Specific therapies of cardiomyopathies

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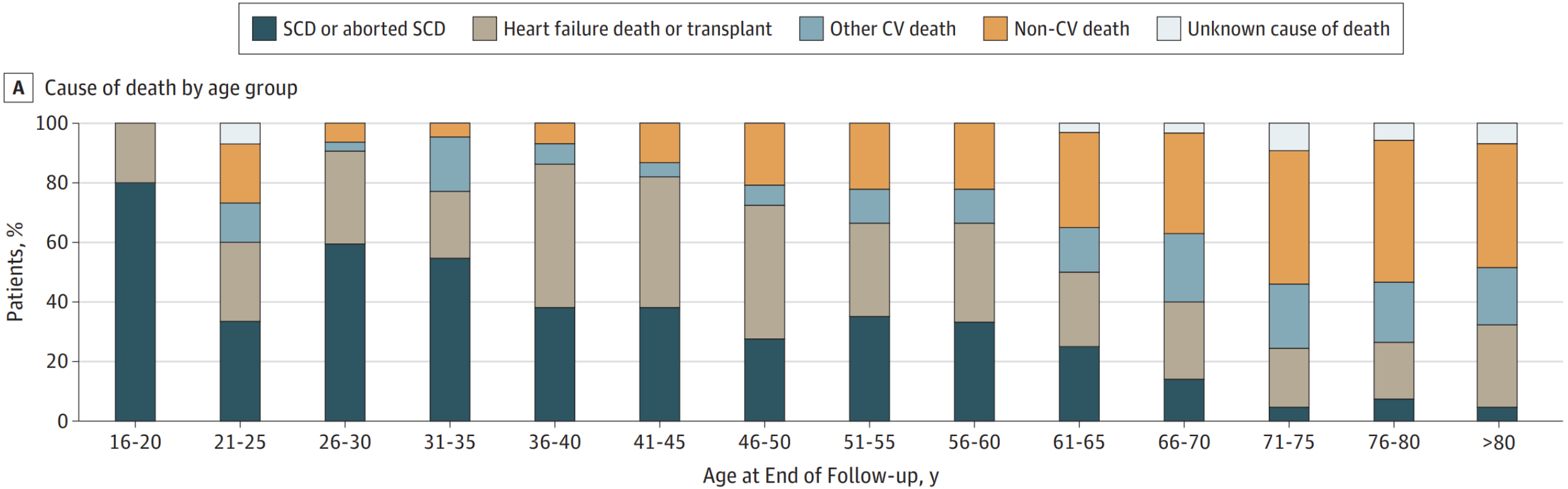
HYPERTROPHIC CARDIOMYOPATHY

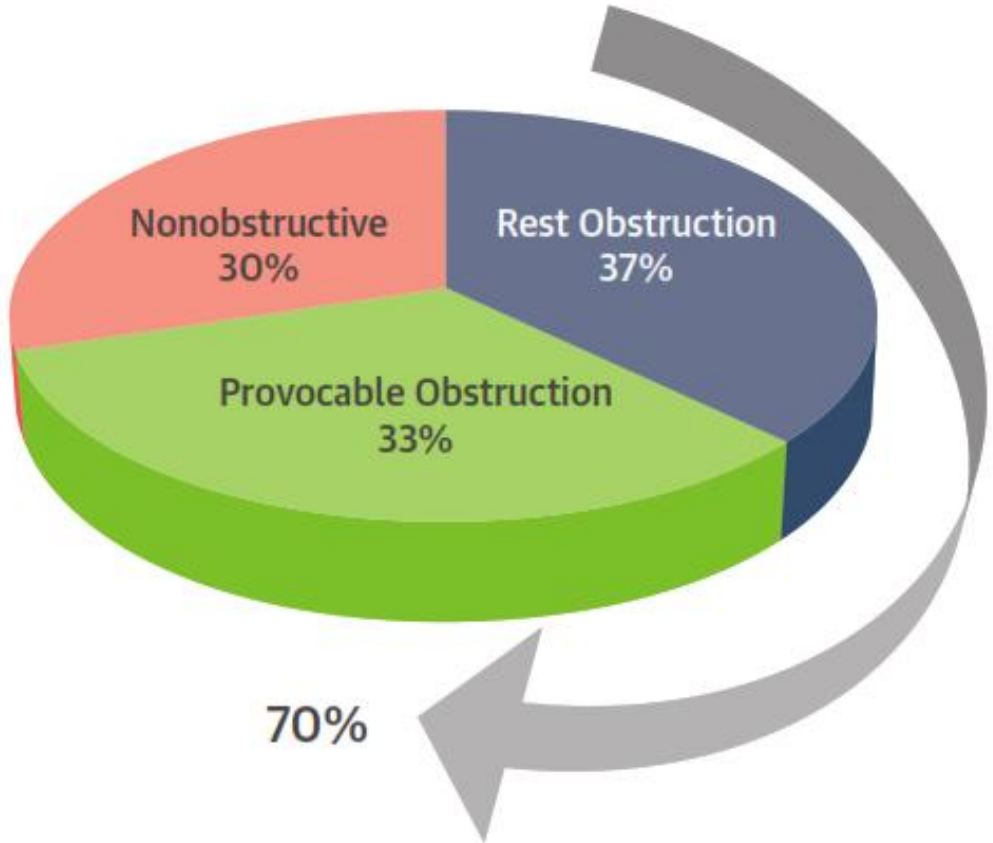
Cause of Death by Age Group

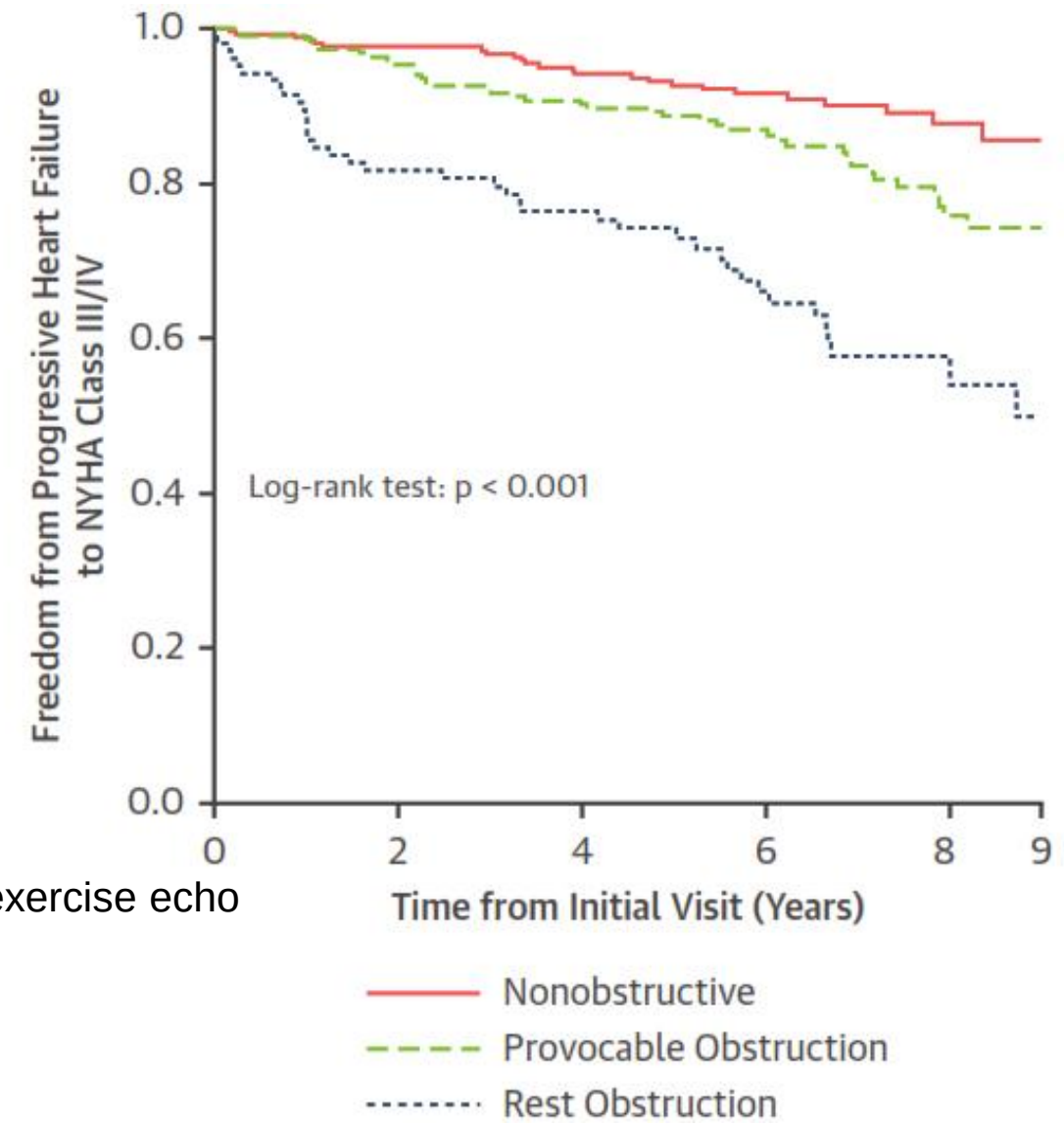
- 4893 patients with HCM, 3126 (63.9%) male,
- age at presentation was 49.2 (16.4) years
- LVOT gradient > 30 mmHg 1372/4238 (32.4)



Lorenzini et al. JAMA Cardiol. 2020;5(1):73-80.

Significance of LVOT gradient in HCM



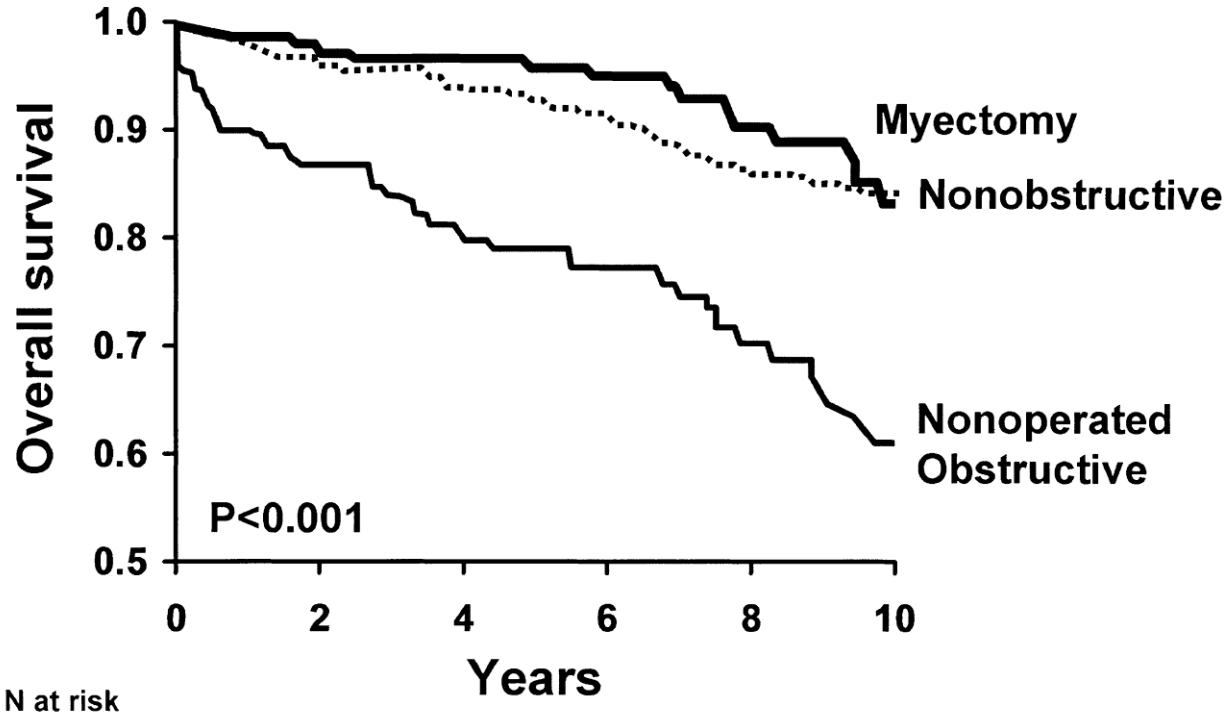


320 consecutive HCM patients (age, 47±17 years),
measuring LVOT gradient at rest, with Valsalva maneuver, and with exercise echo
119 had rest gradients ≥50 mm Hg and were not exercised.

Maron MS, Circulation 2006;114:2232–9.
Maron MS, J Am Coll Cardiol 2016;67:1399–409.
Rowin, E.J. et al. J Am Coll Cardiol Img. 2017;10:1374–86.

Is then septal reduction therapy a solution to prevent sever heart failure?

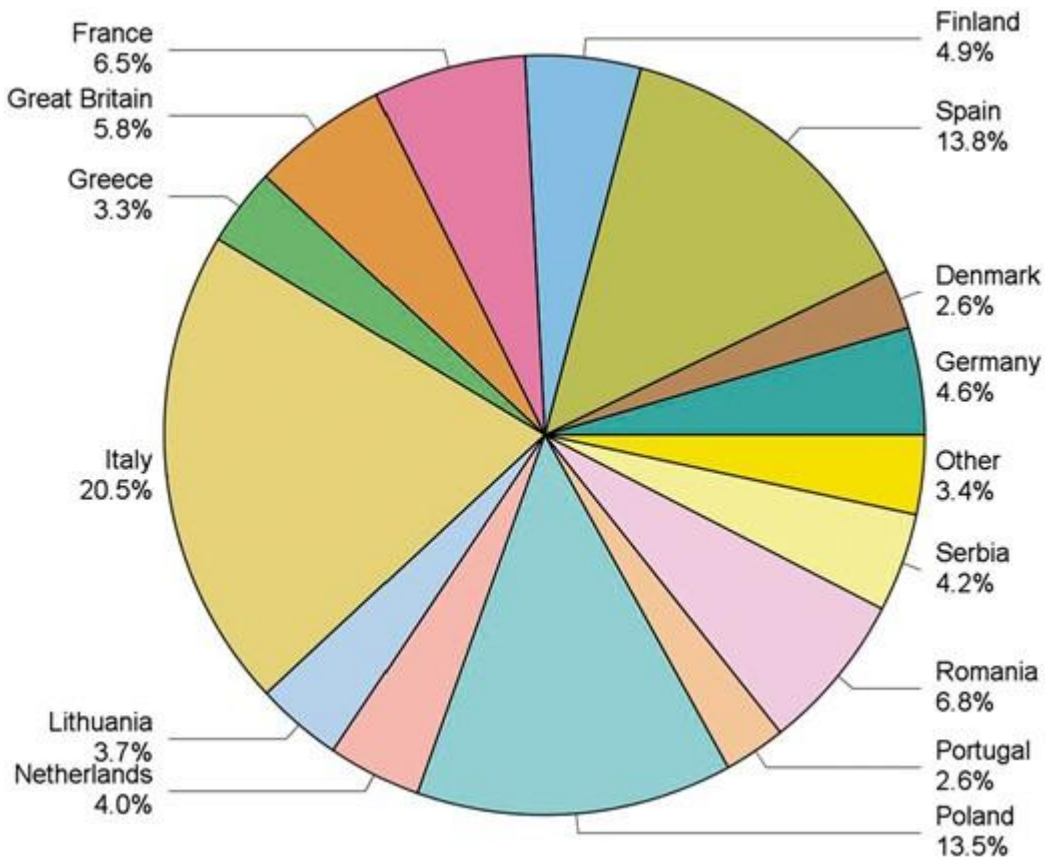
- 1,337 consecutive HCM patients at Mayo clinic
- LVOTO ≥50 mm Hg at rest or with provocative maneuvers
- NYHA III – IV
- Age 45 +/- 20 years
- Procedural risk <1%



N at risk						
Myectomy	289	249	179	108	66	39
Nonobstructive	820	587	490	355	244	201
Nonoperated obstructive	228	146	106	69	42	28

Ommen et al. J Am Coll Cardiol 2005;46:470 – 6

European Experience – EORP registry



- 1739 patients (59.1% males)
- Mean age 55 years

- ICD implantation 19.9%

- Class NYHA II or higher 77.3%
- Symptomatic 84.8%
- Exercise test 39.5%

- Betablockers 74.4%
- **Septal myectomy 4.9%**
- **Alcohol septal ablation 4.0%**

Charron P et al. *European Heart Journal*, Volume 39, Issue 20, 21 May 2018, Pages 1784–1793,

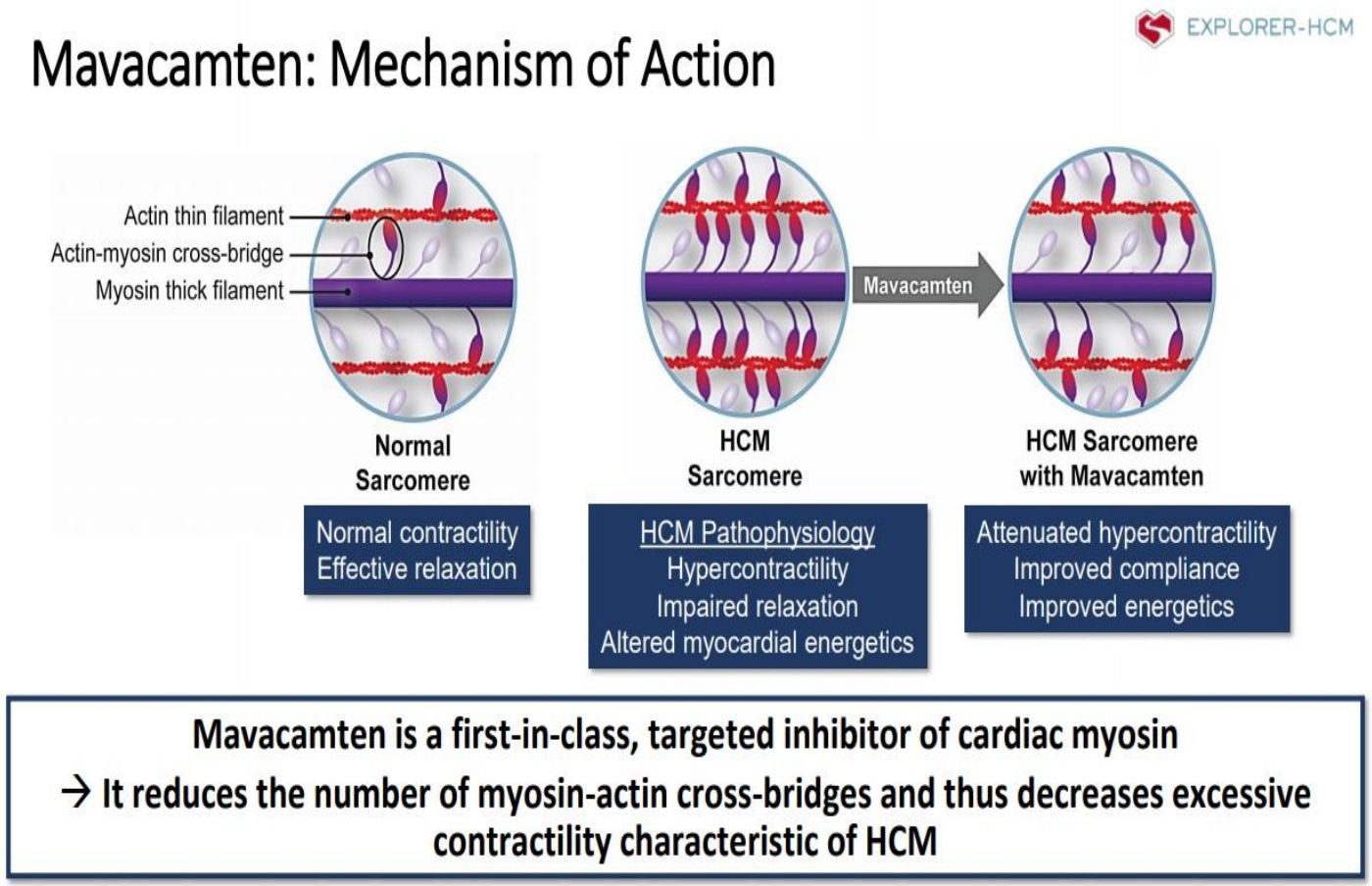
Pharmacological treatment

Standard medication– no data on prognostic improvements, only alleviation of symptoms

- Betablockers
- Calcium channel blockers (verapamil)
- Disopyramide

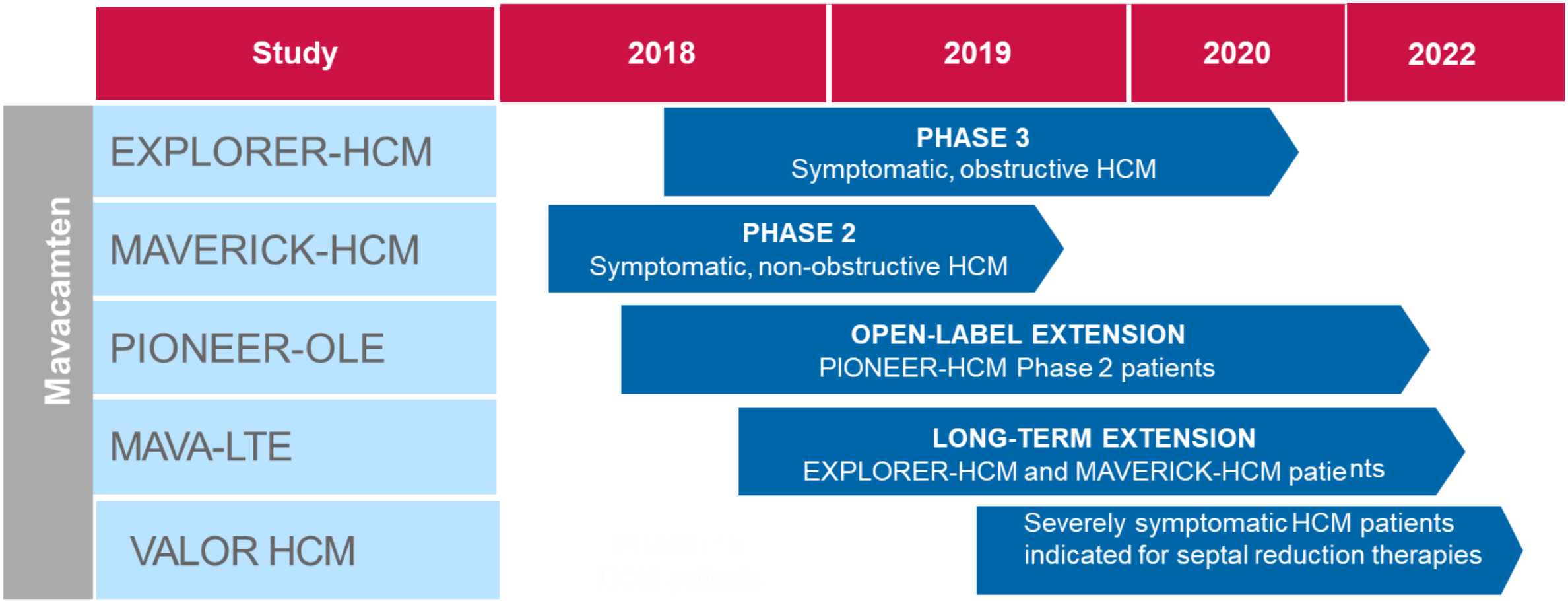
Novel possibilities

- Metabolic modulators (ranolazine, perhexiline)
- Molecular therapy (inhibition of sarcomeric contraction)
  - mavacamten (MYK-461)



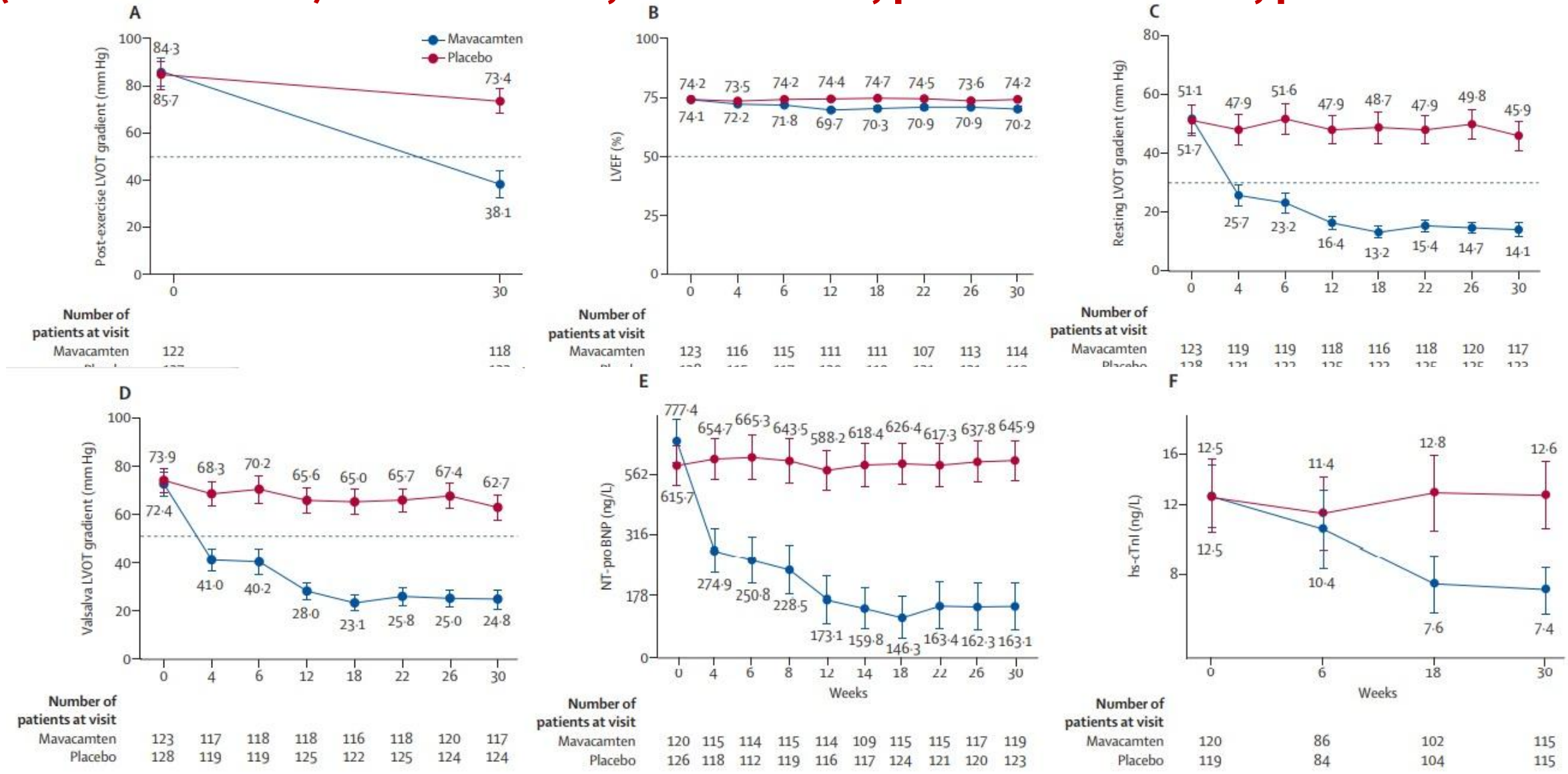
Courtesy – Iacopo Olivotto ESC congress 2020

Mavacamten clinical program



Source: MyoKardia

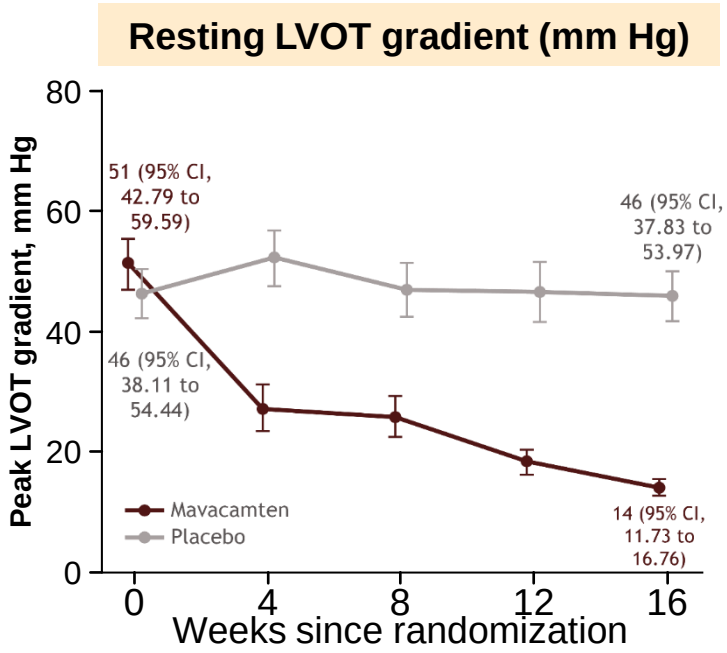
Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

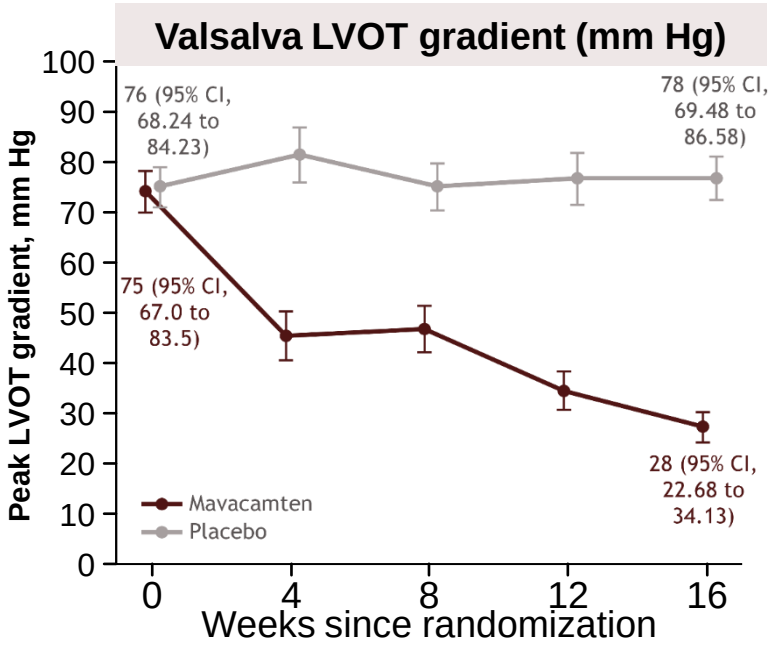


Olivotto I et al. Lancet 2020;396,759-769

VALOR-HCM secondary efficacy end point: Change in LVOT gradient

	Mava	Placebo	Treatment difference
Change from baseline in **post-exercise** LVOT gradient (mmHg)	-39.1 +/- 36.5	-1.8 +/- 28.8	-37.2 (-48.1 to -26.2)

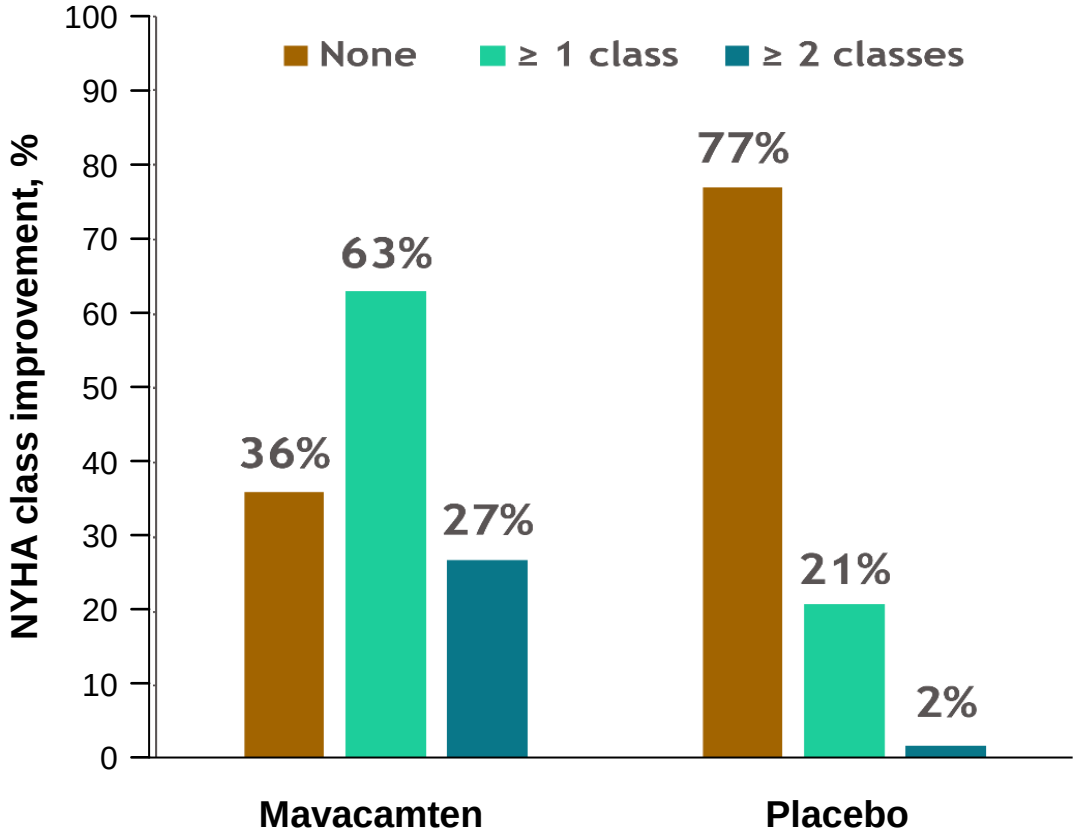




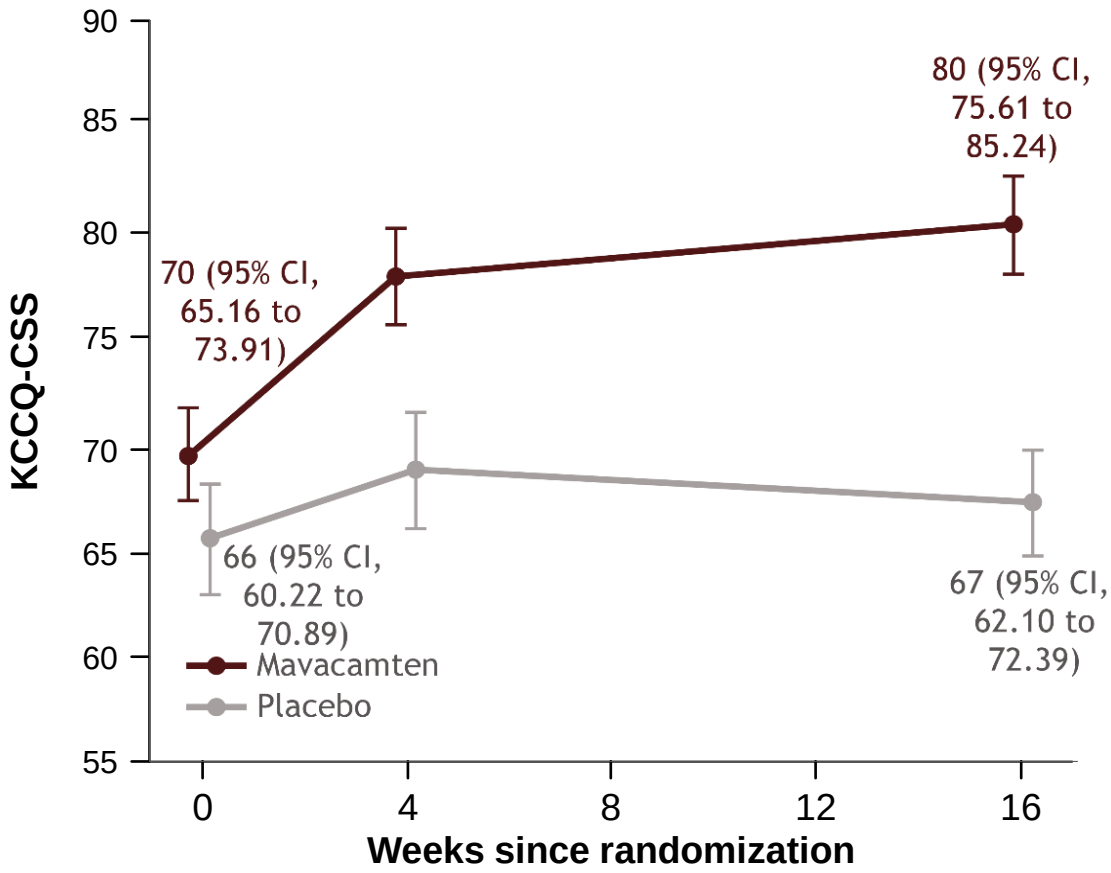
Desai MY. Oral presentation at the American College of Cardiology's 71st Annual Scientific Session & Expo (ACC.22); April 2–4, 2022; Presentation 402-09.

VALOR-HCM secondary efficacy end points: NYHA class and KCCQ-23 CSS improvements

Difference in the proportion of subjects with at least 1 **NYHA functional class improvement**, 41.1% (95% CI: 24.5%-57.7%)



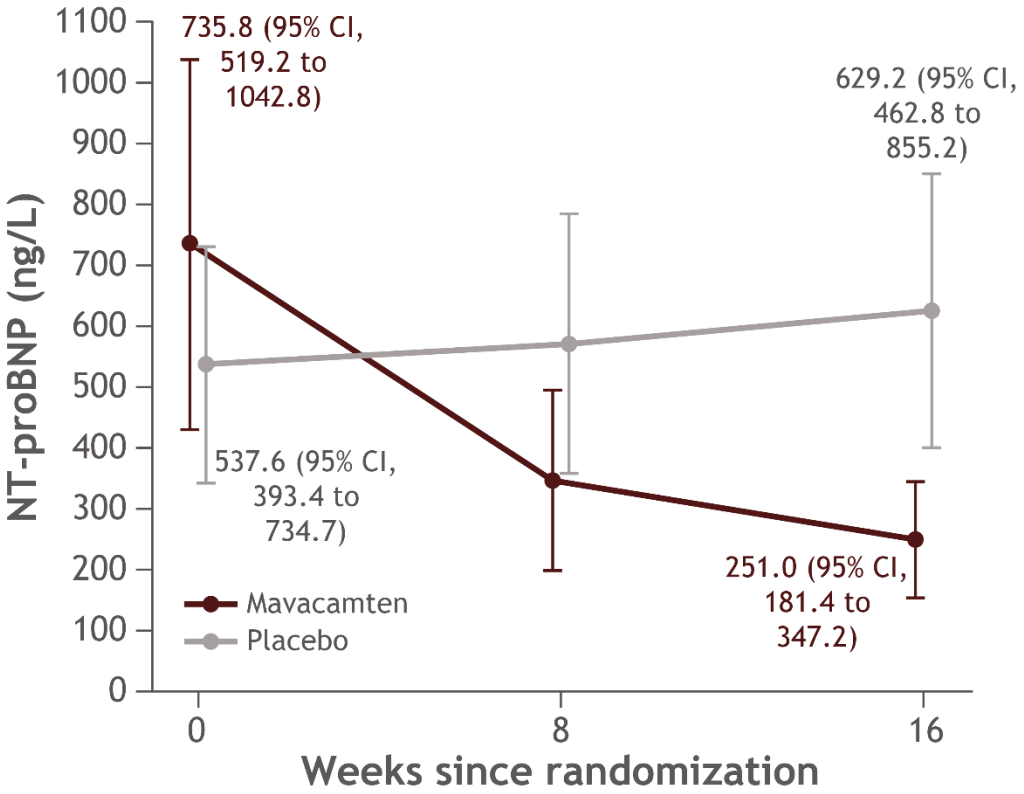
KCCQ-23 CSS difference, 9.4 (4.9 to 14.0) points



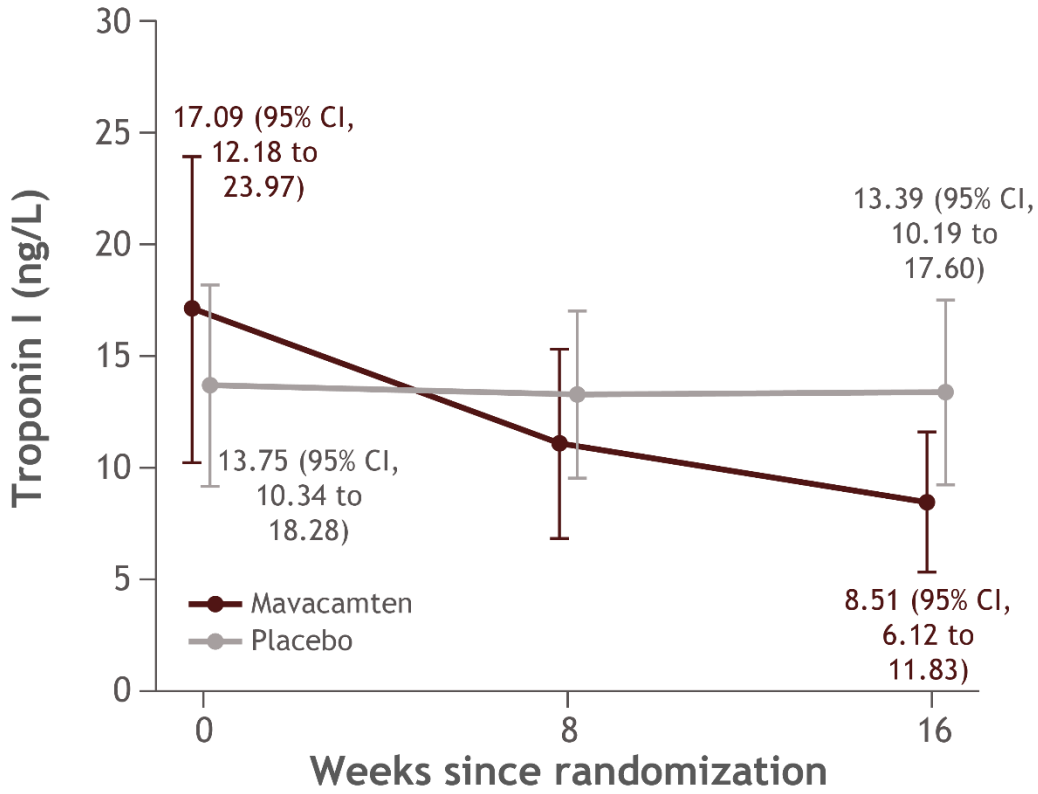
Desai MY. Oral presentation at the American College of Cardiology's 71st Annual Scientific Session & Expo (ACC.22); April 2–4, 2022; Presentation 402-09.

VALOR-HCM secondary efficacy end points: NT-proBNP and Troponin I improvements

NT-proBNP geometric mean ratio difference
0.33 (95% CI, 0.26 to 0.45)



Troponin I geometric mean ratio difference
0.53 (95% CI, 0.41 to 0.70)



Desai MY. Oral presentation at the American College of Cardiology's 71st Annual Scientific Session & Expo (ACC.22); April 2–4, 2022; Presentation 402-09.
NT-proBNP, N-terminal pro B-type natriuretic peptide.

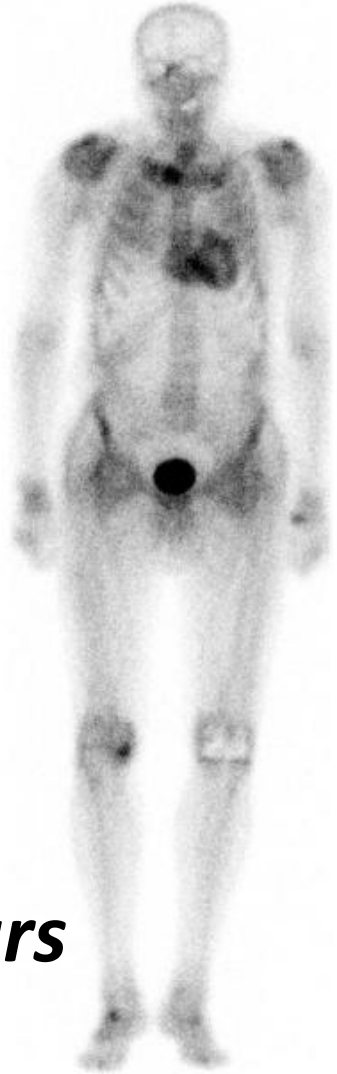
CARDIAC AMYLOIDOSIS

Amyloidosis – ^{99m}Tc-DPD scintigraphy

(99mTc-Diphosphono-Propanodicarboxylic Acid)

Positive

TTR type



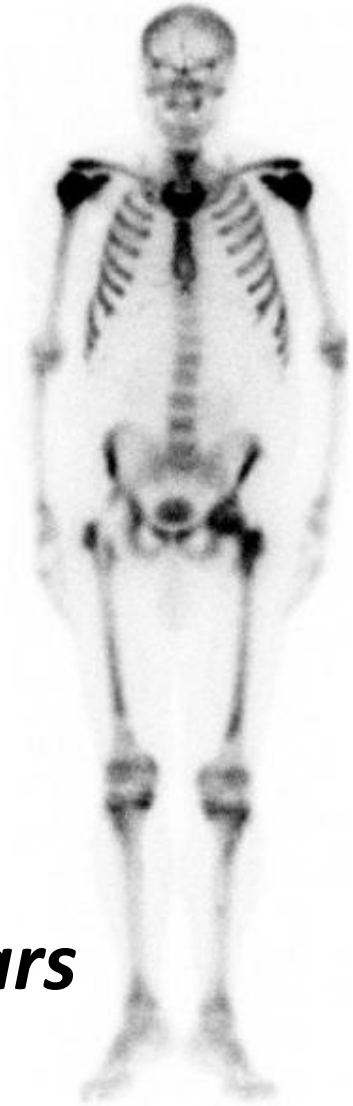
man , 74 years

Negative

AL ?

AA ?

no amyloidosis?

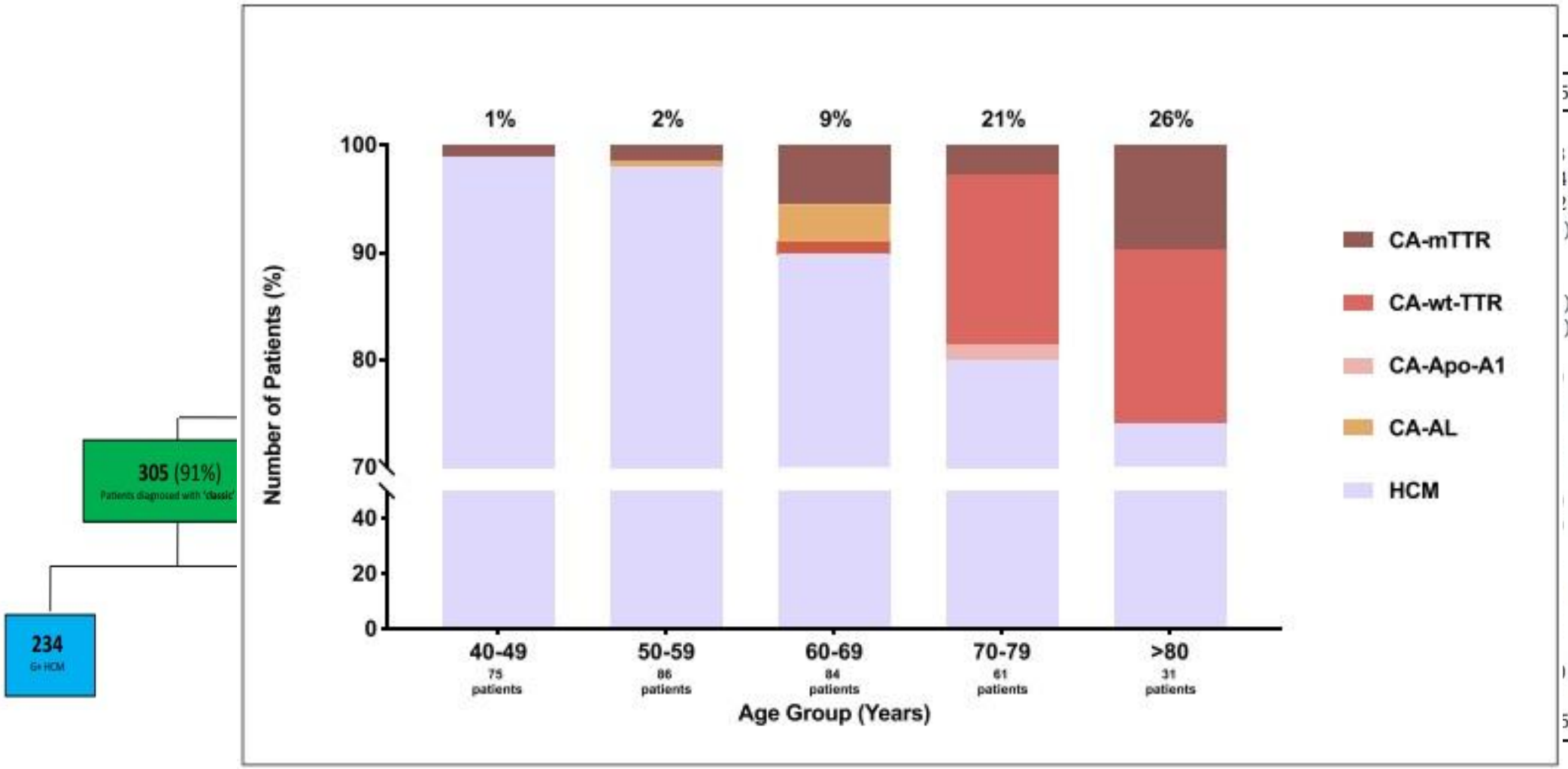


man, 67 years

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

Cases and imaging source: General University Hospital, Prague, CZ

Amyloidosis prevalence in HCM



	CA	AFD
5	$N = 32$	$N = 6$
	$72 \pm 10^{**}$	55 ± 7
4)	$1\ (3.1)^{**}$	1 (17)
2)	$21\ (65.6)^{**}$	1 (17)
)	$26\ (81)^{**}$	5 (83)
)	$5\ (16)^{**}$	5 (83)
)	$16\ (50)^{**}$	1 (17)
	$11\ (34)^{**}$	0
	2 (6.3)	1 (17)
	$13\ (41)^{**}$	1 (17)
	6 (19)	0
	$4\ (13)^{**}$	0
	$7\ (21.8)^{**}$	1 (17)
	2 (6.25)	0
	$62 \pm 31^{**}$	41 ± 3
	$19 \pm 4^{*}$	17 ± 2
	$43 \pm 4^{**}$	42 ± 4
	$11 \pm 4^{**}$	10 ± 4
)	39 ± 14	22 ± 6
	$55 \pm 9^{**}$	59 ± 9
5.5	$11.1 \pm 4.5^{*}$	12.1 ± 2.5

Maurizzi et al. Int J Cardiol 2020;300:191-195

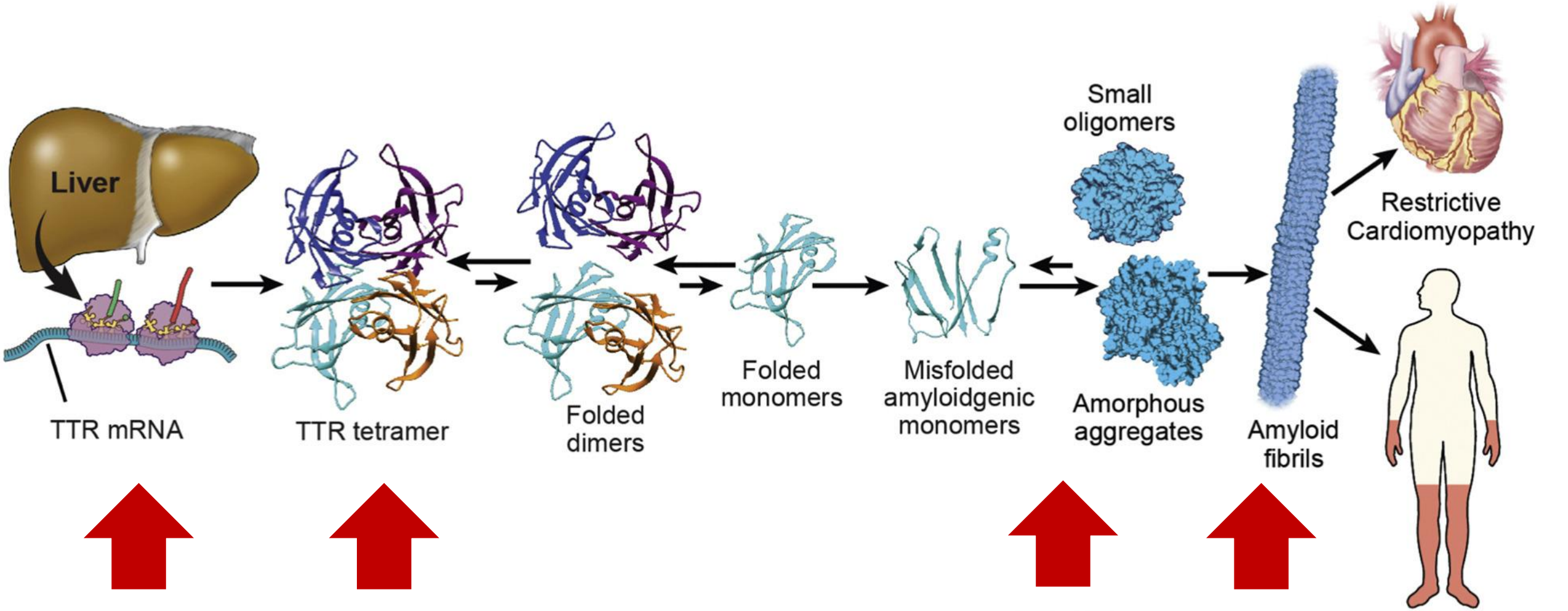
Novel guidance in amlyoidosis

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

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

Garcia-Pavia et al. Eur Heart J 2021; 42:1554-1568

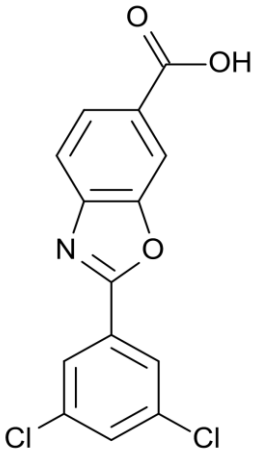
Where and how to intrefere with the disease

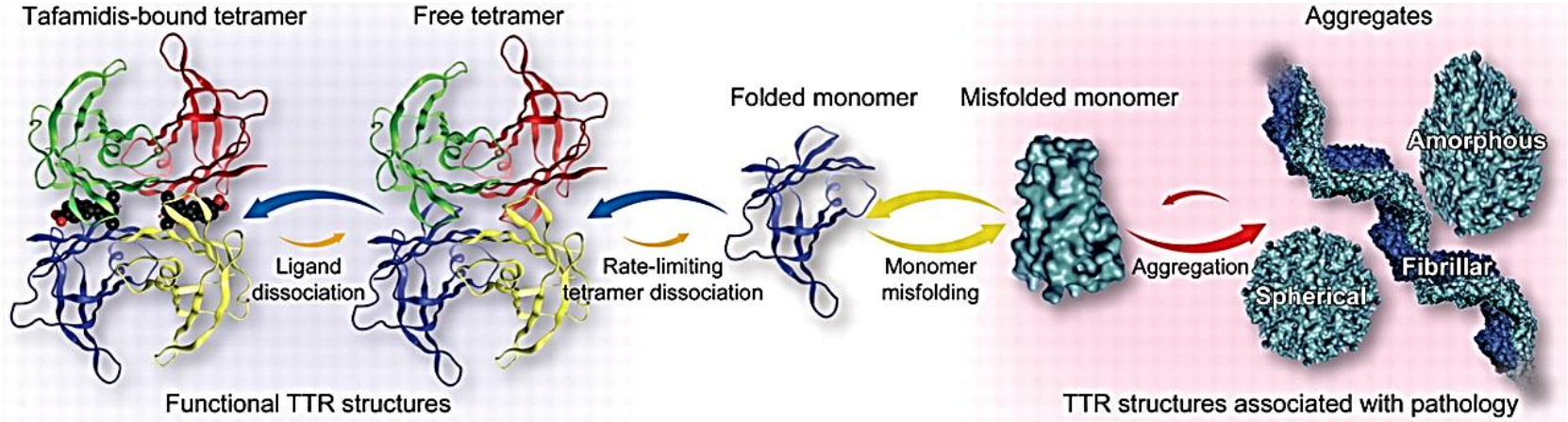


Ruberg et al. J Am Coll Cardiol 2019;73:2872–91

Tafamidis (Vyndaquel®)

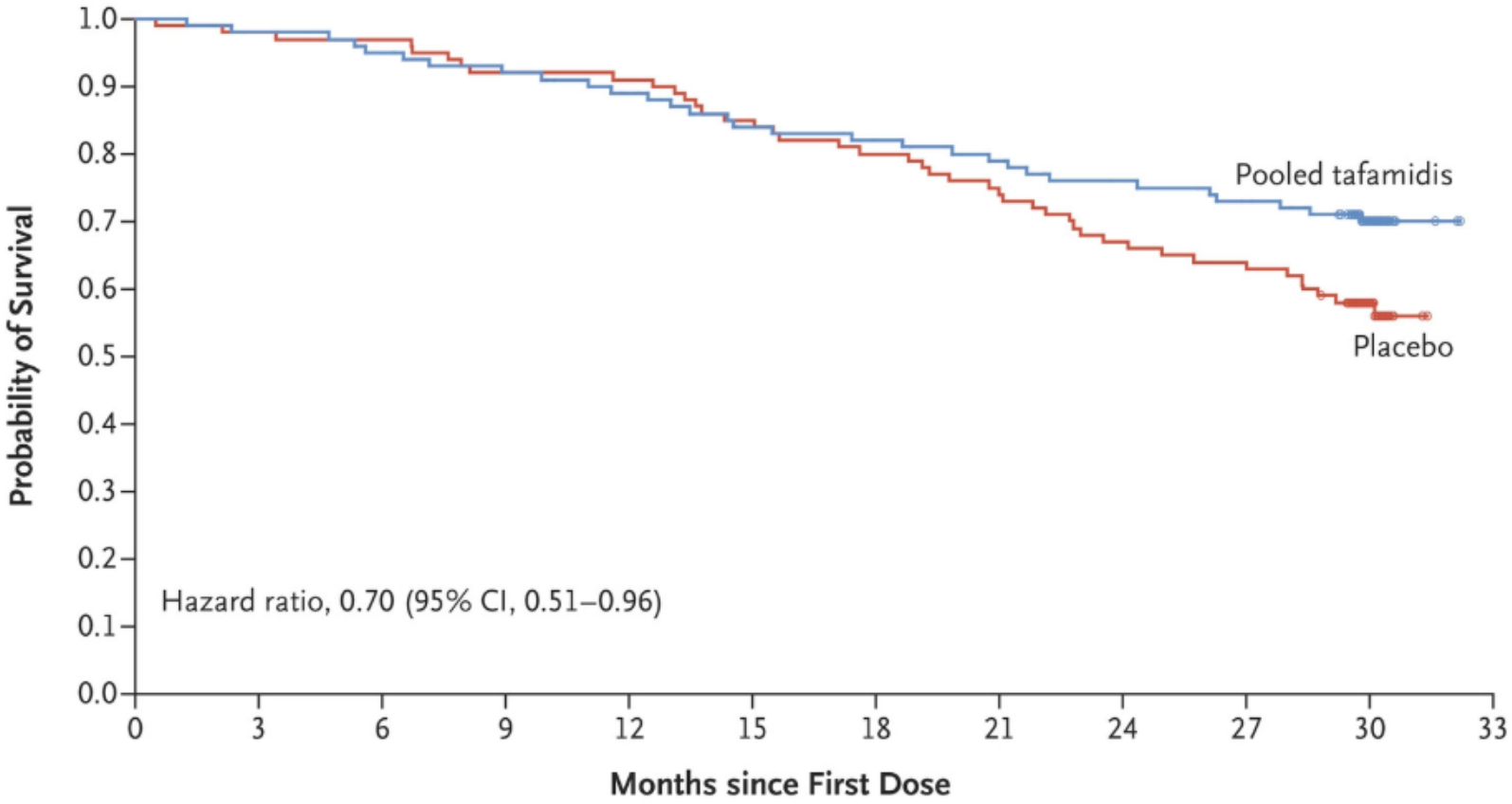
- Léčba hereditární TTR amyloidózy s polyneuropatií (schválen EMA)
- Stabilizace tetramerické formy transthyretinu
- Studie u FAP (familiární polyneuropatie) s pozitivním efektem.
- studie u TTR amyloidotické kardiomyopatie (NCT01994889) –n=400 (FN USA, VFN, IKEM)





Neurology. 2012 Aug 21;79(8):785-92.

ATTR-ACT trial – Tafamidis
All cause mortality



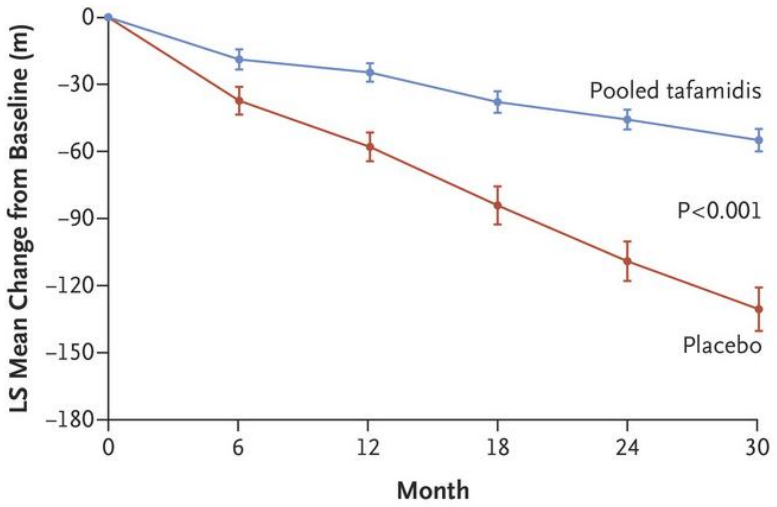
No. at Risk (cumulative no. of events)

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

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

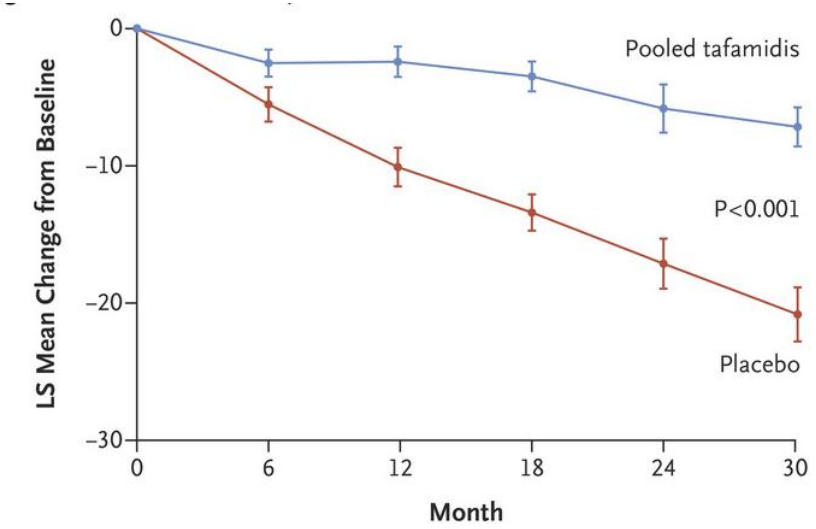
ATTR-ACT trial – Tafamidis

6 minute walk test



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

KCCQ-OS*



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

*Kansas City Cardiomyopathy Questionnaire

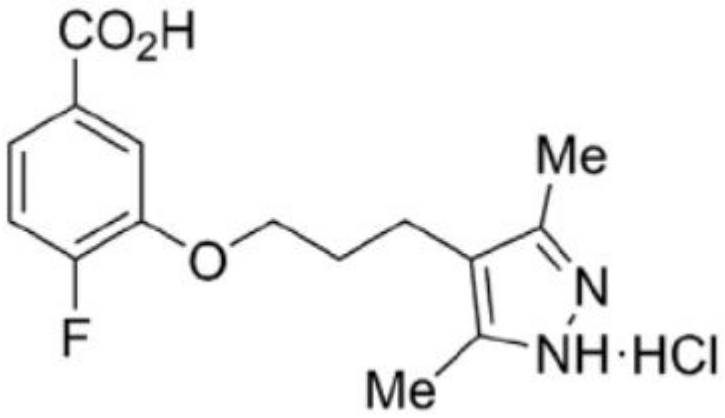
Maurer et al. N Engl J Med 2018; 379:1007-1016

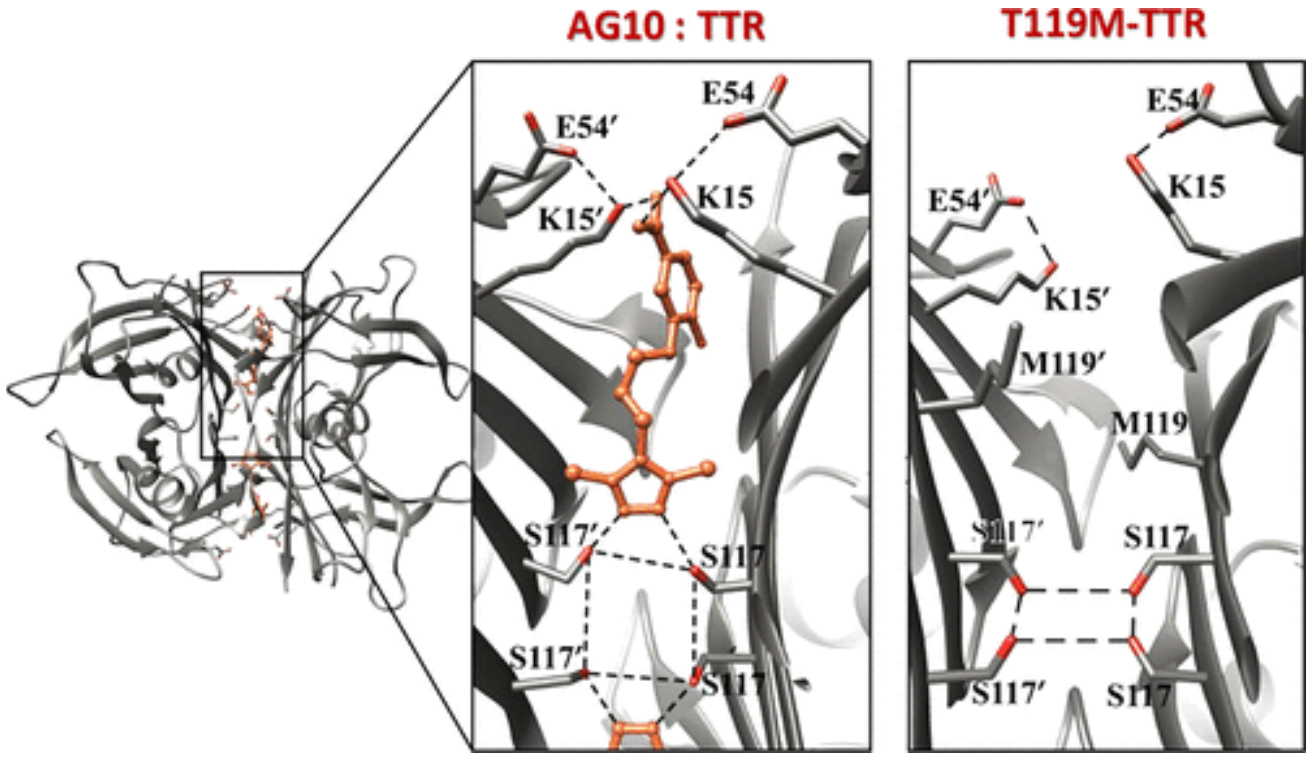
Extenze studie ATTR-ACT

Elliott PM et al.
Circulation: Heart Failure.
2022;15:e008193

AG10

- 2 stabilizing genetic variants in the transthyretin gene (TTR), R104H and T119M
- increased mean plasma transthyretin and thyroxine levels , prolonged life-expectancy[1]
- AG10 is a potent, highly selective TTR stabilizer that was designed to mimic the structural influence of the protective T119M mutation.[2]



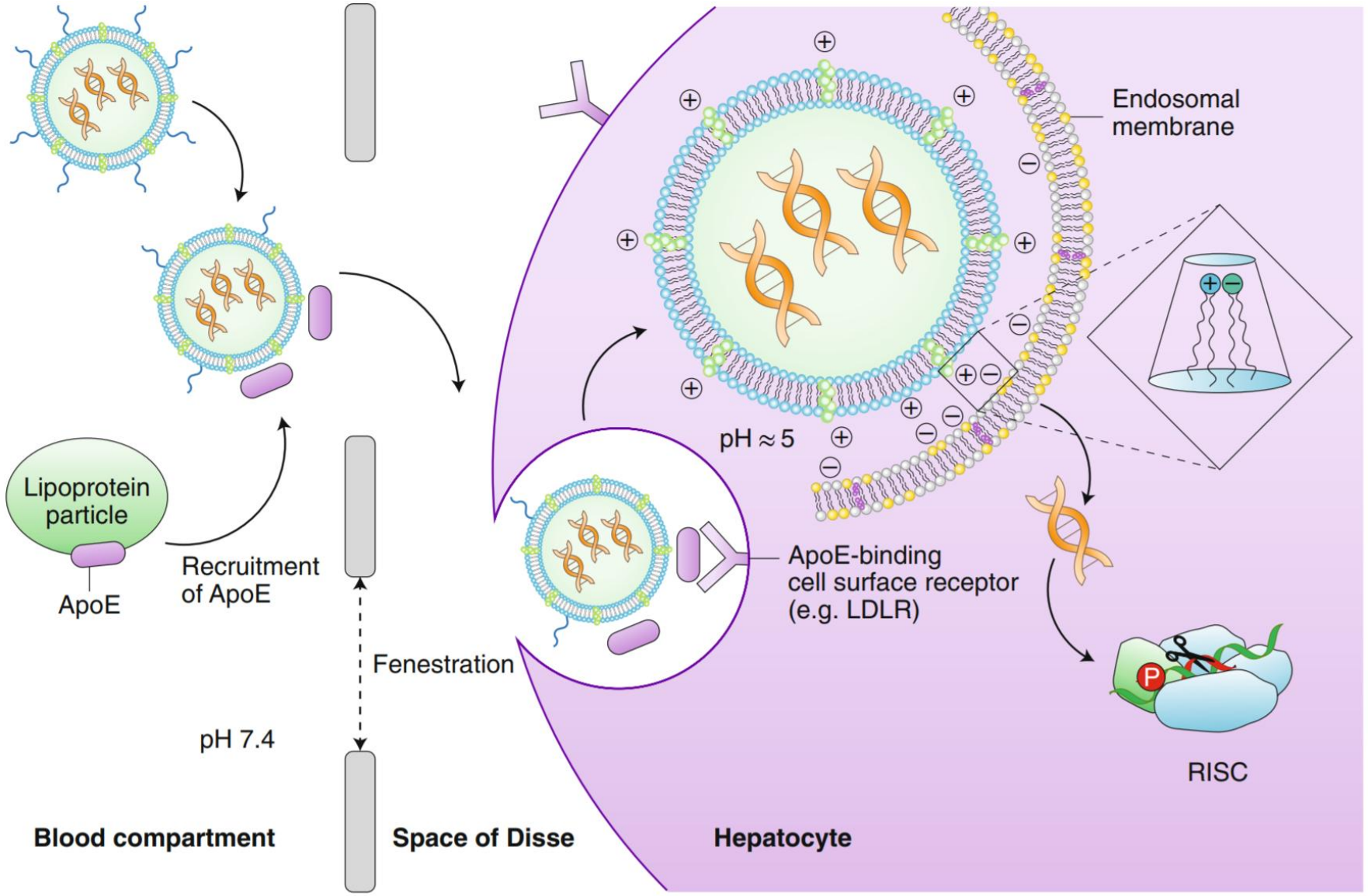


1. Hornstrup LS et al. Arterioscler Thromb Vasc Biol. 2013;33:1441-1447
2. Miller M et al. J Medicinal Chemistry 2018

Small interfering RNA

RISC, RNA-induced silencing complex.

LDLR, low density lipoprotein receptor.



Akinc et al. Nature Nanotechnology volume 14, pages1084–1087(2019)

Mechanisms of siRNA delivery to target tissue

Lipid nanoparticles (LNPs)

- 100 nm size
- Encapsulated siRNA
- Highly efficient liver uptake
- IV administration

- **Patisiran** – clinically validated in APOLLO trial

GalNAc-siRNA conjugates

- N-acetylgalactosamine (GalNAc) ligand conjugated to a modified siRNA
- Targeted to liver delivery
- S.c. administration

- **Revusiran** – stopped after mortality imbalance in phase III trial (ENDEAVOUR)

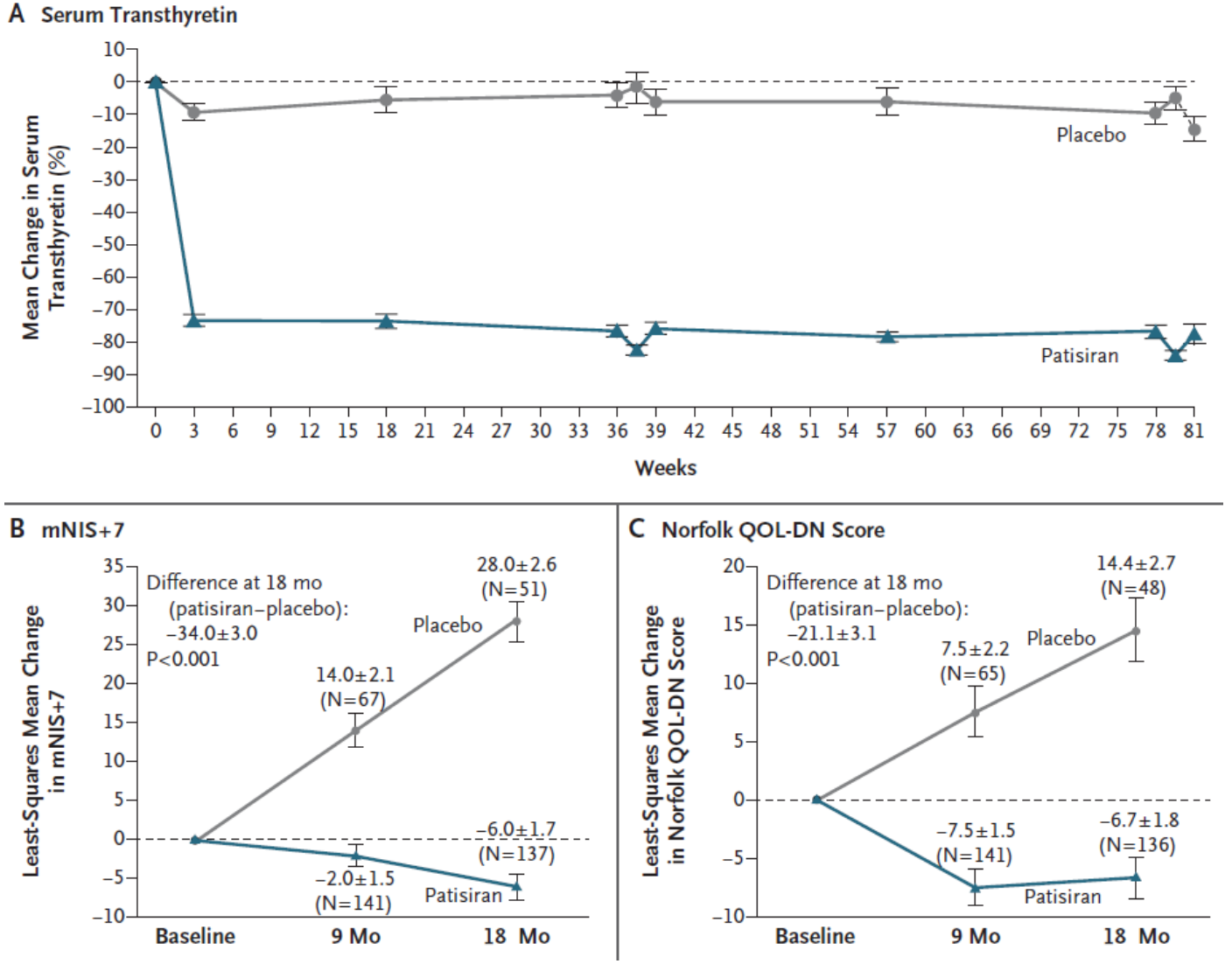
Judge et al.Cardiovascular Drugs and Therapy volume 34, pages357–370(2020)
Adams et al. N Engl J Med 2018;379:11-21.

Randomized trial using patisiran in ATTR neuropathy APOLLO Studv

N = 225
ATTR hereditary neuropathy
i.v. patisiran EOW 0.3 mg/kg

Significant decrease in
- **NT-proBNP**
- **LV mass index**

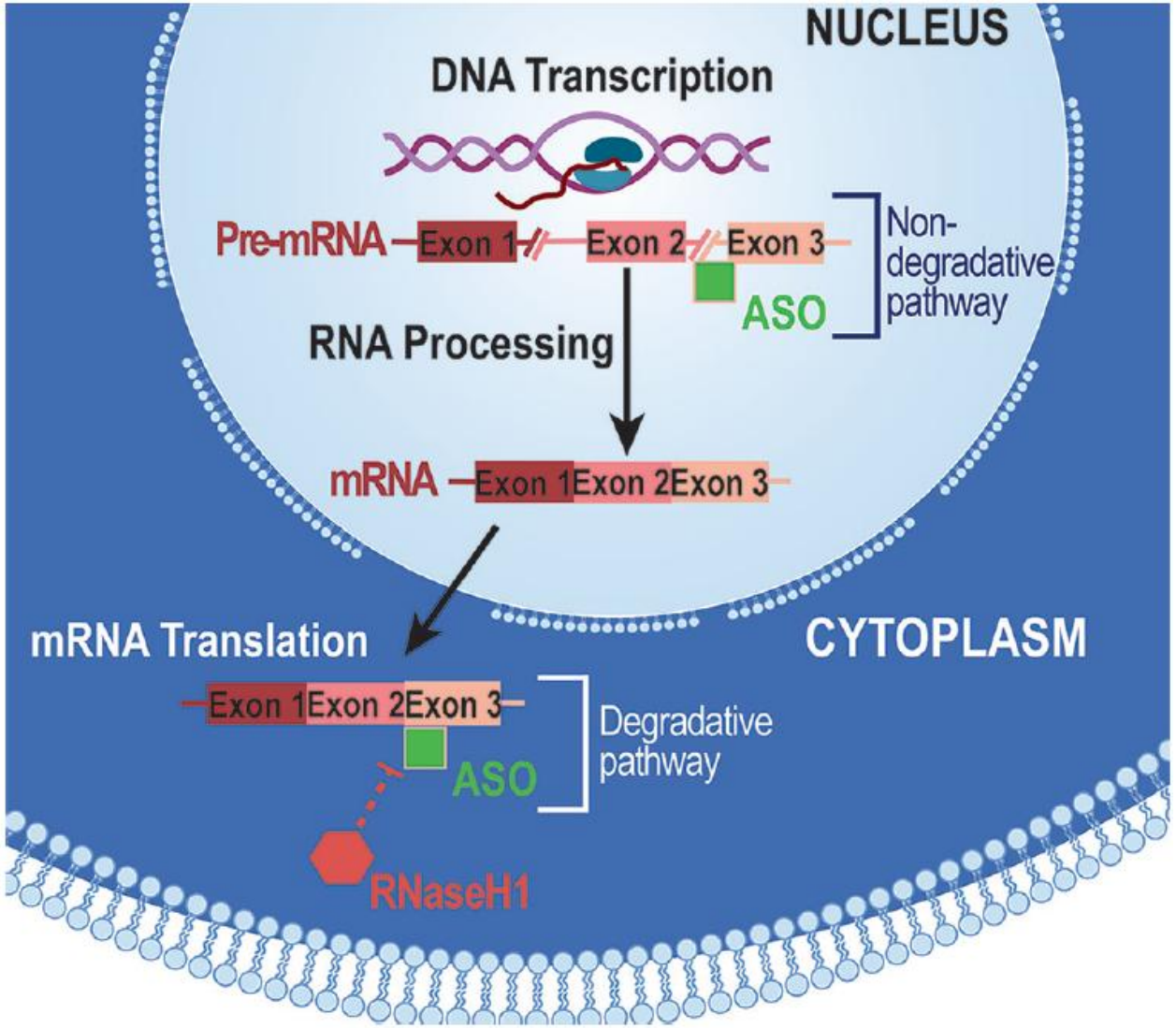
Significant improvement in
- **LV longitudinal strain**



Adams et al. N Engl J Med 2018;379:11-21.

Antisense oligonucleotides

- Synthetically derived short (18-50 base pairs) single-stranded oligonucleotides
- Designed to **target and modify mRNA function by base pairing**.
- The ASOs bind complementarily to
  - pre-mRNA in the nucleus
  - mature mRNA in the cytoplasm,
- Modulation of gene expression

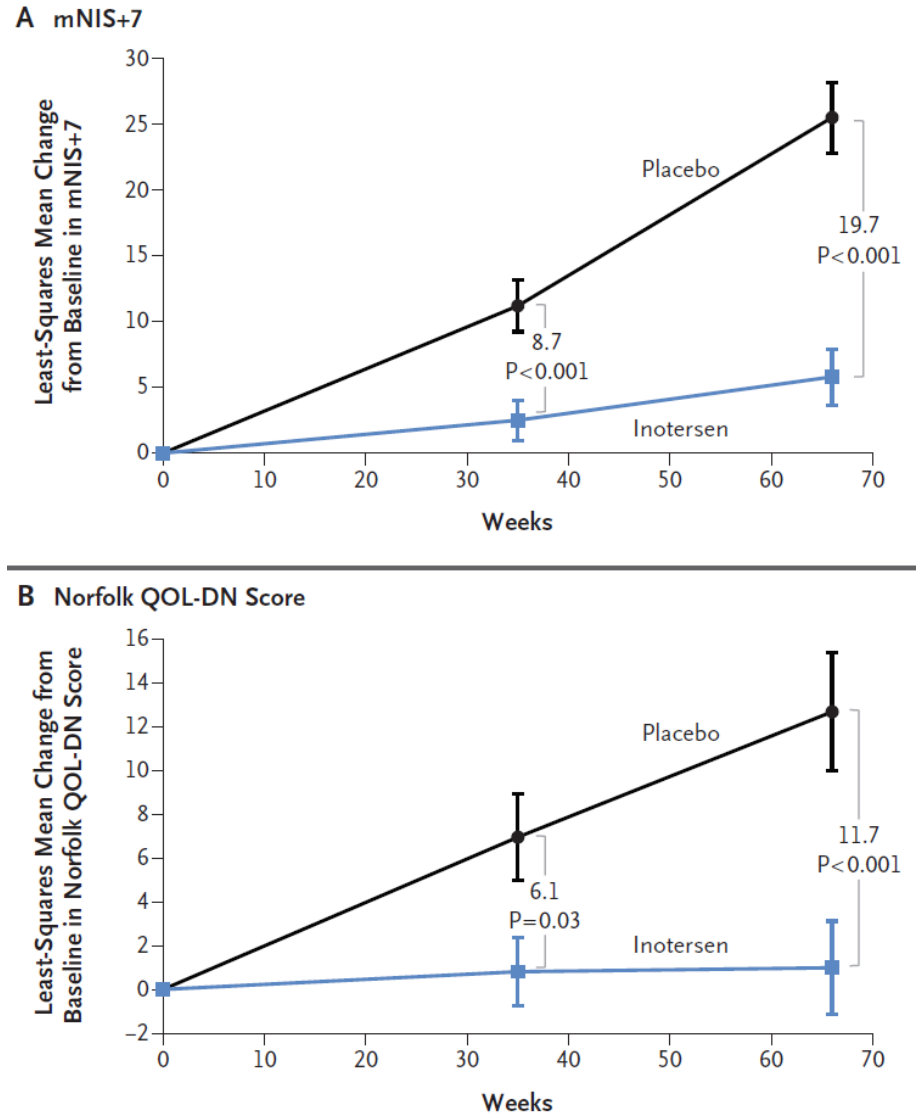


Van Laar and Van Laar, Practical Neurology 2019

Randomized trial with inotersen

- N=173 (2:1)
- **antisense oligonucleotide inhibitor of the hepatic production of TTR**
- ATTR hereditary neuropathy
- 5 deaths with intoresen / 0 with placebo

- Thrombocytopenia



Benson et al. N Engl J Med 2018;379:22-31.

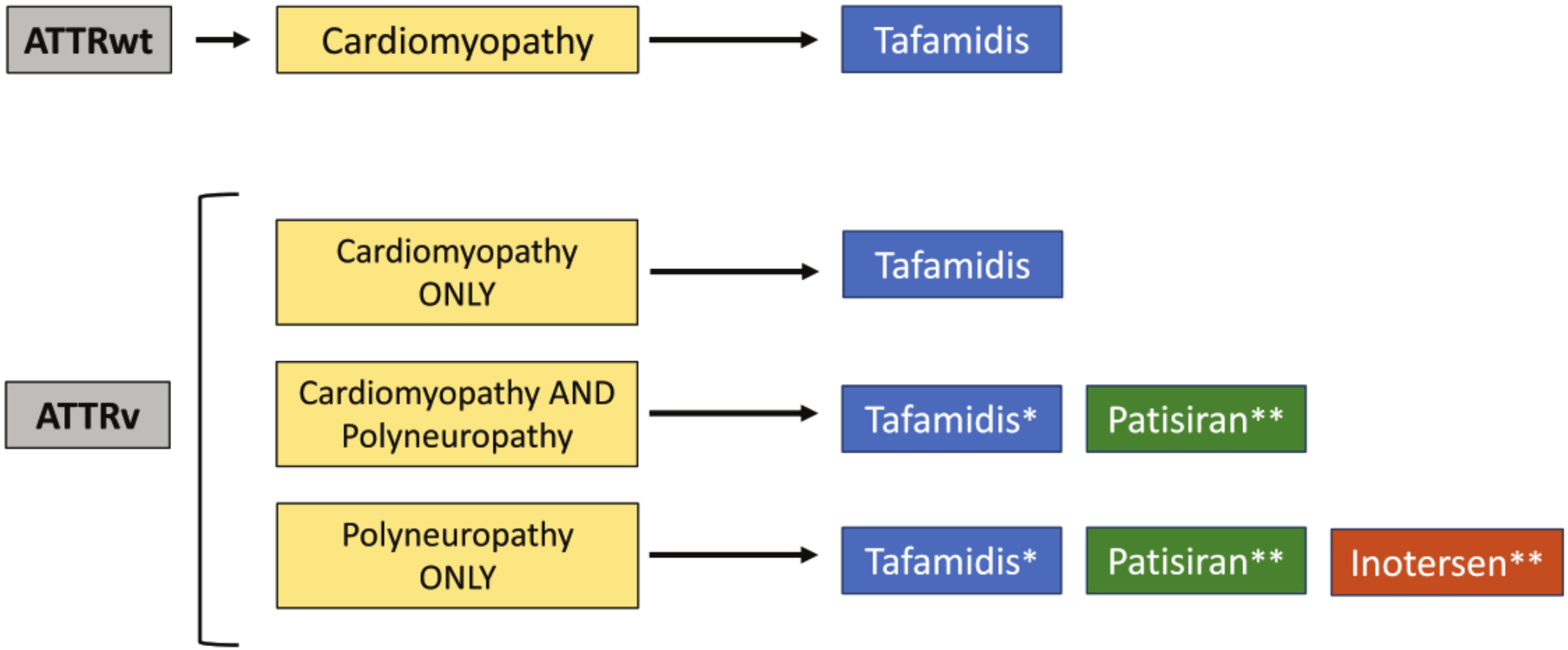
Antibodies targeting serum amyloid P protein or amyloid fibrils

- Serum amyloid P (SAP) is a normal plasma glycoprotein synthetized by the liver, which stabilizes and protects amyloid fibrils from proteolytic degradation
- Miridesap small molecule binding to SAP → hepatic clearance.
- Phase 2 study miridesap followed by antiSAP Ab – prematurely stopped in 2018 – no further development

- Monoclonal antibody targeting TTR amyloid deposits (PRX004) - ongoing phase 1 study on ATTRv.

Emden et al.European Heart Journal (2019) 40, 3699–3706

Therapy of TTR amylodosis according to subtypes



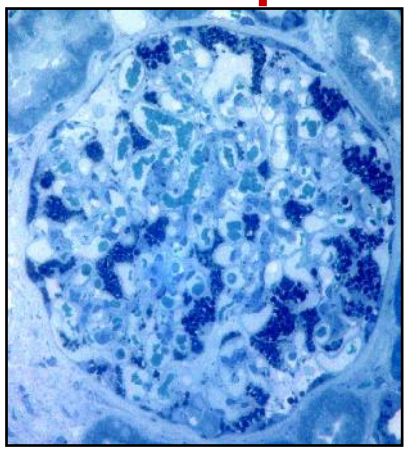
* Polyneuropathy Stage 1
** Polyneuropathy Stage 1 & 2

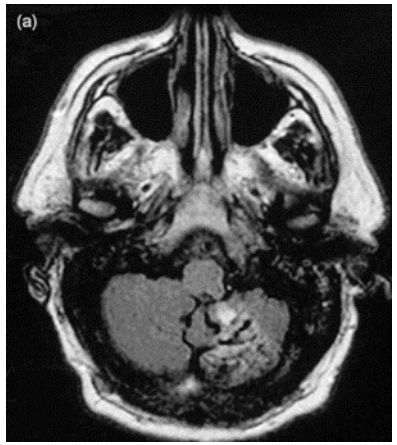
Garcia-Pavia P. European Journal of Heart Failure (2021)

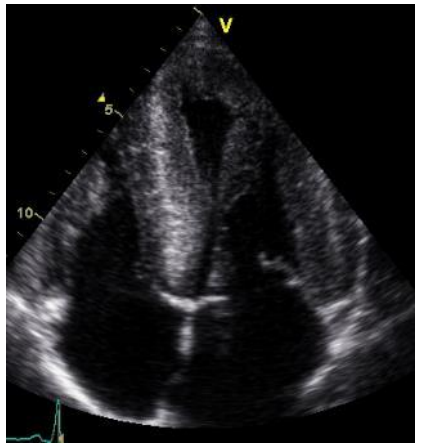
FABRY DISEASE

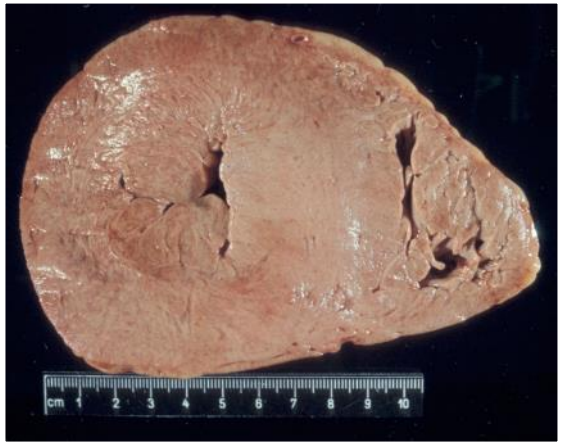
Fabry phenotypes

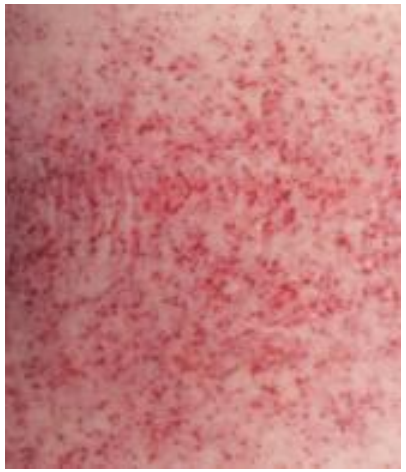
- **Classical / multiorgan**
- **Late onset / variant**

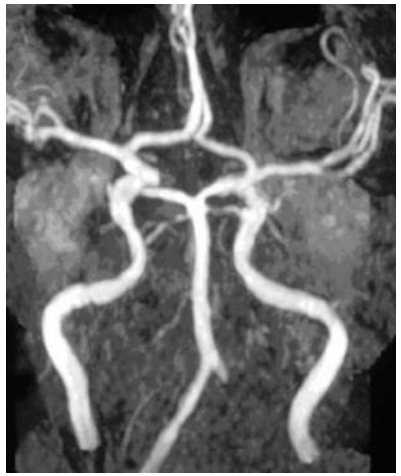












Adapted from: Mehta et al. Eur J Clin Invest 2004;34: 236–242; Hegemann, S. Eur J Clin Invest. 2006;36:654-62.; Burlina et al. J Neurol 2008;255:738–744; Elleder et al. Virchows Arch A Pathol Anat Histopathol. 1990;417:449-55.

Targeted therapies in Fabry disease

- Enzyme replacement therapy
  - Agalsidase alfa (0.2 mg/kg/EOW)[1]
  - Agalsidase beta (1mg/kg/EOW) [2]
- Chaperone
  - Migalastat 123 mg orally, every other day [3]

- In development
  - Novel enzymes (pegylated plant-derived enzyme) [4]
  - Substrate-reduction therapies[5]
  - Genetic therapies[6]

1. Schiffmann et al., JAMA 2001;285:2743-9
2. Eng MC et al., NEJM 2001;345:9-16
3. Germain et al. N Engl J Med 2016; 375: 545–555.
4. Schiffmann et al. J Inherit Metab Dis. 2019 May;42(3):534-544
5. Viel et al. Sci Rep 11, 20945 (2021)
6. Domm et al. Mol Genet Metab 2021;134:117-131

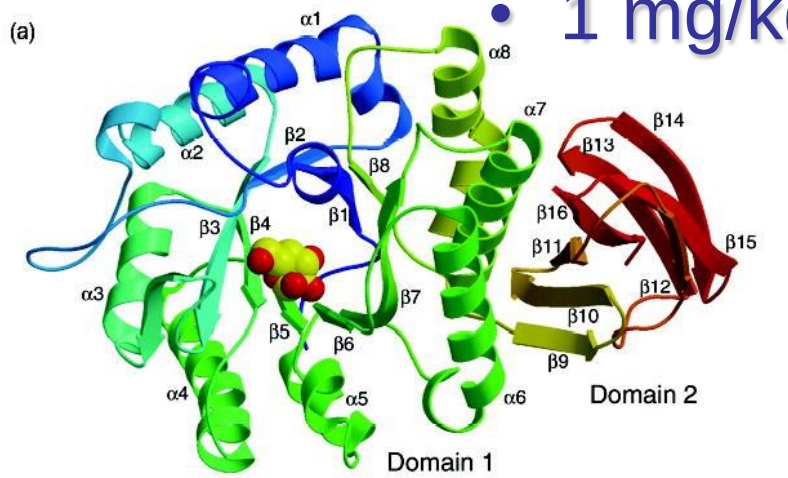
Enzyme replacement therapy

AGALSIDASE ALFA

- *Schiffmann R and Brady RO, JAMA 2001;285:2743-9*
- human fibroblasts
- 0.2 mg/kg EOW

AGALSIDASE BETA

- *Eng MC and Desnick RJ, NEJM 2001;345:9-16*
- chinese hamster ovary
- 1 mg/kg EOW



Aminoacid sequence almost identical (minimal posttranslational differences), differ in glycosylation (sialylation, mannose-6-phosphate)

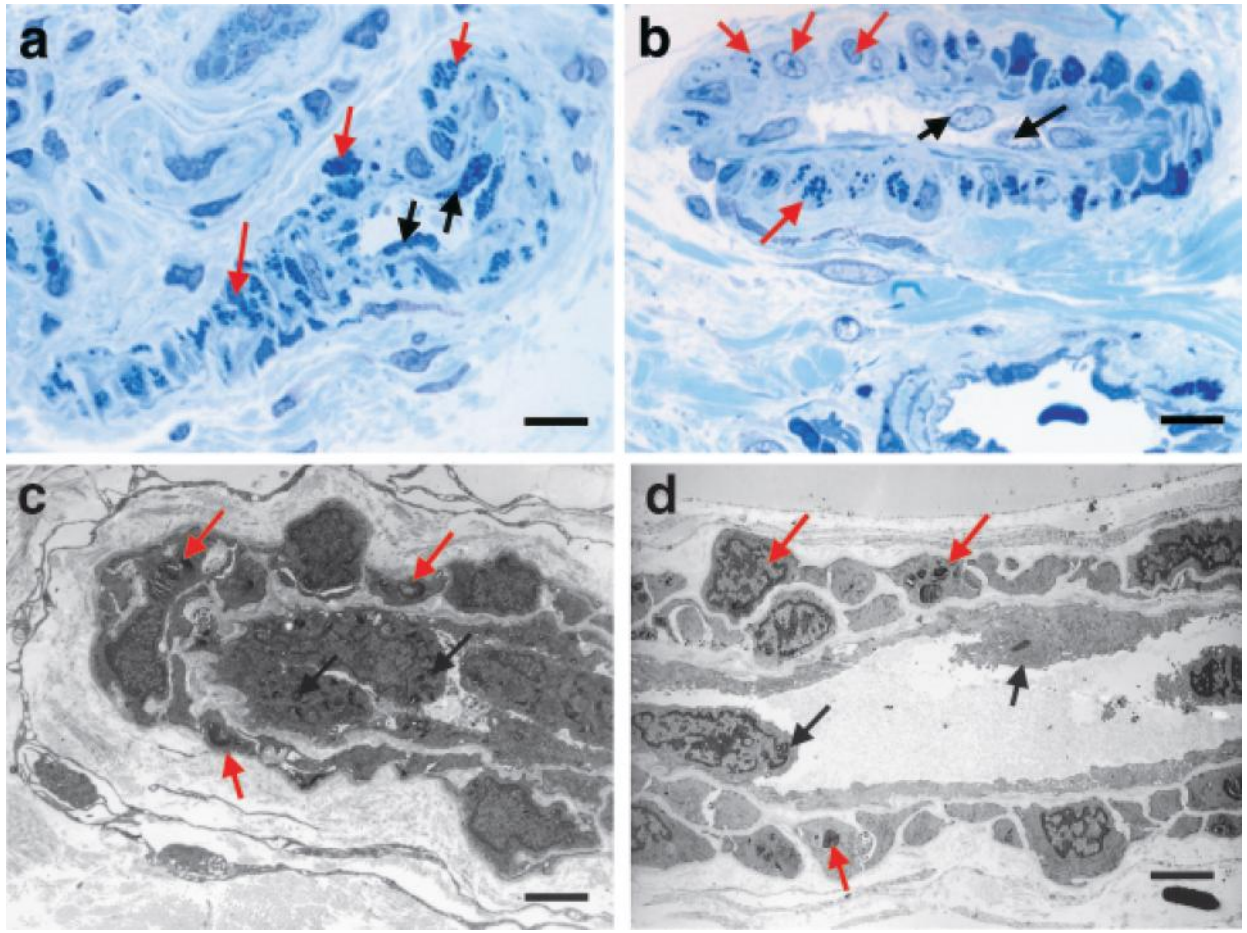
Lee k. et al. Glycobiology. 2003 Apr;13(4):305-13.

After ERT – Gb_3 is cleared from endothelial cells and reduced in smooth muscle cells

Enzyme replacement therapy (ERT) = Agalsidase beta – 36 months

Skin biopsy

Red arrows = endothelial cells
Black arrows = smooth mucle cells



pre-treatment post-treatment

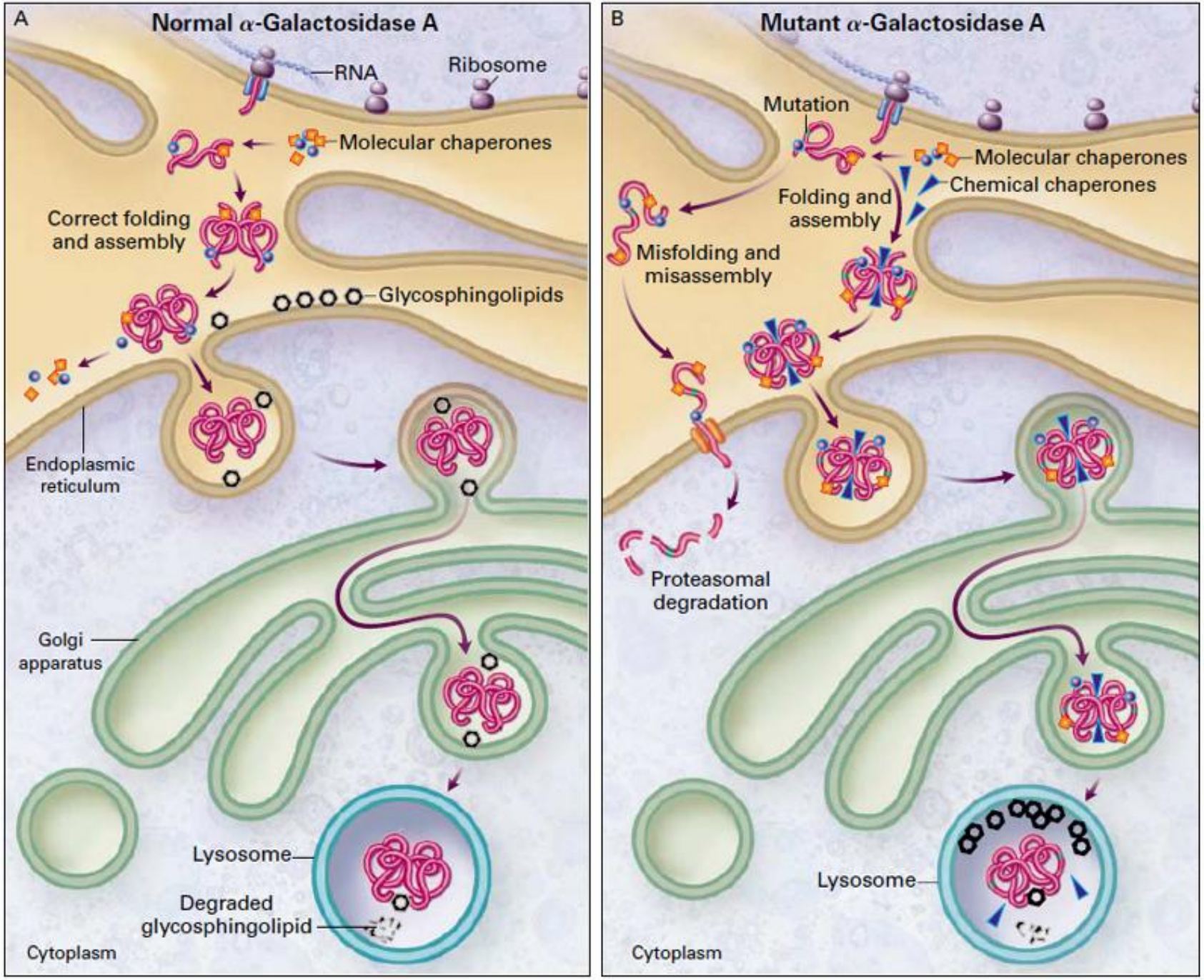
(a and b – magnification x100, scale bar = 10 μm).
(c - electron microscopy magnification x 3000, scale bar = 2.43 μm).
(d - electron microscopy -magnification x 2000, scale bar = 2.95 μm)

Thurberg BL et al. J Invest Dermatol. 2004 Apr;122(4):900-8.

Approved enzyme replacement therapies for LSDs

Disease	Product (generic name)	Manufacturer
Fabry Disease	Fabrazyme® (agalsidase beta)	SanofiGenzyme
	Replagal® (agalsidase alfa)	Shire Human Genetic Therapies, Inc.
Gaucher Disease Type 1	Cerezyme® (imiglucerase)	SanofiGenzyme
	VPRIV™ (velaglucerase alfa)	Shire Human Genetic Therapies, Inc.
	Elelyso™ (taliglucerase)	Pfizer Labs
Glycogen storage disease type II. Pompe	Myozyme® (alglucosidase alfa)	SanofiGenzyme
	Lumizyme® (alglucosidase alfa)	SanofiGenzyme
MPS I (Hurler, Hurler-Scheie, Scheie)	Aldurazyme® (laronidase)	SanofiGenzyme
MPS II (Hunter)	Elaprase® (idursulfase intravenous)	Shire Human Genetic Therapies, Inc.
MPS VI (Maroteaux-Lamy syndrome)	Naglazyme™ (galsulfase)	BioMarin Pharmaceutical, Inc.

Adapted from Ratko TA, Marbella A, Godfrey S, et al. Technical Briefs, No. 12.;2013

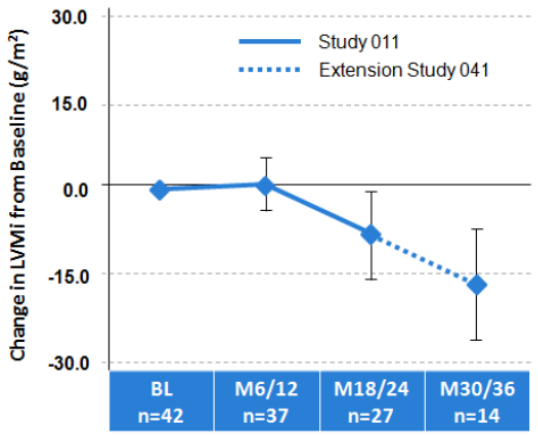

A
Normal α-Galactosidase A
RNA
Ribosome
Molecular chaperones
Correct folding and assembly
Glycosphingolipids
Endoplasmic reticulum
Golgi apparatus
Lysosome
Degraded glycosphingolipid
Cytoplasm
B
Mutant α-Galactosidase A
Mutation
Molecular chaperones
Chemical chaperones
Folding and assembly
Misfolding and misassembly
Proteasomal degradation
Lysosome
Cytoplasm

LV mas changes in two independent randomized controlled trials (FACETS and ATTRACT)

- ATTRACT – 18 mo., open label, ERT switch to migalastat (n=36) or continue ERT (n=24)
- FACETS – 6 mo, double-blind, Rx naïve, migalastat (n=34) or placebo (n=33)
- Open-label extensions

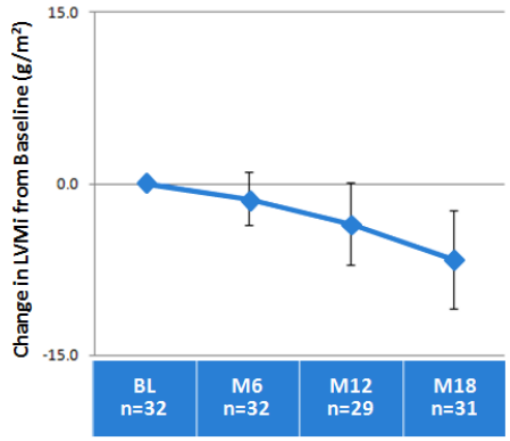
FACETS

AT1001-011+041 (ERT Naïve): LVMi CFB on Migalastat



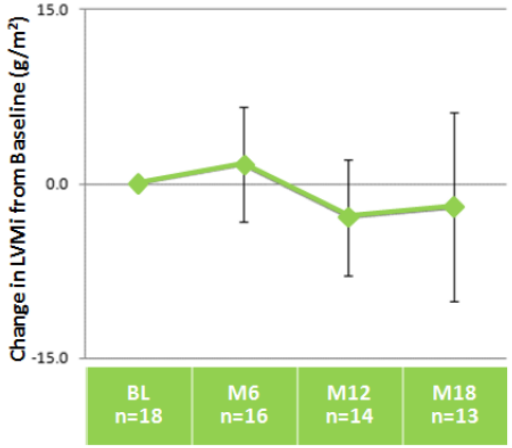
ATTRACT – migalastat

AT1001-012 (ERT Switch): LVMi CFB on Migalastat



ATTRACT - ERT

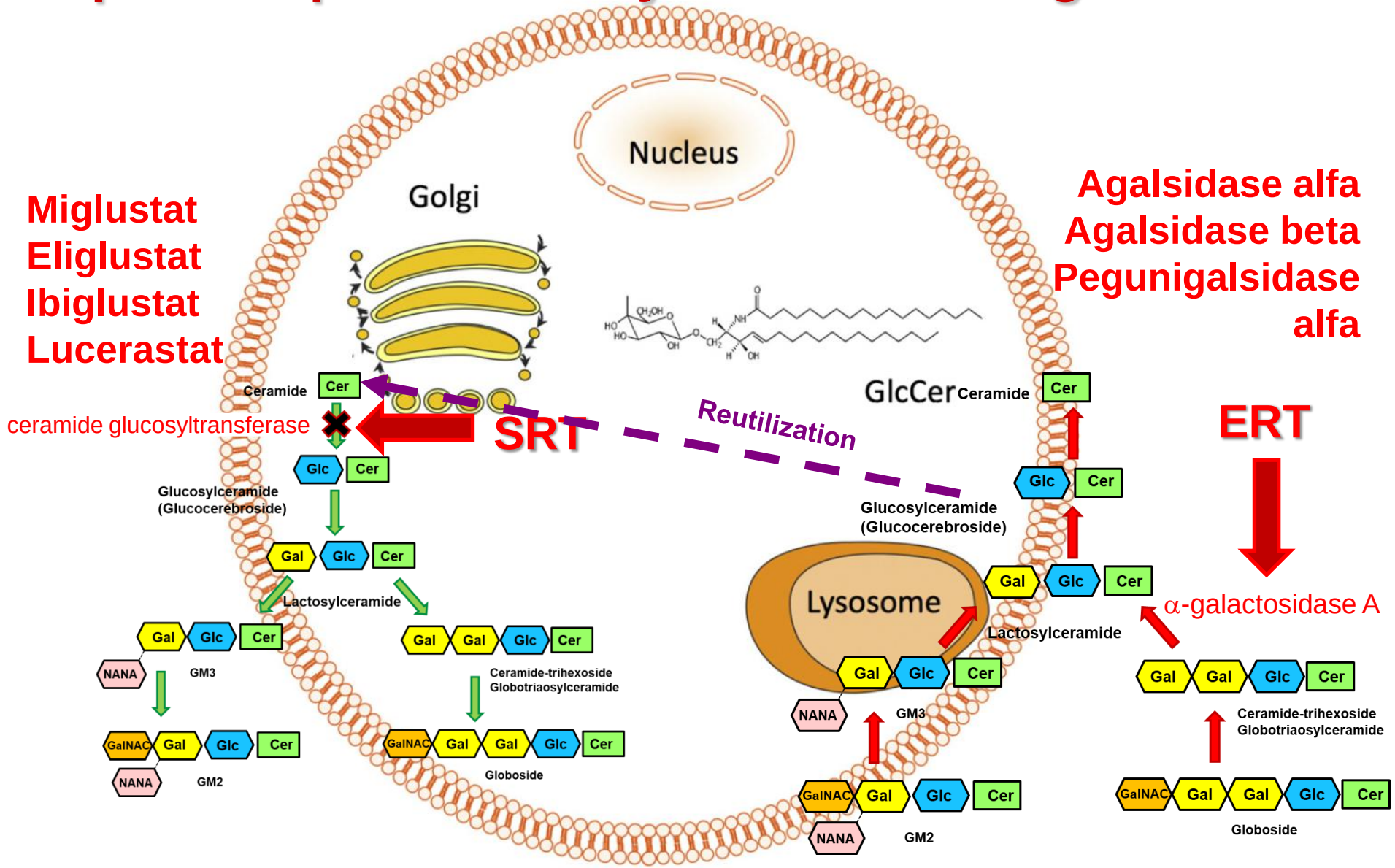
AT1001-012 (ERT): LVMi CFB on ERT



mITT analysis – excluding patients with „non-amenable“ mutations

Germain et al. N Engl J Med 2016;375:545-55.
Hughes DA, et al. J Med Genet 2017;54:288–296.
Bichet DG et al. Mol Genet Metab Rep. 2021

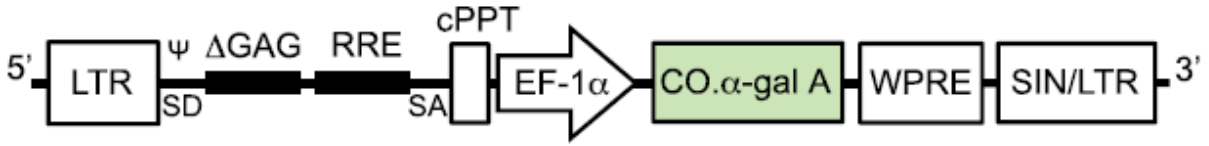
Spatial separation of synthesis and degradation

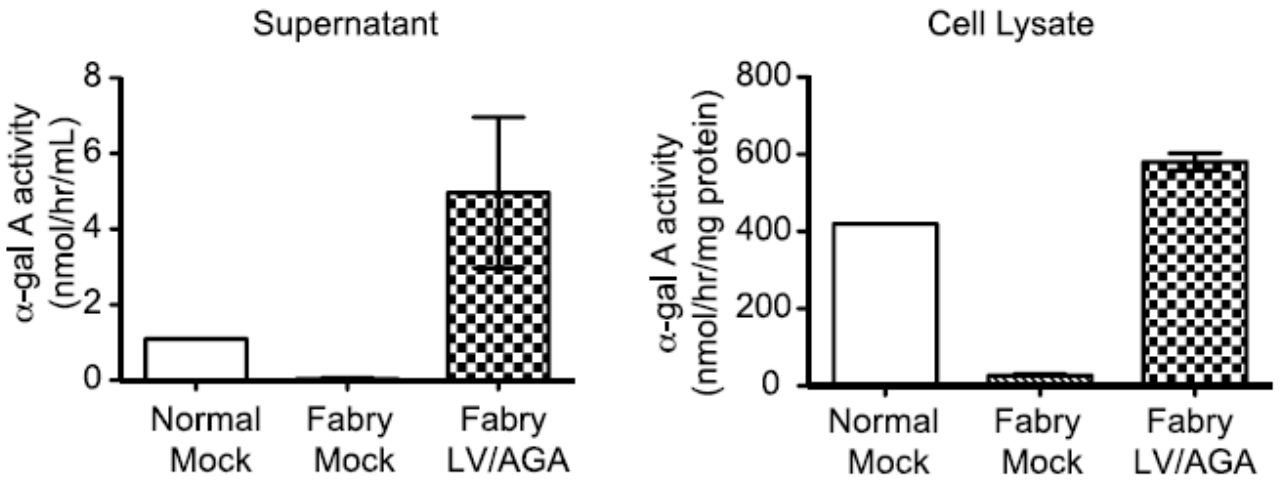


Modified from Futterman and Platt Molecular Genetics and Metabolism 120 (2017) 22–26

Gene Therapy - The near future?

- Lentivirus vectors
- Fabry patients transduced CD34+ hematopoietic cells
- Tested in Fabry mice models
- First-in-the-world trial approved and started in Canada





Huang J et al. Molecular Therapy: Methods & Clinical Development 2017;5:241-7

Conclusions:

- **Therapeutic approach „one size fits all“ comes to its end**
- **Mavacamten as myosin inhibitor in HOCM may be the last molecule used in a wide spectrum of mutations**
- **Understanding disease heterogeneity and cpecific diagnosis will be the key for targeted therapies**
- **Amyloidosis and lysosomal storage diseases demonstrate that understanding the patophysiological process in details leads to rapid discovery of multiple therapies**