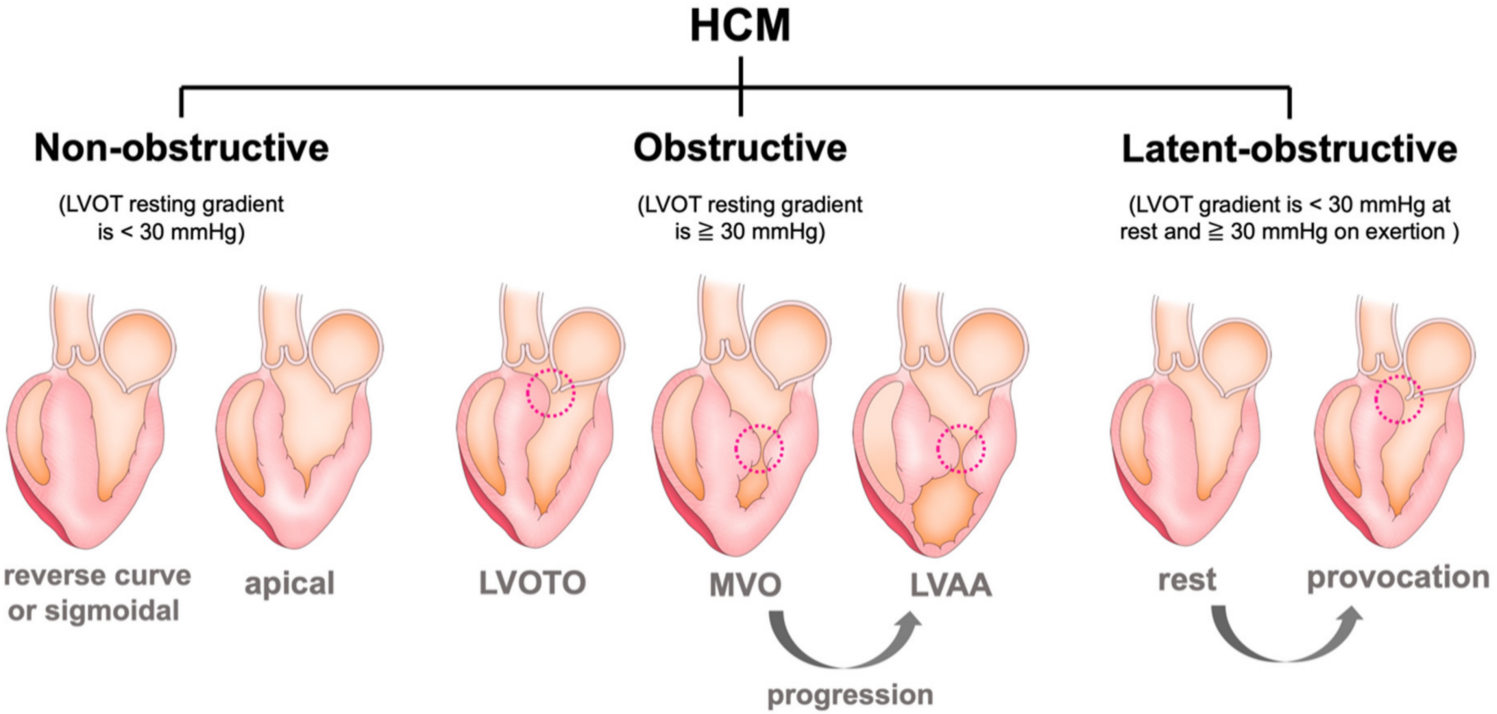
NOUVEAUX TRAITEMENTS DES CMH

Olivier LAIREZ
Centre hospitalier universitaire de Toulouse

AVANT-PROPOS

Hôpitaux de Toulouse

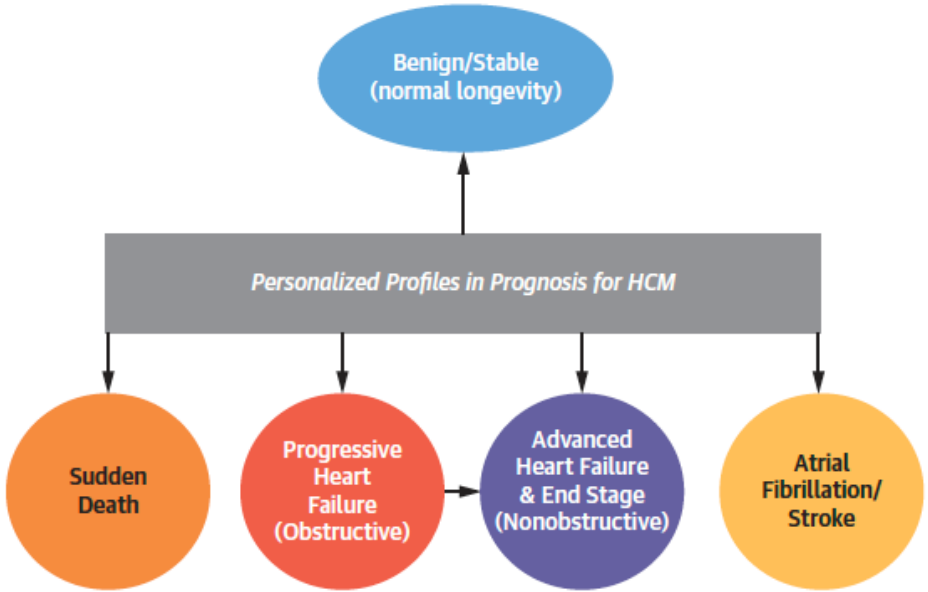
LES CMH

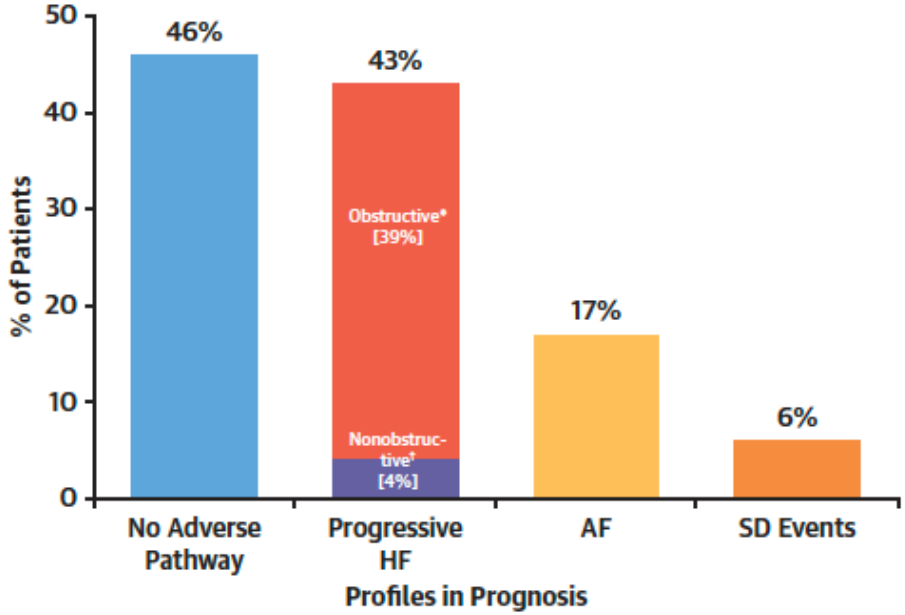


Hôpitaux de Toulouse

Kitai T, et al. *J Cardiovasc Dev Dis.* 2022;9:169

PROFILS & RISQUES DES CMH

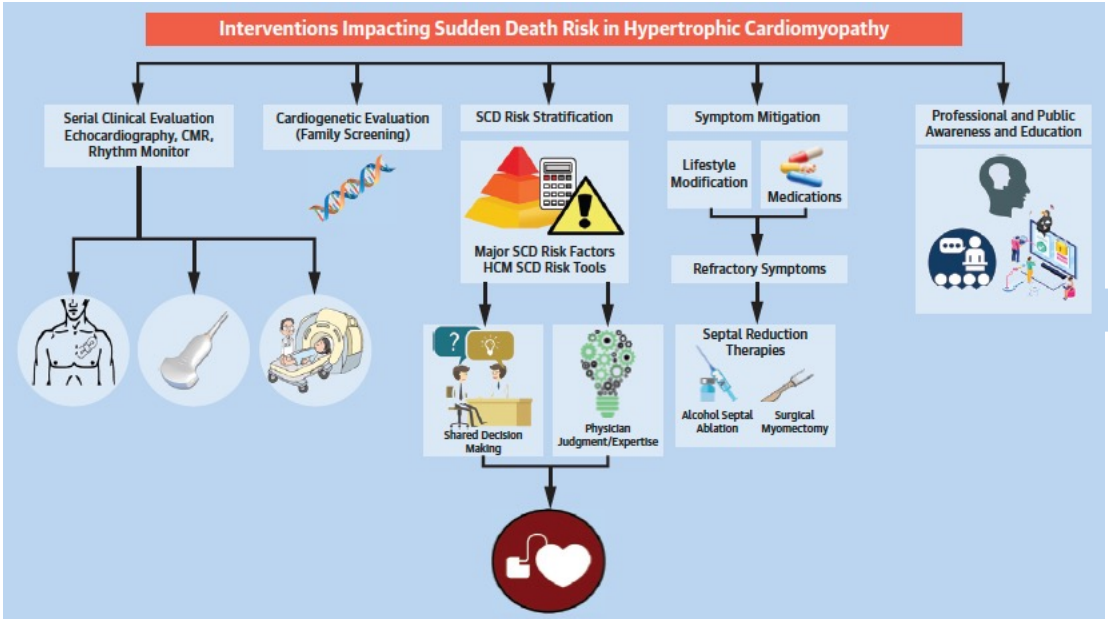


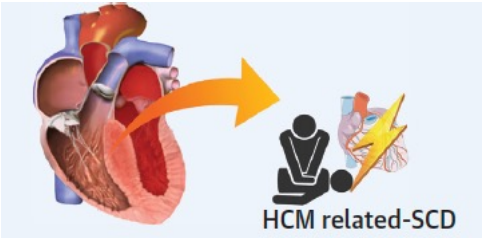


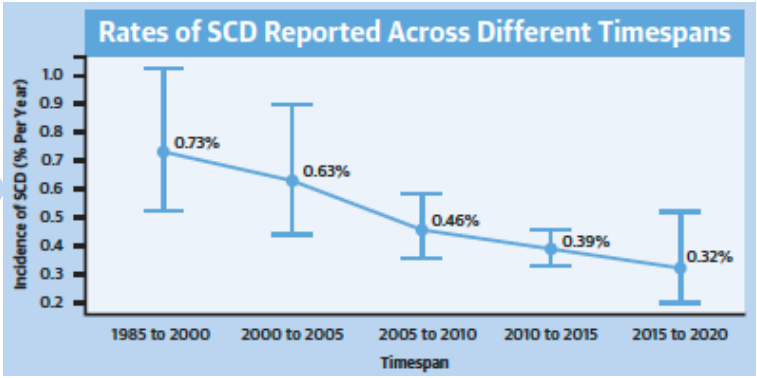
Hôpitaux de Toulouse

Maron BJ et al, *J Am Coll Cardiol.* 2022;79:372–389

PRÉVENTION DE LA MORT SUBITE





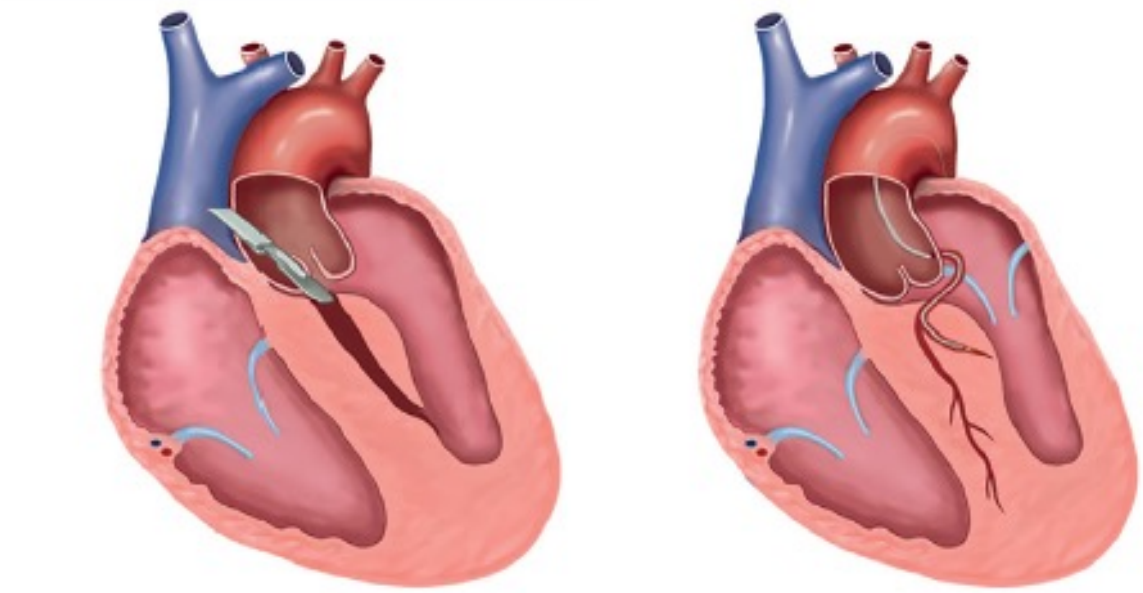


Hôpitaux de Toulouse

Abdelfattah OM, et al. *J Am Coll Cardiol EP*. 2022;8:1417–1427

APPROCHE MÉCANISTIQUE

TRAITEMENT MÉCANIQUE DE L'OBSTRUCTION

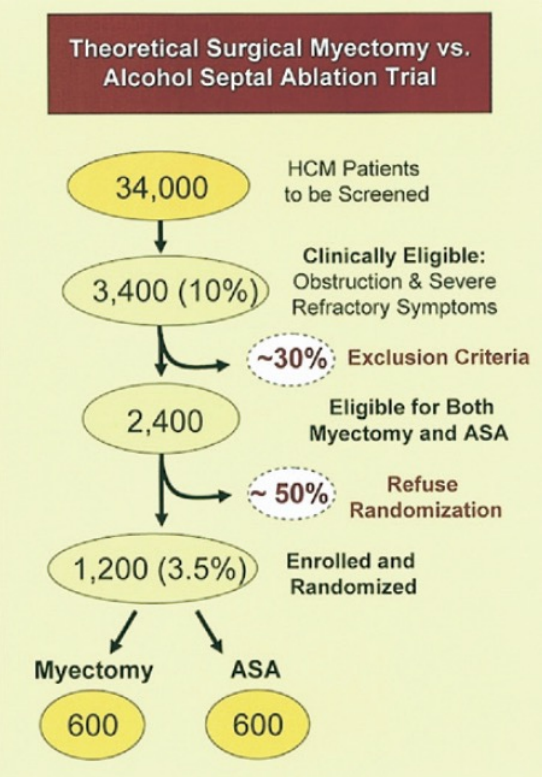


Myomectomie **Alcoolisation septale**

Hôpitaux de Toulouse

Mentias A, et al. *J Am Coll Cardiol*. 2023;81:105–115

UN ESSAI RANDOMISÉ POUR LES CMHO



Conclusions and Future Perspectives

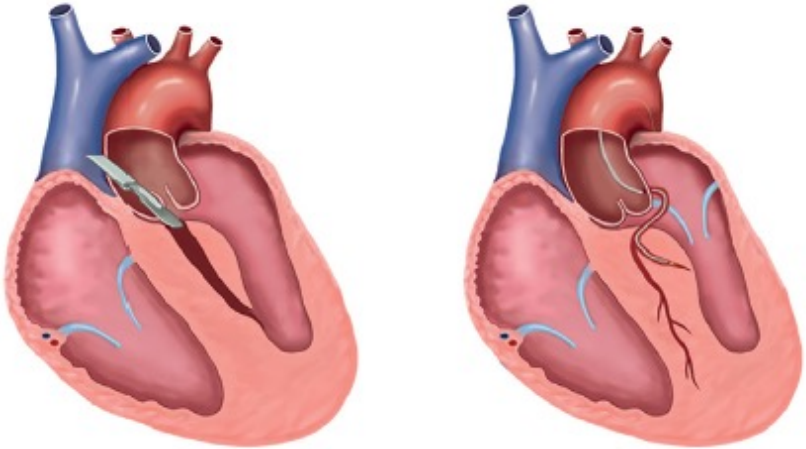
An adequately powered randomized trial comparing long-term benefits of myectomy and ASA in severely symptomatic patients with obstructive HCM is not feasible and unlikely to be undertaken at any time. Alternative strategies would include carefully conducted prospective, non-randomized studies assessing the long-term clinical outcome associated with both procedures, with particular regard to the risk of late sudden cardiac death.

Hôpitaux de Toulouse

Olivotto I, et al. *J Am Coll Cardiol.* 2007;50:831-4

Survival After Septal Reduction in Patients >65 Years Old With Obstructive Hypertrophic Cardiomyopathy

Septal Myectomy (SM) N = 3,680	Alcohol Septal Ablation (ASA) N = 1,999

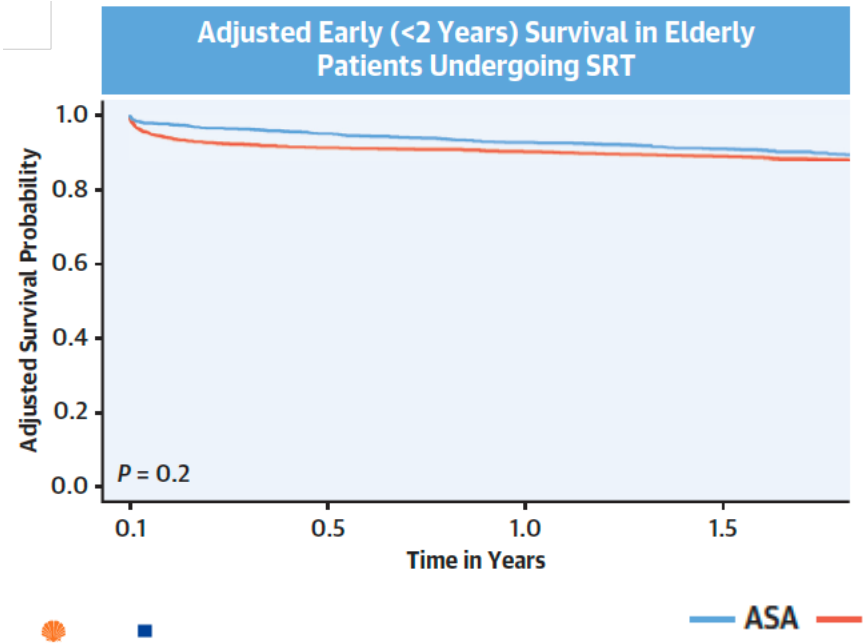


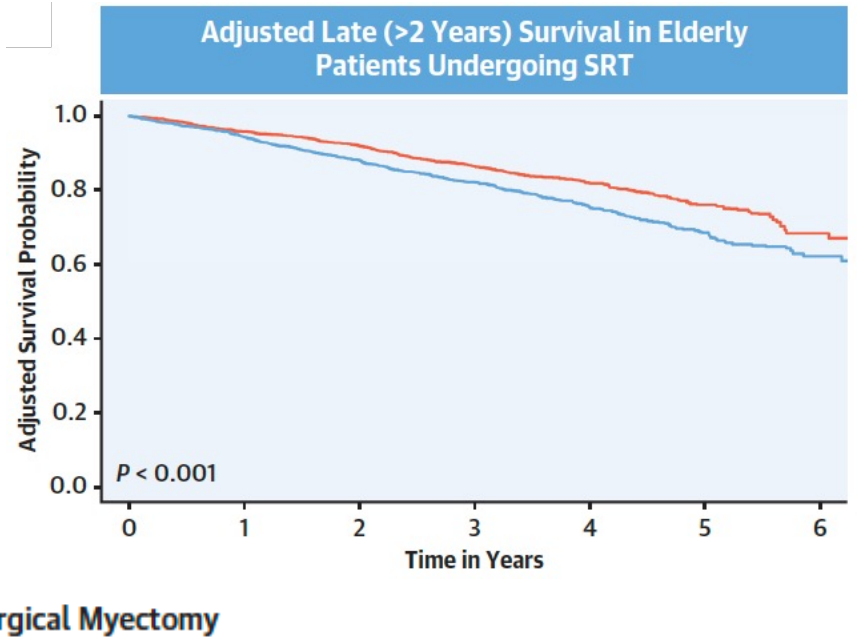
- ↑ Higher complications up to 3 months following SM vs ASA
- ↓ Need for redo SRT after SM vs ASA (HR: 0.10, 95% CI: 0.0607-0.1915, *P < 0.001*)
- ↓ Both SRT reduced HF readmission burden

Hôpitaux de Toulouse

Mentias A, et al. *J Am Coll Cardiol*. 2023;81:105–115

Survival After Septal Reduction in Patients >65 Years Old With Obstructive Hypertrophic Cardiomyopathy





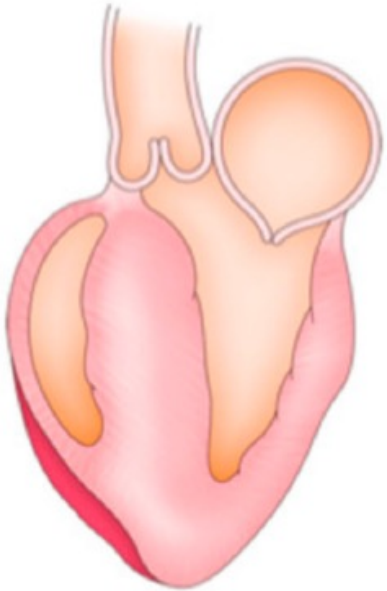
ASA — Surgical Myectomy

Hôpitaux de Toulouse

Mentias A, et al. *J Am Coll Cardiol*. 2023;81:105–115

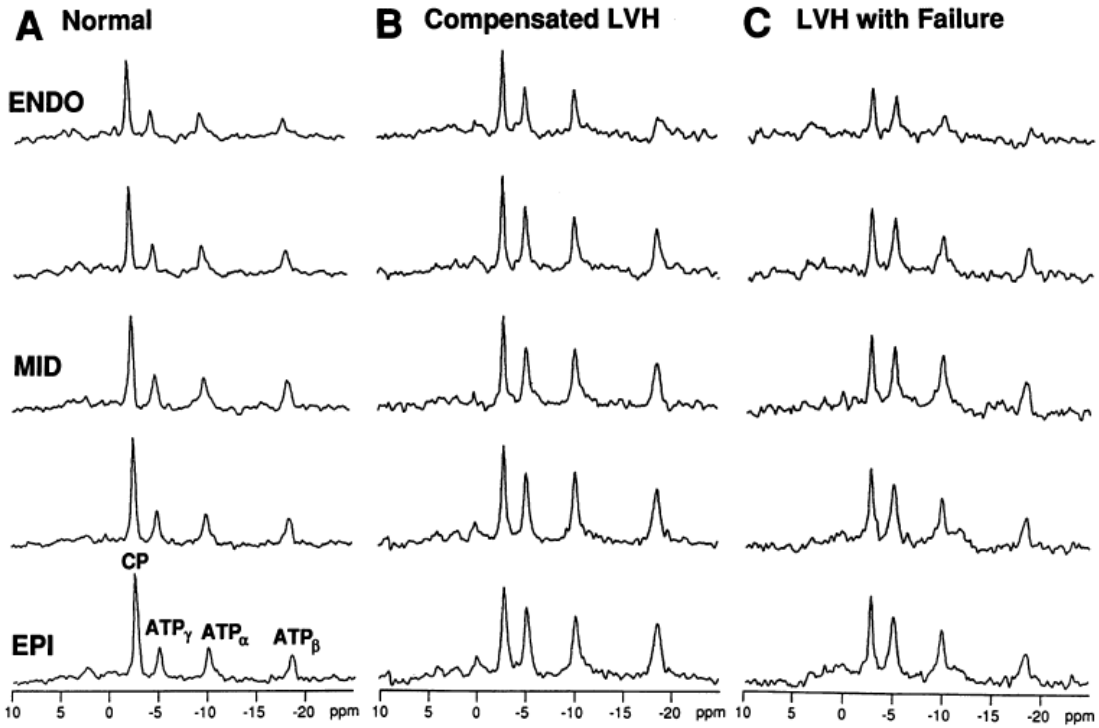
APPROCHE PHÉNOTYPIQUE

Approche phénotypique



Hypertrophie ventriculaire gauche

SPECTROSCOPIE PAR RÉSONNANCE DU PHOSPHORE



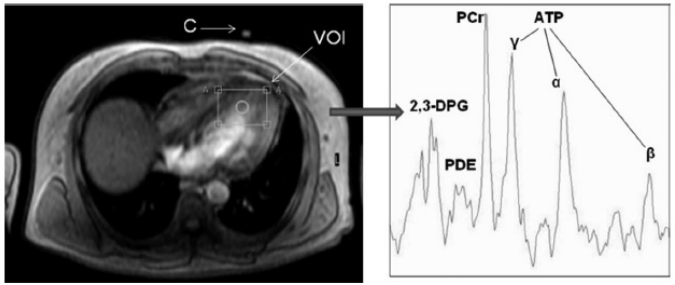
Hôpitaux de Toulouse

Zhang J, et al. *J Clin Invest.* 1993;92:993-1003

Metabolic Modulator Perhexiline Corrects Energy Deficiency and Improves Exercise Capacity in Symptomatic Hypertrophic Cardiomyopathy

Perhexiline

Modulateur métabolique, inhibiteur de la carnitine palmitoyltransférase 1.

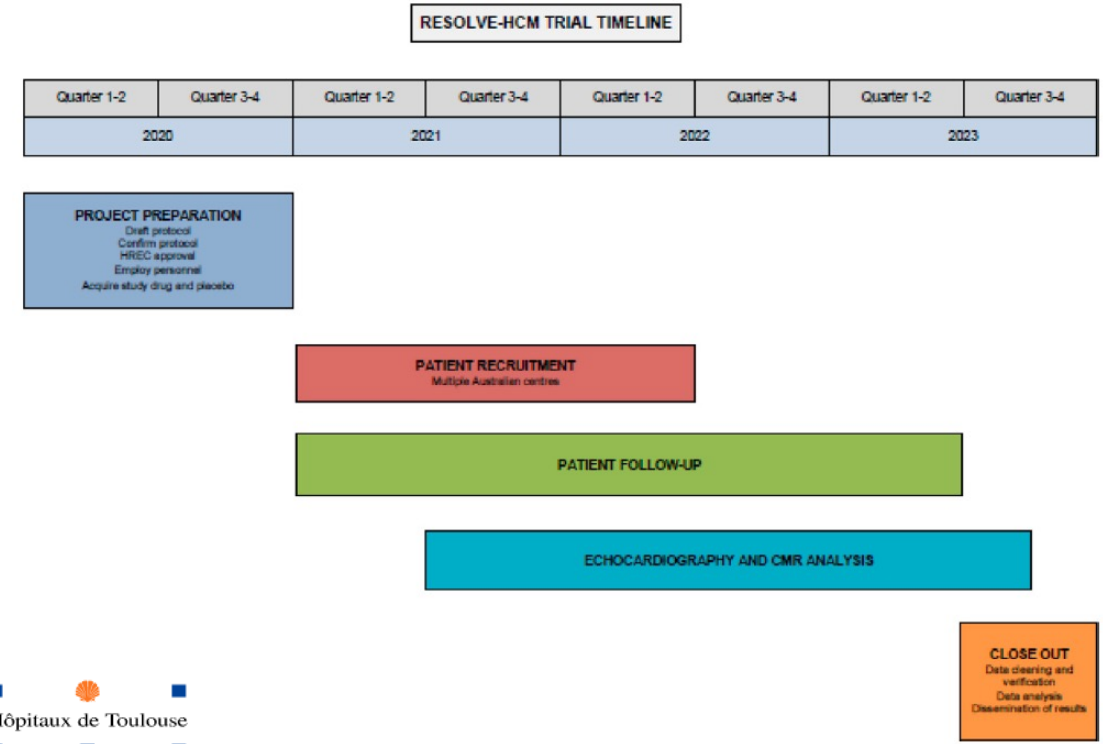


Parameter	Perhexiline Group		Placebo Group		
	Baseline	Follow-Up	Baseline	Follow-Up	*P*, ANCOVA
Metabolic exercise parameters					
Peak $\dot{V}o_2$, mL · kg^{-1} · min^{-1}	22.2±0.2	24.3±0.2	23.6±0.3	22.3±0.2	0.003*
$\dot{V}o_2$-AT, mL · kg^{-1} · min^{-1}	16±0.11	15±0.1	17±0.23	16±0.15	0.85
$\dot{V}E/\dot{V}co_2$ slope	30±0.12	32±0.12	30±0.23	32±0.3	0.99
Myocardial energetic status					
PCr/ATP ratio	1.27±0.02	1.73±0.02	1.29±0.01	1.23±0.01	0.003*
Symptomatic status					
MLHFQ score	36±0.94	28±0.75	37±1.21	34±1.25	<0.001*
LV systolic function (at rest and during exercise), %†					
Resting EF	68±0.51	67±0.49	66±0.46	65±0.42	0.22
Exercise EF	72±0.75	69±0.45	73±0.56	75±0.39	0.07

Hôpitaux de Toulouse

Abozguia K, *Circulation*. 2010;122:1562-9

Randomized controlled trial of perhexiline on regression of left ventricular hypertrophy in patients with symptomatic hypertrophic cardiomyopathy (RESOLVE-HCM trial)



ClinicalTrials.gov Identifier: NCT04426578

Recruitment Status : Recruiting
First Posted : June 11, 2020
Last Update Posted : March 11, 2021

Hôpitaux de Toulouse

Ananthakrishna R, et al. *Am Heart J*. 2021;240:101-113

ÉTUDES EN COURS

Trientine

Chélateur sélectif du cuivre

(Effets sur la réponse hypertrophique chez l'animal)

The Efficacy and Mechanism of Trientine in Patients With Hypertrophic Cardiomyopathy (TEMPEST)

ClinicalTrials.gov Identifier: NCT04706429

Recruitment Status : Recruiting
First Posted : January 12, 2021
Last Update Posted : March 17, 2021

Éléclazine

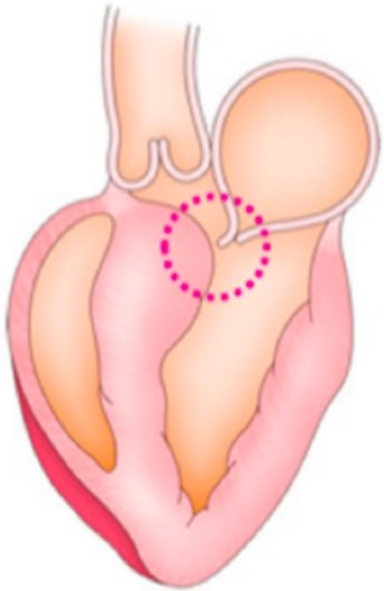
Inhibiteur sélectif du courant sodique tardif

Effect of Eleclazine (GS-6615) on Exercise Capacity in Subjects With Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM)

ClinicalTrials.gov Identifier: NCT02291237

Recruitment Status : Terminated
First Posted : November 14, 2014
Results First Posted : March 22, 2018
Last Update Posted : September 24, 2018

APPROCHE PHÉNOTYPIQUE



Cardiomyopathie hypertrophique obstructive

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy

Recommendations on medical treatment of LVOTO

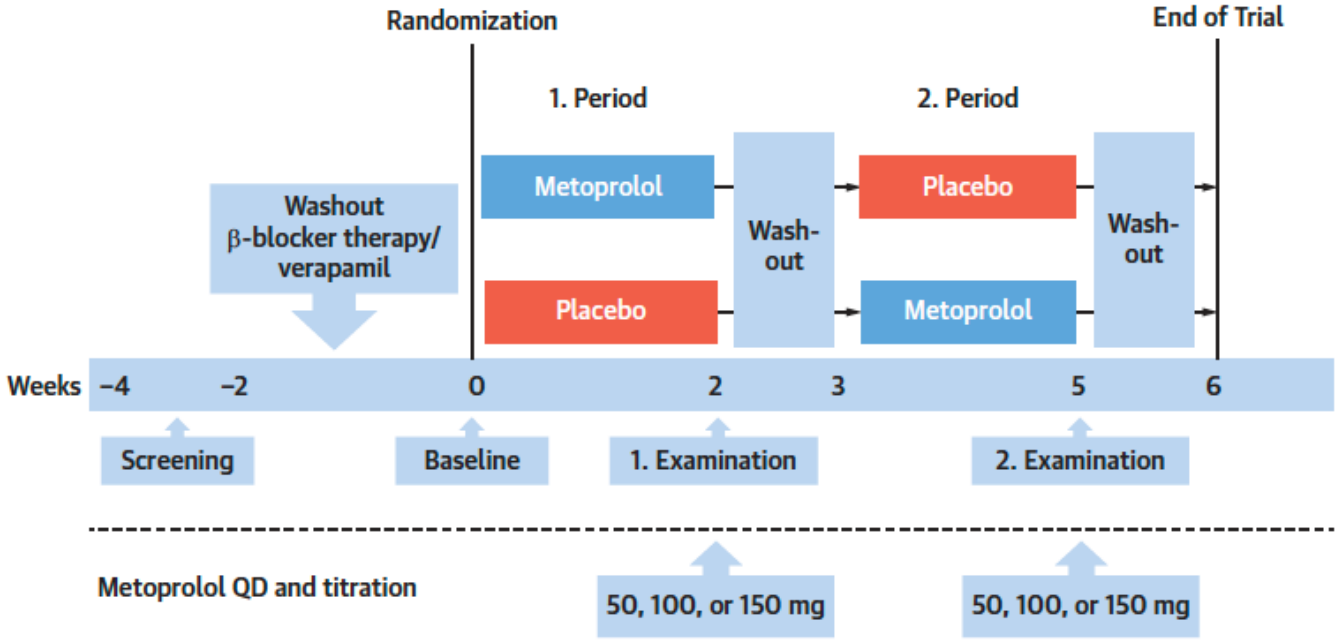
Recommendations	Class[a]	Level[b]
Non-vasodilating ß-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provoked[d] LVOTO.	I	B
Verapamil, titrated to maximum tolerated dose, is recommended to improve symptoms in patients with resting or provoked[d] LVOTO, who are intolerant or have contraindications to ß-blockers.	I	B
Disopyramide, titrated to maximum tolerated dose,[e] is recommended in addition to a ß-blocker (or, if this is not possible, with verapamil) to improve symptoms in patients with resting or provoked[d] LVOTO.	I	B

Recommendations	Class[a]	Level[b]
Disopyramide, titrated to maximum tolerated dose,[e] may be considered as monotherapy to improve symptoms in patients with resting or provoked[d] LVOTO (exercise or Valsalva manoeuvre) taking caution in patients with—or prone to—AF, in whom it can increase ventricular rate response.	IIb	C

Hôpitaux de Toulouse

Elliott PM , et al. *Eur Heart J* 2014;35:2733–2779

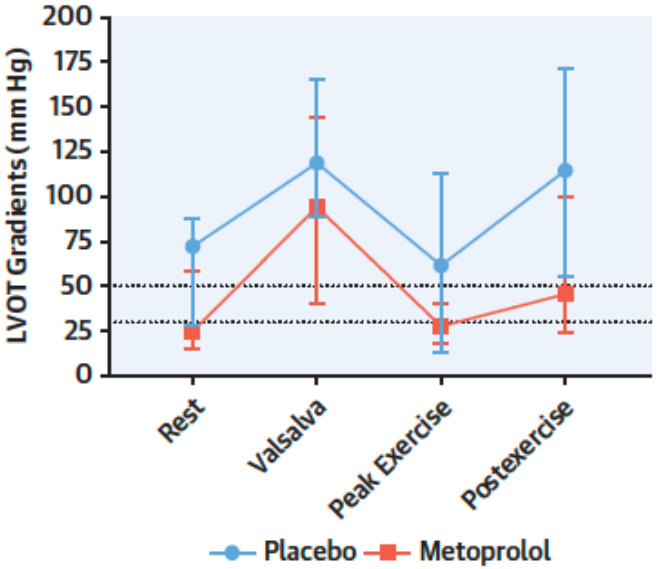
Randomized Trial of Metoprolol in Patients With Obstructive Hypertrophic Cardiomyopathy

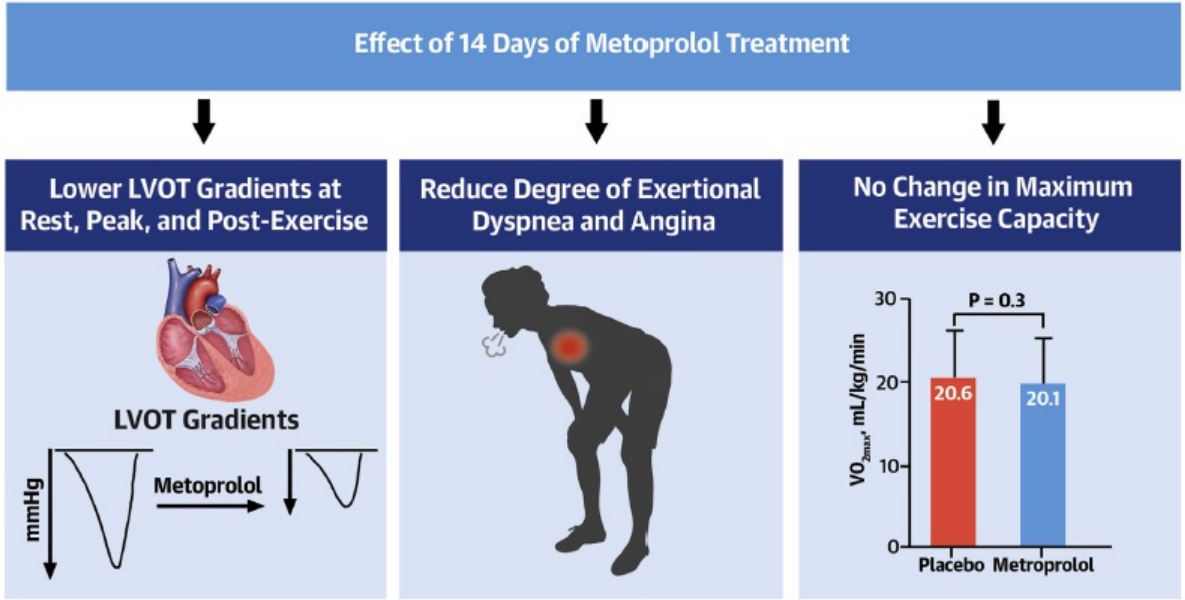


Hôpitaux de Toulouse

Dybro AM, et al. *J Am Coll Cardiol.* 2021;78:2505-2517

Randomized Trial of Metoprolol in Patients With Obstructive Hypertrophic Cardiomyopathy

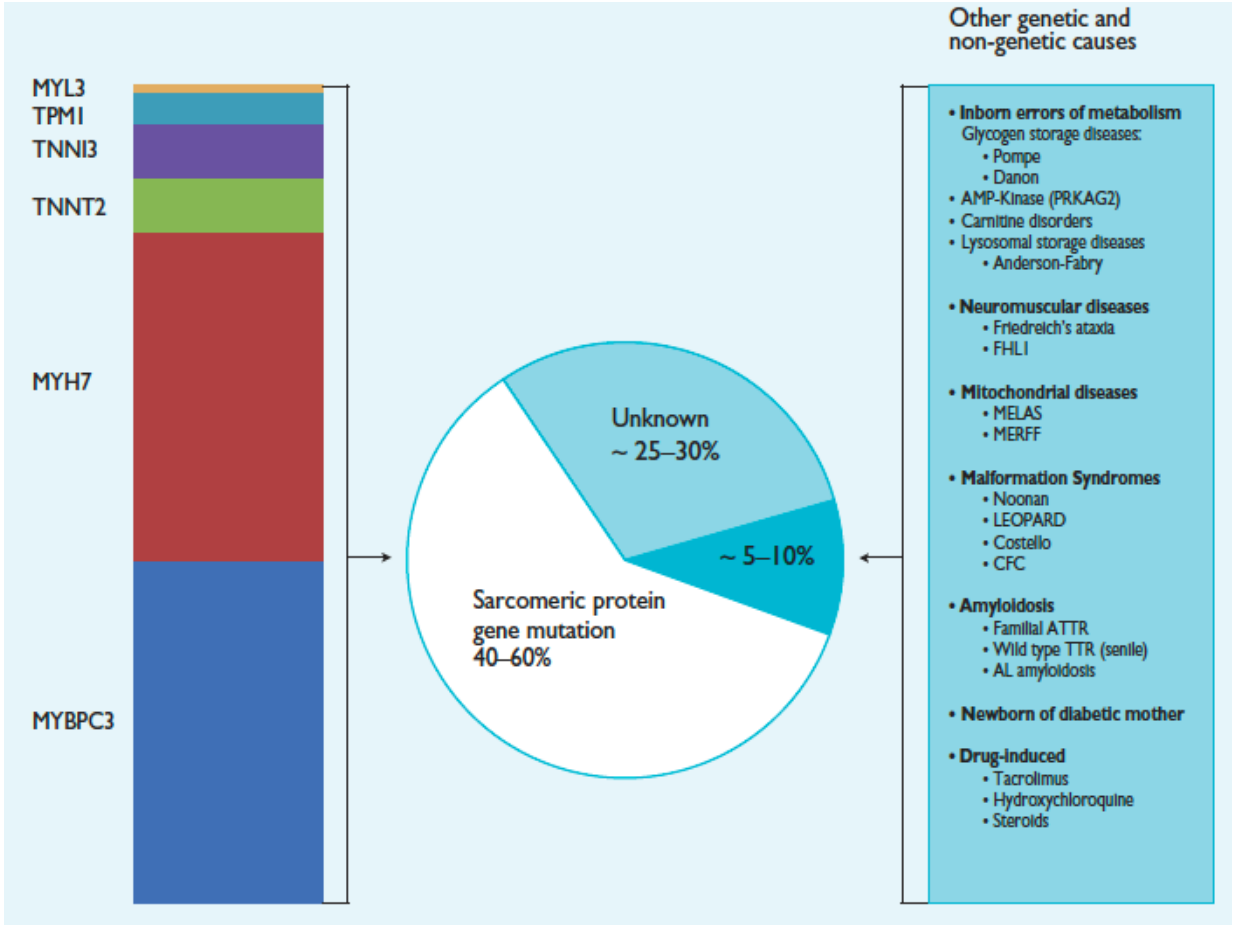




Hôpitaux de Toulouse

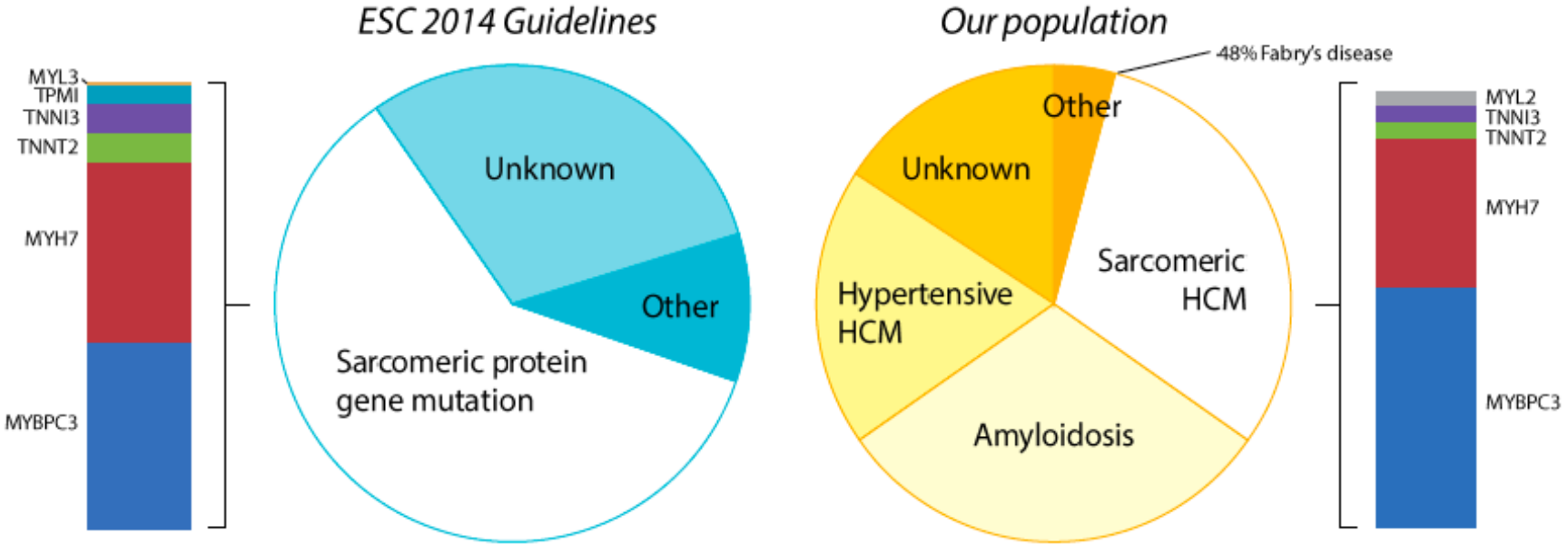
Dybro AM, et al. *J Am Coll Cardiol.* 2021;78:2505-2517

APPROCHE ÉTIOLOGIQUE



Hôpitaux de Toulouse

Elliott PM, et al. *Eur Heart J* 2014; 35, 2733–2779



Hôpitaux de Toulouse

Beneyto M, et al. *Open Heart*. 2021;8:e001462

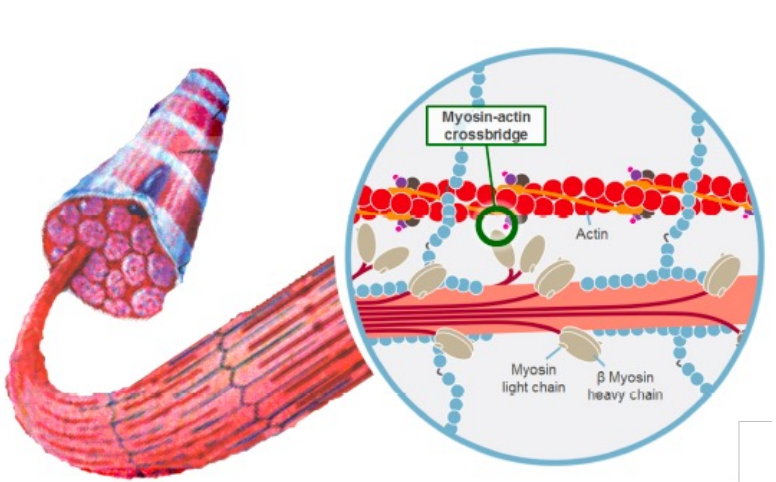
CMH SARCOMÉRIQUES

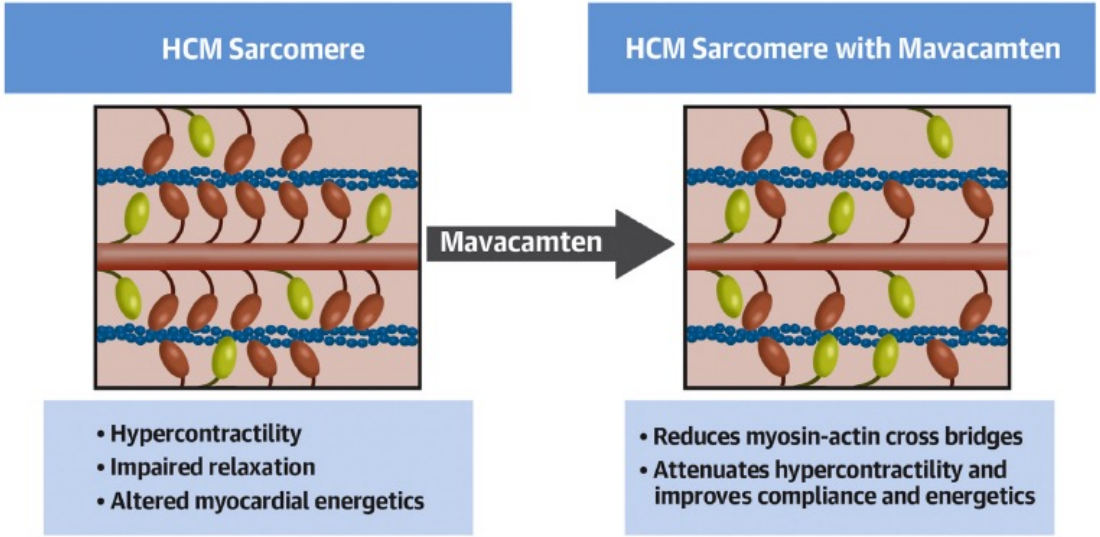
Hôpitaux de Toulouse

CMH OBSTRUCTIVE

Mavacamten

Modulateur de la β-myosine cardiaque réduisant l'hypercontractilité myocardique





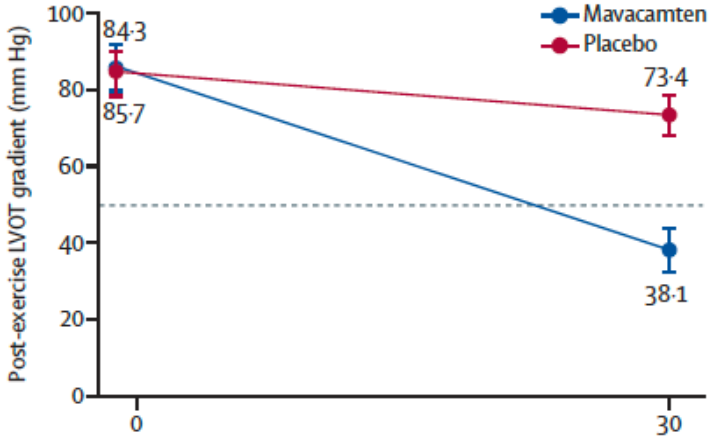
Hôpitaux de Toulouse

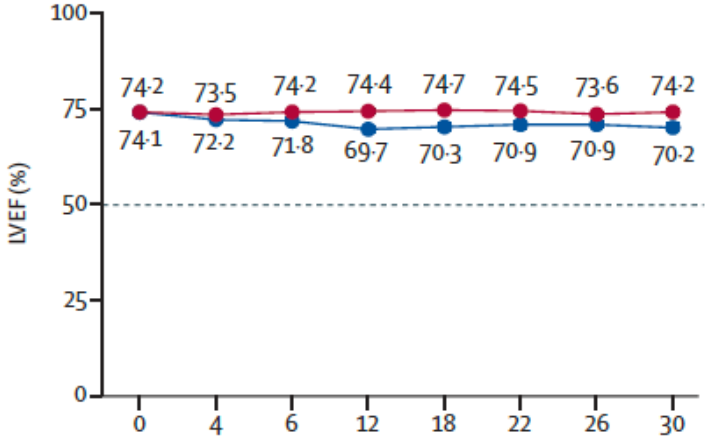
Vaughan T, et al. *Eur J Heart Fail.* 2020;22:228-240

Desai MY, et al. *J Am Coll Cardiol*. 2022;80:95–108

Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

251 patients symptomatiques (NYHA II ou III) avec une obstruction ≥ 50 mmHg.
Critère principal : augmentation de la VO2max de 1,5 mL/kg/min et amélioration d'une classe NYHA ou augmentation de la VO2max de 3 mL/kg/min sans dégradation de la classe NYHA
Suivi 30 semaines



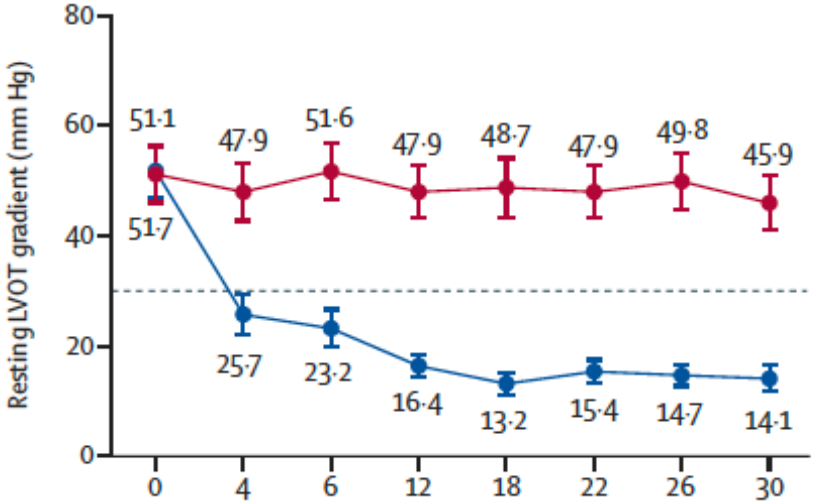


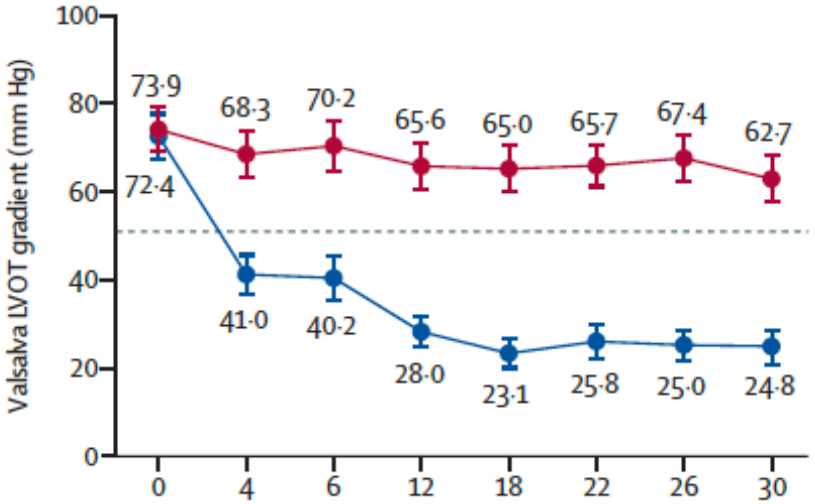
Hôpitaux de Toulouse

Olivotto I, et al. *Lancet.* 2020;396:759-769

Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

37% des patients sous mavacamten contre 17% sous placebo ont atteint le critère primaire
(différence +19,4%, IC95% 8,7 to 30,1; p=0,0005)





Hôpitaux de Toulouse

Olivotto I, et al. *Lancet.* 2020;396:759-769

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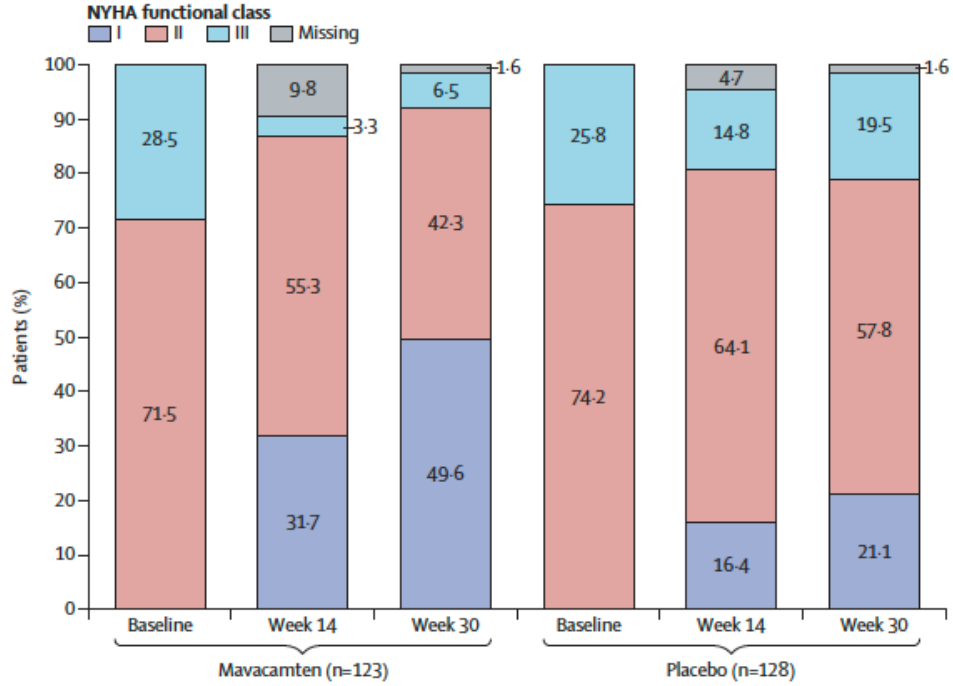
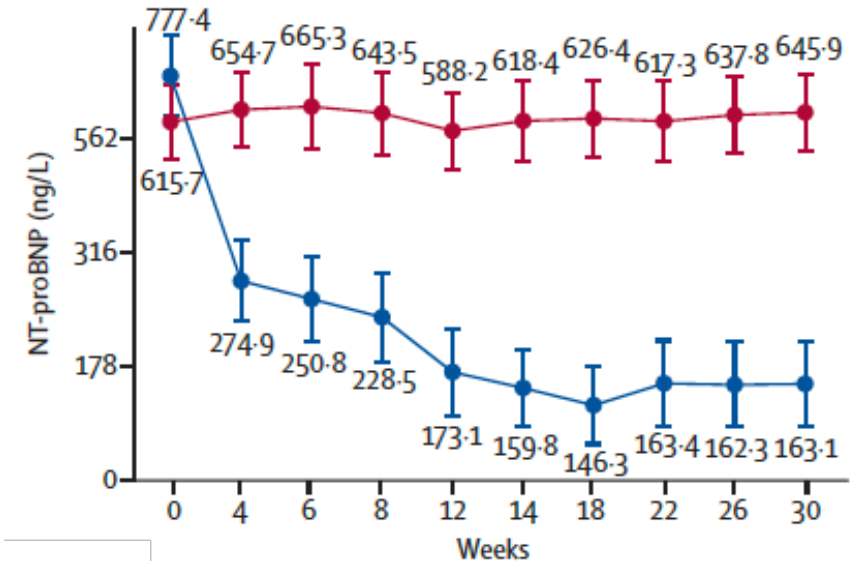
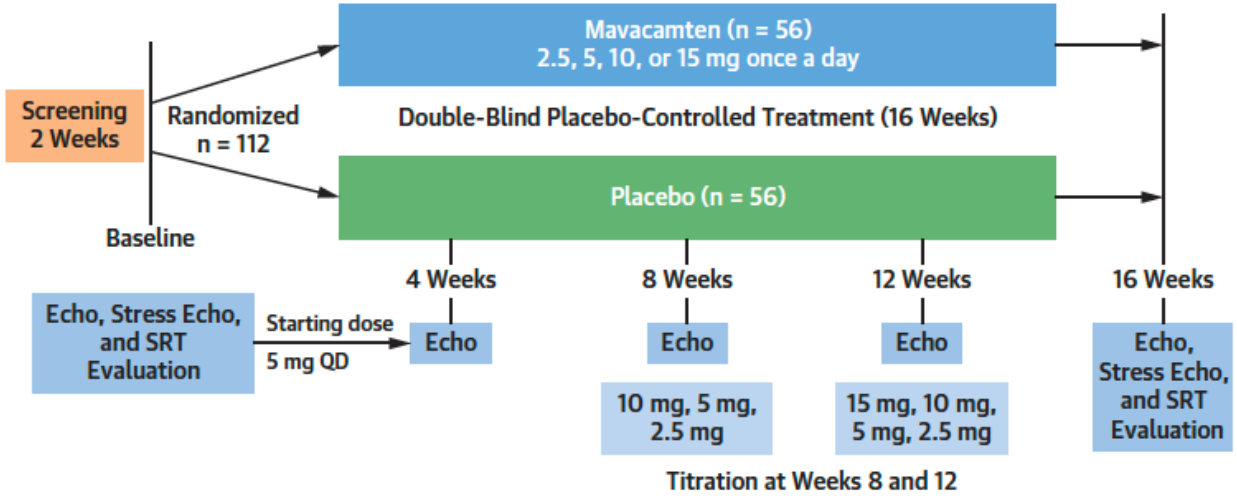


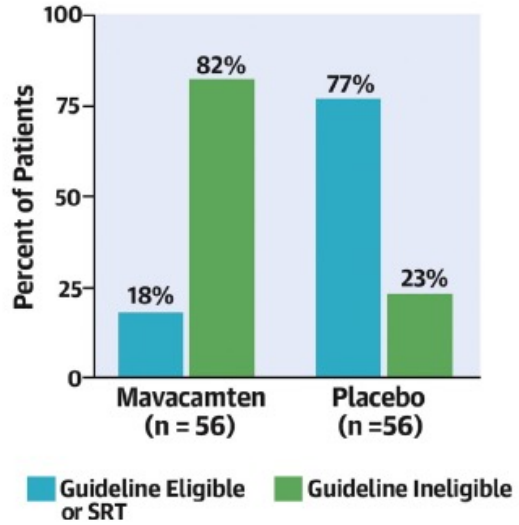


Hôpitaux de Toulouse

Olivotto I, et al. *Lancet.* 2020;396:759-769

Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy



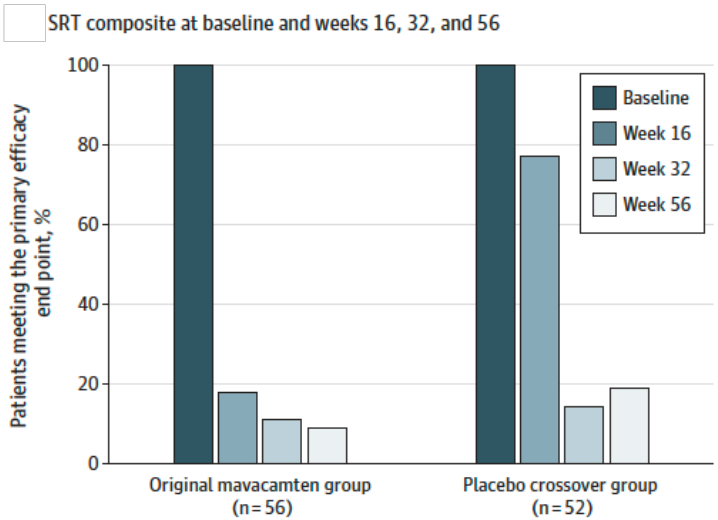


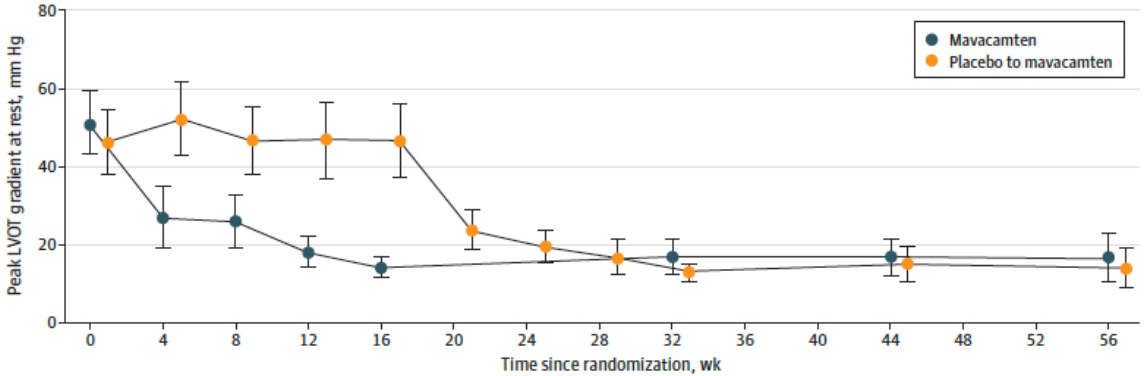
Hôpitaux de Toulouse

Desai MY, et al. *J Am Coll Cardiol*. 2022;80:95–108

Mavacamten in Patients With Hypertrophic Cardiomyopathy Referred for Septal Reduction

Week 56 Results From the VALOR-HCM Randomized Clinical Trial

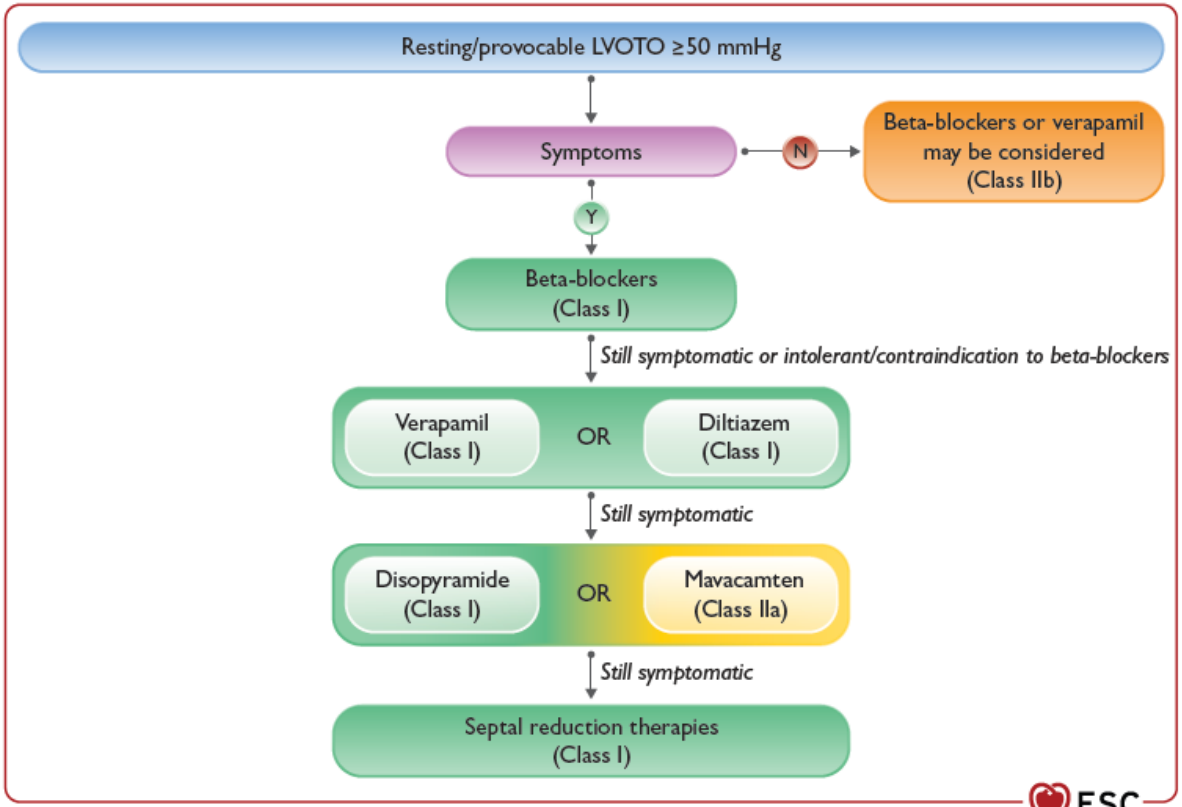




Hôpitaux de Toulouse

Deasi MY et al. *JAMA Cardiol.* 2023;e233342

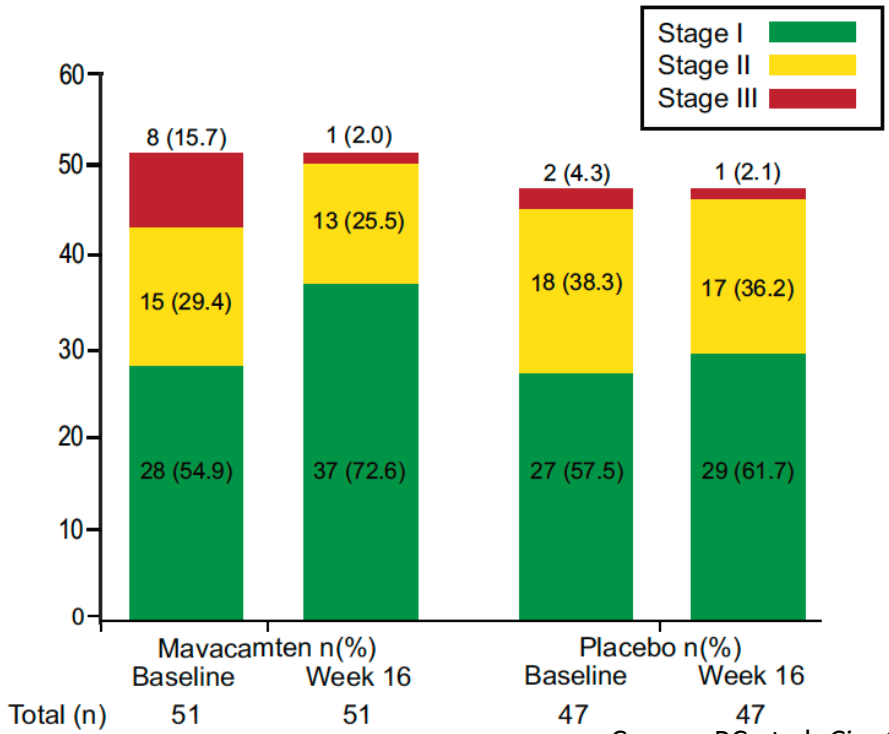
2023 ESC Guidelines for the management of cardiomyopathies



Hôpitaux de Toulouse

Arbelo E, et al. *Eur Heart J.* 2023

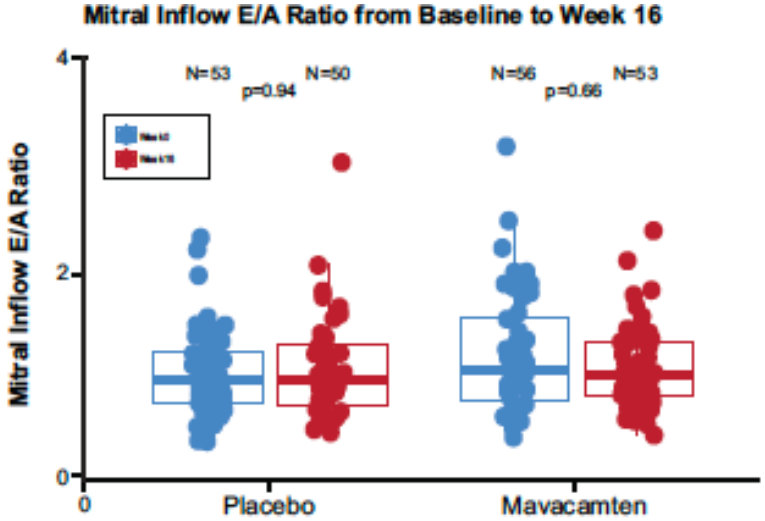
Myosin Inhibition and Left Ventricular Diastolic Function in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy: Insights From the VALOR-HCM Study

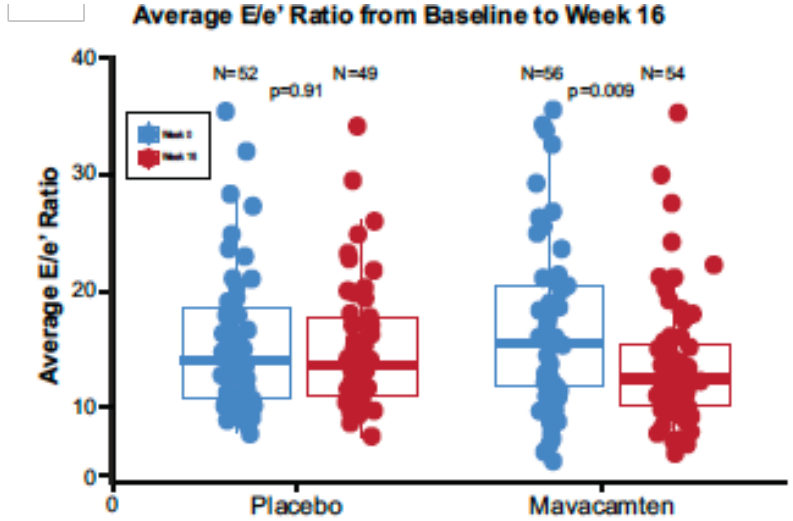


Hôpitaux de Toulouse

Cremer PC et al. *Circ Cardiovasc Imaging.* 2022;15:e014986

Myosin Inhibition and Left Ventricular Diastolic Function in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy: Insights From the VALOR-HCM Study





Hôpitaux de Toulouse

Cremer PC et al. *Circ Cardiovasc Imaging.* 2022;15:e014986

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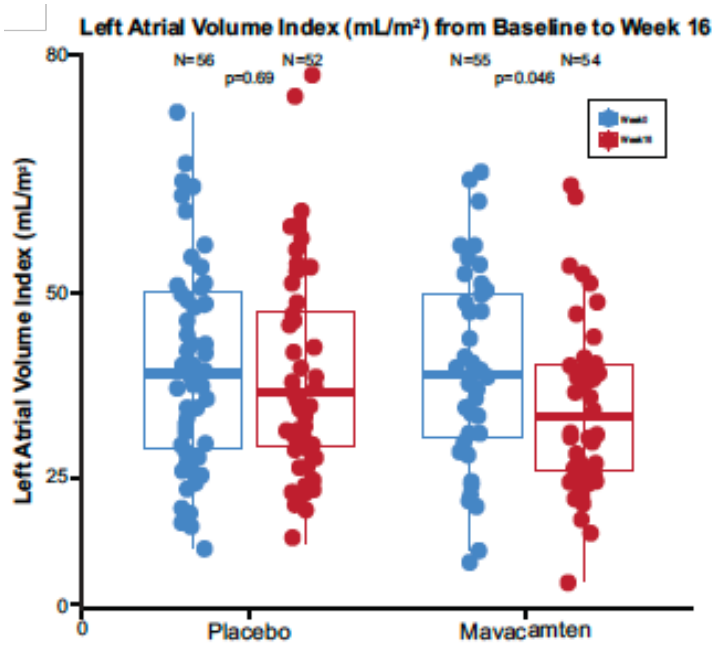
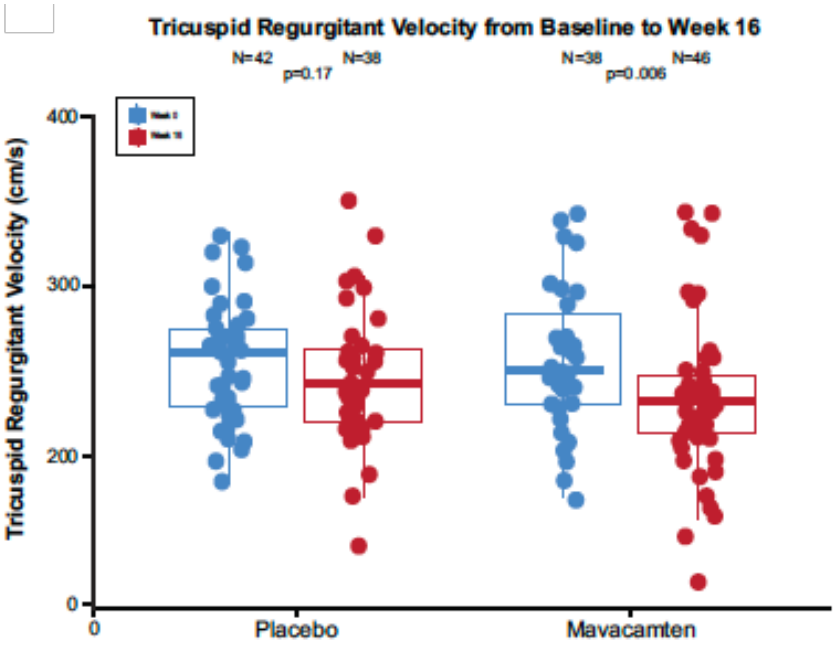
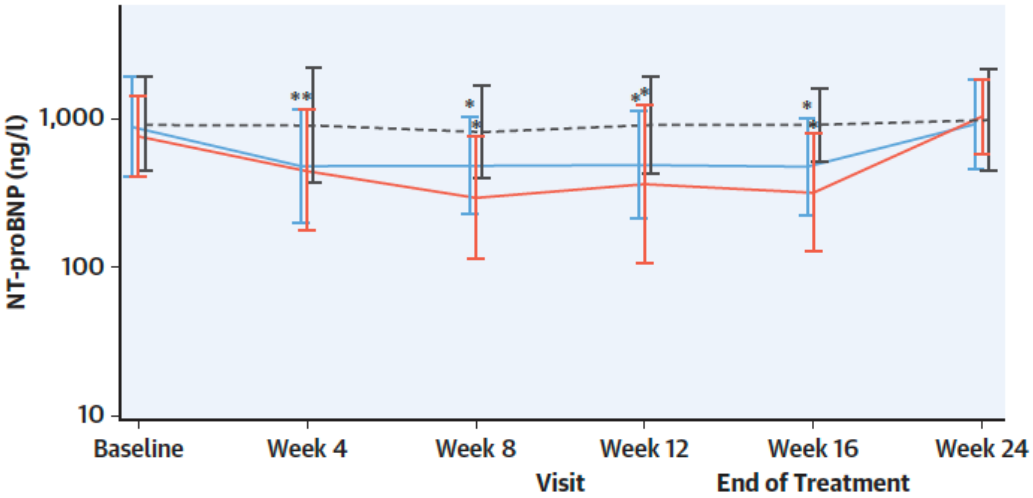


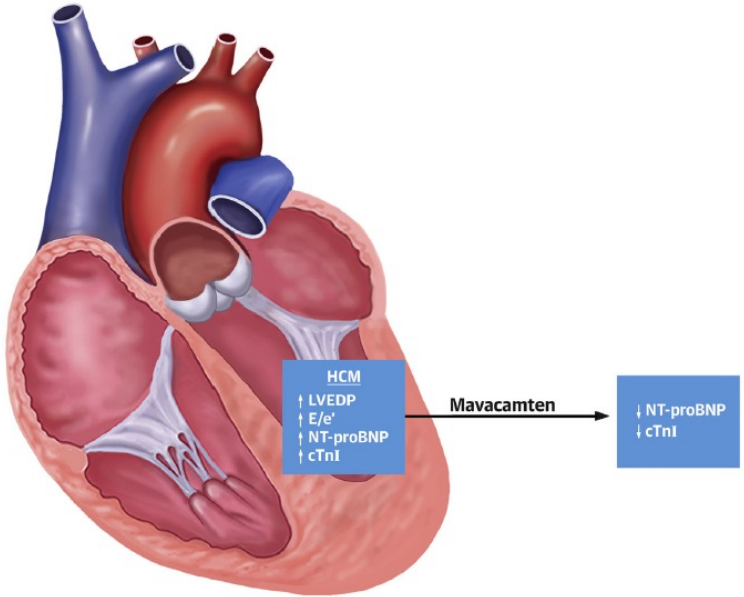


Hôpitaux de Toulouse

Cremer PC et al. *Circ Cardiovasc Imaging.* 2022;15:e014986

Evaluation of Mavacamten in Symptomatic Patients With Nonobstructive Hypertrophic Cardiomyopathy

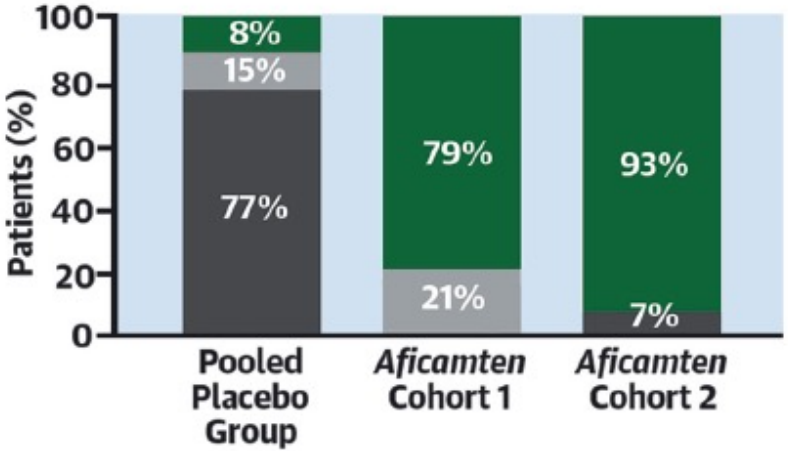


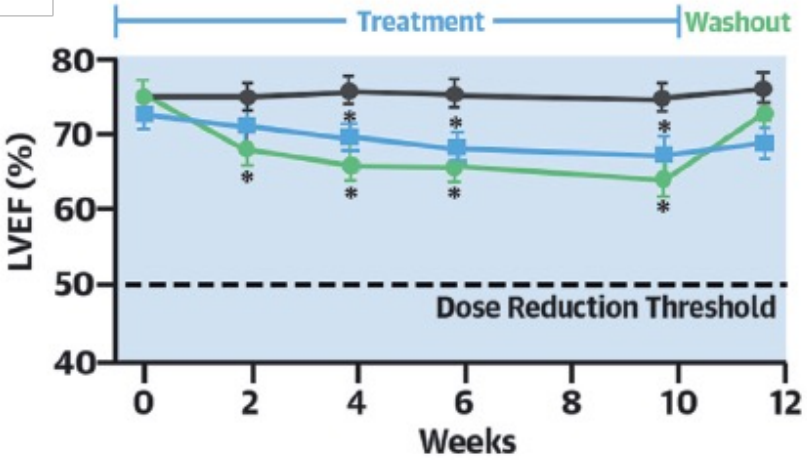


Hôpitaux de Toulouse

Ho C, et al. *J Am Coll Cardiol* 2020;75:2649–60

Phase 2 Study of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy





Panel C Key:

- Complete: Resting LVOT-G <30 + Valsalva LVOT-G <50 mm Hg
- Partial: Resting LVOT-G <30 + Valsalva LVOT-G ≥50 mm Hg
- None: Resting LVOT-G ≥30 + Valsalva LVOT-G ≥50 mm Hg

Panel A, B, and D Key:

- Pooled placebo group (n = 13)
- *Aficamten* cohort 1 (n = 14)
- *Aficamten* cohort 2 (n = 14)

Hôpitaux de Toulouse

Maron MS, et al. *J Am Coll Cardiol* 2023;81:34–45

ÉTUDES EN COURS

Aficamten

Modulateur de la β-myosine cardiaque

CY 6031 Study Will Evaluate the Effects of Treatment With Aficamten (CK-3773274) Over a 24-week Period on Cardiopulmonary Exercise Capacity and Health Status in Patients With Symptomatic oHCM (SEQUOIA-HCM)

ClinicalTrials.gov Identifier: NCT05186818

Recruitment Status : Recruiting
First Posted : January 11, 2022
Last Update Posted : January 9, 2023

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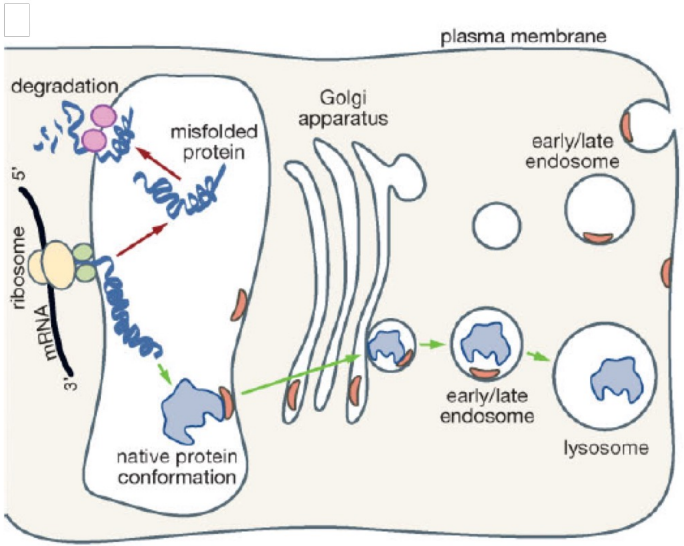
www.clinicaltrials.gov

MALADIE DE FABRY

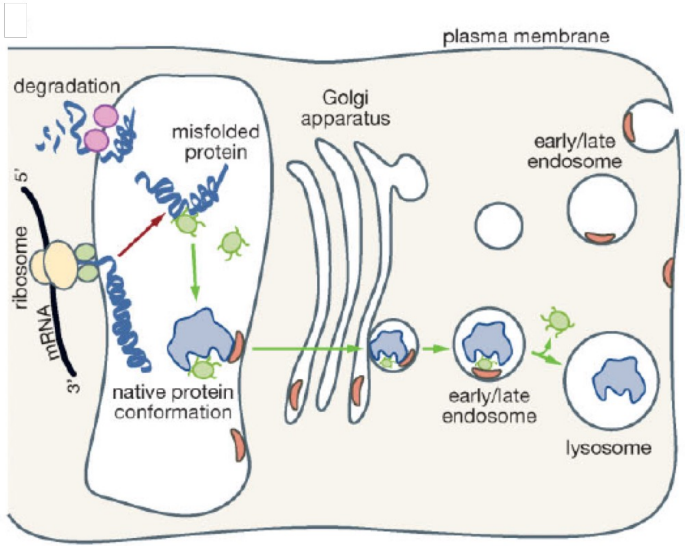
Hôpitaux de Toulouse

Maladie de Fabry

Enzymothérapie de substitution :
apport exogène pour tous les patients



Molécule chaperon :
restauration de l'activité endogène
chez les patients avec mutations sensibles



Hôpitaux de Toulouse

Parenti G, et al. *EMBO Mol Med*. 2009;1:268-79

Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study

52 patients (34 dans le groupe migalastat et 18 dans le groupe enzymothérapie substitutive)
Critère principal : masse ventriculaire gauche indexée mesurée en ETT
Suivi 18 mois

Parameter	Baseline mean	Change from baseline to month 18 (95% CI)
Migalastat: LVMi (g/m^2)		
All (n=33) (% abnormal)	95.3 (39)	−6.6 (−11.0 to −2.2)*
LVH† at baseline (9 females and 4 males)	116.7	−8.4 (−15.7 to 2.6)
ERT: LVMi (g/m^2)		
All (n=16) (% abnormal)	92.9 (31)	−2.0 (−11.0 to 7−0)
LVH† at baseline (n=5) (1 female and 4 males)	123.3 (100%)	4.5 (−20.9 to 30.0)

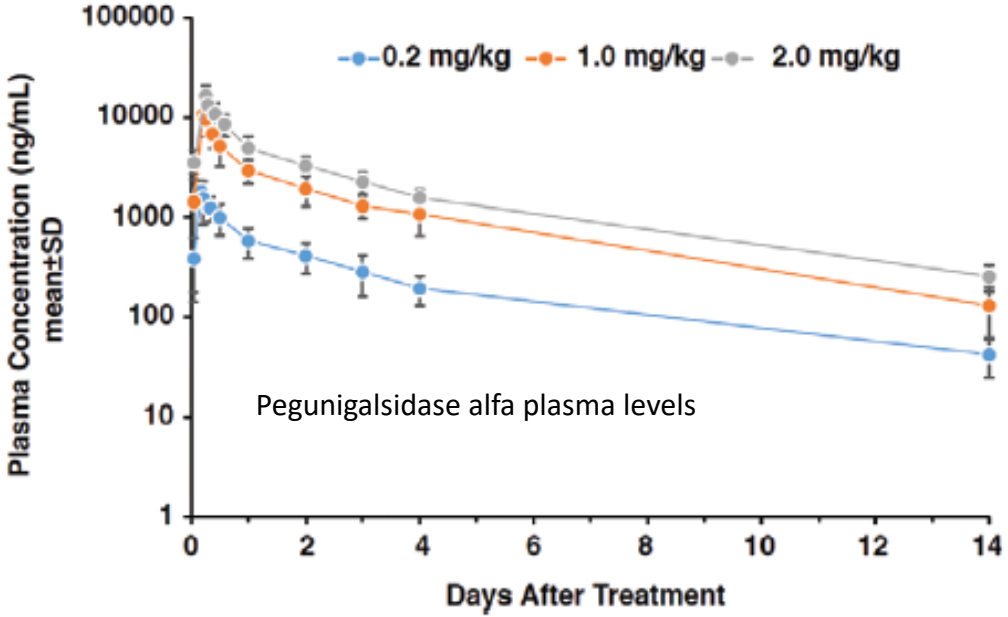
Composite clinical outcome: number of patients (mITT population)

Component	Migalastat (n=34)	ERT (n=18)
Renal	8 (24%) ↑Proteinuria (6), ↓GFR (2)	6 (33%) ↑Proteinuria (4), ↓GFR (3)
Cardiac	2 (6%) Chest pain, VT/chest pain	3 (17%) Cardiac failure, dyspnoea, arrhythmia
CNS	0 (0%)	1 (6%) TIA
Death	0 (0%)	0 (0%)
Any	10 (29%)	8 (44%)

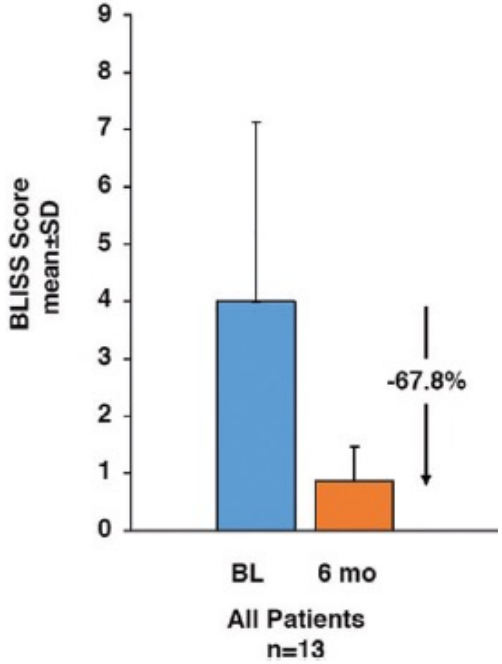
Hôpitaux de Toulouse

Hughes D, et al. *J Med Genet.* 2017;54:288-296

Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: A 1-year Phase 1/2 clinical trial



Pegunigalsidase alfa plasma levels



Hôpitaux de Toulouse

Schiffmann R, et al. *Inherit Metab Dis.* 2019;42:534–544

ÉTUDES EN COURS

Pegunigalsidase

Enzymothérapie substitutive végétale

Extension Study of 1 mg/kg Pegunigalsidase Alfa in Patients With Fabry Disease

ClinicalTrials.gov Identifier: NCT03566017

Recruitment Status : Enrolling by invitation
First Posted : June 21, 2018
Last Update Posted : February 21, 2022

Lucerastat

Enzymothérapie substitutive orale

Efficacy and Safety of Lucerastat Oral Monotherapy in Adult Subjects With Fabry Disease (MODIFY)

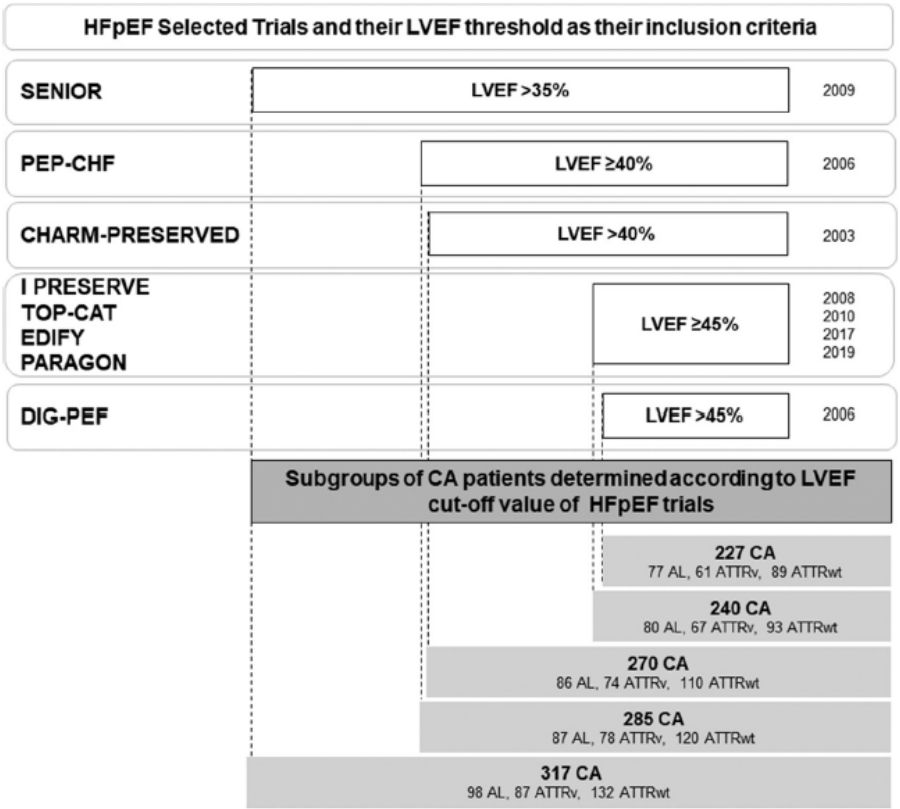
ClinicalTrials.gov Identifier: NCT03425539

Recruitment Status : Completed
First Posted : February 7, 2018
Last Update Posted : October 29, 2021

AMYLOSE À TRANSTHYRÉTINE

Hôpitaux de Toulouse

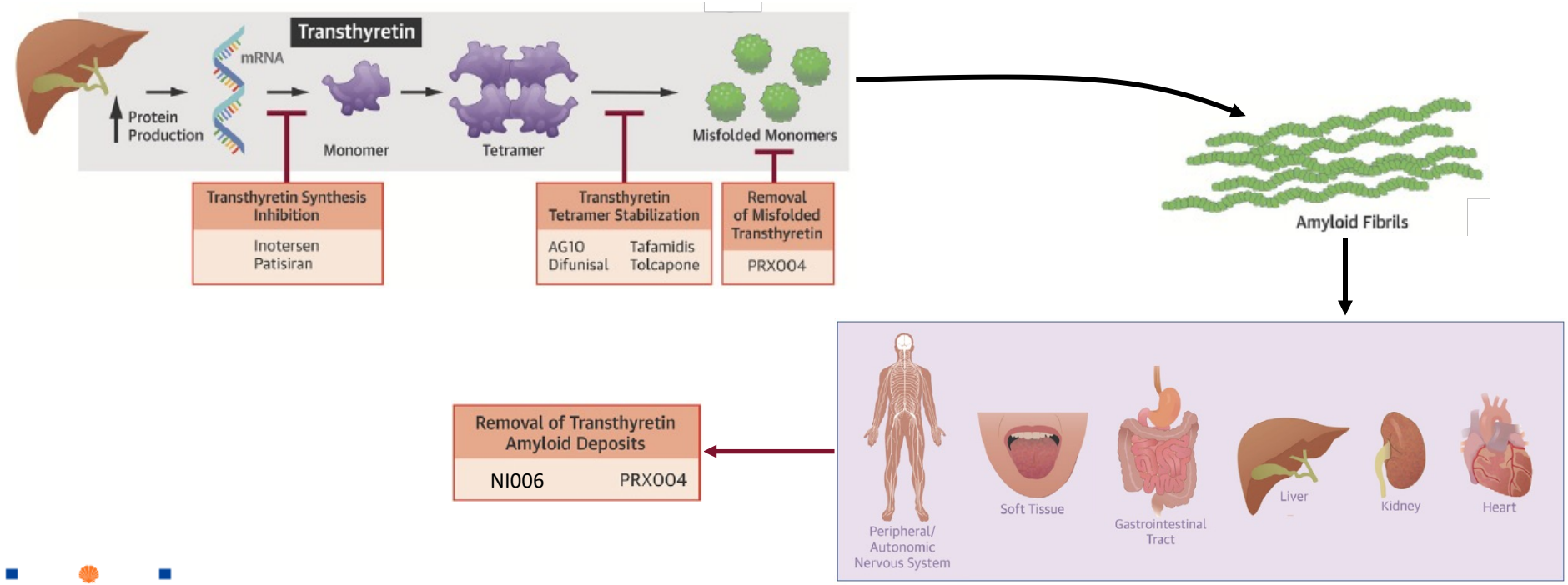
The Impact of Patients With Cardiac Amyloidosis in HFpEF Trials



Hôpitaux de Toulouse

Oghina S, et al. *J Am Coll Cardiol HF* 2021;9:169-178

AMYLOSE CARDIAQUE À TRANSTHYRÉTINE



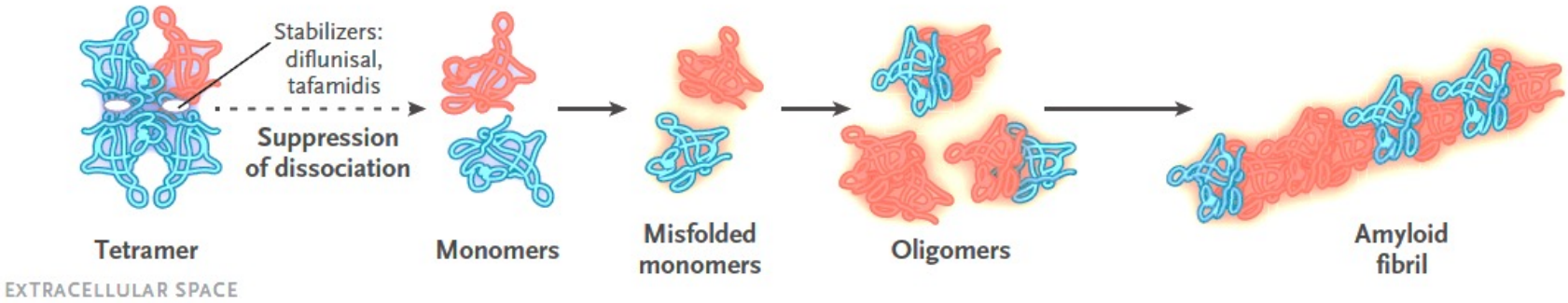
Hôpitaux de Toulouse

Zhang KW, et al. *JACC Basic Transl Sci.* 2019;4:438-448

STABILISATEURS DU TÉTRAMÈRE

Tafamidis

Stabilisateur du tétramère

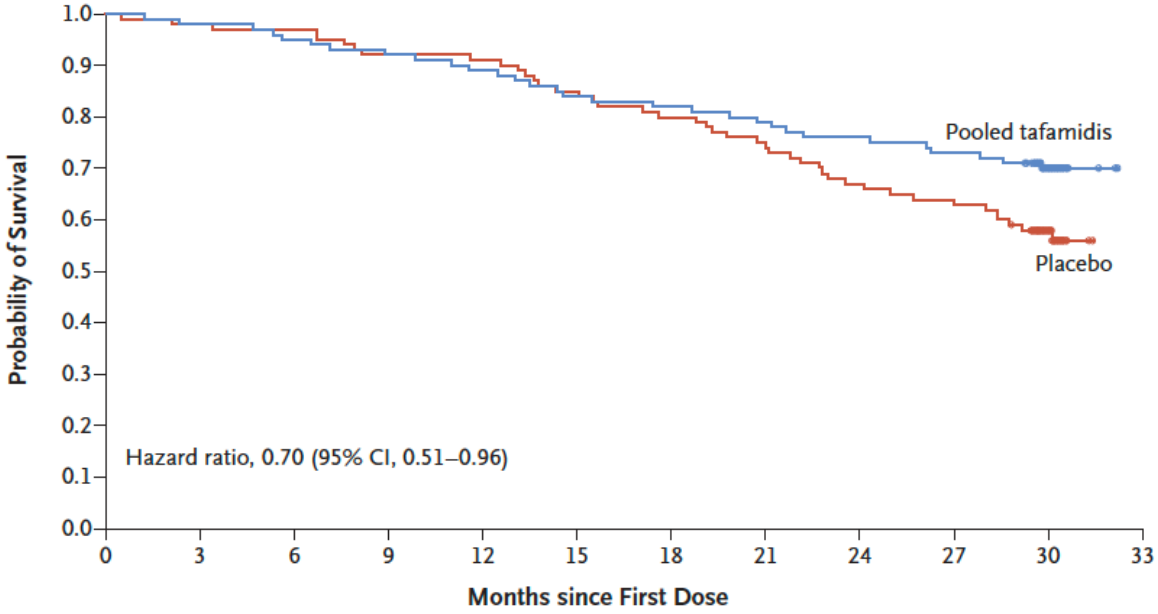


Hôpitaux de Toulouse

Buxaum JN. *N Engl J Med* 2018;379:208

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

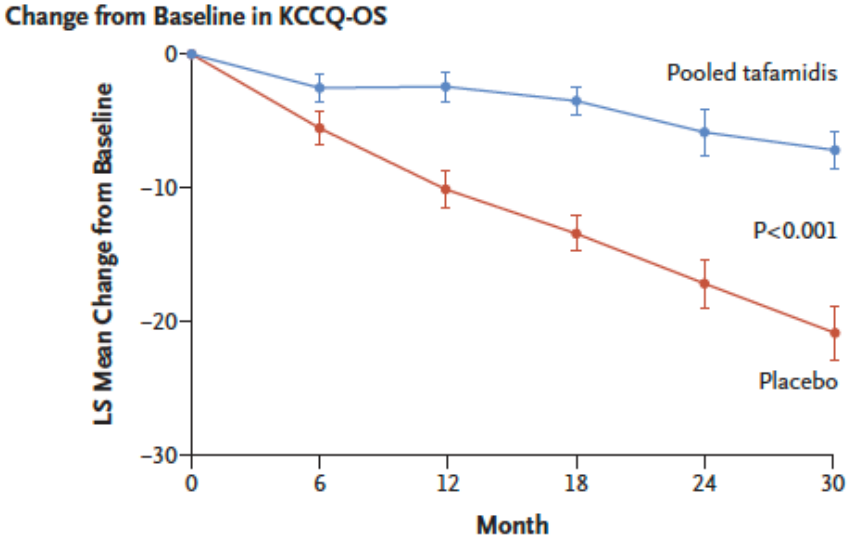
441 patients
Critère principal : mortalité et hospitalisations pour insuffisance cardiaque
Suivi 30 mois

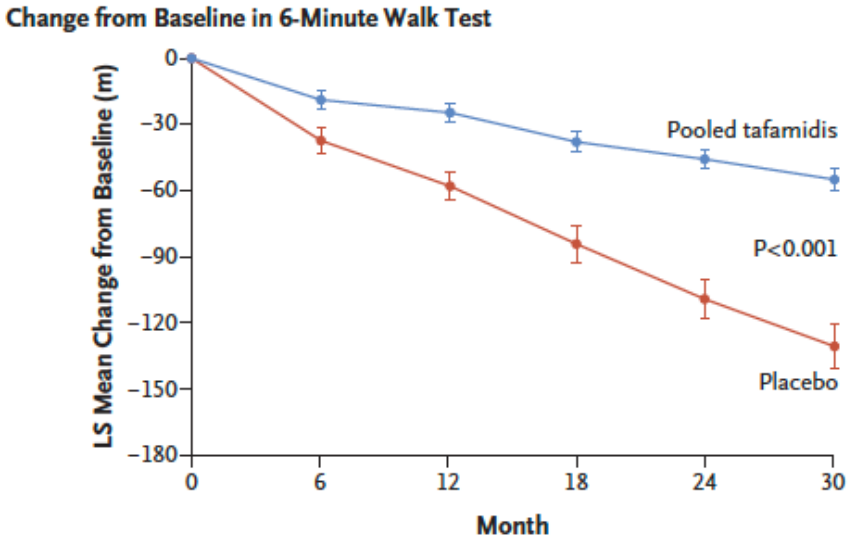


Hôpitaux de Toulouse

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

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy



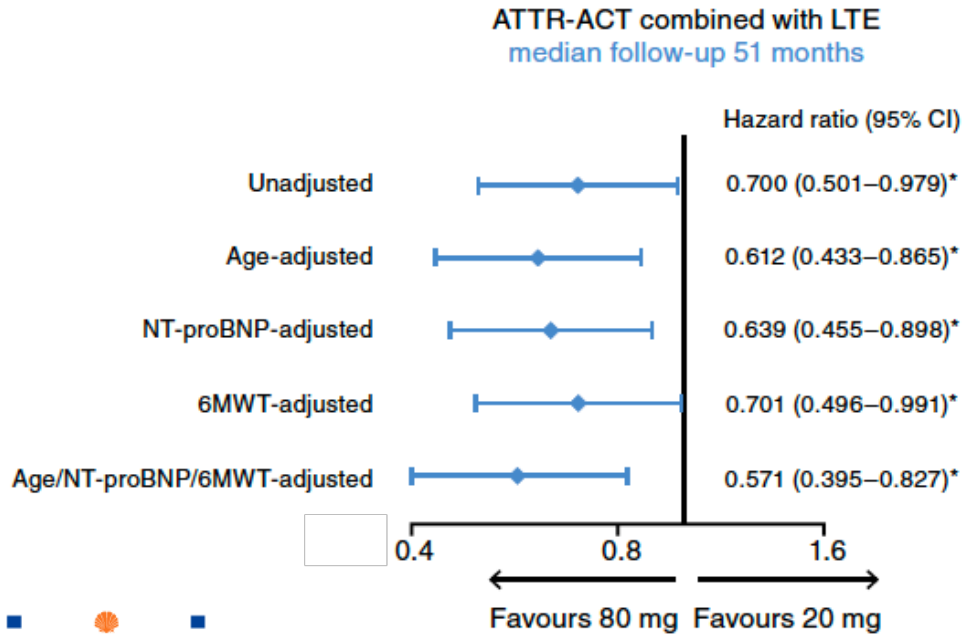


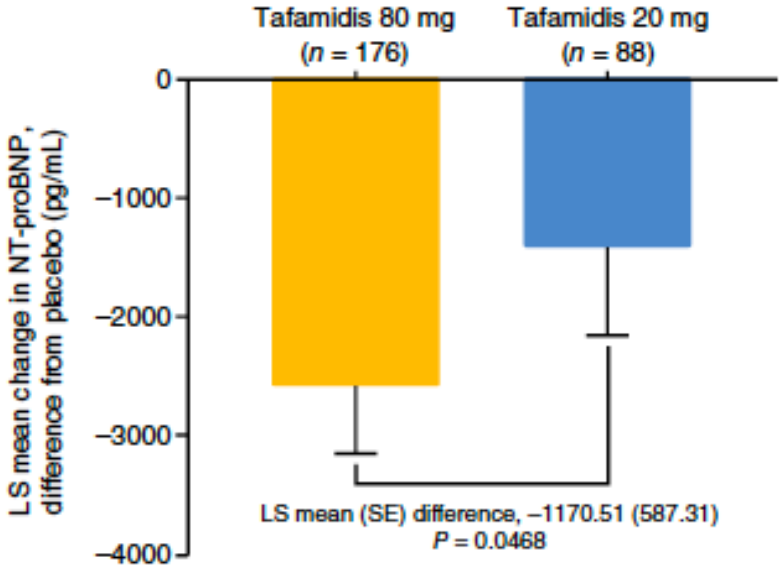
Hôpitaux de Toulouse

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

Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study

Mortalité totale

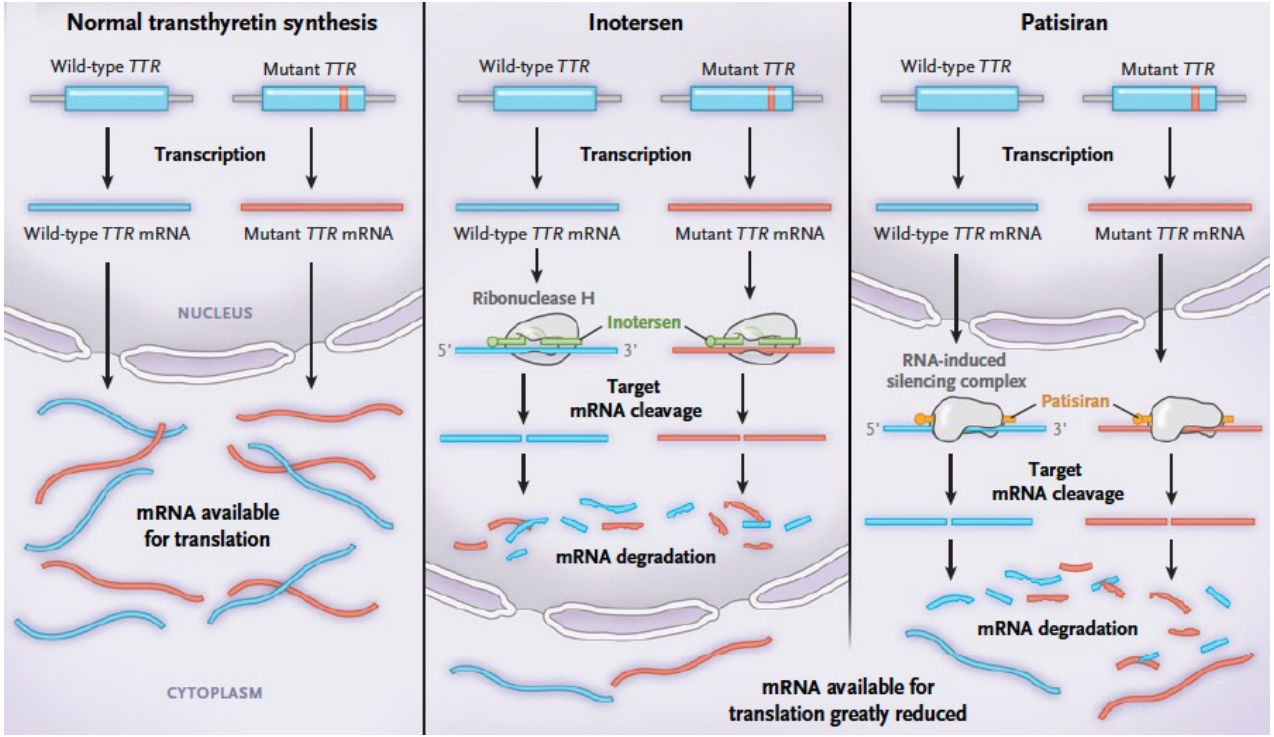




Hôpitaux de Toulouse

Damy T, et al. *Eur J Heart Fail.* 2021;23:277-285

OLIGONUCLÉOTIDES

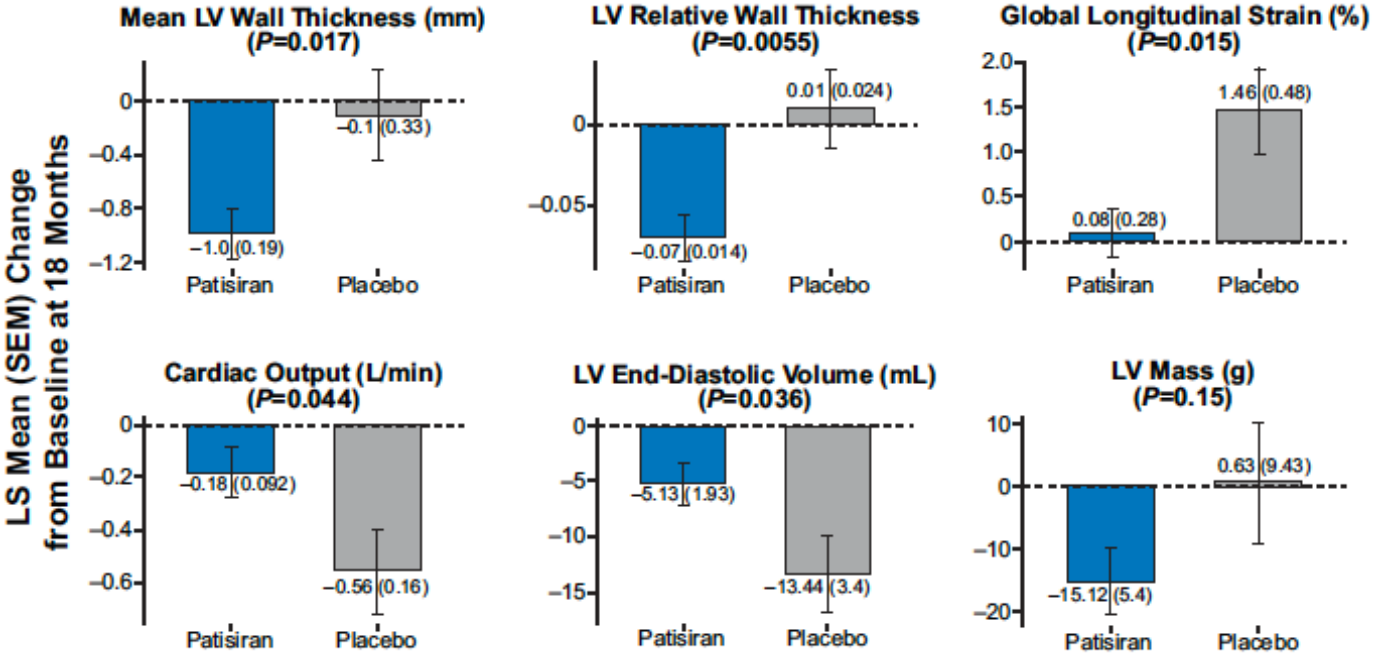


Hôpitaux de Toulouse

Buxaum JN. *N Engl J Med* 2018;379:208

Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis

Analysis of the APOLLO Study



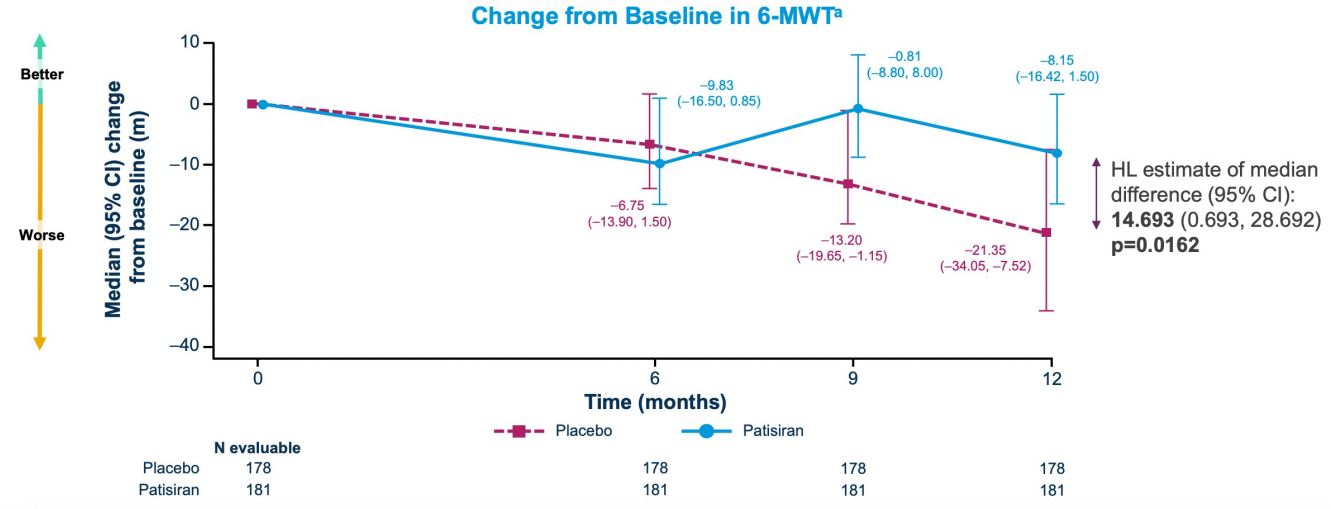
Hôpitaux de Toulouse

Solomon SD, et al. *Circulation* 2019;139:431-443

Alnylam Reports Positive Topline Results from APOLLO-B Phase 3 Study of Patisiran in Patients with ATTR Amyloidosis with Cardiomyopathy

360 patients : 181 dans le bras Patisiran et 179 dans le bras placebo
Suivi : 12 mois

Primary Endpoint: Patisiran Demonstrated Significant Clinical Benefit in Functional Capacity (6-MWT) Compared to Placebo at Month 12



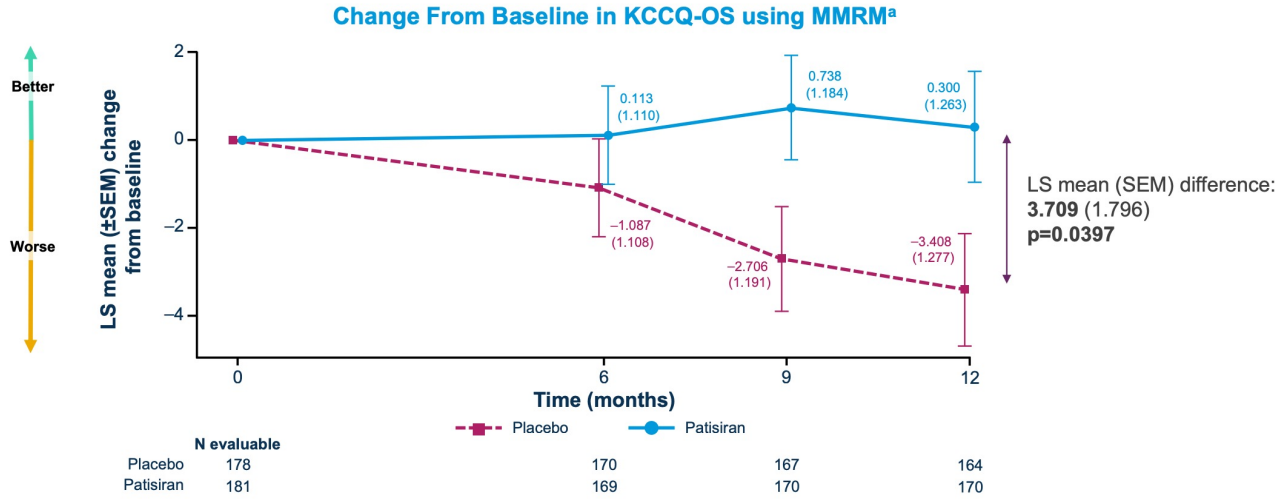
Hôpitaux de Toulouse

https://investors.alnylam.com/press-release

Alnylam Reports Positive Topline Results from APOLLO-B Phase 3 Study of Patisiran in Patients with ATTR Amyloidosis with Cardiomyopathy

360 patients : 181 dans le bras Patisiran et 179 dans le bras placebo
Suivi : 12 mois

Secondary Endpoint: Patisiran Demonstrated Significant Clinical Benefit in Health Status and Quality of Life (KCCQ-OS) Compared to Placebo at Month 12

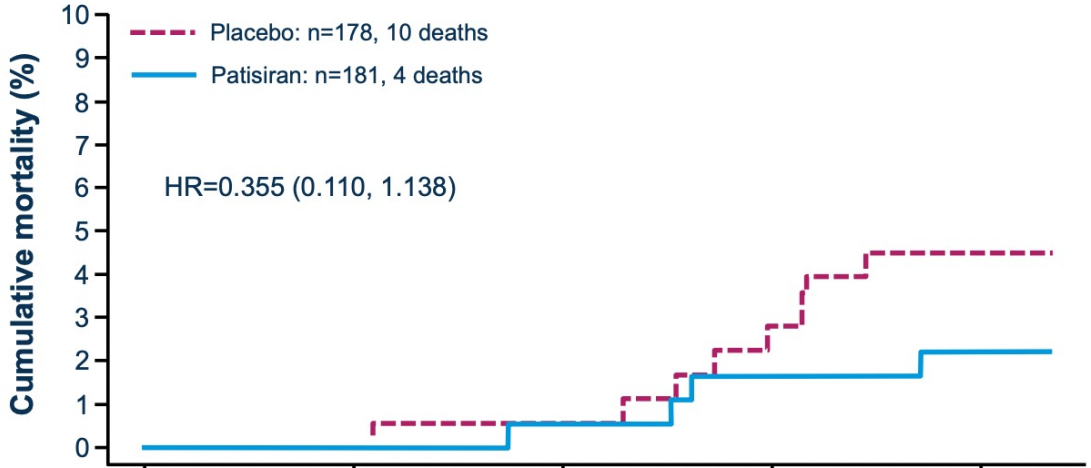


Hôpitaux de Toulouse

https://investors.alnylam.com/press-release

Alnylam Reports Positive Topline Results from APOLLO-B Phase 3 Study of Patisiran in Patients with ATTR Amyloidosis with Cardiomyopathy

All-Cause Mortality During the 12-Month Double-Blind Period[a,b]



N at risk (deaths)					
Placebo	178 (0)	178 (0)	177 (1)	173 (5)	170 (8)
Patisiran	181 (0)	181 (0)	180 (1)	178 (3)	176 (4)

Hôpitaux de Toulouse

https://investors.alnylam.com/press-release

ÉTUDES EN COURS

Vutrisiran

ARN interférent

HELIOS-B: A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy

ClinicalTrials.gov Identifier: NCT04153149

Recruitment Status : Active, not recruiting
First Posted : November 6, 2019
Last Update Posted : March 8, 2022

Eplontersen

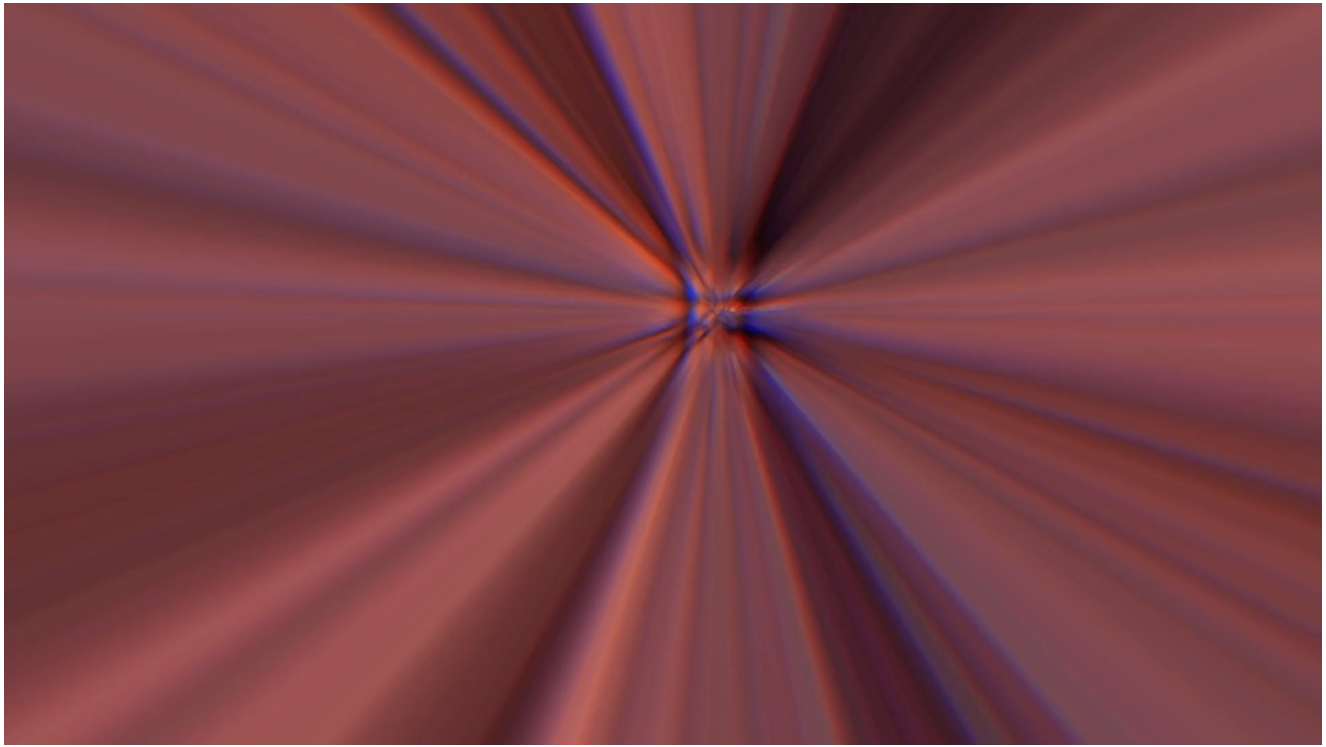
ARN anti-sens

24 Month Open Label Study of the Tolerability and Efficacy of Inotersen in TTR Amyloid Cardiomyopathy Patients

ClinicalTrials.gov Identifier: NCT03702829

Recruitment Status : Active, not recruiting
First Posted : October 11, 2018
Last Update Posted : December 7, 2020

ANTICORPS MONOCLONAUX

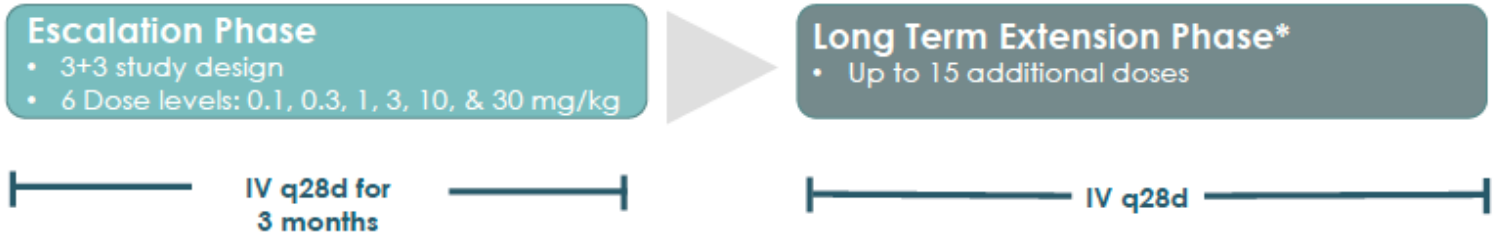


Hôpitaux de Toulouse

https://www.prothena.com

PRX004, the First Investigational Anti-Amyloid Immunotherapy for the Treatment of ATTR Amyloidosis

9-month results from a Phase 1 long-term extension study



Primary Objectives:
- Evaluate safety, tolerability, PK and target engagement (misTTR assay)
- Determine MTD or RP2D(s)

Secondary Objective:
- Evaluate immunogenicity

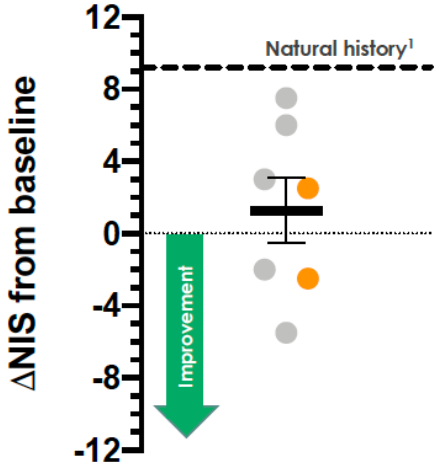
Exploratory Objective:
- Characterize efficacy (NIS) in patients with hATTR-PN with or without hATTR-CM (Cohorts 4-6)

Hôpitaux de Toulouse

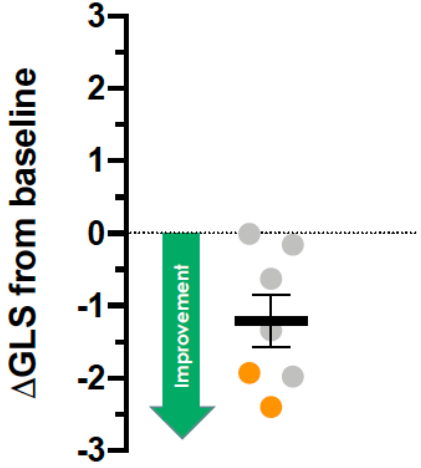
https://www.prothena.com

PRX004, the First Investigational Anti-Amyloid Immunotherapy for the Treatment of ATTR Amyloidosis

9-month results from a Phase 1 long-term extension study



	PRX004 Phase 1	
	All	PRX004 Alone
ΔNIS mean* (n)	**+1.29** (n=7)	0.00 (n=2)
Time point	9 months	

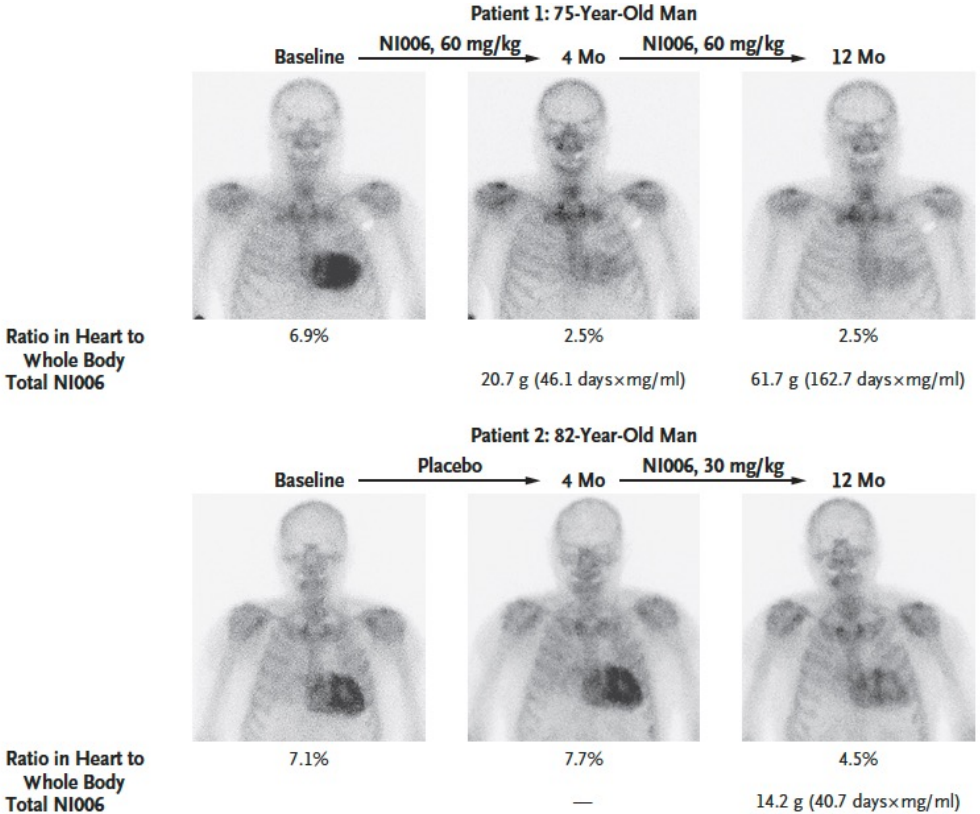


	PRX004 Phase 1	
	All	PRX004 Alone
ΔGLS mean* (n)	**–1.21%** (n=7)	–2.16% (n=2)
Time point	9 months	

Hôpitaux de Toulouse

https://www.prothena.com

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



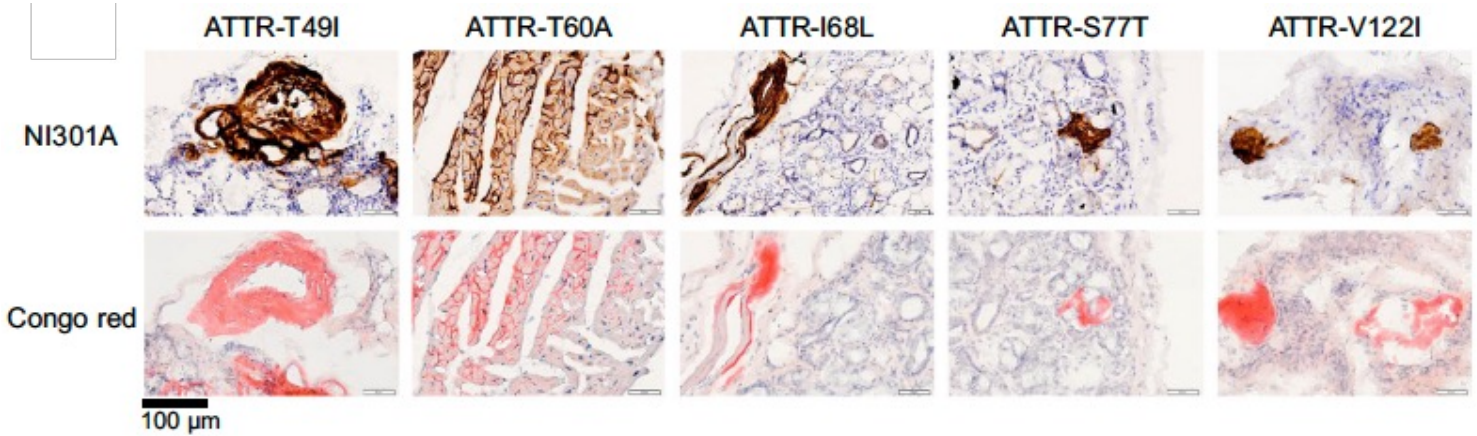
Hôpitaux de Toulouse

Garcia-Pavia P, et al. *N Engl J Med*. 2023;389:239-250

A human antibody selective for transthyretin amyloid removes cardiac amyloid through phagocytic immune cells

NI301A

Anticorps monoclonal anti-transthyrétine



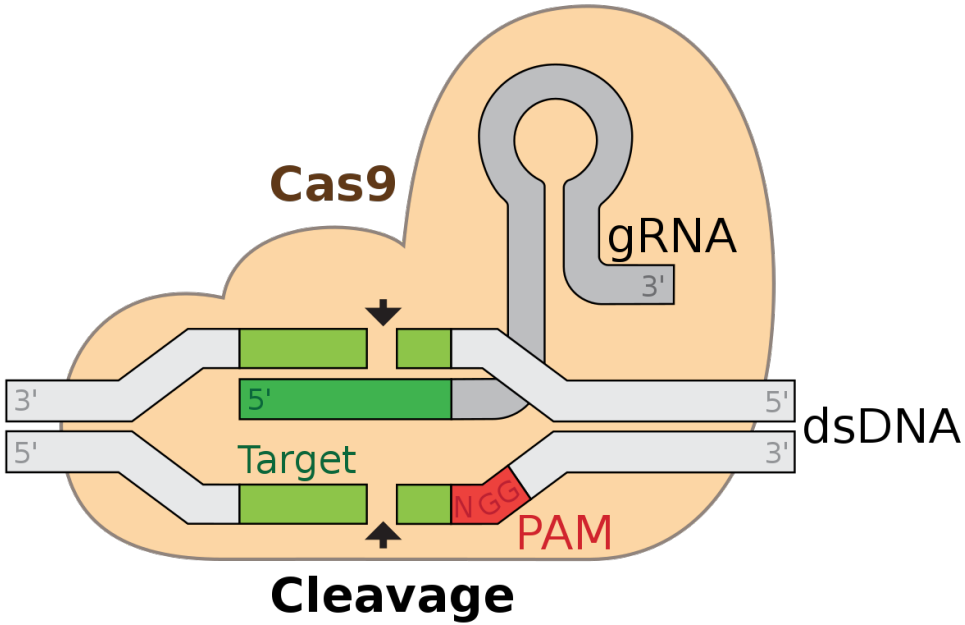
Hôpitaux de Toulouse

Michalon A, et al. *Nat Commun*. 2021;12:3142

ÉDITION GÉNIQUE CRIPR-CAS9

NTLA-2001

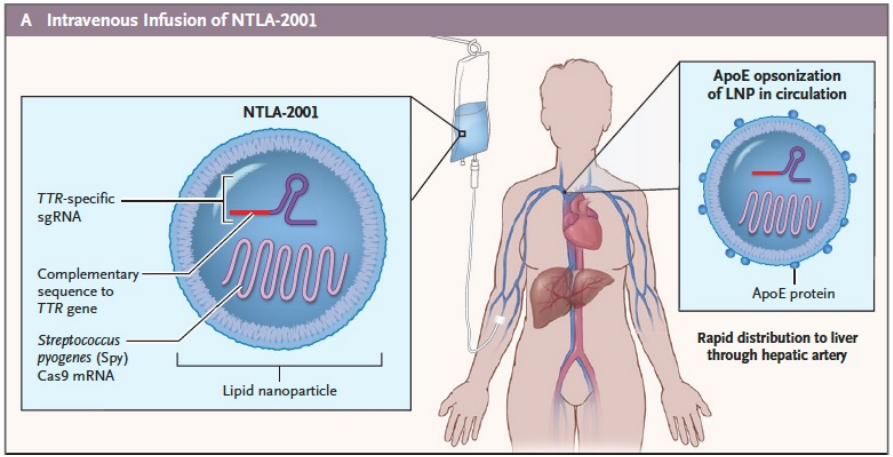
Suppression du gène de la transthyrétine

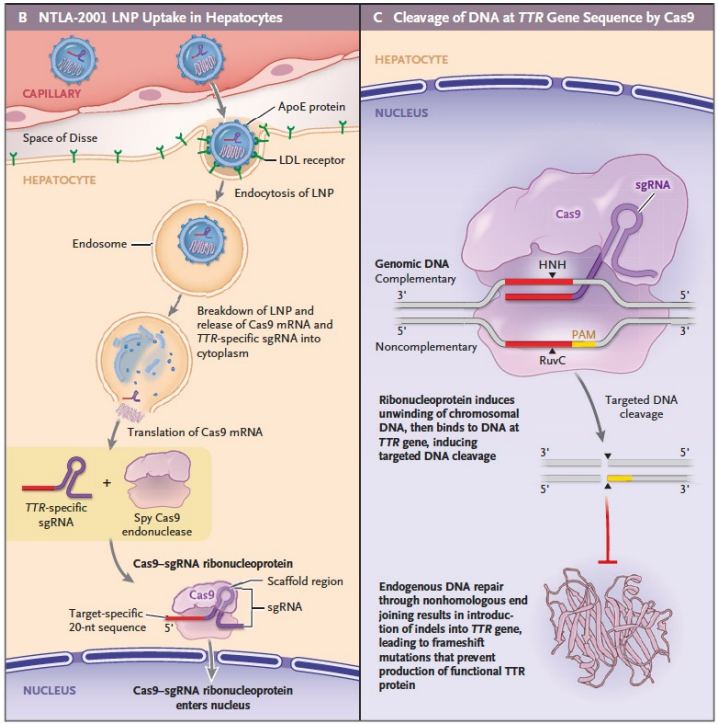


Hôpitaux de Toulouse

The NEW ENGLAND JOURNAL of MEDICINE

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis



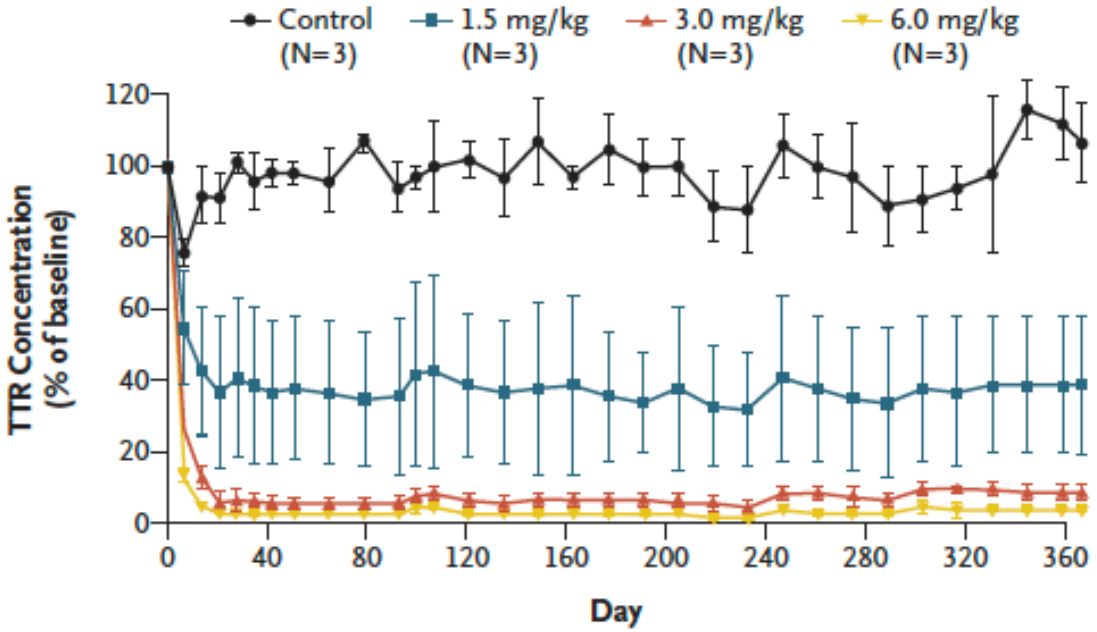


Hôpitaux de Toulouse

Gillmore JD, et al. *N Engl J Med.* 2021;385:493-502

The NEW ENGLAND JOURNAL of MEDICINE

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis



Hôpitaux de Toulouse

Gillmore JD, et al. *N Engl J Med.* 2021;385:493-502

SYNTHÈSE

Hôpitaux de Toulouse

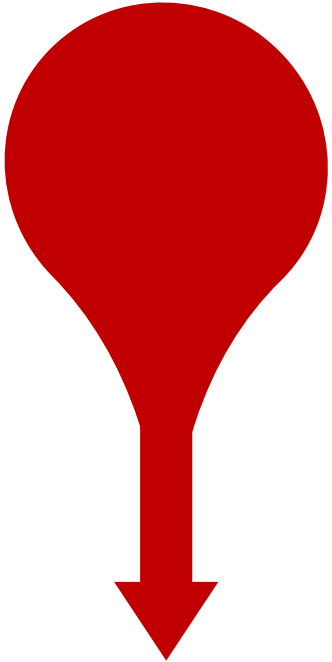
NOUVEAUX TRAITEMENTS DES CMH

Approche mécanistique

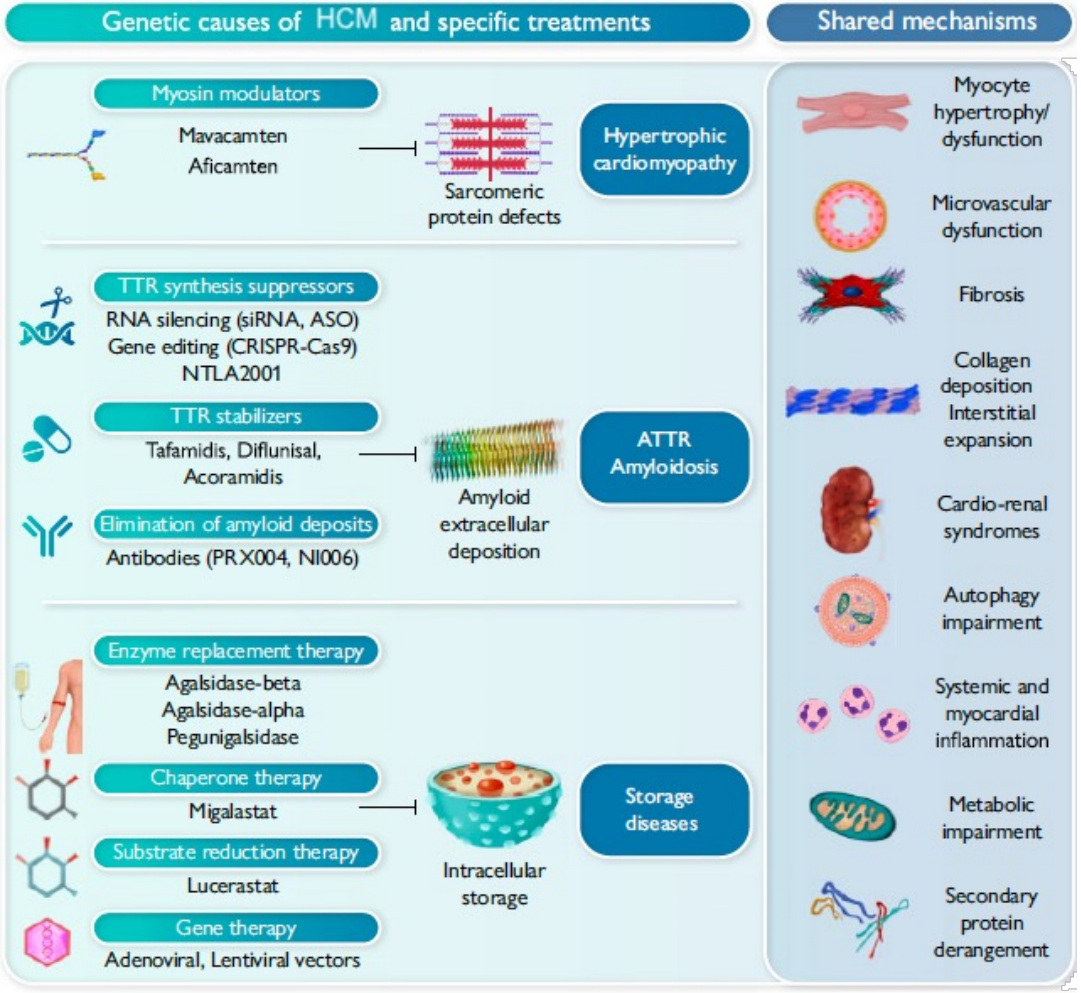
Approche phénotypique

Approche étiologique

Approche génétique ?



Hôpitaux de Toulouse



Hôpitaux de Toulouse

Olivotto I, et al. *Eur Heart J* 2022;00:1–12