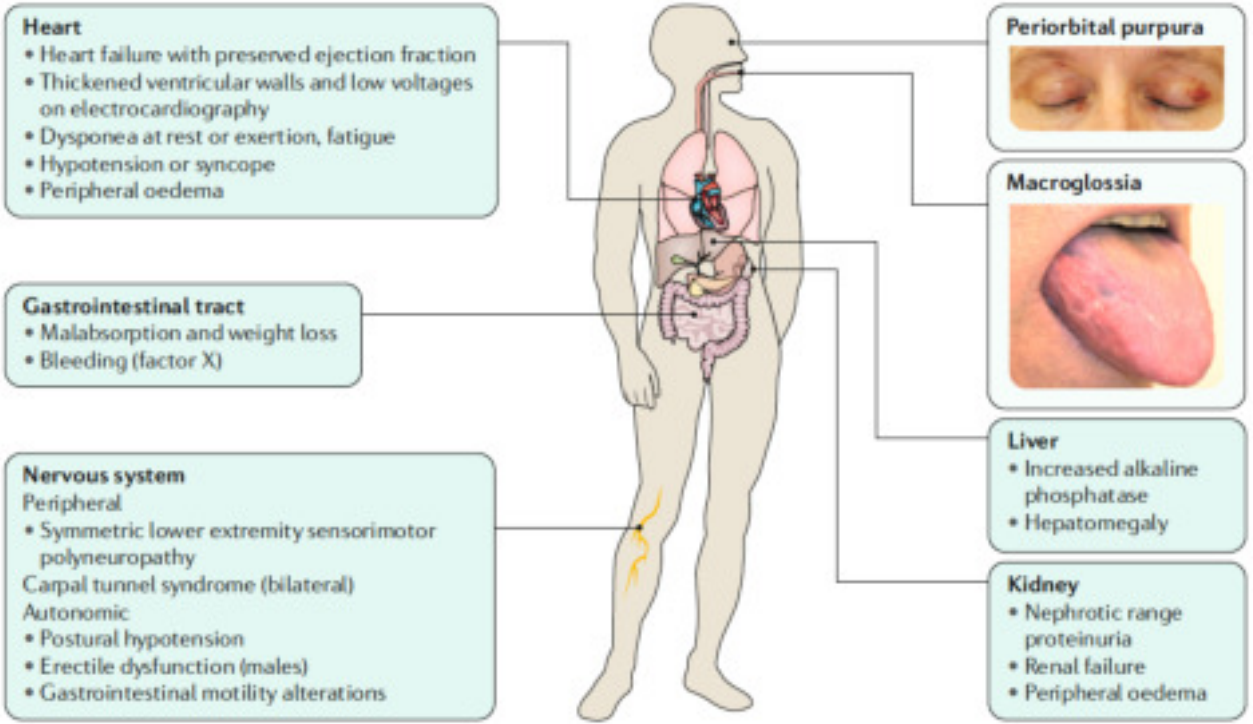
Olivier LAIREZ
Fédération de cardiologie
Centre d'imagerie cardiaque
Hôpital Rangueil, Toulouse

TTR02-FRA-00174 – Décembre 2020

AMYLOIDOSIS

Hôpitaux de Toulouse

AMYLOIDOSIS



Hôpitaux de Toulouse

Merlini M, *Nat Rev Dis Primers* 2018 ;4:38

AMYLOIDOSIS

Classification of cardiac amyloid types		
Amyloidosis type	**Precursor**	**Comment**
Light chain or light chain/heavy chain	Immunoglobulin light chain	Systemic plasma cell dyscrasia
Mutant transthyretin-related	*TTR* point mutation	Inherited autosomal-dominant mutation, expressed after fifth decade
Wild-type transthyretin-related	None	Formerly known as senile cardiac amyloidosis
Amyloid A	Serum amyloid A	Sustained inflammatory process, cardiac involvement rare

Hôpitaux de Toulouse

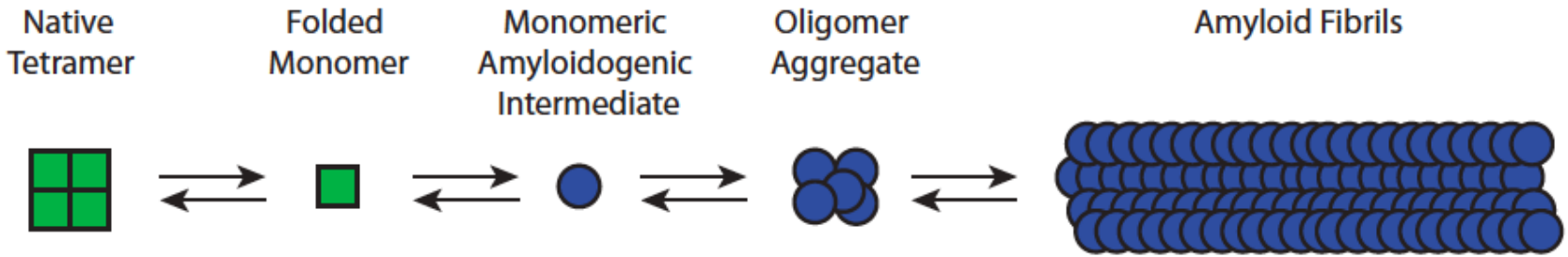
Gertz MA, *Nat. Rev Cardiol* 2015;12:91-102

TRANSTHYRETIN

Tetrameric protein physiologically present in human serum and responsible for the transport of thyroxine and retinol-binding protein

Synthesized mainly by the liver

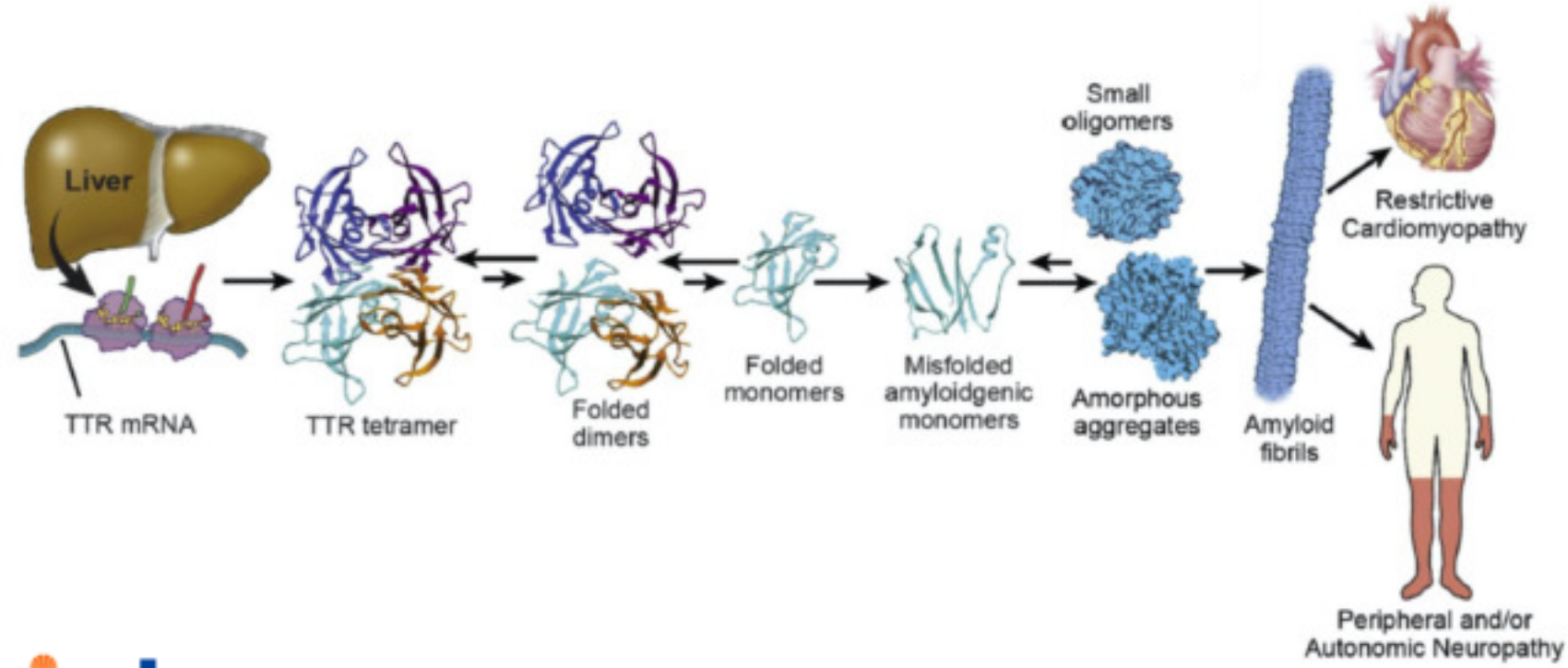
Aggregation capacity of insoluble amyloid fibrils



Hôpitaux de Toulouse

Galant NJ, *Clinical Science* 2017;131:395-409

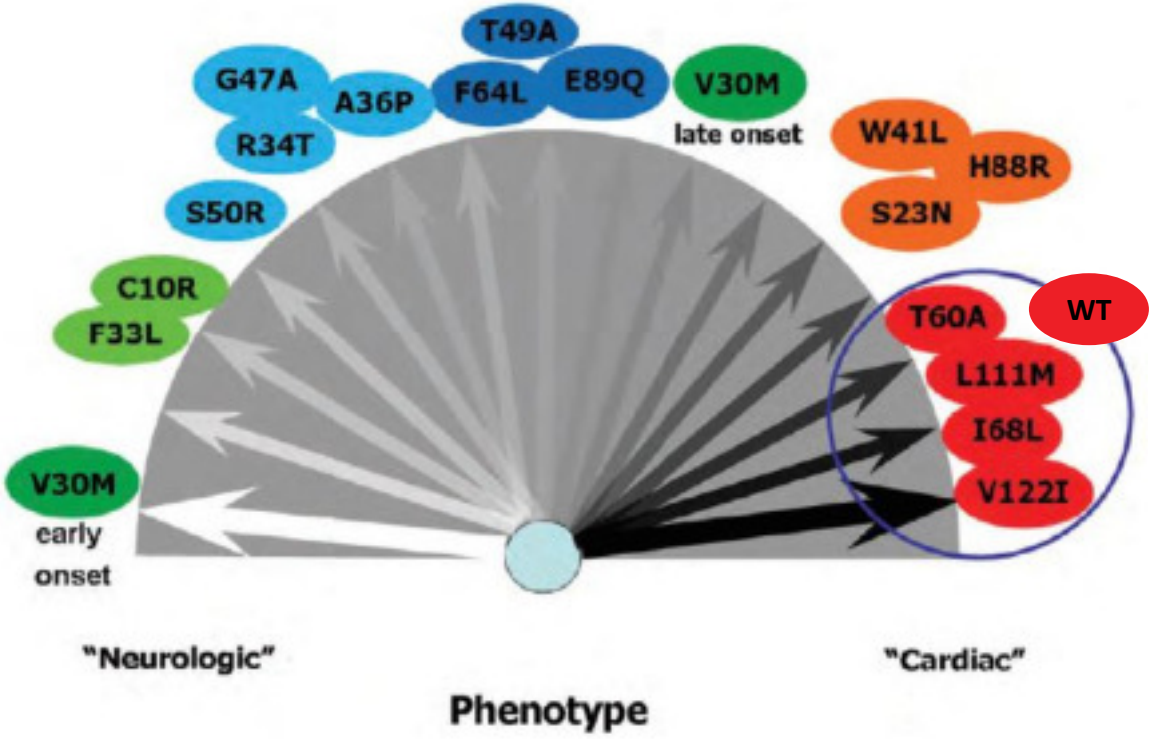
TRANSTHYRETIN AMYLOIDOSIS



Hôpitaux de Toulouse

Ruberg FL, et al. *J Am Coll Cardiol* 2019;73:2872–91

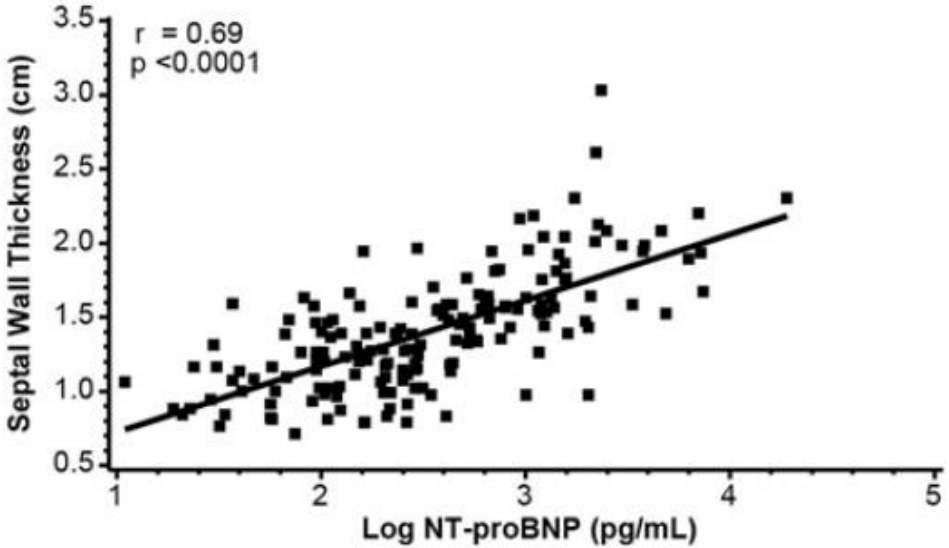
TRANSTHYRETIN AMYLOIDOSIS

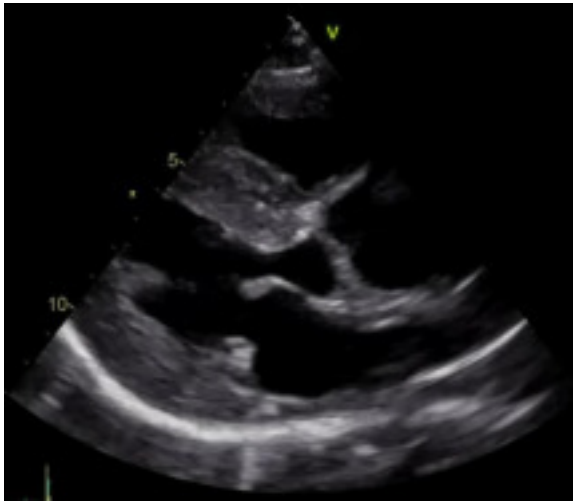


Hôpitaux de Toulouse

Rapezzi C, et al. *Eur Heart J.* 2013;34:520-8

FIBRILS ACCUMULATION WITHIN THE MYOCARDIUM

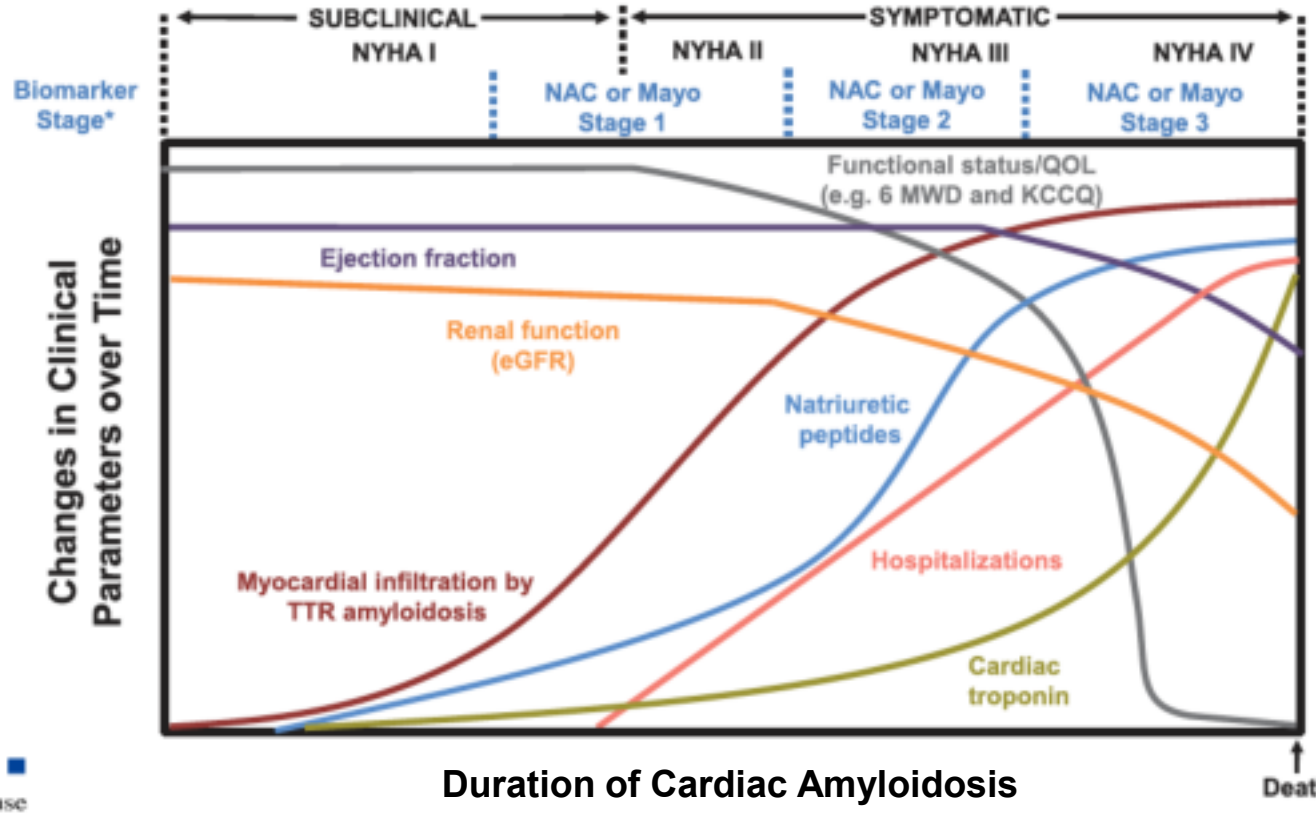




Hôpitaux de Toulouse

Waddington-Cruz M, *Amyloid.* 2018:1-9

NATURAL HISTORY OF CARDIAC AMYLOIDOSIS



Hôpitaux de Toulouse

Grodin JL, et al. Circulation. 2019;140:27-30

PREVALENCE

Hôpitaux de Toulouse

AUTOPSY SERIES

85 postmortem examinations of subjects over 80-year-old
Age ranging from 80 to 98-year-old (mean 85-year-old)

Frequency of Localized and Generalized Cardiovascular Amyloid in 85 Elderly Patients

Type of Amyloid	Number of Patients	Percentage
Senile aortic amyloid	85	100
Isolated atrial amyloid	66	78
ASc_1	21	25

Hôpitaux de Toulouse

Cornwell GG, et al. *Am J Med*. 1983;75:618-23

AUTOPSY SERIES

256 postmortem examinations of subjects over 85 years
Age ranging from 85 to 106-year-old (mean 93-year-old)

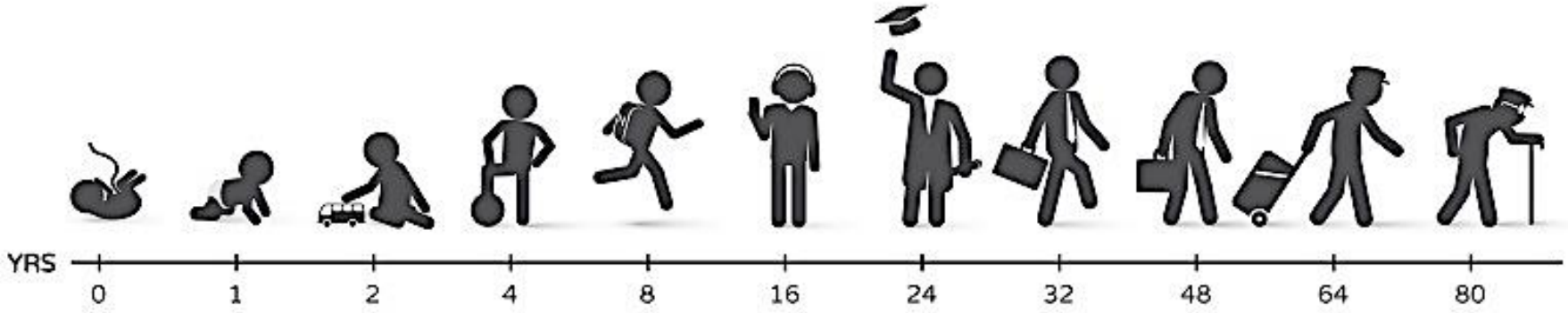
ATTR cardiomyopathy:

- 25% (63/256) of the whole study population
- 17% (11/65) among 85–89-year-old
- 23% (29/127) among 90–94-year-old
- 32% (18/56) among 95–100-year-old
- 63% (5/8) among > 100-year-old

Hôpitaux de Toulouse

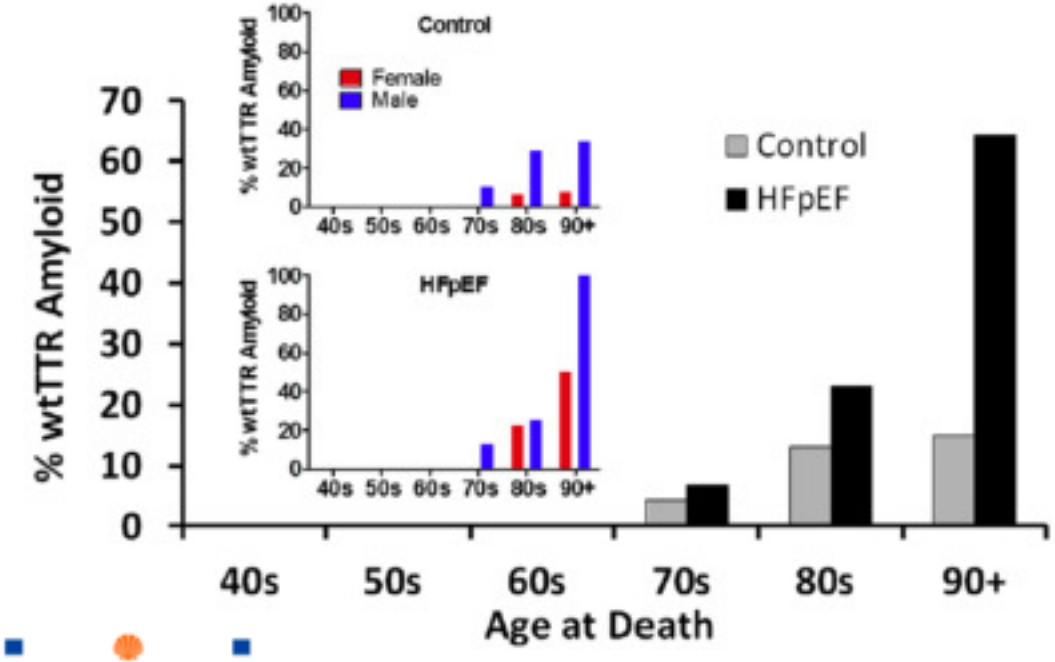
Tanskanen M, *Ann Med.* 2008;40:232-9

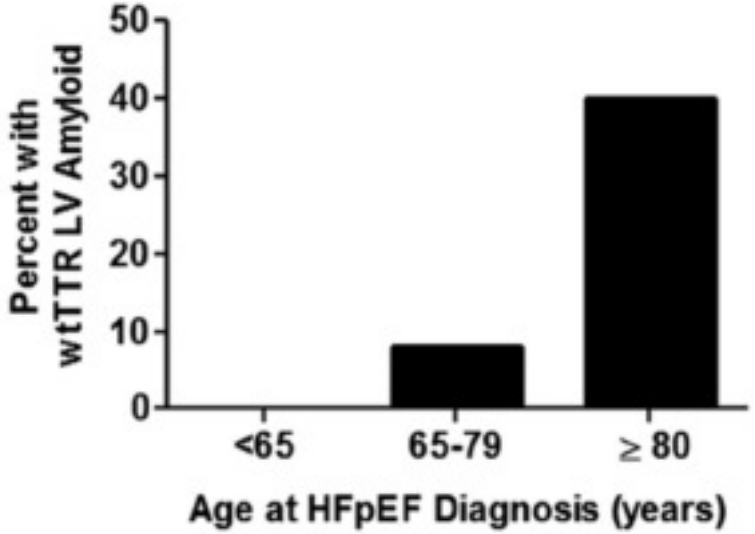
Is TTR deposition a part of the physiological aging process?



Hôpitaux de Toulouse

Left Ventricular Amyloid Deposition in Patients With Heart Failure and Preserved Ejection Fraction





Hôpitaux de Toulouse

Mohammed SF, *J Am Coll Cardiol HF* 2014;2:113-22

IN CLINICAL PRACTICE

Patient populations deemed at-risk of ATTR-CM

Heart failure OR presence of "red flag" signs/symptoms

AND

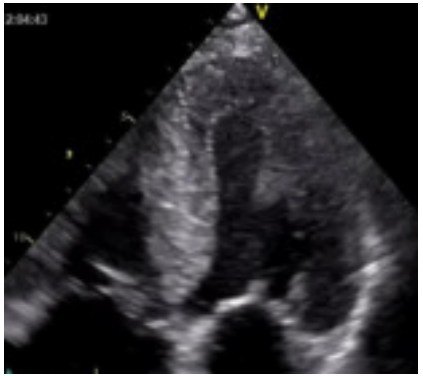
Increased wall thickness ≥14 mm

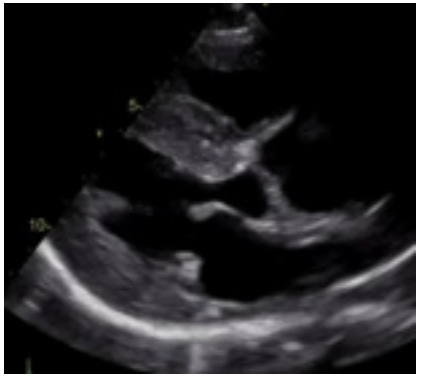
+

Male >65 years

OR

Female >70 years





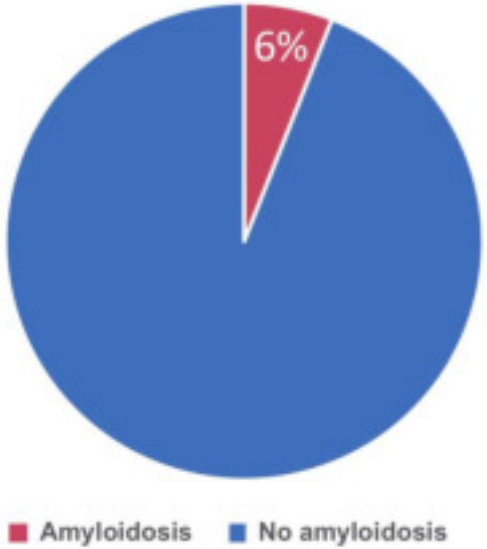
Hôpitaux de Toulouse

Witteles RM, *J Am Coll Cardiol HF* 2019;7:709-16

Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis

Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement

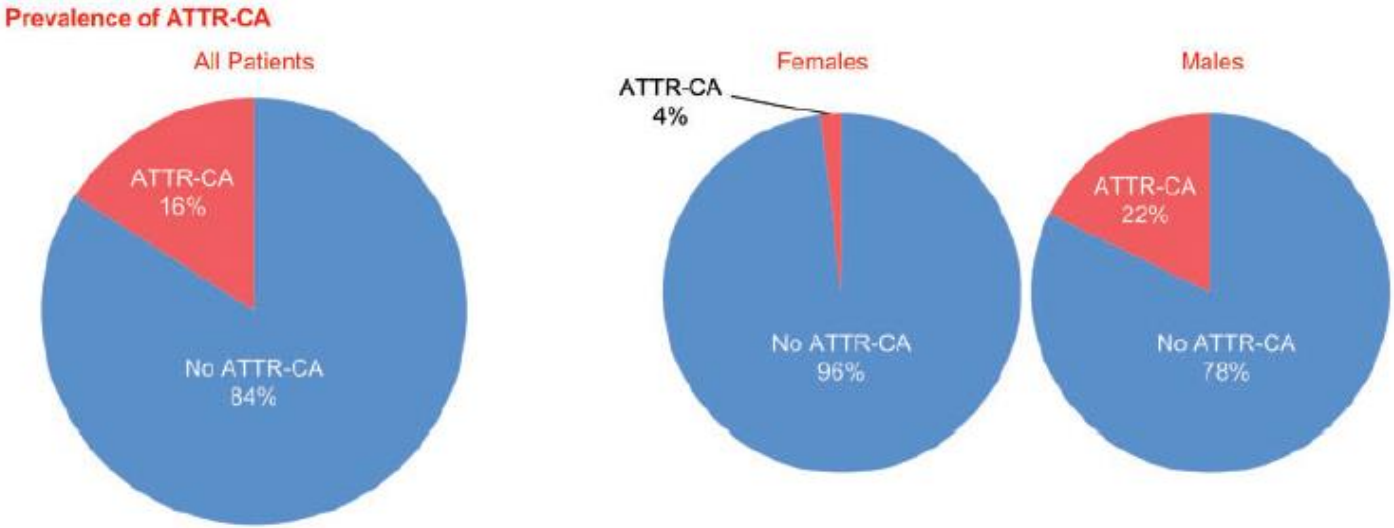
Prevalence of ATTR cardiomyopathy of 6% among patients > 65-year-old referred for surgical aortic valve replacement



Hôpitaux de Toulouse

Treibel TA, *Circ Cardiovasc Imaging*. 2016;9:e005066

Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement



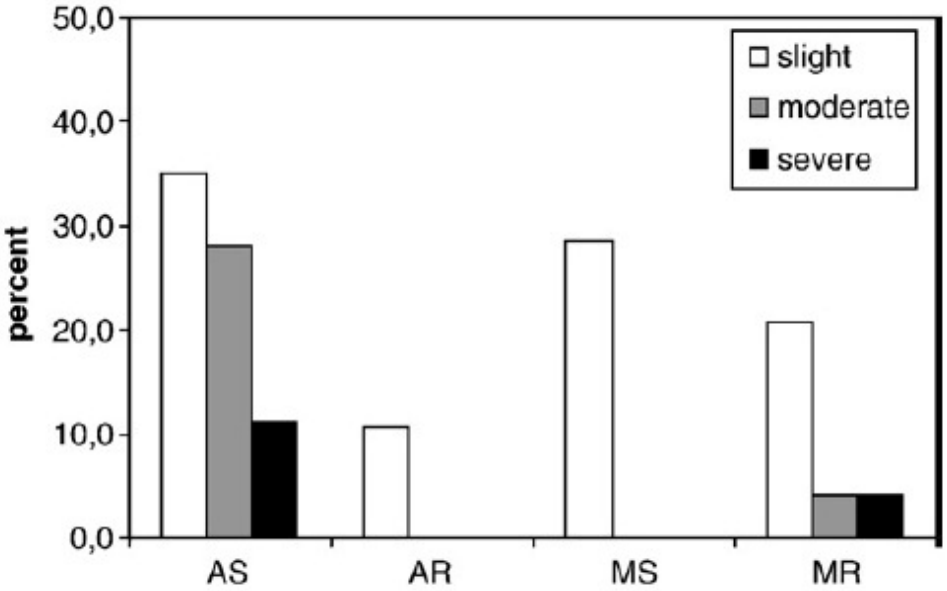
Hôpitaux de Toulouse

Castano A, *European Heart Journal* 2017;38:2879-2887

High prevalence of amyloid in 150 surgically removed heart valves—a comparison of histological and clinical data reveals a correlation to atheroinflammatory conditions

150 surgically resected heart valve specimens
Amyloid found in 55% specimens with highest prevalence in AS

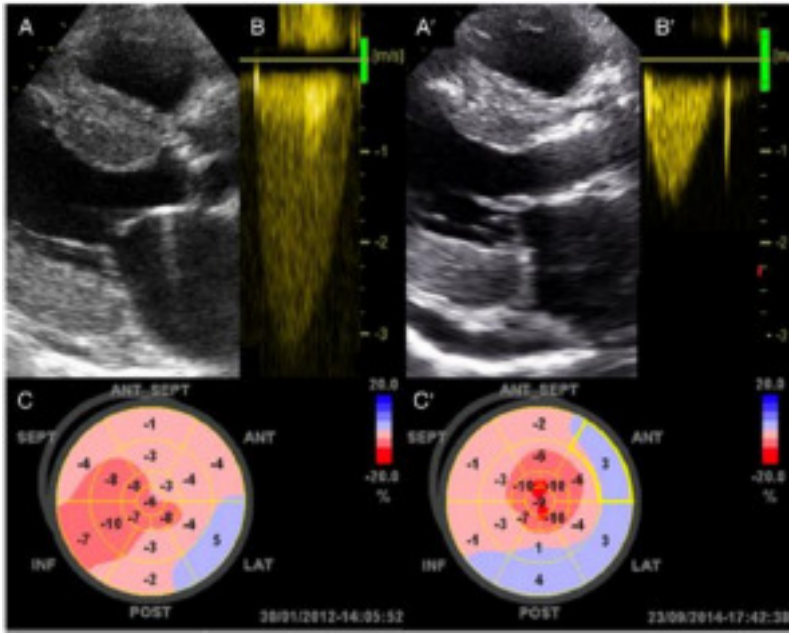
AS	
Without amyloid (n=26)	With amyloid (n=74)

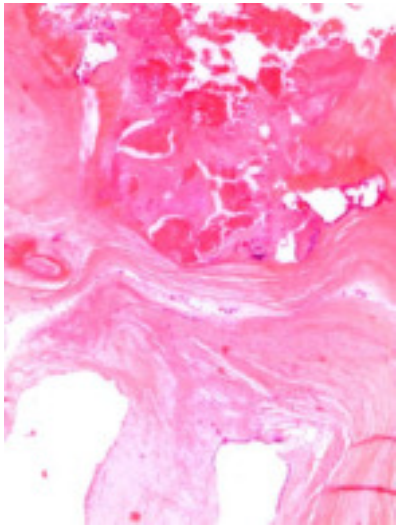


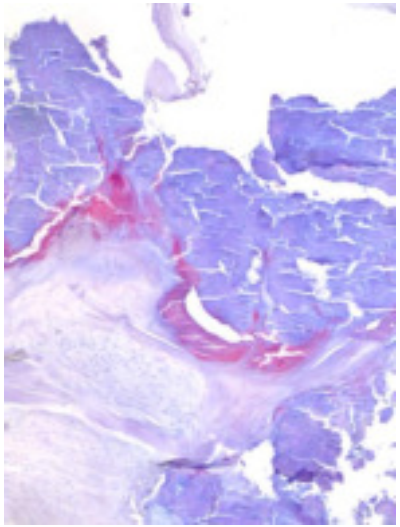
Hôpitaux de Toulouse

Kristen AV, et al. *Cardiovasc Pathol*. 2010;19:228-35

Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg?







Hôpitaux de Toulouse

Galat A, et al. *Eur Heart J*. 2016;37:3525-3531

Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology

Consensus recommendation

Older patients with symptomatic HF, particularly those with HFpEF (who are not hypertensive) or those who have features of hypertrophic or restrictive cardiomyopathy, or degenerative aortic stenosis and end-diastolic interventricular septal wall thickness exceeding 12 mm, *should be considered for screening* for cardiac transthyretin amyloidosis (ATTR).

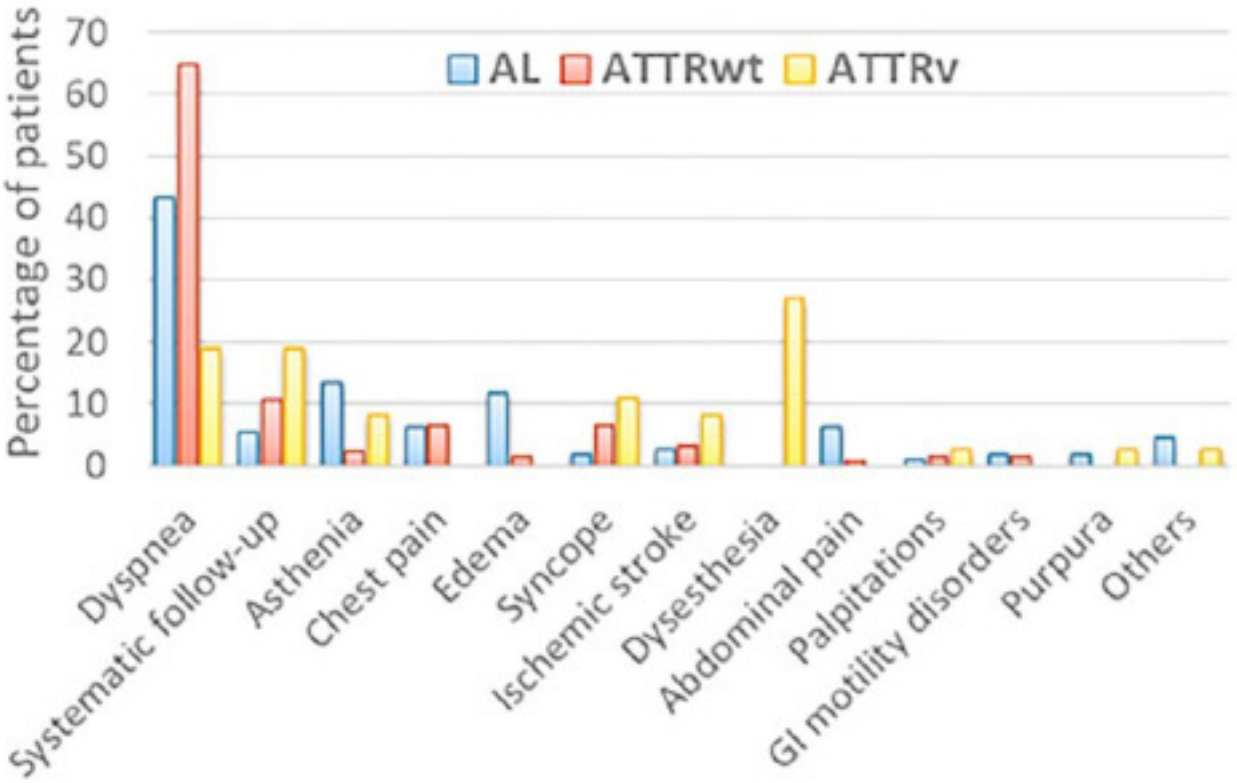
Hôpitaux de Toulouse

Seferovic PM, et al. *Eur J Heart Fail.* 2019;21:1169-1186

GATEWAY & JOURNEY

Hôpitaux de Toulouse

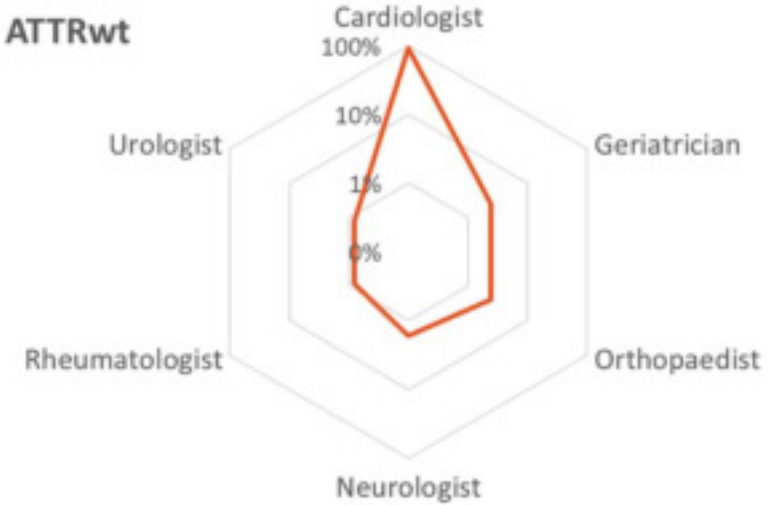
FIRST SYMPTOM

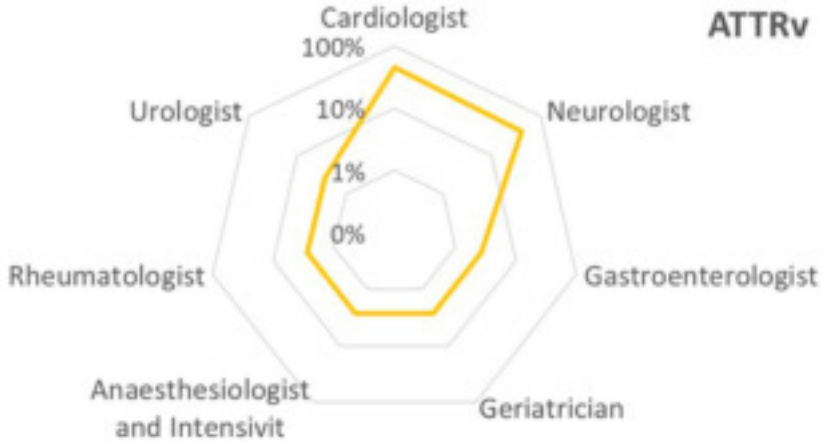


Hôpitaux de Toulouse

Dang D, et al. *ESC Heart Fail*. 2020;7:2418-2430

FIRST SPECIALIST

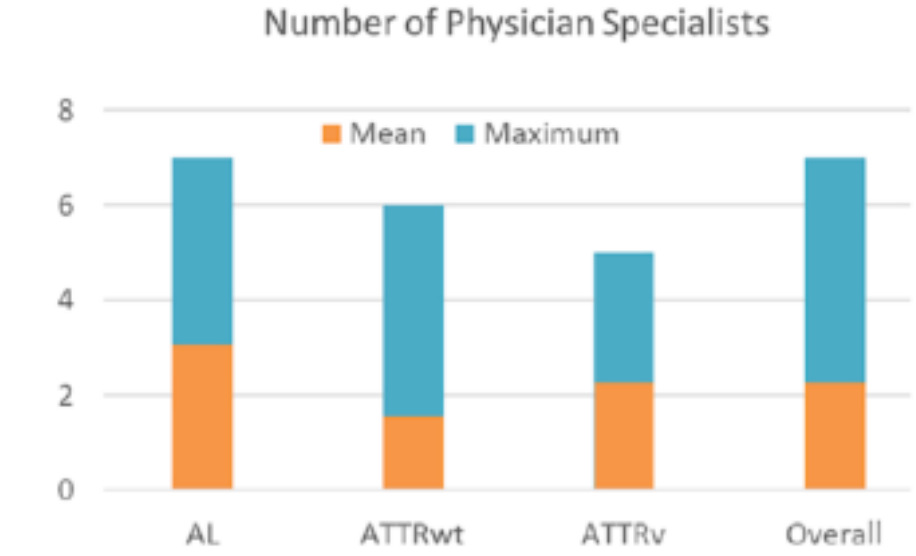


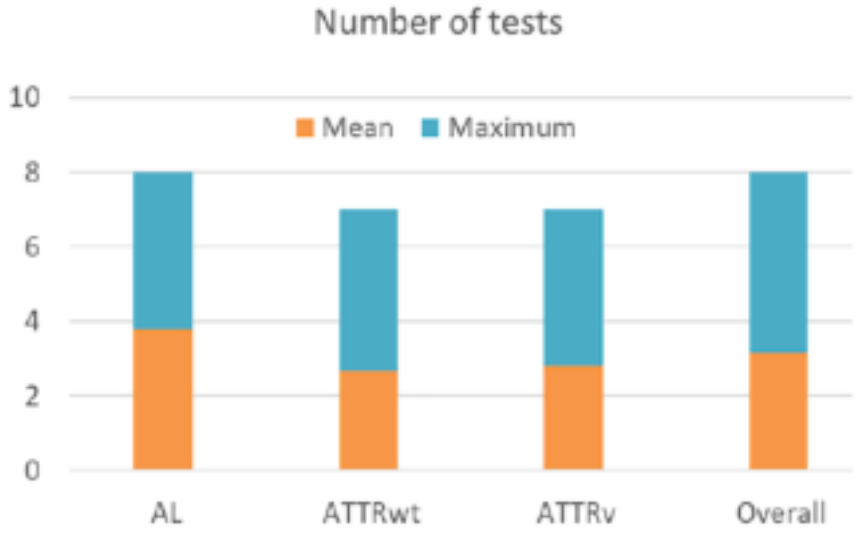


Hôpitaux de Toulouse

Dang D, et al. *ESC Heart Fail*. 2020;7:2418-2430

NUMBER OF SPECIALISTS AND TESTS

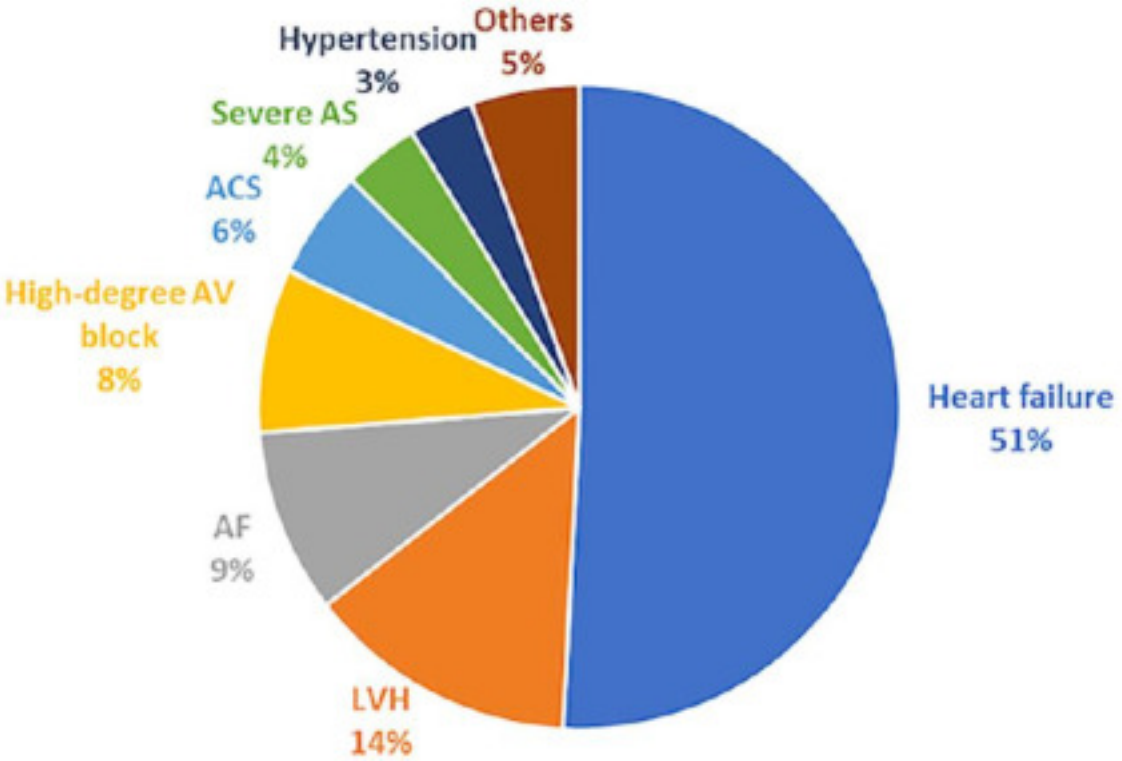




Hôpitaux de Toulouse

Dang D, et al. *ESC Heart Fail*. 2020;7:2418-2430

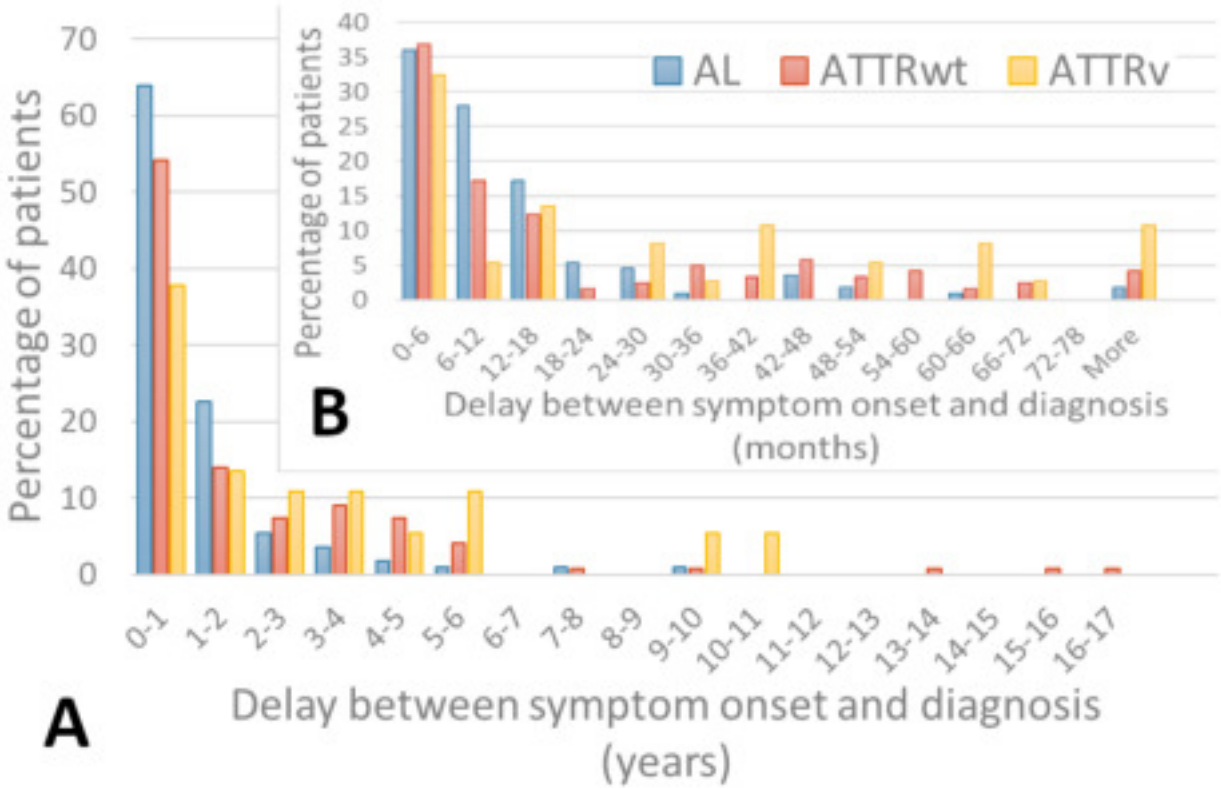
GATEWAY IN CARDIOLOGY



Hôpitaux de Toulouse

Dang D, et al. *ESC Heart Fail*. 2020;7:2418-2430

DELAY



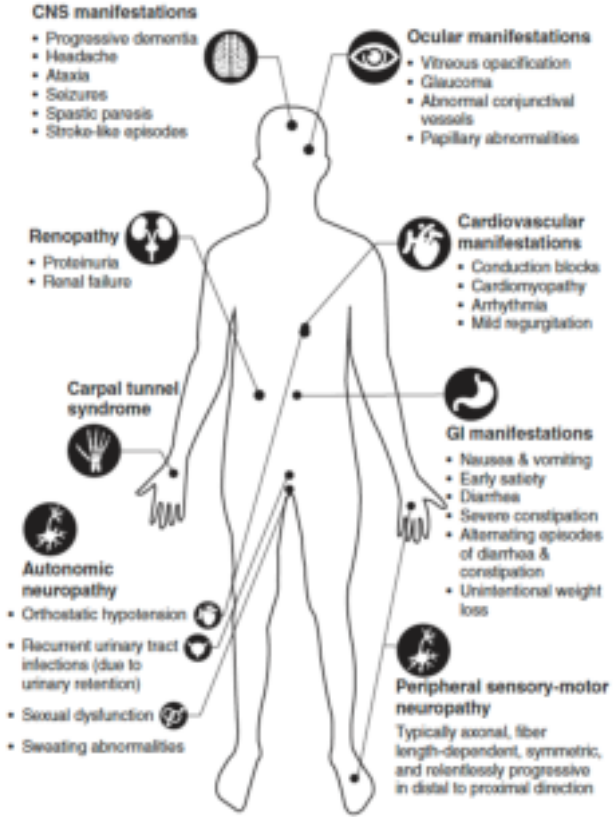
Hôpitaux de Toulouse

Dang D, et al. *ESC Heart Fail*. 2020;7:2418-2430

‘RED FLAGS’ SIGNS

Hôpitaux de Toulouse

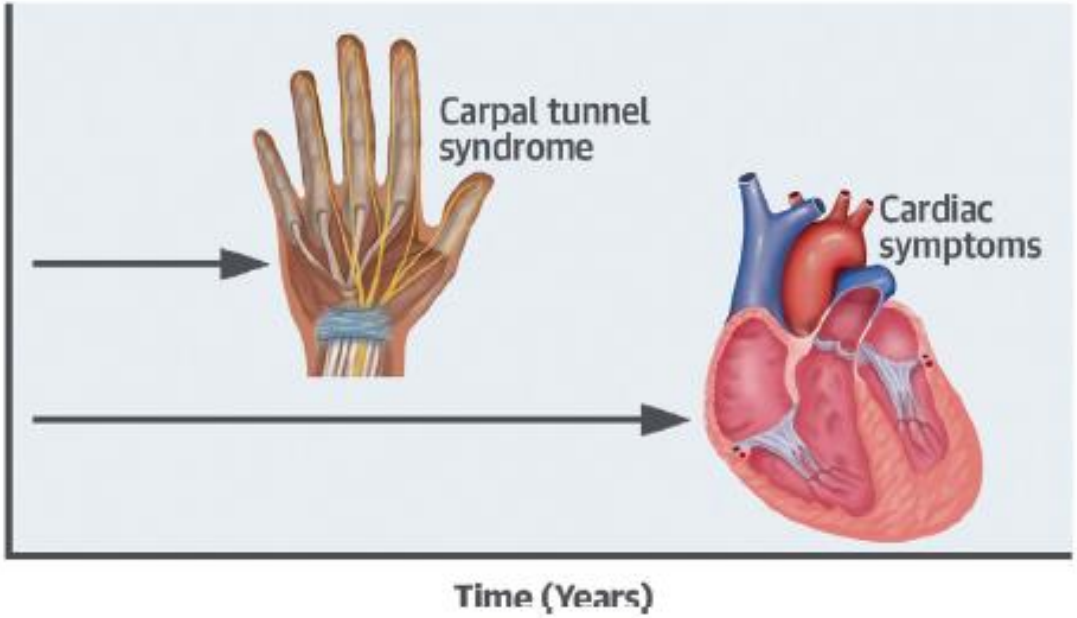
SYSTEMIC DISEASE



Hôpitaux de Toulouse

Conceição I, *J Peripher Nerv Syst*. 2016;21:5-9

Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release



Hôpitaux de Toulouse

Sperry BW, *J Am Coll Cardiol* 2018;72:2040-50

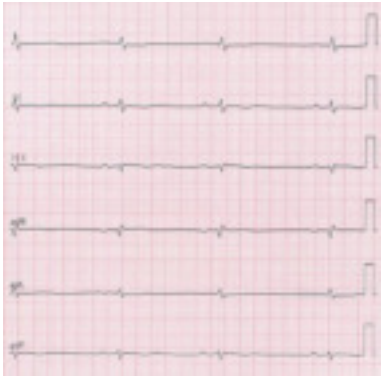
POPEYE'S SIGN

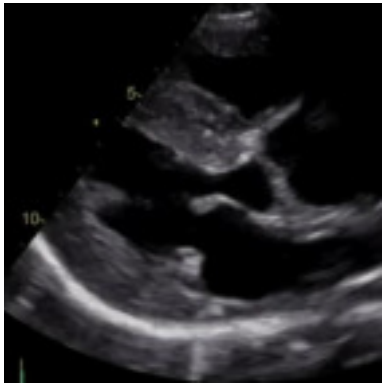
Hôpitaux de Toulouse

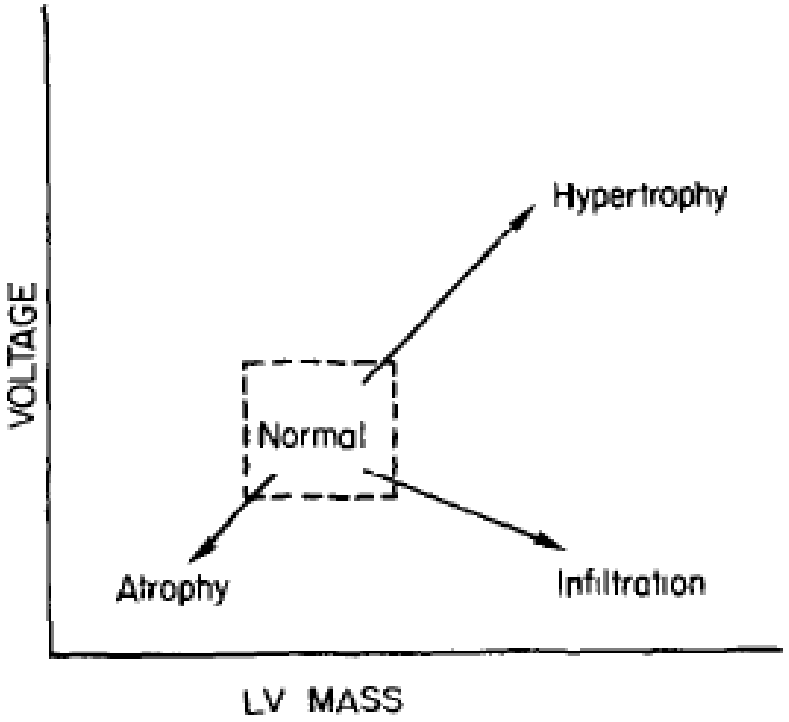
SUSPECT AMYLOIDOSIS

Hôpitaux de Toulouse

ECG & IMAGING DISCREPANCY



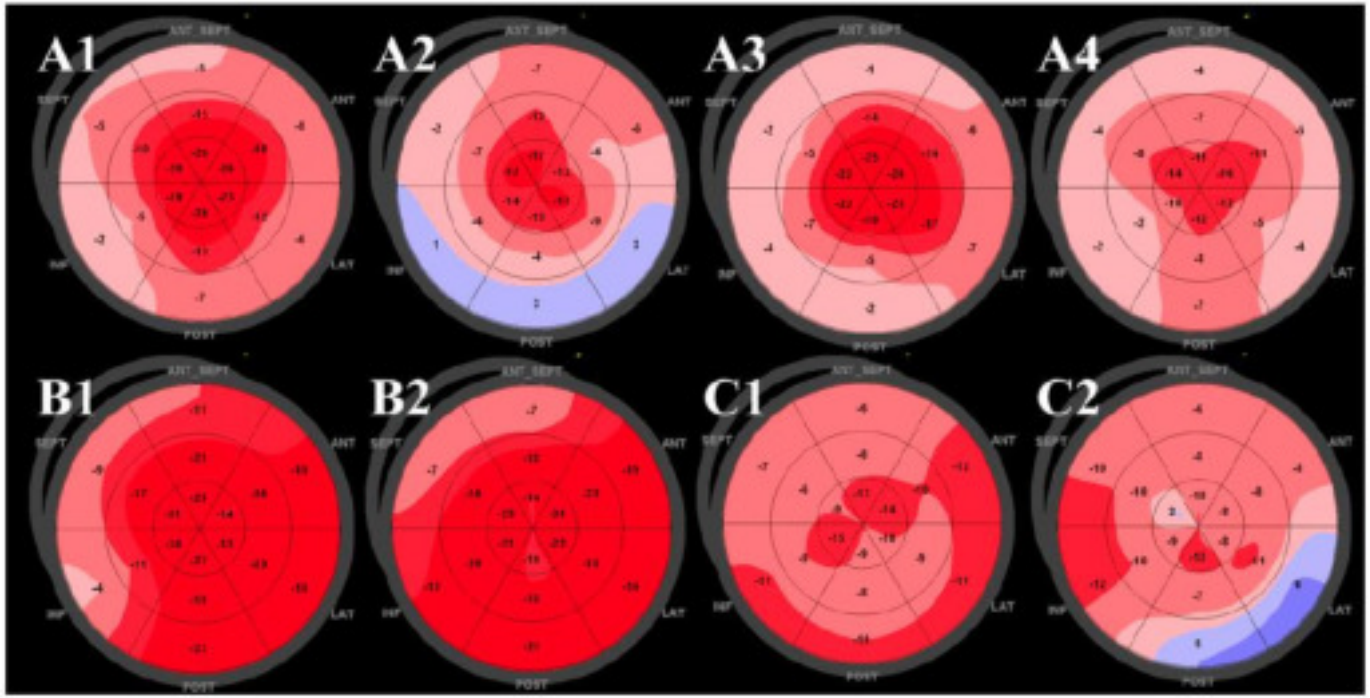




Hôpitaux de Toulouse

Carroll JD, *Am J Cardiol.* 1982;49:9-13

Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis



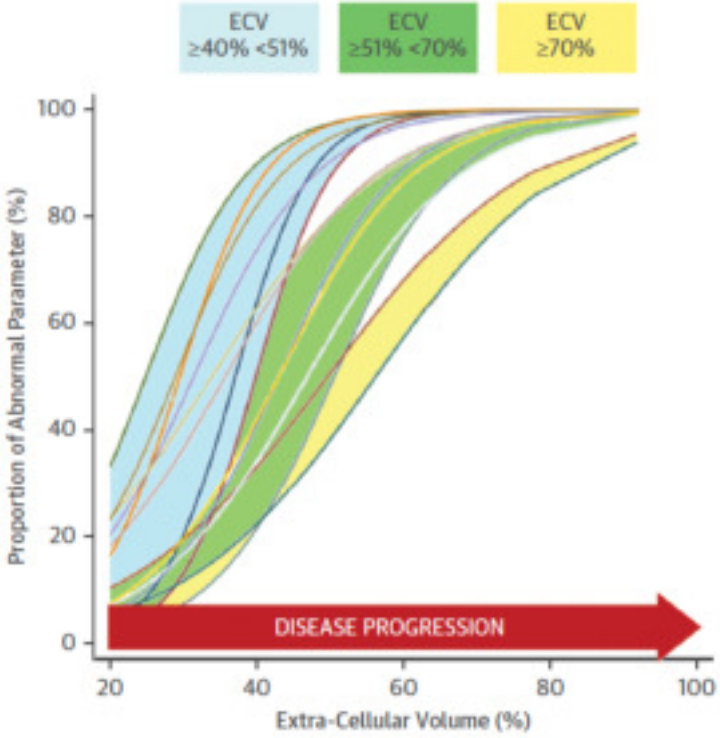
Hôpitaux de Toulouse

Phelan D. *Heart* 2012;98:1442e1448

Multiparametric Echocardiography Scores for the Diagnosis of Cardiac Amyloidosis

Variable Cut-Offs and Details About Calculation of the AL and IWT Scores

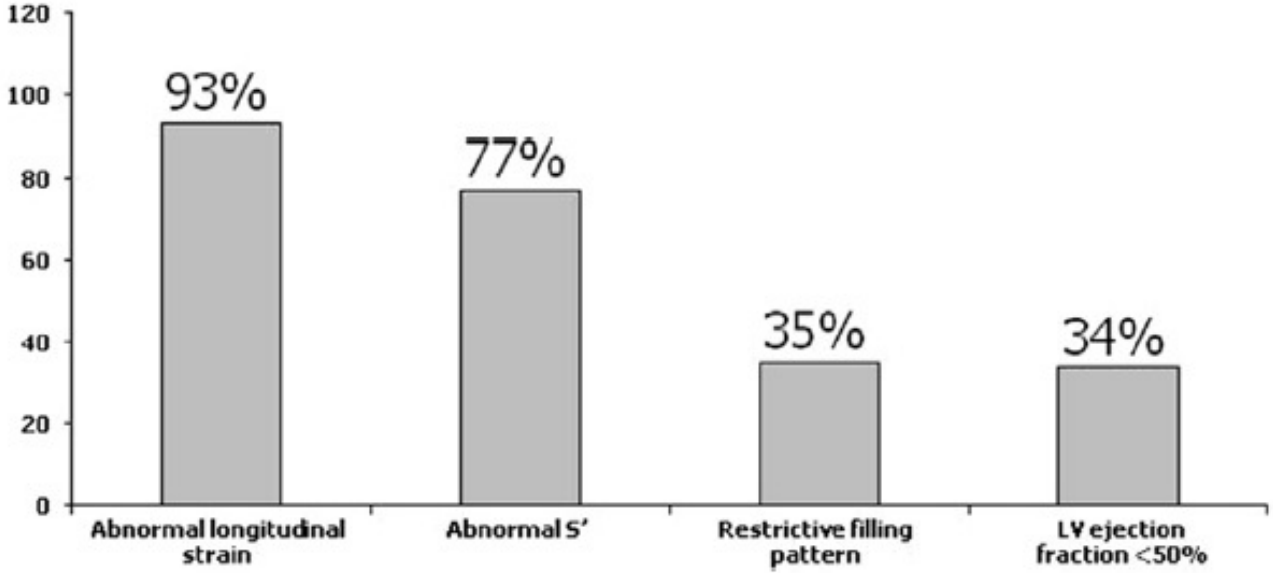
	Cut-Off	Points
AL score		
RWT	>0.52	2
E/e'	>10	2
TAPSE, mm	≤19	1
LS, %	≥−14	1
IWT score		
RWT	>0.6	3
E/e'	>11	1
TAPSE, mm	≤19	2
LS, %	≥−13	1
SAB	>2.9	3



Hôpitaux de Toulouse

Boldrini M, et al. *JACC Cardiovasc Imaging.* 2020;13:909-920

LEFT VENTRICULAR STRUCTURE & FUNCTION



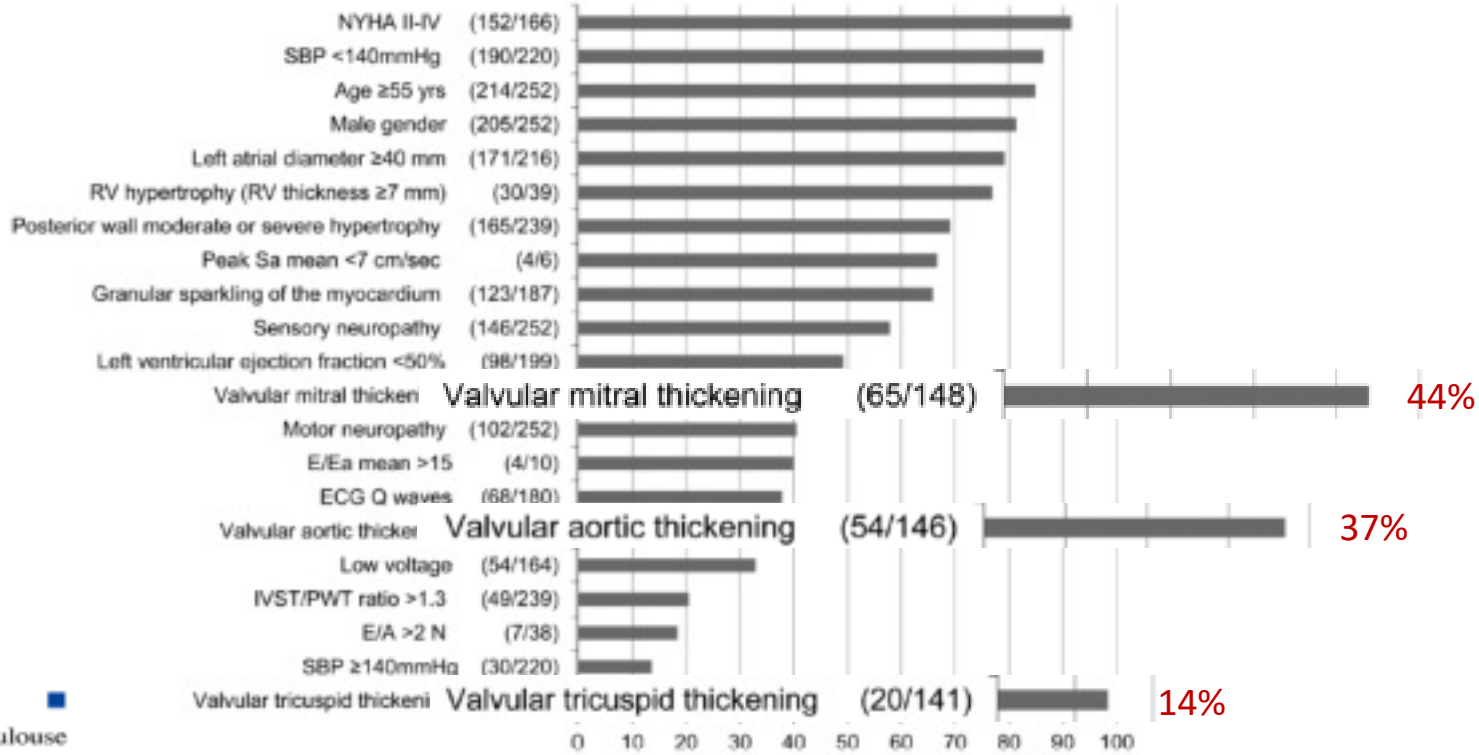
Hôpitaux de Toulouse

Quarta CC, et al. *Circulation.* 2014;129:1840-1849

VALVULAR THICKENING

Hôpitaux de Toulouse

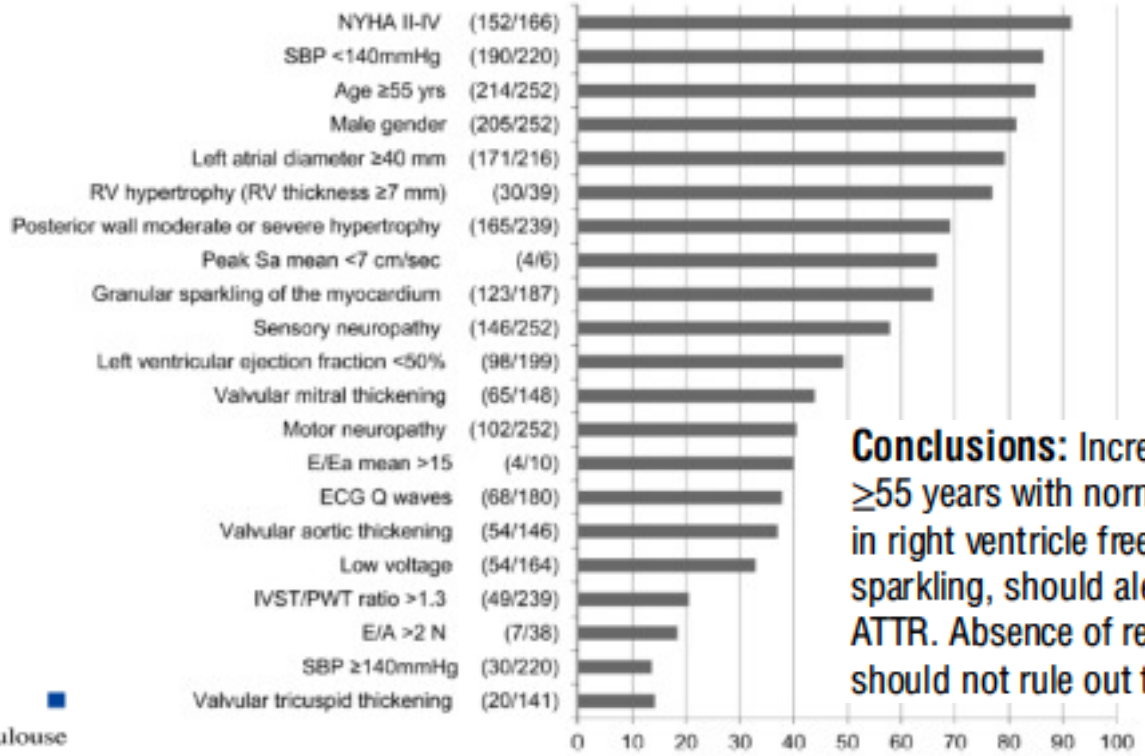
Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy



Hôpitaux de Toulouse

Damy T, *Open Heart* 2016;3:e000289

Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy

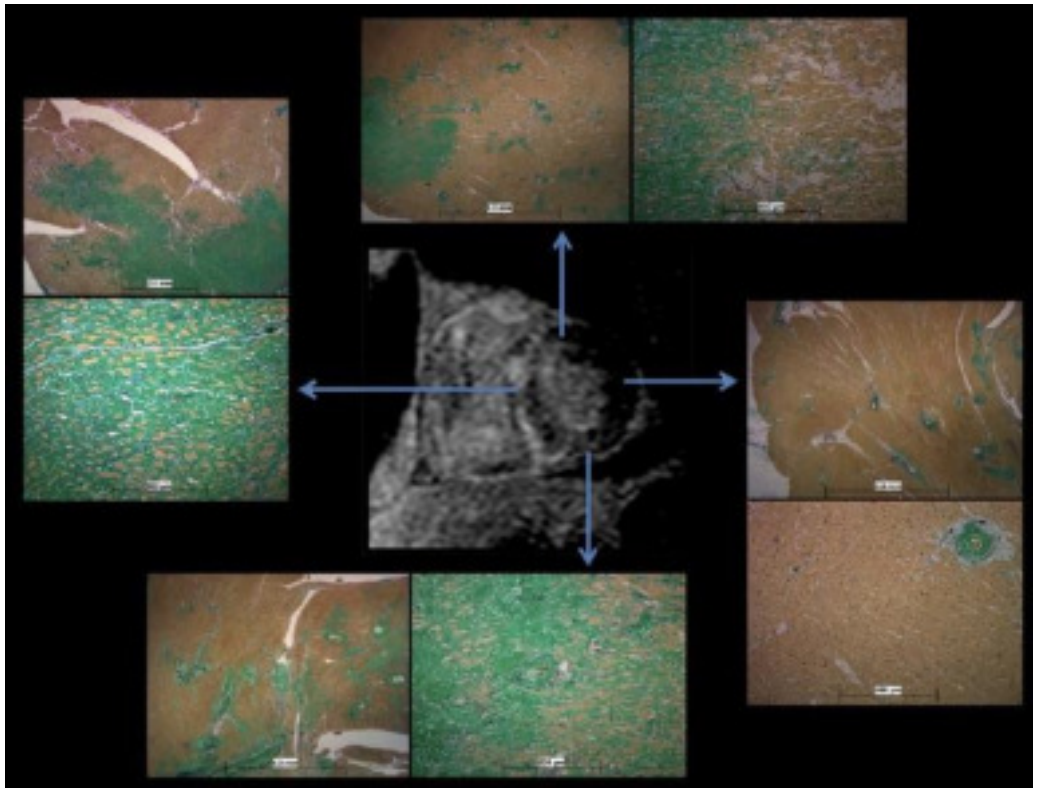


Conclusions: Increased IVST, especially in men ≥55 years with normal systolic blood pressure, increase in right ventricle free wall and valve thicknesses, and sparkling, should alert practitioners to the possibility of ATTR. Absence of restrictive pattern and low voltage should not rule out the suspicion.

Hôpitaux de Toulouse

Damy T, *Open Heart* 2016;3:e000289

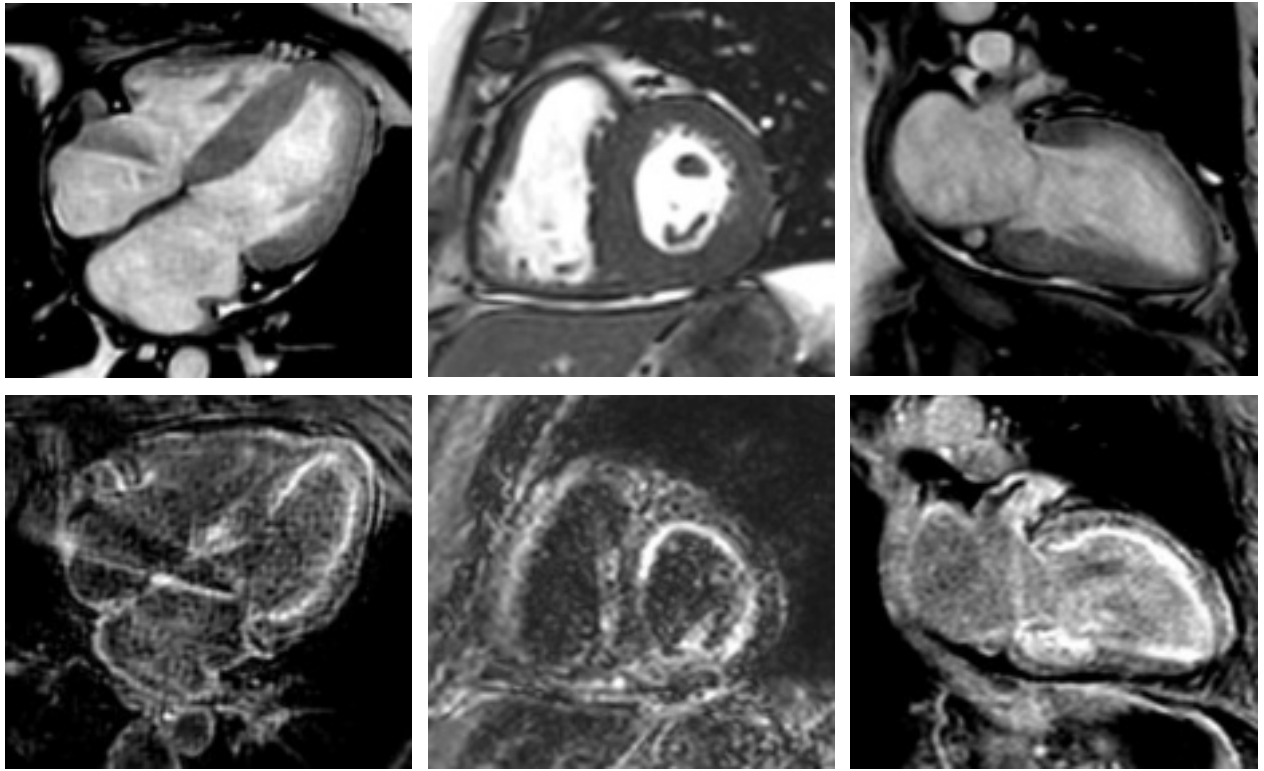
VALUE OF CARDIAC MRI



Hôpitaux de Toulouse

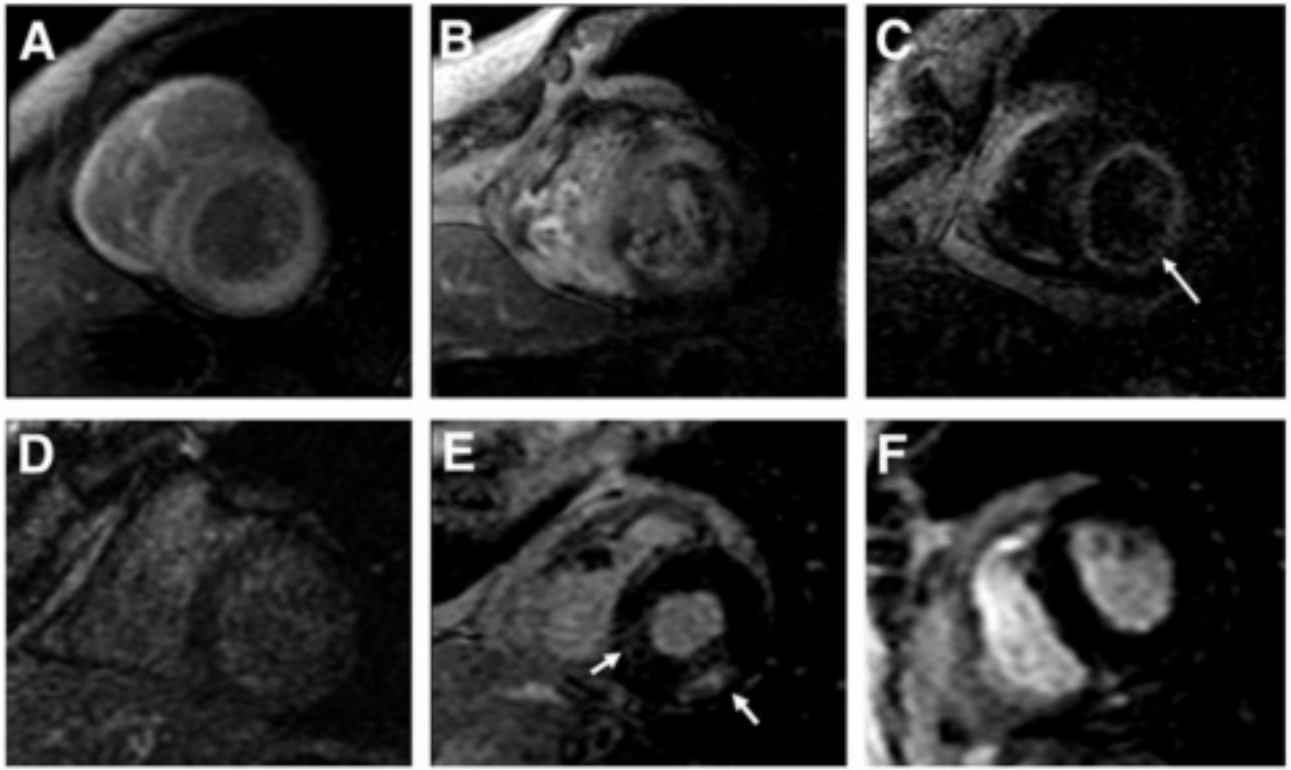
Syed IS, *J Am Coll Cardiol Img* 2010;3:155-164

LATE GADOLINIUM ENHANCEMENT



Hôpitaux de Toulouse

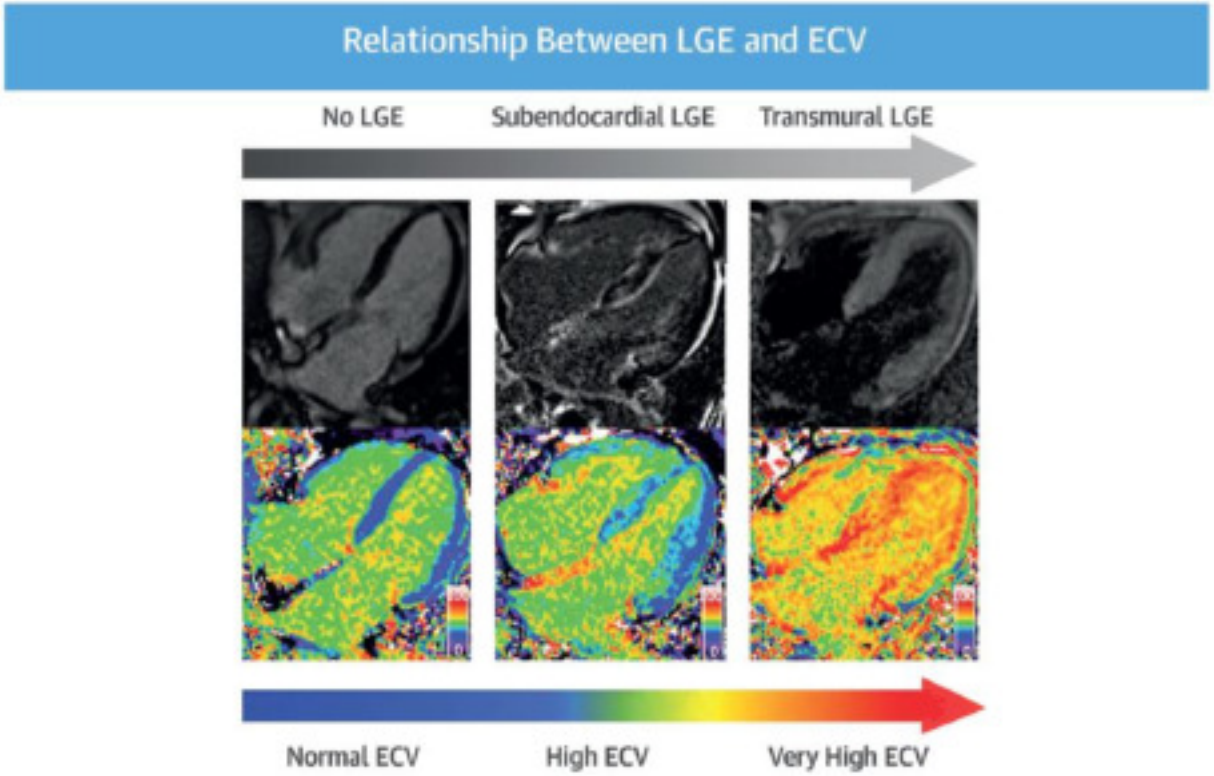
VALUE OF CARDIAC MRI



Hôpitaux de Toulouse

Syed IS, *J Am Coll Cardiol Img* 2010;3:155-164

VALUE OF CARDIAC MRI



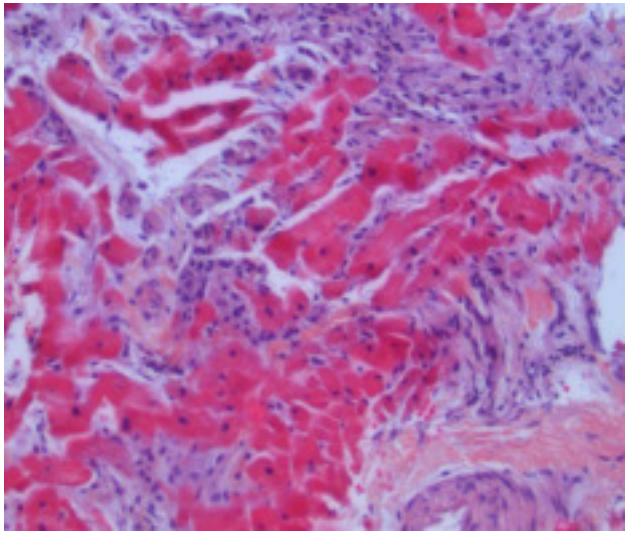
Hôpitaux de Toulouse

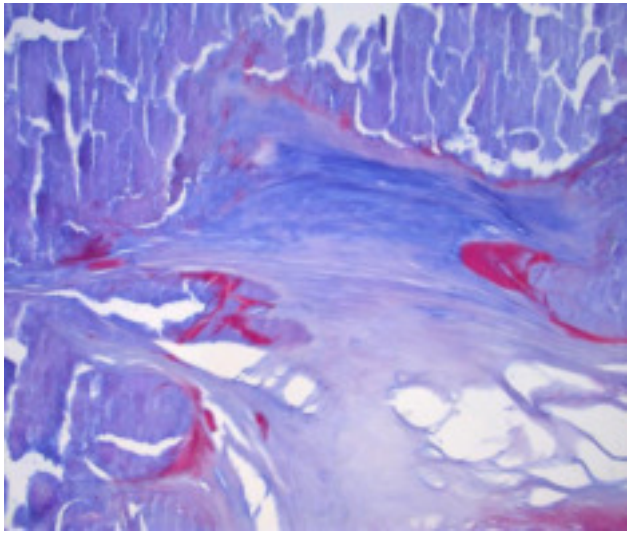
Martinez-Naharro A, *J Am Coll Cardiol* 2017;70:466-77

TYPE AMYLOIDOSIS

Hôpitaux de Toulouse

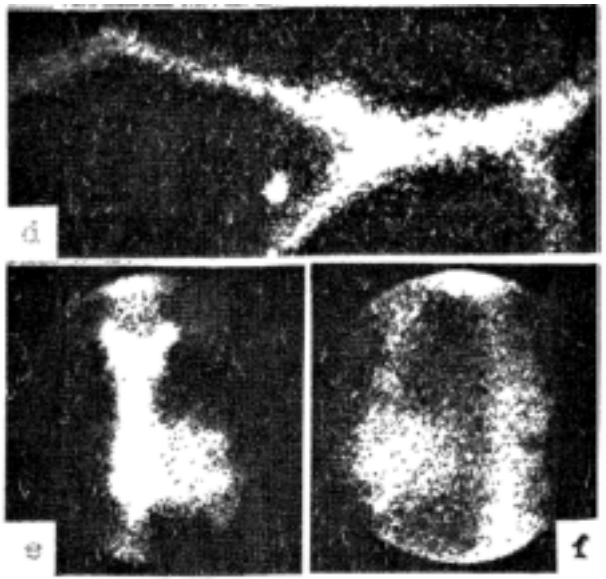
TISSUE BIOPSY & IMMUNOSTAINING





Hôpitaux de Toulouse

HISTORY OF BONE SCINTIGRAPHY IN THE FIELD OF AMYLOIDOSIS



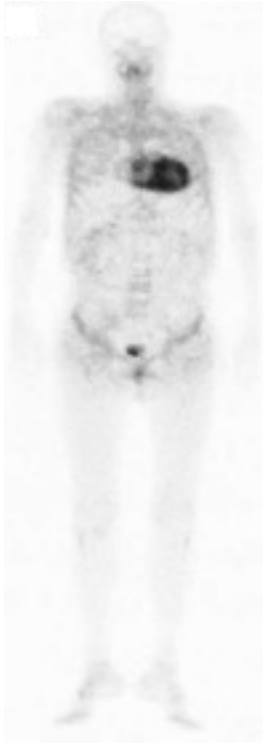
SCANNING FOR SOFT-TISSUE AMYLOID

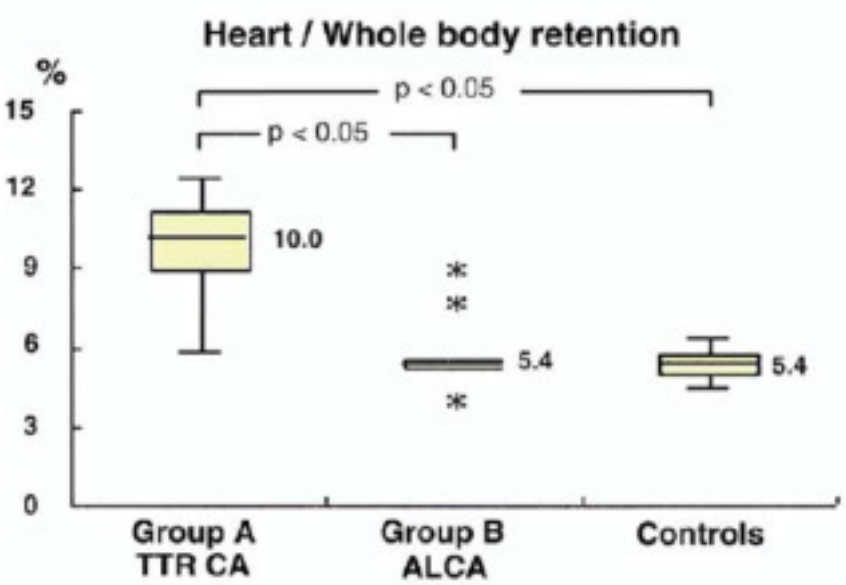
SIR,—Two patients, a 15-year-old girl with hereditary amyloidosis and a 59-year-old man with amyloidosis associated with a kappa light-chain myeloma, showed excessive, diffuse soft-tissue localisation when individual limbs were scanned 5–6 h after the administration of 10 mCi technetium-99m diphosphonate.[1] The soft-tissue localisation was so great that it obscured the normal bone localisation

Hôpitaux de Toulouse

Kula RW, et al. *Lancet* 1977;1:92-3

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

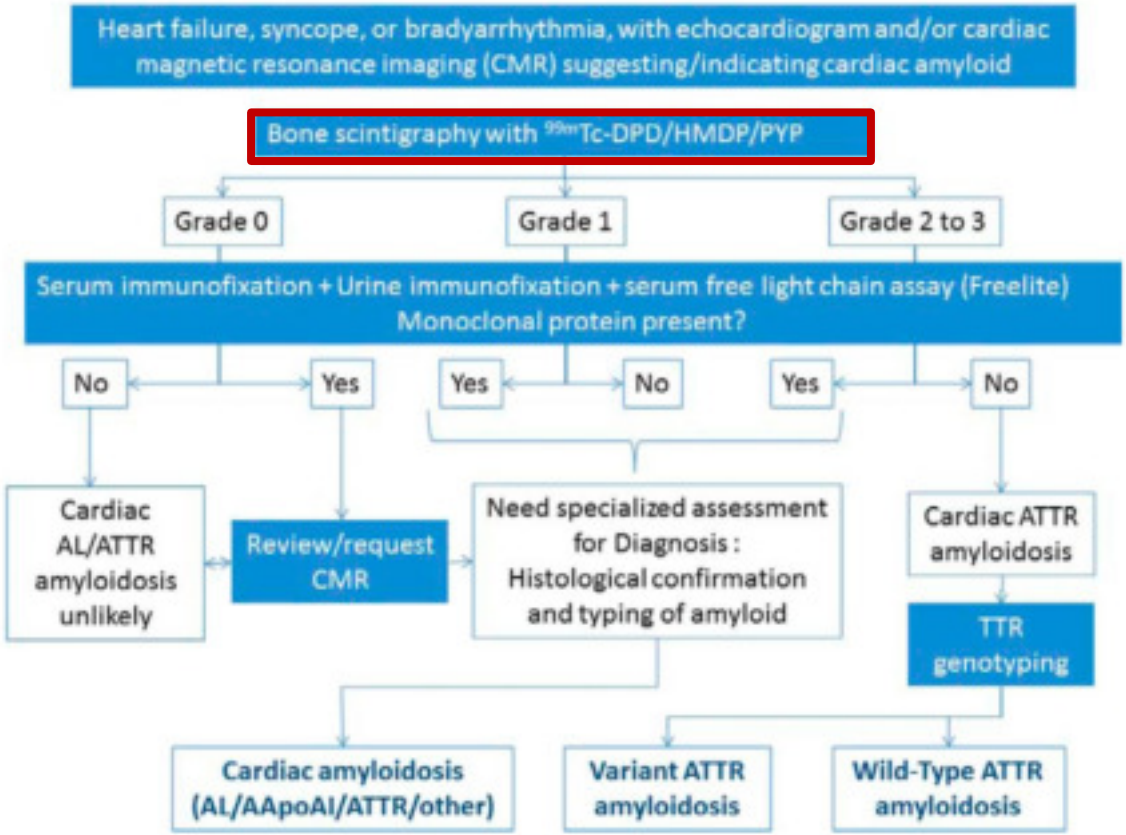




Hôpitaux de Toulouse

Perugini E, et al. *J Am Coll Cardiol* 2005;46:1076–84

Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis



Hôpitaux de Toulouse

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

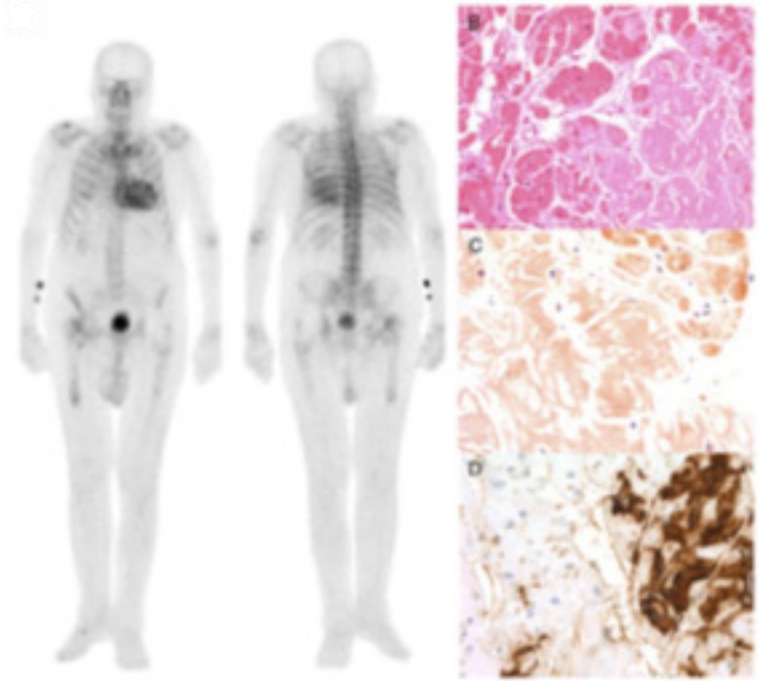
THE ROLE OF BONE SCINTIGRAPHY

Hôpitaux de Toulouse

Martinez-Naharro A, et al. *Nat Rev Cardiol.* 2020;17:413-426

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

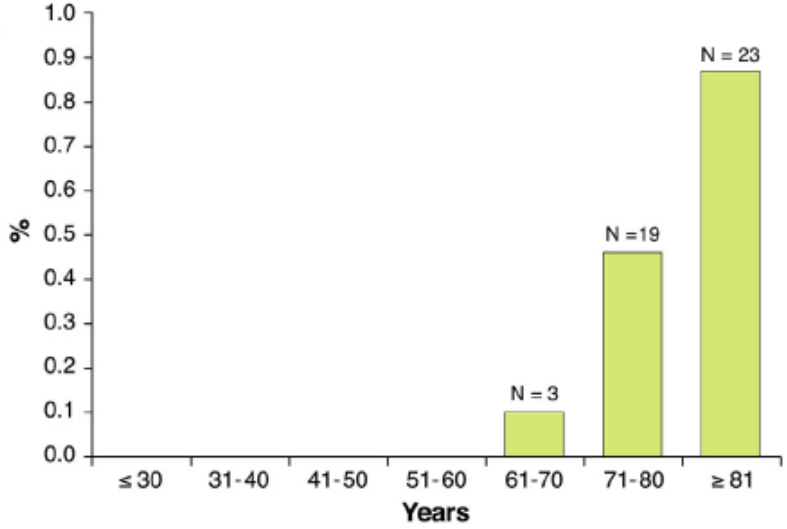
Thirteen percent of ^{99m}Tc-DPD scintigraphy myocardial uptake among patients over 60-year-old admitted for HFpEF with left ventricular hypertrophy (≥ 12 mm)

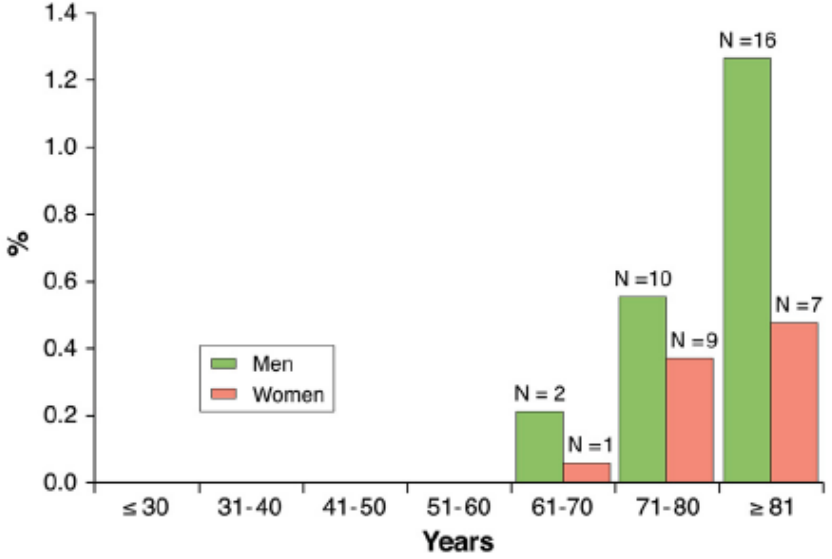


Hôpitaux de Toulouse

González-López E, et al. *Eur Heart J* 2015;36:2585-94

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



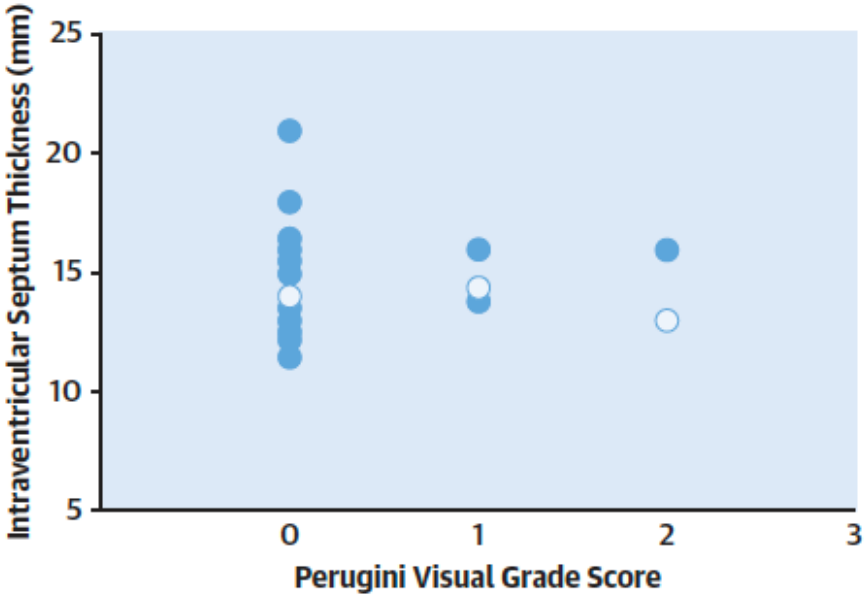


Hôpitaux de Toulouse

Longhi S, et al. *JACC Cardiovasc Imaging* 2014;7:531–2

Low Sensitivity of Bone Scintigraphy in Detecting Phe64Leu Mutation-Related Transthyretin Cardiac Amyloidosis

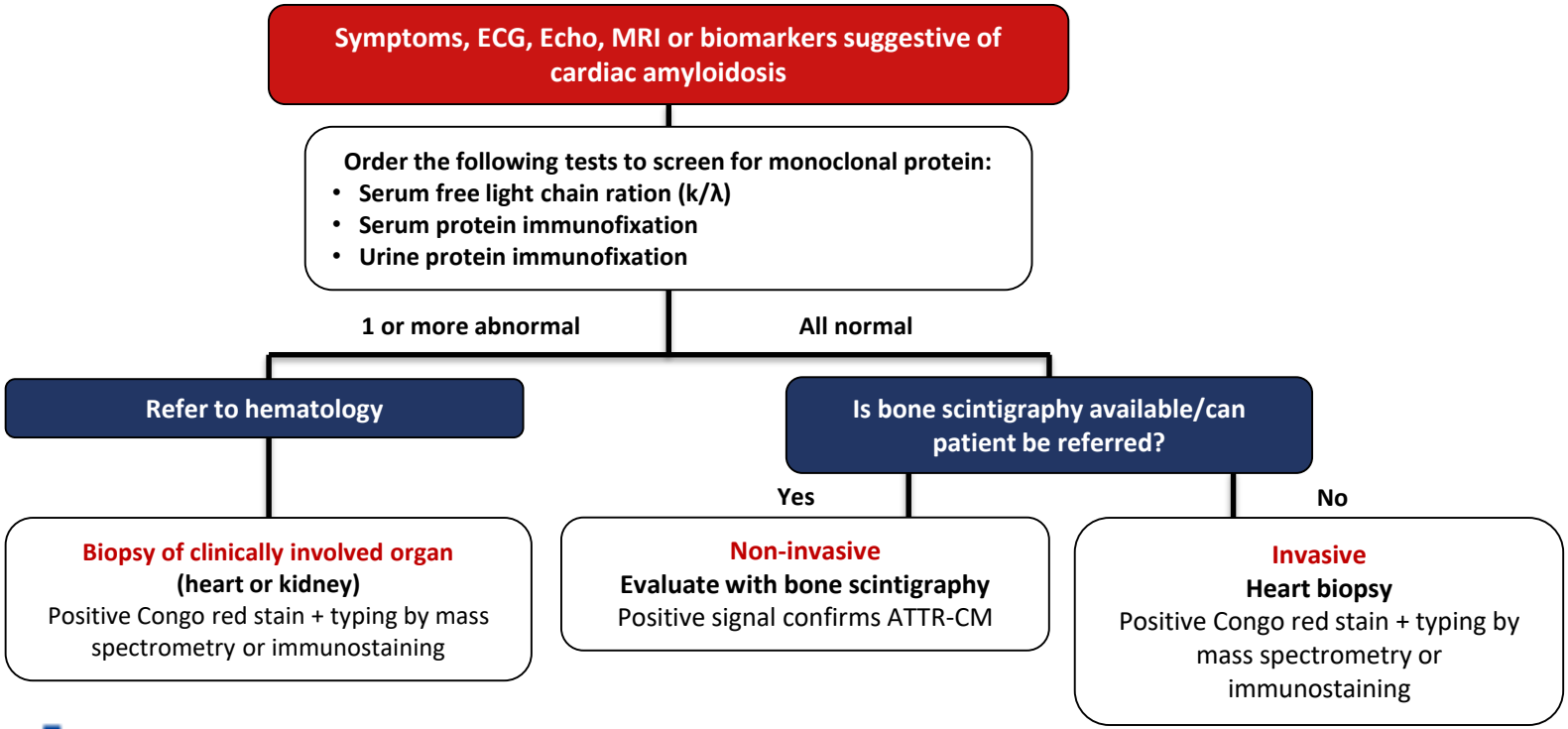
55 patients with Phe64Leu TTR mutation.
26 patients with cardiac involvement (IVS≥12 mm).
19 underwent bone scintigraphy.
17 (89.5%) patients had low or absent myocardial bone tracer uptake.
2 (10.5%) showed high-grade myocardial uptake.



Hôpitaux de Toulouse

Musumeci MB, et al. *JACC Cardiovasc Imaging.* 2020;13:1314-1321

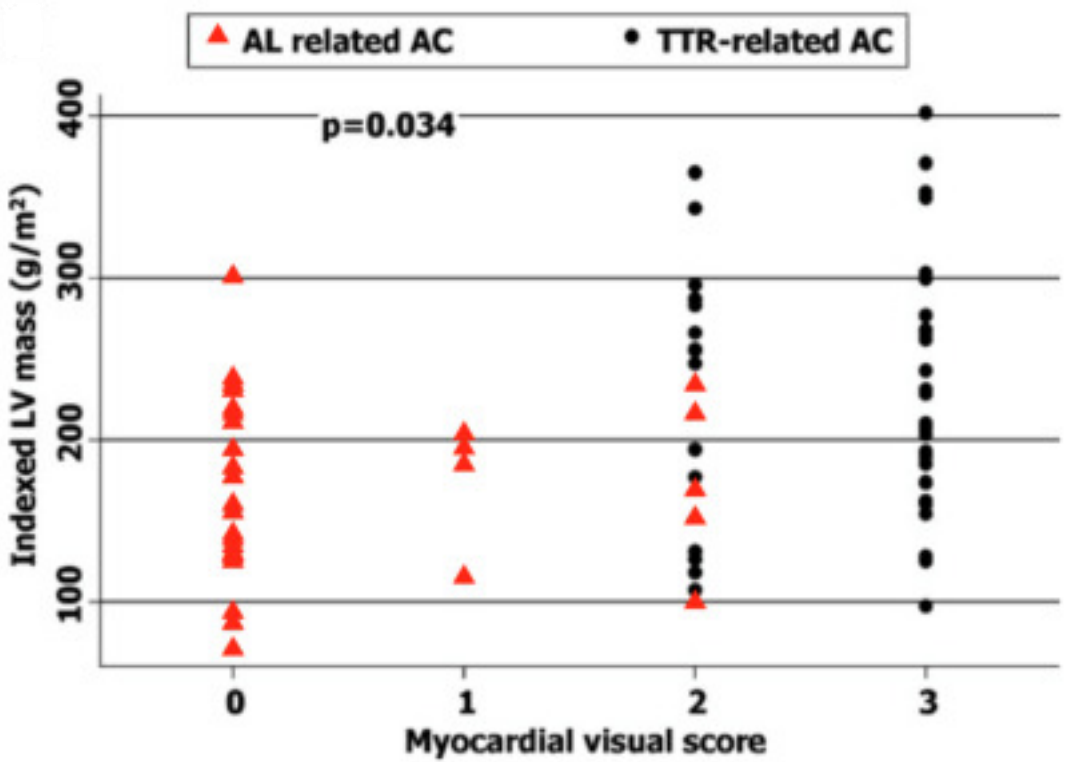
DIAGNOSTIC ALGORITHM



Hôpitaux de Toulouse

Maurer MS, et al. *Circ Heart Fail.* 2019;12:e006075

TRAPS OF BONE SCINTIGRAPHY

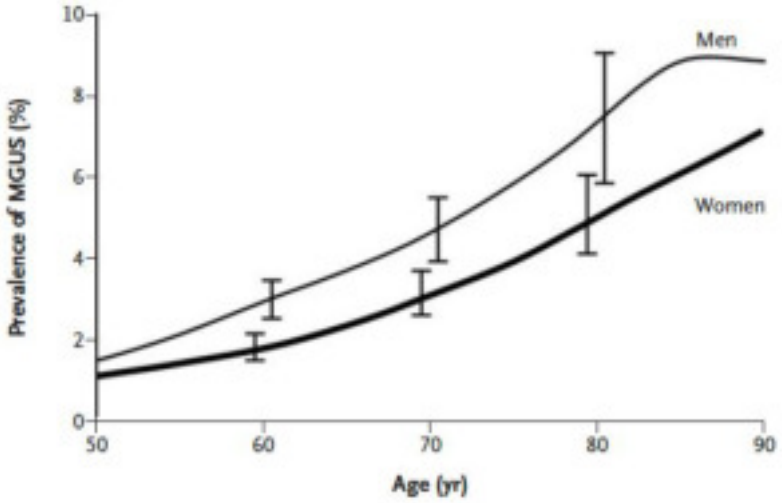


Hôpitaux de Toulouse

Rapezzi C, et al. *Eur J Nucl Med Mol Imaging.* 2011;38:470-8

Prevalence of Monoclonal Gammopathy of Undetermined Significance

Age	Men	Women	Total
	*number/total number (percent)**		
50–59 yr	82/4038 (2.0)	59/4335 (1.4)	141/8373 (1.7)
60–69 yr	105/2864 (3.7)	73/3155 (2.3)	178/6019 (3.0)
70–79 yr	104/1858 (5.6)	101/2650 (3.8)	205/4508 (4.6)
≥80 yr	59/709 (8.3)	111/1854 (6.0)	170/2563 (6.6)
Total	350/9469 (3.7)†	344/11,994 (2.9)†	694/21,463 (3.2)†‡



Hôpitaux de Toulouse

Kyle RA, et al. *N Engl J Med* 2006;354:1362-9

Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis

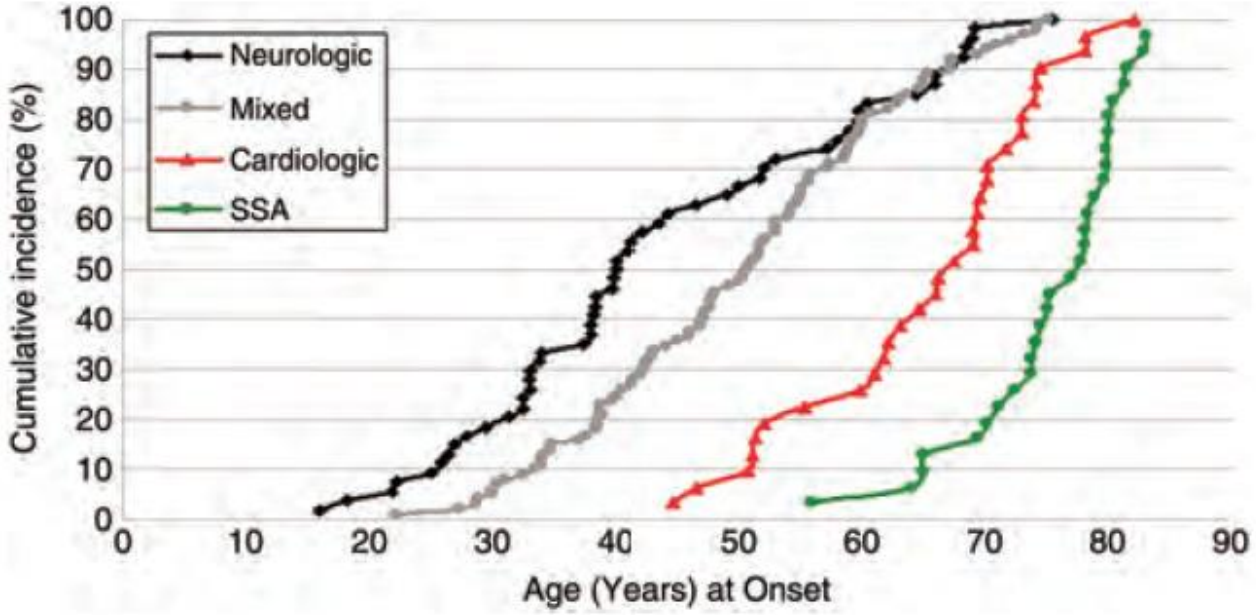
Diagnostic sensitivity of fat pad fine needle aspiration in different cardiac amyloidoses

Amyloid type	*n*	Number positive by Congo red staining	Diagnostic sensitivity (CI)
Systemic AL amyloidosis	216	181	84% (78–88%)
ATTRm	113	51	45% (36–54%)
Val122Ile	69	23	33%
Thr60Ala	21	14	67%
ATTRwt	271	42	15% (11–20%)

Hôpitaux de Toulouse

Quarta CC, et al. *Eur Heart J.* 2017;38:1905-1908

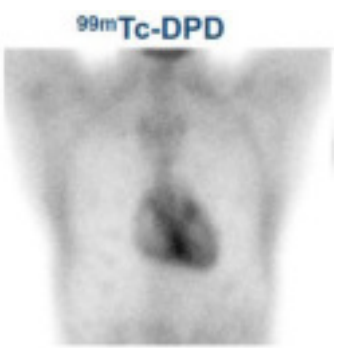
Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective

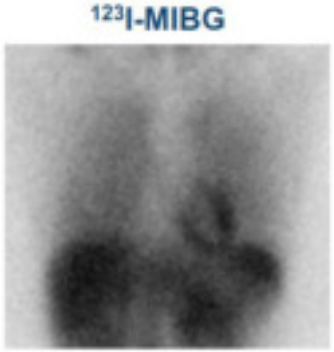


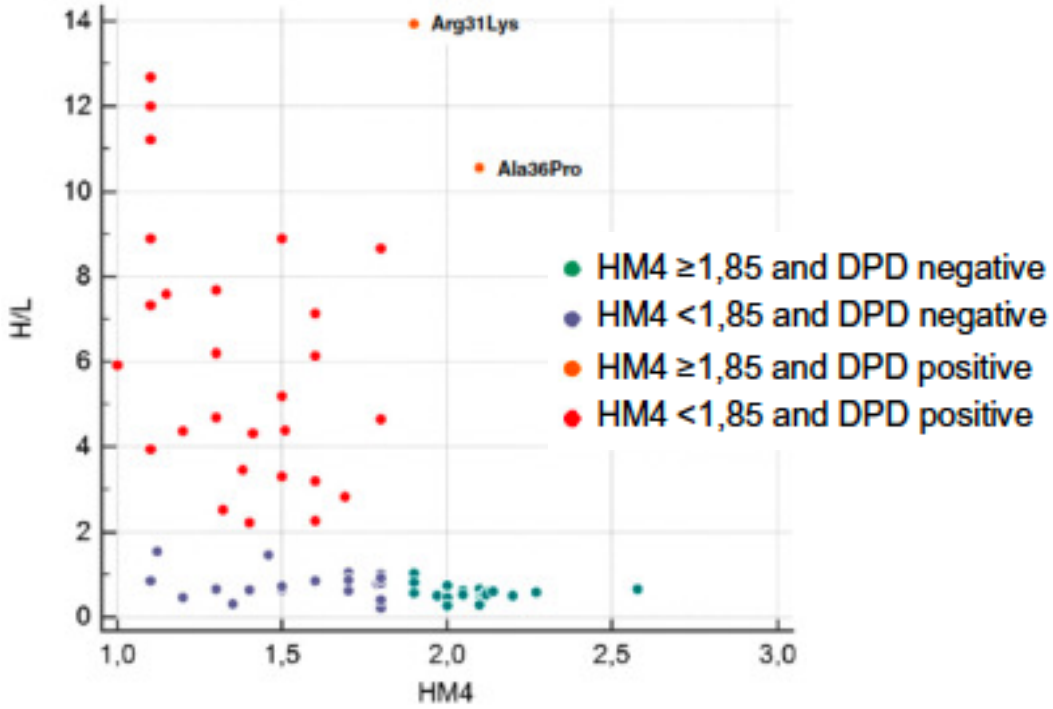
Hôpitaux de Toulouse

Rapezzi C, et al. *Eur Heart J.* 2013 Feb;34(7):520-8

Cardiac denervation evidenced by MIBG occurs earlier than amyloid deposits detection by diphosphonate scintigraphy in TTR mutation carriers







Hôpitaux de Toulouse

Piekarski E, et al. *Eur J Nucl Med Mol Imaging.* 2018;45:1108-1118

TREATMENTS

Hôpitaux de Toulouse

Treatment of cardiac transthyretin amyloidosis: an update

Diuretic therapy for dyspnea

Avoid beta-blockers

ACEI & ARB can be poorly tolerated but are not contra-indicated

Avoid digoxin (?)

Non-dihydropyridine calcium channel blockers contraindicated because of their negative inotropic effect

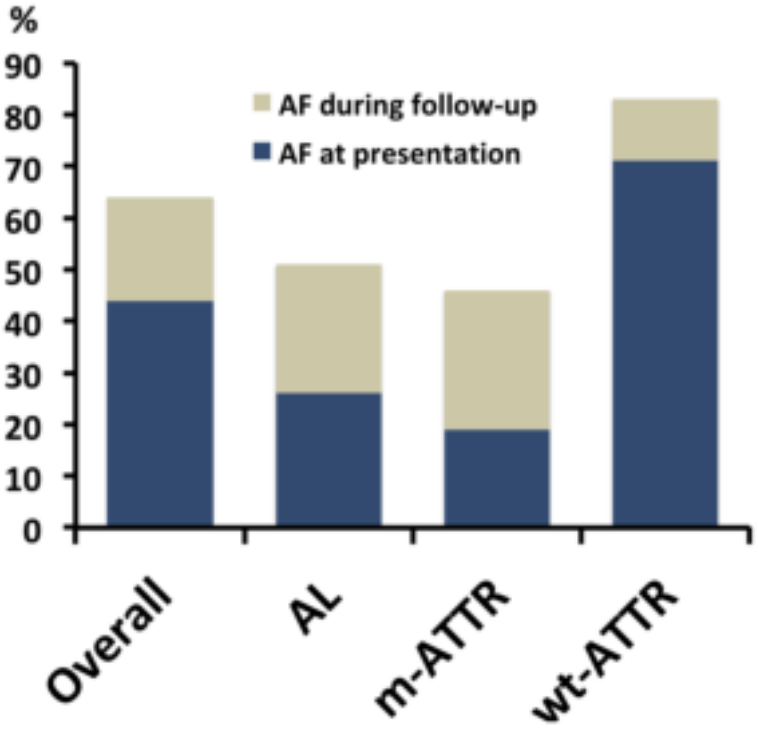
Impaired chronotropic reserve with amiodarone

Increased risk of atrial thrombosis even in sinus rhythm, likely because of a loss of atrial mechanical function

Hôpitaux de Toulouse

Emdin M, *Eur Heart J*. 2019;40:3699-3706

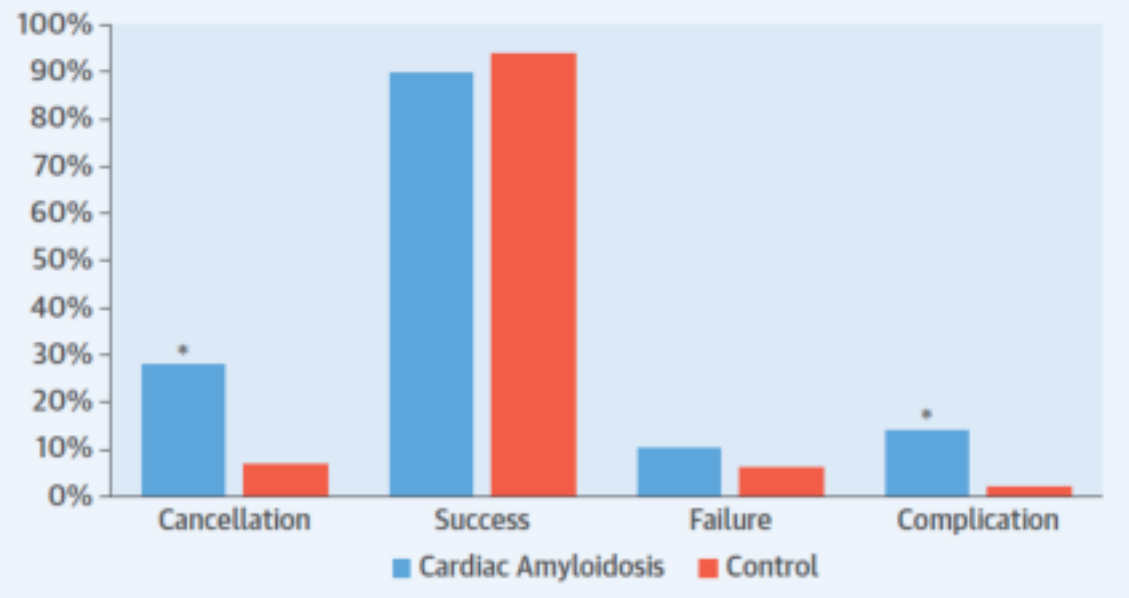
ATRIAL FIBRILLATION



Hôpitaux de Toulouse

Sanchis K, *Amyloid.* 2019;26:128-138

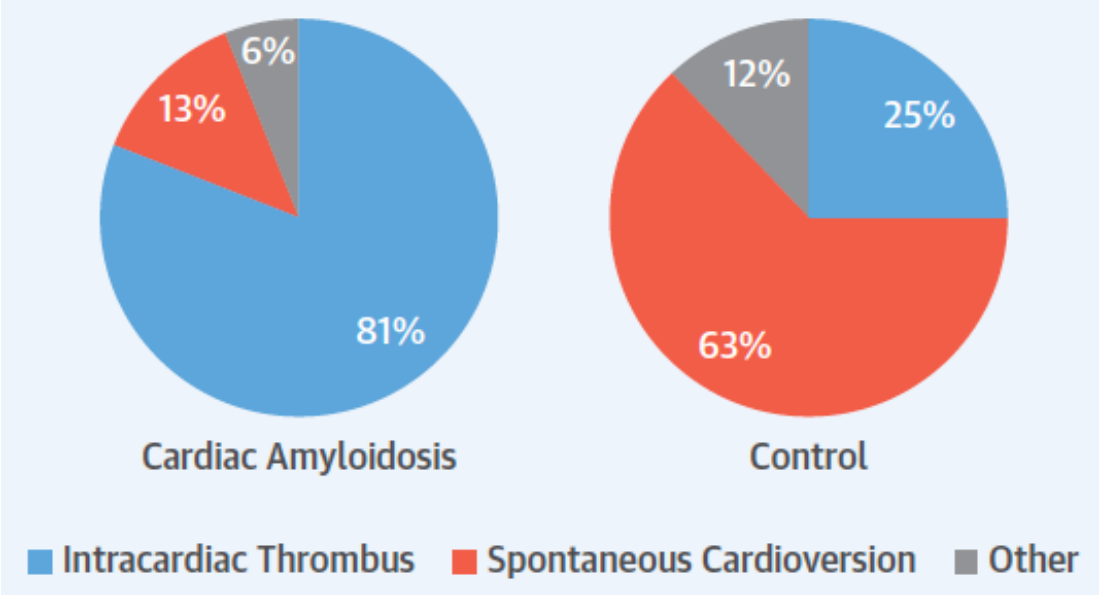
Direct Current Cardioversion of Atrial Arrhythmias in Adults With Cardiac Amyloidosis



Hôpitaux de Toulouse

El-Am EA, *J Am Coll Cardiol* 2019;73:589-97

Direct Current Cardioversion of Atrial Arrhythmias in Adults With Cardiac Amyloidosis



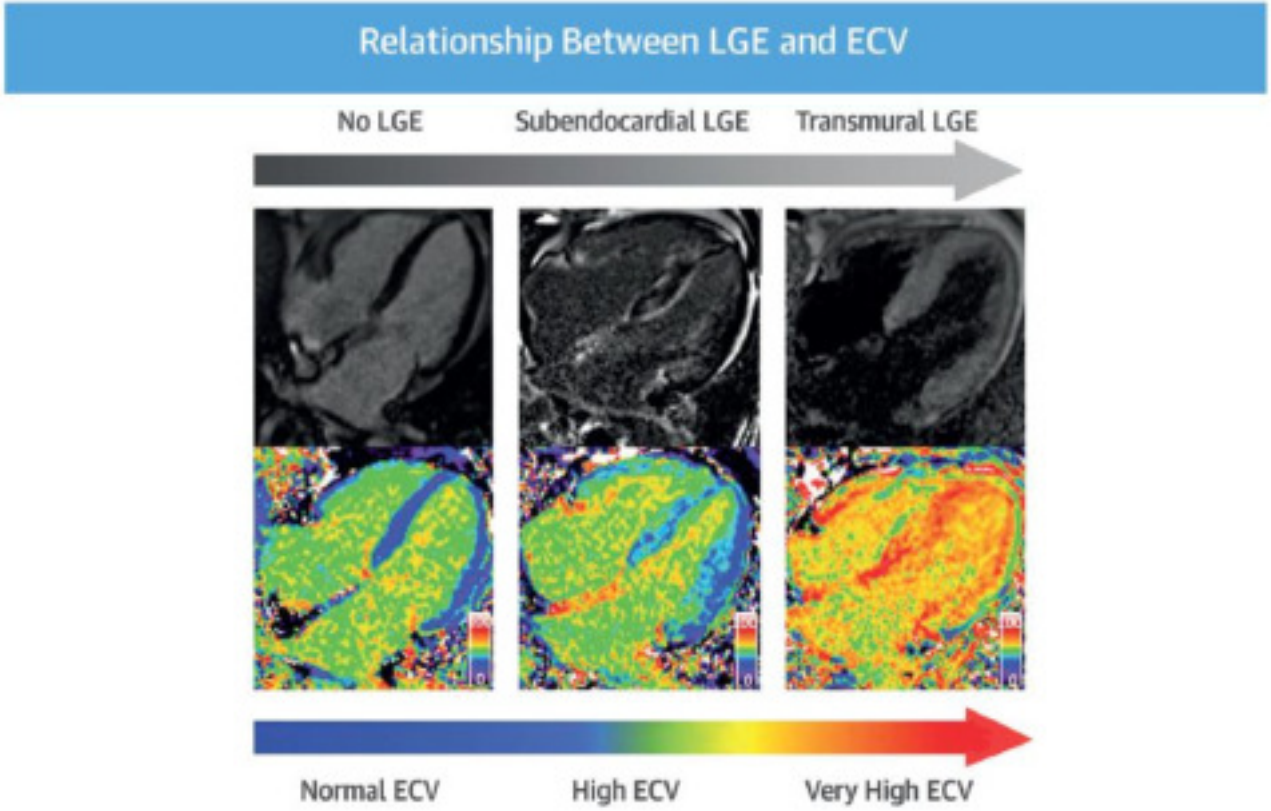
Hôpitaux de Toulouse

El-Am EA, *J Am Coll Cardiol* 2019;73:589-97

FOLLOW-UP

Hôpitaux de Toulouse

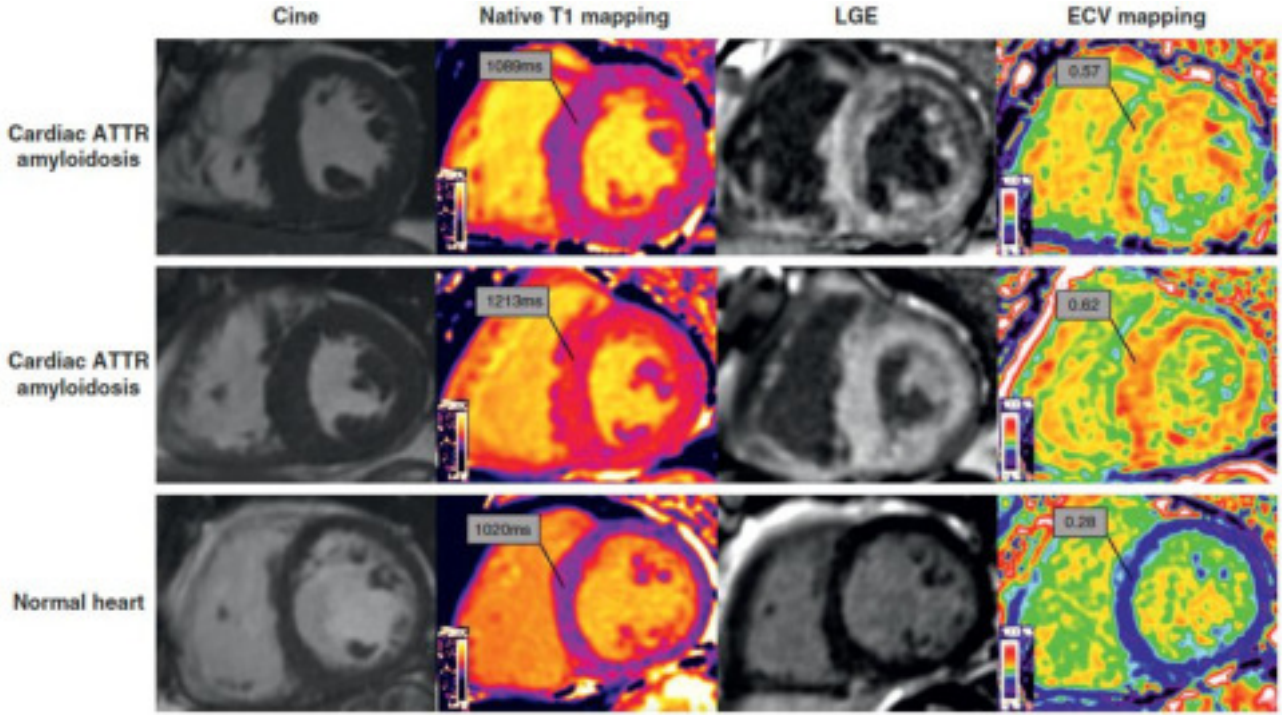
CARDIAC MRI



Hôpitaux de Toulouse

Martinez-Naharro A, *J Am Coll Cardiol* 2017;70:466-77

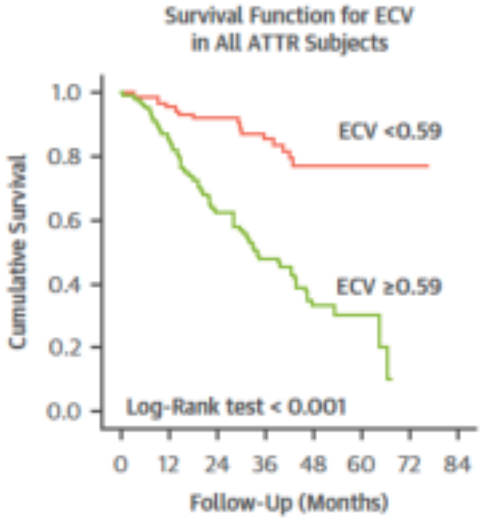
NATIVE T1 & EXTRACELLULAR VOLUME

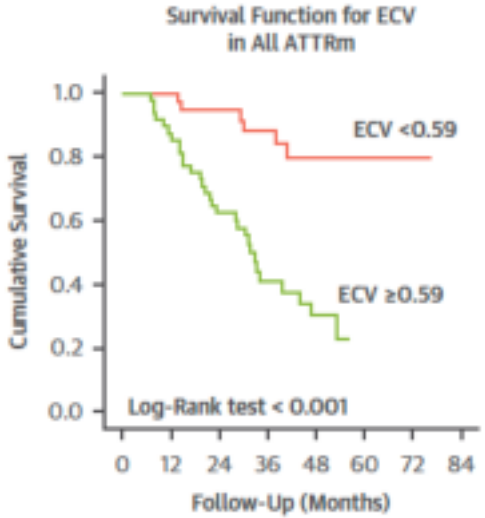


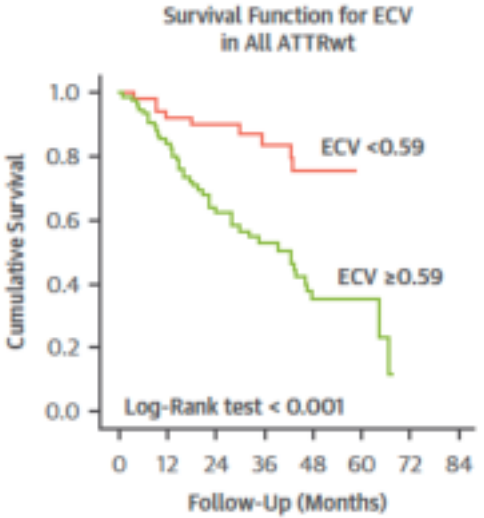
Hôpitaux de Toulouse

Martinez-Naharro A, et al. *JACC Cardiovasc Imaging* 2019;12:810-819

CARDIAC MRI
FOR THE QUANTIFICATION & THE FOLLOW-UP







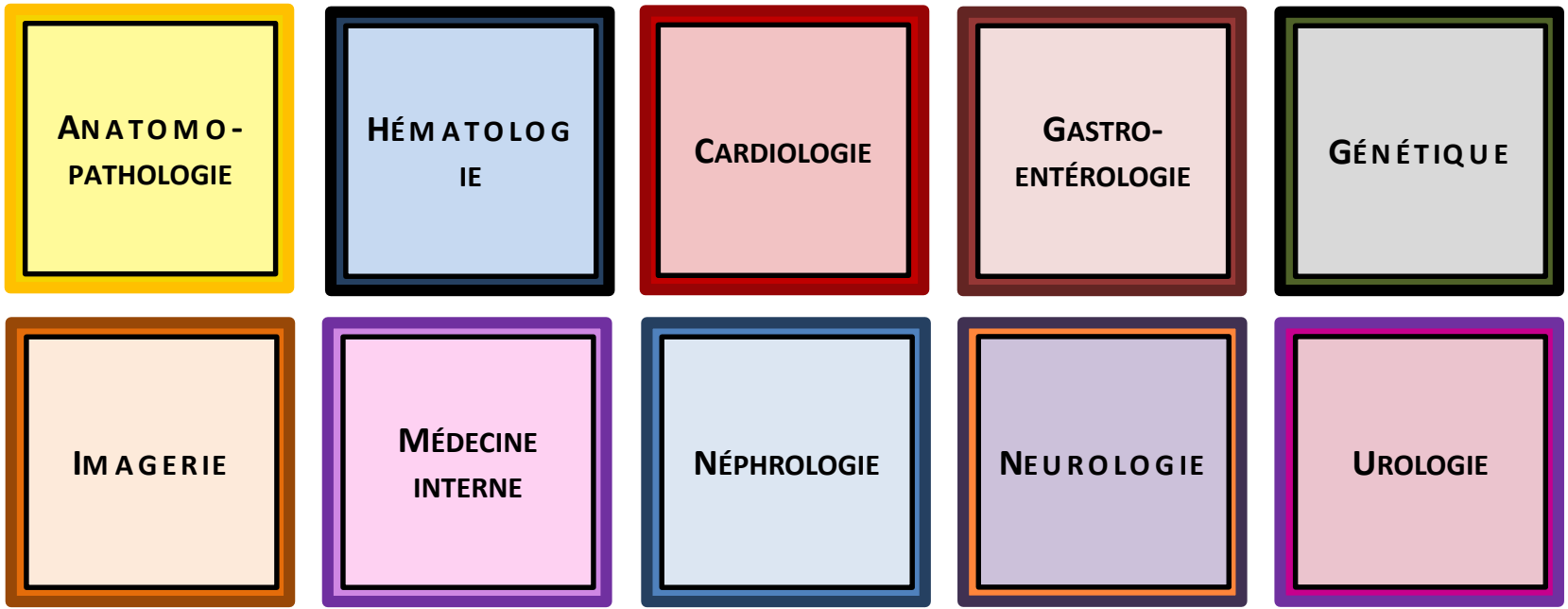
Hôpitaux de Toulouse

Martinez-Naharro A, et al. *JACC Cardiovasc Img* 2019;12:810-819

MANAGEMENT

Hôpitaux de Toulouse

MULTIDISCIPLINARY APPROACH



Hôpitaux de Toulouse

Martinez-Naharro A, *J Am Coll Cardiol* 2017;70:466-77

MULTIDISCIPLINARY APPROACH

CARDIOLOGIE

IMAGEURS
INTERVENTIONNELS
RYTHMOLOGUES

CLINICIENS

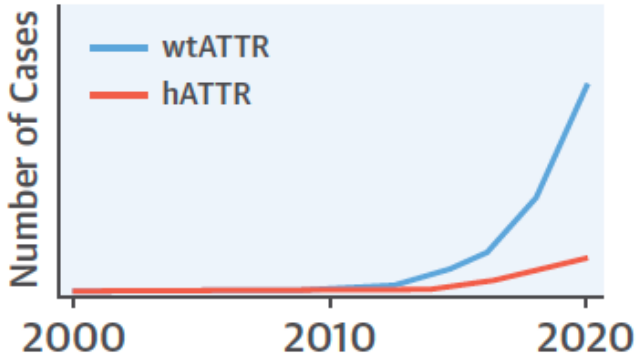
Hôpitaux de Toulouse

TAKE HOME MESSAGES

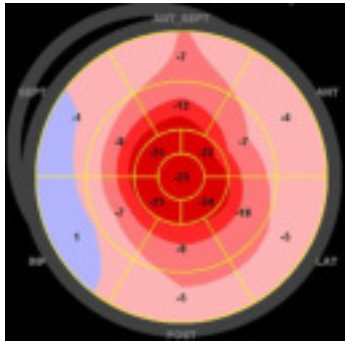
Hôpitaux de Toulouse

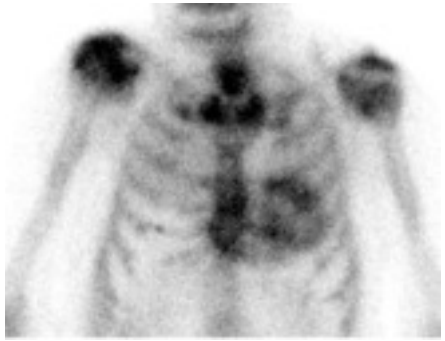
TAKE HOME MESSAGES

Recognition of ATTR-CM



Noninvasive- Imaging

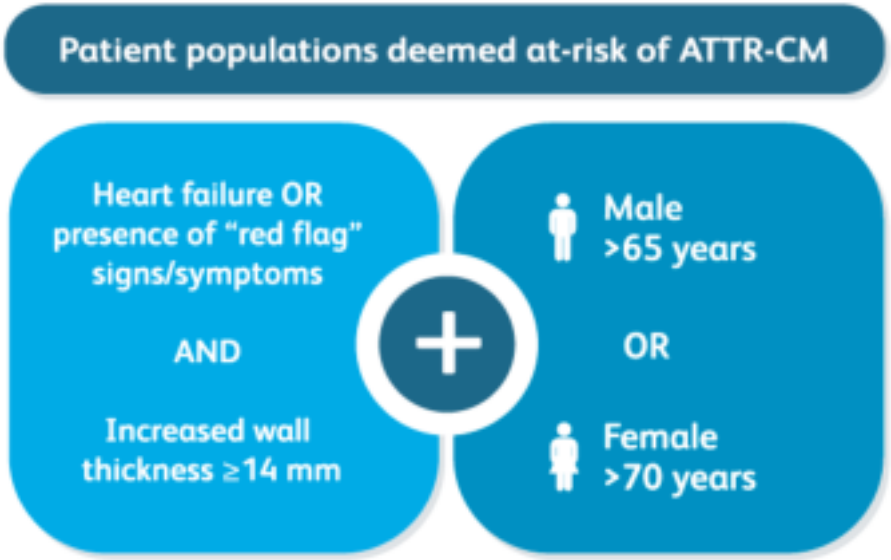




Hôpitaux de Toulouse

Ruberg FL, et al. *J Am Coll Cardiol* 2019;73:2872–91

TAKE HOME MESSAGES



Hôpitaux de Toulouse

Witteles RM, et al. *J Am Coll Cardiol HF*. 2019;7:709-16

Diastolic Heart Failure

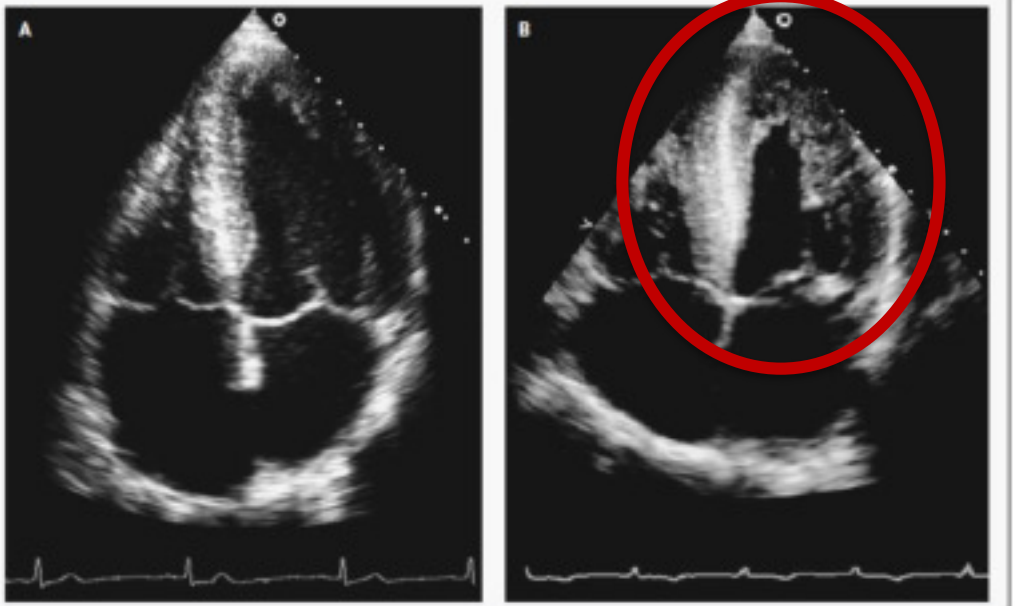


Figure 1. Echocardiographic Images in a Normal Person (Panel A) and the Patient with Diastolic Heart Failure (Panel B). The patient with diastolic heart failure has a thickened left ventricular wall and a normal left chamber volume.

Hôpitaux de Toulouse

Aurigemma GP, et al. *N Engl J Med* 2004;351:1097-105

TTR02-FRA-00174 – Décembre 2020

Hôpitaux de Toulouse