7th Advances in Heart Failure 2024

10 e 11 de Outubro

FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

Terapêuticas inovadoras na Miocardiopatia hipertrófica

Nuno Cardim, MD, PhD, FESC, FACC
S. Cardiologia, Hospital CUF-Descobertas, Lisbon, Portugal
Nova Medical School, Lisbon, Portugal

Disclosures

Myokardia/BMS EXPLORER & LTE investigator, mavacamten advisory board member

Cytokinetics SEQUOIA: initial investigator, aficamten advisory board member

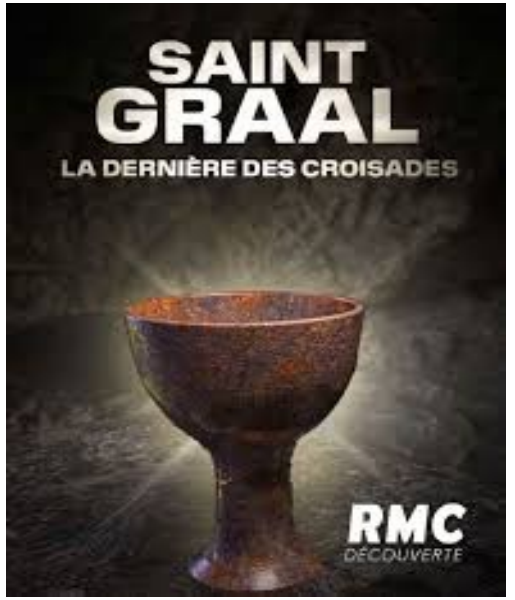
The advent of "pathophysiology- targeted" treatments for HCM

1. Non genetic

- Modulation of m… (perhexiline, trimetazidine, ninerafaxstat)
- Inhibition of late- sodium channels (ranolazine and eleclazine)
- Reduction of fibrosis (spironolactone, valsartan, losartan)
- Stabilization of mutant prot… …ators of MYBCP)
- SGLTsi
- **Myosin inhibitors**

2. Genetic therapy

- Editing
- Replacement
- Silencing
- Modulation



Myosin inhibitors

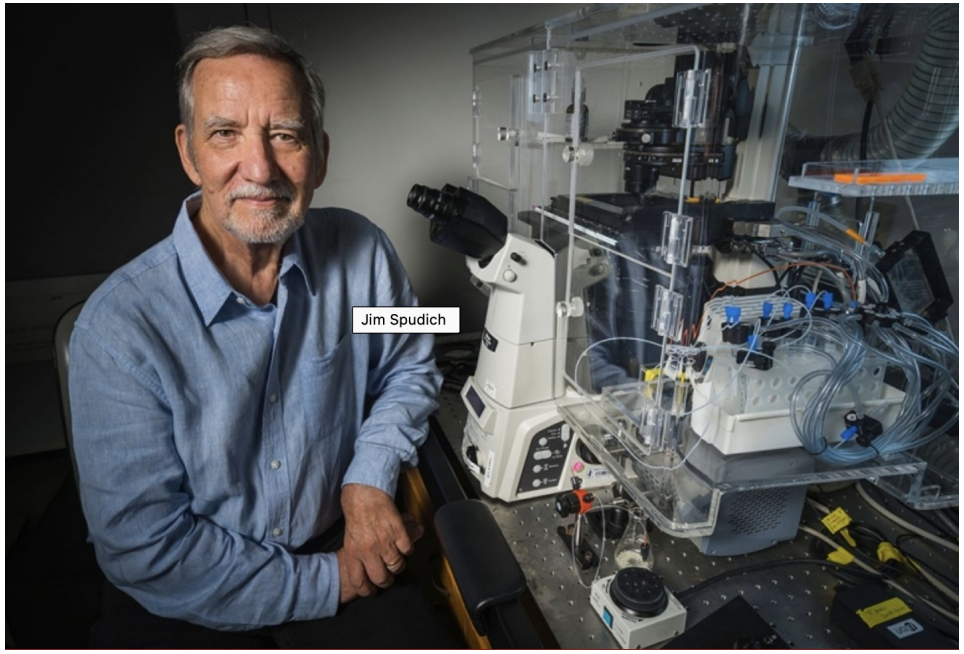
Myosin inhibitors

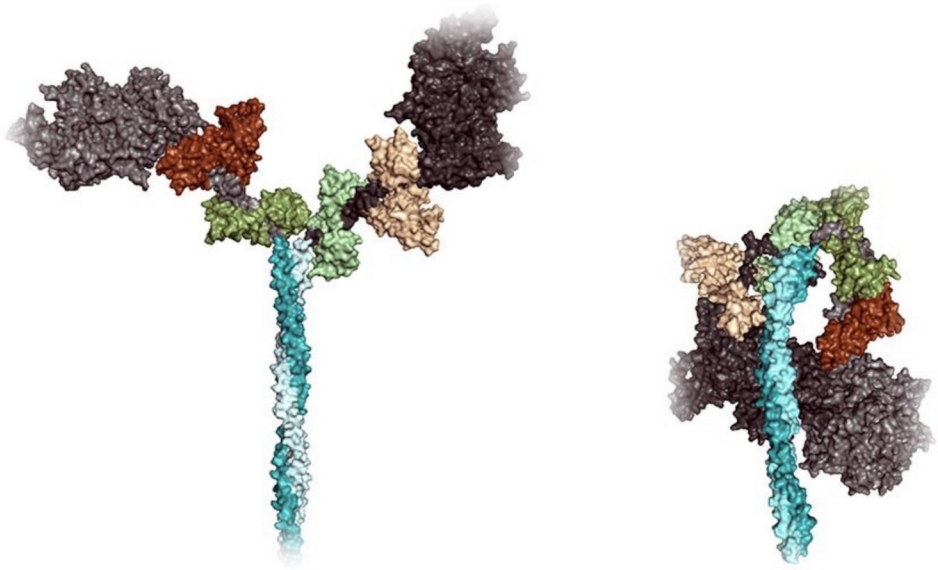
Mystery novel and dream spur key scientific insight into heart defect

On Dec. 14, 2014, after many months of not getting expected results, biochemist Jim Spudich got into bed, read a chunk of a novel, fell asleep and had a dream that would change the thinking in his field about what causes a common and often lethal heart defect.

2014

%"on-off" myosin-actin crossbridges

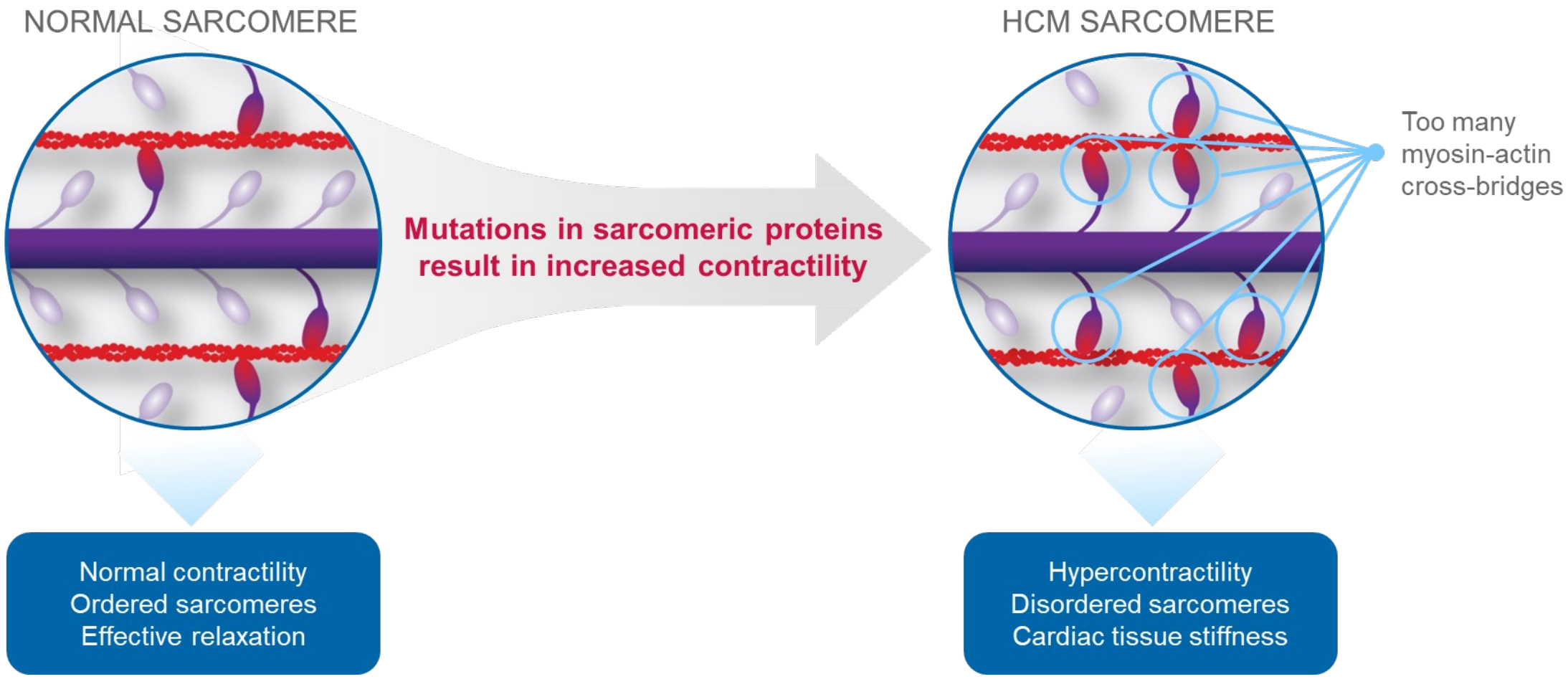




cofounder and member of the scientific advisory boards of **MyoKardia** and of **Cytokinetics**

https://med.stanford.edu/news/all-news/2019/03/mystery-novel-and-dream-spur-key-scientific-insight.html

HCM: a myosin-actin cross bridges disease



Libby P et al. Braunwald's Heart Disease. 11th ed. 2018.

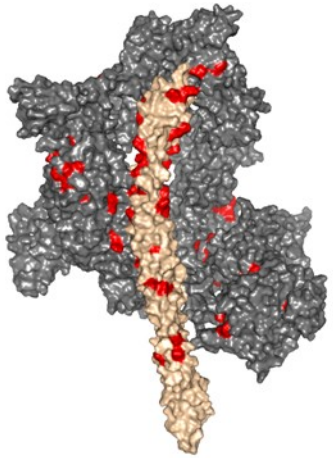
Myosin in sarcomeric HCM

Normals: 50-60% myosins " "on"

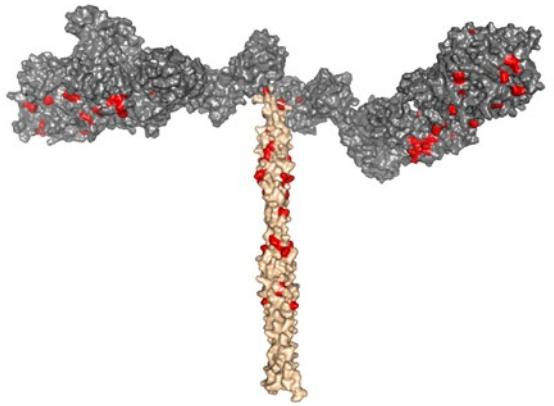
In a healthy heart, 40-50% of myosins are in an "off" state

HCM: 80-85% myosins "on"

In HCM, many mutations destabilize this state, and 15-20% of myosins are in an "off" state



"Off" state
No contraction



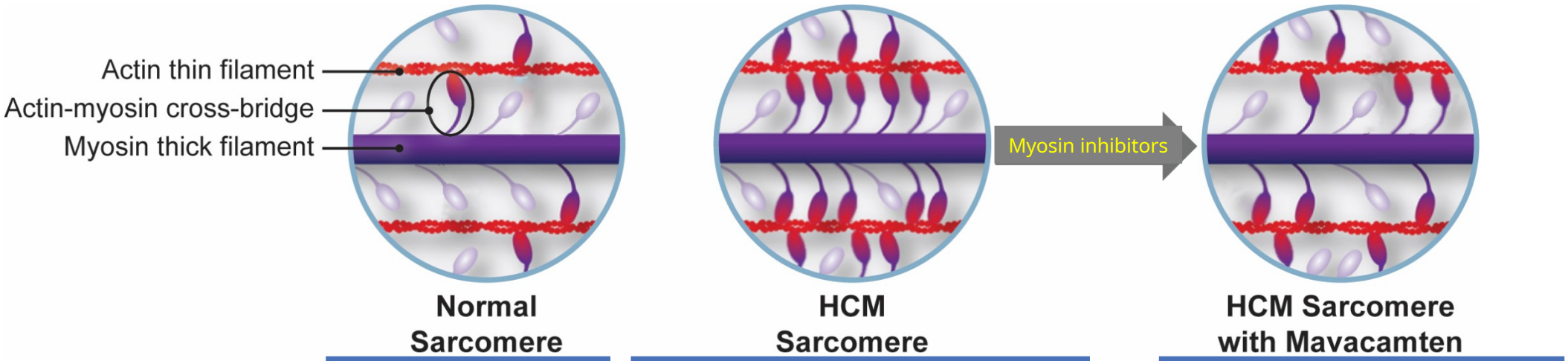
"On" state
Able to contract

Too many myosins in the "on" state in HCM are thought to engage **too many cross-bridges** leading to **excess contractility** and **impaired relaxation**

L et al. eLife 6, e24634. 2017. Trivedi DV et al. Biophys Rev 110, 27-48. 2018.
Anderson RL et al. Proc Natl Acad Sci U S A 115:E8143-E8152. 2018.

Alosteric inhibitor: modifies the active site of myosin to the" off state" so that actin binding is reduced

Myosin inhibitors: Mechanism of Action

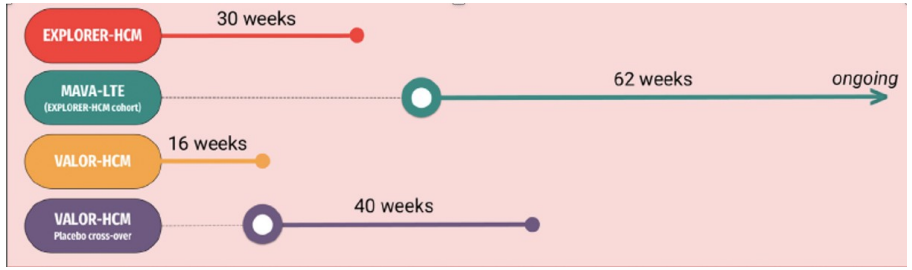


Normal Sarcomere	HCM Sarcomere	HCM Sarcomere with Mavacamten
Normal contractility Effective relaxation	**HCM Pathophysiology** "Hypercontractility" Impaired relaxation Altered myocardial energetics	Attenuated hypercontractility ?Improved relaxation ?Improved energetics

Myosin inhibitors are selective allosteric inhibitor of cardiac myosin

→ Reduce the number of myosin-actin cross-bridges and thus decreases excessive contractility characteristic of HCM

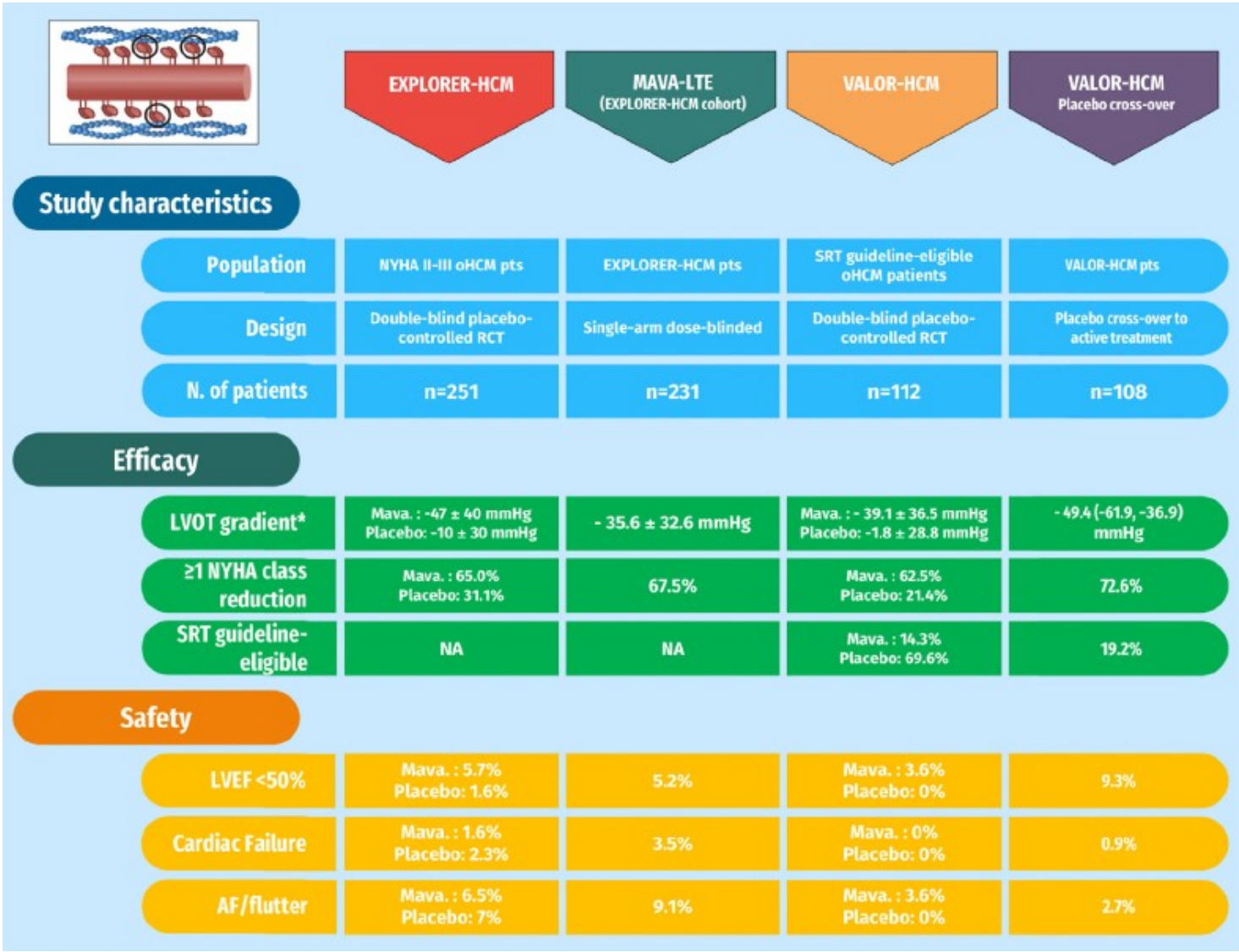
Mavacamten



Effective & safe

> exercise capacity, < LVOTO, > diastolic function < biomarkers, <symptoms & > health status in oHCM ...

EF, interactions, dosage titration...



	EXPLORER-HCM	MAVA-LTE (EXPLORER-HCM cohort)	VALOR-HCM	VALOR-HCM Placebo cross-over
Study characteristics				
Population	NYHA II-III oHCM pts	EXPLORER-HCM pts	SRT guideline-eligible oHCM patients	VALOR-HCM pts
Design	Double-blind placebo-controlled RCT	Single-arm dose-blinded	Double-blind placebo-controlled RCT	Placebo cross-over to active treatment
N. of patients	n=251	n=231	n=112	n=108
Efficacy				
LVOT gradient*	Mava. : -47 ± 40 mmHg Placebo: -10 ± 30 mmHg	- 35.6 ± 32.6 mmHg	Mava. : - 39.1 ± 36.5 mmHg Placebo: -1.8 ± 28.8 mmHg	- 49.4 (-61.9, -36.9) mmHg
≥1 NYHA class reduction	Mava. : 65.0% Placebo: 31.1%	67.5%	Mava. : 62.5% Placebo: 21.4%	72.6%
SRT guideline-eligible	NA	NA	Mava. : 14.3% Placebo: 69.6%	19.2%
Safety				
LVEF <50%	Mava. : 5.7% Placebo: 1.6%	5.2%	Mava. : 3.6% Placebo: 0%	9.3%
Cardiac Failure	Mava. : 1.6% Placebo: 2.3%	3.5%	Mava. : 0% Placebo: 0%	0.9%
AF/flutter	Mava. : 6.5% Placebo: 7%	9.1%	Mava. : 3.6% Placebo: 0%	2.7%

Ammirati,JACC HF 2024

Mavacamten

THE LANCET

This journal · Journals · Publish · Clinical · Global health · Multimedia · Events · About

ARTICLES · Volume 396, Issue 10253, P759-769, September 12, 2020 · Download Full Issue

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

Dr Iacopo Olivotto, MD [a,b] · Artur Oreziak, MD [c] · Roberto Barriales-Villa, MD [d,e,f,g,h] · Prof Theodore P Abraham, MD [i] · Ahmad Masri, MD [j] · Pablo Garcia-Pavia, MD [h,k,l] · et al. Show more

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 80, NO. 2, 2022

ORIGINAL INVESTIGATIONS

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

Milind Y. Desai, MD, MBA,[a,b,c] Anjali Owens, MD,[d] Jeffrey B. Geske, MD,[e] Kathy Wolski, MPH,[b,c] Srihari S. Naidu, MD,[f] Nicholas G. Smedira, MD, MBA,[a,g] Paul C. Cremer, MD, MS,[b,c] Hartzell Schaff, MD,[h] Ellen McErlean, RN, MSN,[b,c] Christina Sewell, RN,[b,c] Wanying Li, PhD,[i] Lulu Sterling, PhD,[i] Kathy Lampl, MD,[i] Jay M. Edelberg, MD, PhD,[i] Amy J. Sehnert, MD,[i] Steven E. Nissen, MD[b,c]

Mavacamten

Circulation

AHA Journals | Journal Information | All Issues | Subjects | Features | Resources & E

Home > Circulation > Vol. 143, No. 6 > Mavacamten Favorably Impacts Cardiac Structure in Obstructive Hypertrophic Cardiomyopathy

FREE ACCESS
LETTER
PDF/EPUB

Mavacamten Favorably Impacts Cardiac Structure in Obstructive Hypertrophic Cardiomyopathy

EXPLORER-HCM Cardiac Magnetic Resonance Substudy Analysis

Clinical Trial > JACC Heart Fail. 2024 Jan;12(1):164-177. doi: 10.1016/j.jchf.2023.09.028.

Mavacamten Treatment for Symptomatic Obstructive Hypertrophic Cardiomyopathy: Interim Results From the MAVA-LTE Study, EXPLORER-LTE Cohort

Long-term effects of mavacamten treatment in obstructive hypertrophic cardiomyopathy (HCM): updated cumulative analysis of the EXPLORER cohort of MAVA-long-term extension (LTE) study up to 120 weeks FREE

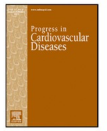
JAMA Cardiology | Original Investigation

Mavacamten in Patients With Hypertrophic Cardiomyopathy Referred for Septal Reduction

Week 56 Results From the VALOR-HCM Randomized Clinical Trial

Journal Pre-proof

Real-world experience with mavacamten in obstructive hypertrophic cardiomyopathy: Observations from a tertiary care center



Milind Y. Desai, Adel Hajj-Ali, Katy Rutkowski, Susan Ospina, Andrew Gaballa, Michael Emery, Craig Asher, Bo Xu, Maran Thamilarasan, Zoran B. Popovic

Mavacamten in Obstructive Hypertrophic Cardiomyopathy Patients Referred for Septal Reduction

Health Status Analysis Through Week 56 in VALOR-HCM Trial

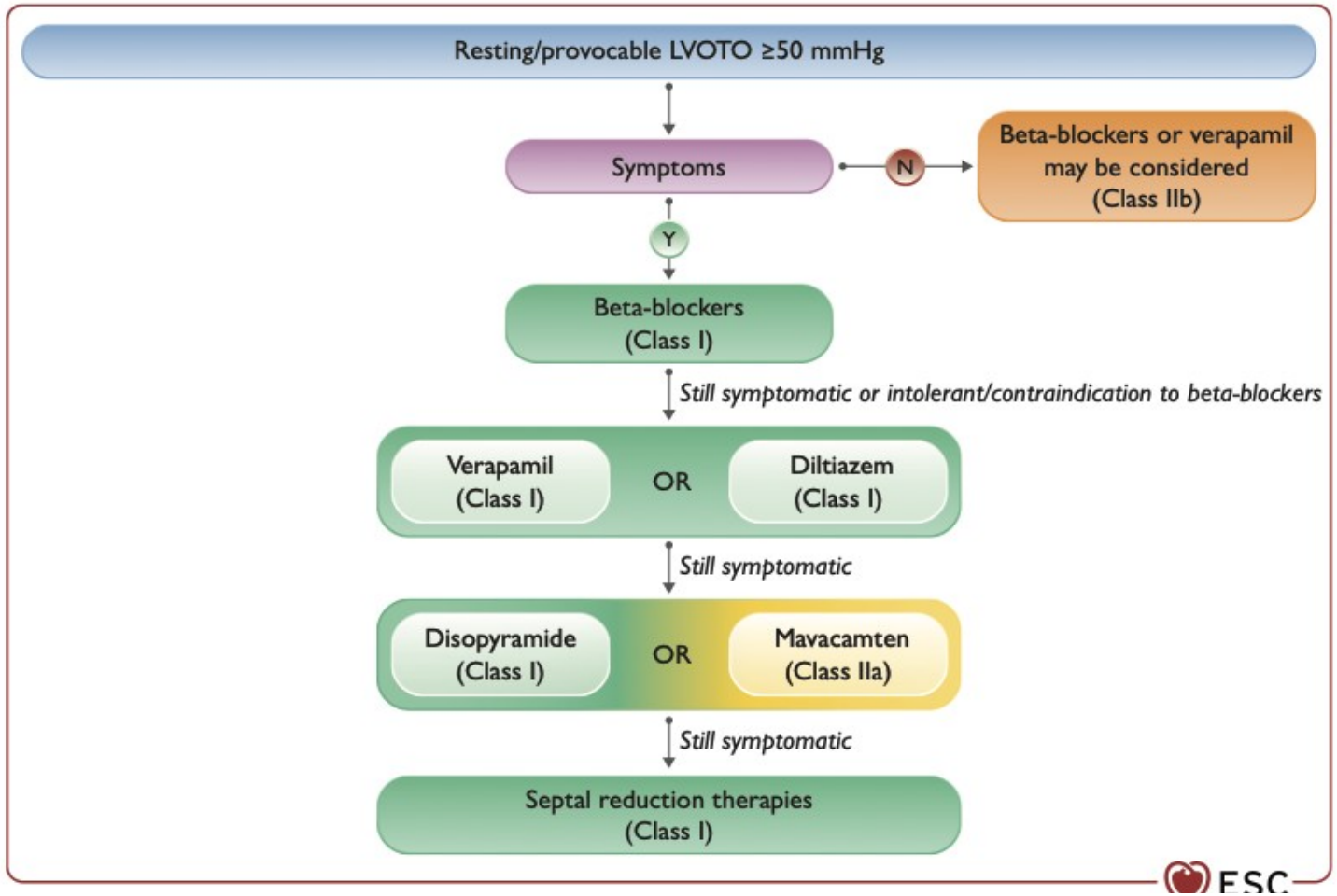
Mavacamten-Associated Temporal Changes in Left Atrial Function in Obstructive HCM

Insights From the VALOR-HCM Trial

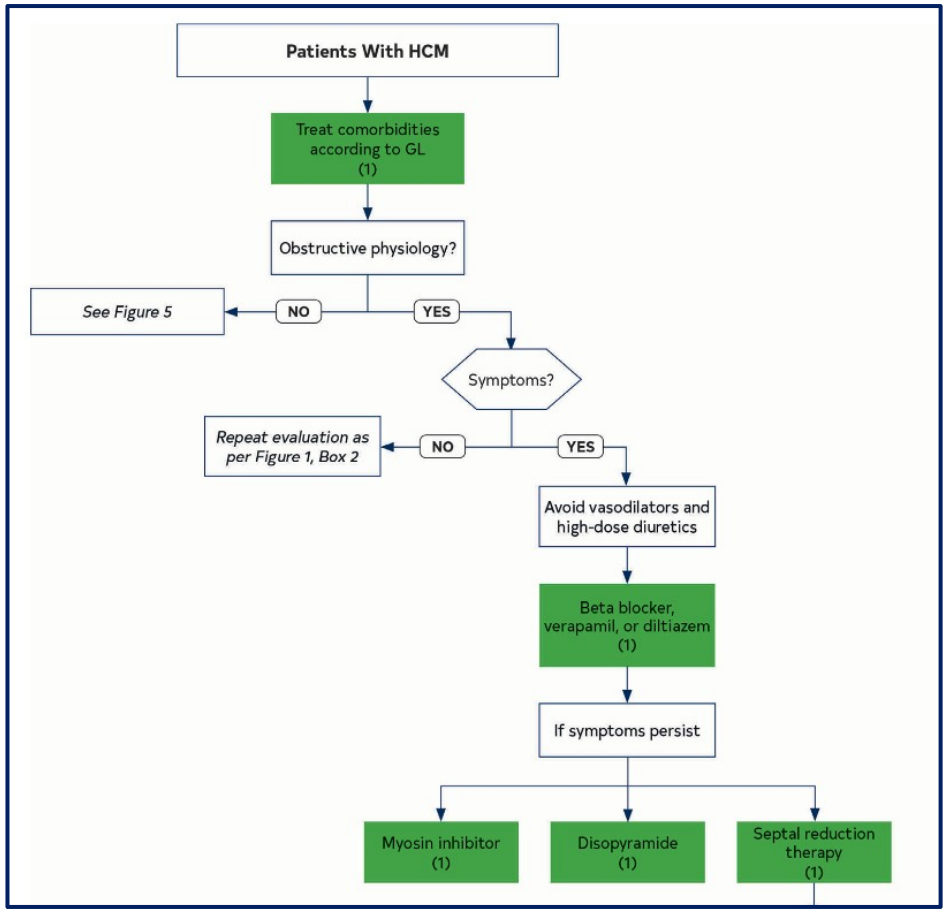
Mavacamten in the guidelines

Effective & safe

ESC 2023, IIa



AHA-ACC 2024, Ia



Mavacamten issues..

- CYP2C19 **metaboliser** phenotype (18% Asians, 2% Europeans are **poor/slow metabolisers**)
- Use of CYP2C19 **inhibitors (& inducers)**
- **LVEF < 50%** small and rare but real - Echo guided dose titration

FDA

April 2022

REMS

(risk evaluation and mitigation strategy)
Echo guided dose titration (7 first year, 4 after)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 2023

CYP genotype

to determine the appropriate dose
Echo guided dose titration

*Negative inotropism + > the duration of transition from diastole to systole and prolongs time from the onset to the peak in systole

Aficamten

Binds to cardiac myosin at a distinct allosteric binding site

Potential “in vivo” pharmacodynamic advantages (different binding site):

-faster **onset** of action (steady state 2 weeks)

-shorter half life -rapid **reversibility** of effect (no interruption but dose reduction)

-minimal drug **interactions** (multiple elimination pathways)

-favorable tolerability

-easy titration of dosage

-no reduced effect under BB

- under review by the FDA
- EMA will follow

MYK-581 and MYK-224 will follow...

The NEW ENGLAND JOURNAL of MEDICINE

SEQUOIA-HCM

ORIGINAL ARTICLE

Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

Authors: Martin S. Maron, M.D., Ahmad Masri, M.D., Michael E. Nassif, M.D., Roberto Barriales-Villa, M.D., Ph.D., Michael Arad, M.D., Nuno Cardim, M.D., Ph.D., Lubna Choudhury, M.D., +26, for the SEQUOIA-HCM Investigators* Author Info & Affiliations

Published May 13, 2024 | N Engl J Med 2024;390:1849-1861 | DOI: 10.1056/NEJMoa2401424 | VOL. 390 NO. 20

	Aficamten[b]
	SEQUOIA-HCM
	24 weeks (n = 282)
	• LVEF ≥60% • LVOT gradient ≥30 mm Hg at rest and ≥50 mm Hg after Valsalva • NYHA class II or III • decreased exercise capacity, defined by a predicted peak oxygen uptake of 90% or less based on age and sex
	• mean age 59 years • 59% men • 76% NYHA class II, 24% class III/IV • 61% on beta blockers (11% on disopyramide) • 15% not on background HCM therapy
	5 mg/day with dose titration at 2, 4, and 6 weeks
	change in pVO_2 from baseline to week 24
	change from baseline to week 24:
	• KCCQ-23 CSS • NYHA class • LVOT Valsalva gradient • Valsalva LVOT gradient < 30 mm Hg • duration of eligibility for SRT • total workload on CPET
	change from baseline to week 12:
	• KCCQ-23 CSS • NYHA functional class • LVOT Valsalva gradient • Valsalva LVOT gradient <30 mm Hg

LVOT gradients, LA size, LV diastolic function indices, markers of LV filling pressures
Correlations with improvements in pVO_2, KCCQ-CSS, NT-proBNP
Modest reduction in LVEF

Maron M, Cardim N, et al NEJM 2024

Effect of Aficamten on Health Status Outcomes in Obstructive Hypertrophic Cardiomyopathy

Results from SEQUOIA-HCM

Impact of Aficamten on Disease and Symptom Burden in Obstructive Hypertrophic Cardiomyopathy

Results From SEQUOIA-HCM

FOREST HCM

Effect of Aficamten on Cardiac Structure and Function in Obstructive Hypertrophic Cardiomyopathy

SEQUOIA-HCM CMR Substudy

Impact of Aficamten on Echocardiographic Cardiac Structure and Function in Symptomatic Obstructive Hypertrophic Cardiomyopathy

Mavacamten vs Aficamten

Commentary

Two cardiac myosin inhibitors in the treatment of obstructive hypertrophic cardiomyopathy

Milind Y. Desai[1,3,*] and Eugene Braunwald[2]

No direct comparisons possible
Trials too diferentt for comparisons

Table 1. Key characteristics of all phase 3 trials on cardiac myosin inhibitors for patients with symptomatic obstructive hypertrophic cardiomyopathy

	Mavacamten[a]			Aficamten[b]
	EXPLORER-HCM	VALOR-HCM	EXPLORER-CN	SEQUOIA-HCM
Phase 3 trials (number of patients)	30 weeks (n = 251)	16 weeks (n = 112)	30 weeks (n = 81)	24 weeks (n = 282)
Key inclusion criteria	• peak LVOT gradient of ≥50 mm Hg at rest or after Valsalva • LVEF of ≥55% • NYHA class II or III	• peak LVOT gradient of ≥50 mm Hg at rest or after Valsalva • LVEF of ≥60% • NYHA class III/IV or class II with exertional syncope • referred for and actively considering SRT • on maximally tolerated background HCM therapy	• peak LVOT gradient of ≥50 mm Hg at rest or after Valsalva • LVEF of ≥55% • NYHA class II or III	• LVEF ≥60% • LVOT gradient ≥30 mm Hg at rest and ≥50 mm Hg after Valsalva • NYHA class II or III • decreased exercise capacity, defined by a predicted peak oxygen uptake of 90% or less based on age and sex
Key patient characteristics	• mean age 59 years • 59% men • 73% NYHA class II, 27% class III/IV • 75% on beta blockers	• mean age 60 years • 51% men • 93% NYHA class III/IV, 7% class II • 75% on beta blockers (36% on combination therapy, including disopyramide)	• mean age 52 years • 72% men • 82% NYHA class II, 18% class III • 89% on beta blockers	• mean age 59 years • 59% men • 76% NYHA class II, 24% class III/IV • 61% on beta blockers (11% on disopyramide) • 15% not on background HCM therapy
Starting dose and dose titration	5 mg/day with dose titration at 8 and 12 weeks		2.5 mg/day with dose titration at 8, 14, and 20 weeks	5 mg/day with dose titration at 2, 4, and 6 weeks
Key primary endpoint(s)	1.5 mL/kg/min or greater increase in pVO_2 and at least one NYHA class reduction or 3.0 mL/kg/min or greater increase in pVO_2 without NYHA class worsening	patient deciding to proceed with SRT or continuing to meet guideline eligibility for SRT	change in Valsalva LVOT peak gradient from baseline to week 30	change in pVO_2 from baseline to week 24
Key secondary endpoints	change from baseline to week 30: • post-exercise LVOT gradient • pVO_2 • proportion of patients with at least one NYHA class improvement • KCCQ-23 CSS • HCMSQ subscore	change from baseline to week 16: • post-exercise LVOT gradient • NYHA functional class • KCCQ-23 CSS • NT-proBNP • cardiac troponin I	proportion of patients at week 30 with • Valsalva LVOT peak gradient <30 mm Hg • Valsalva LVOT peak gradient <50 mm Hg • at least 1 NYHA class improvement change from baseline to week 30: • resting LVOT peak gradient • KCCQ-23 CSS • NT-proBNP • high-sensitivity cardiac troponin I • LVMI evaluated by cardiac magnetic resonance	change from baseline to week 24: • KCCQ-23 CSS • NYHA class • LVOT Valsalva gradient • Valsalva LVOT gradient < 30 mm Hg • duration of eligibility for SRT • total workload on CPET change from baseline to week 12: • KCCQ-23 CSS • NYHA functional class • LVOT Valsalva gradient • Valsalva LVOT gradient <30 mm Hg
Criteria for therapy interruption	LVEF <50% for temporary interruption or <30% for permanent discontinuation			LVEF <40%
Dose adjustments and therapy interruptions	core-lab			site-read

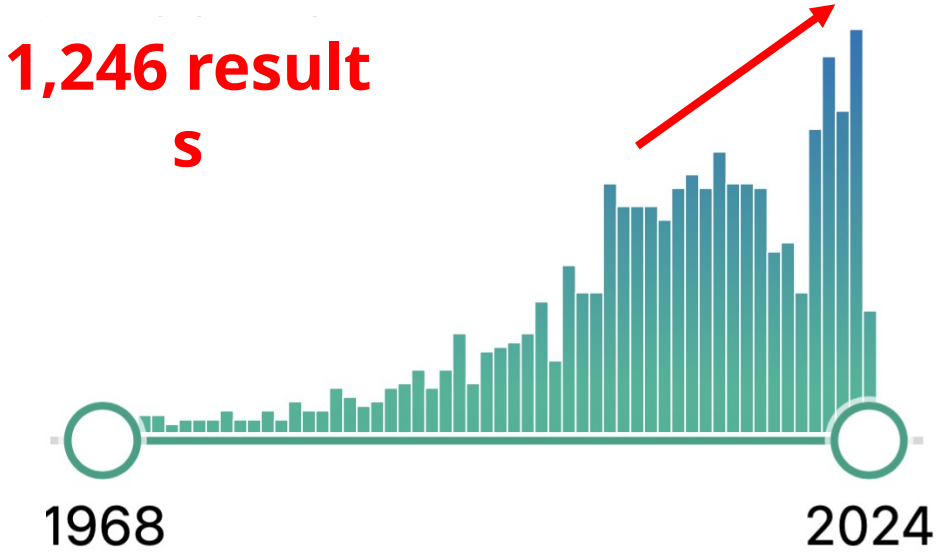
Table 1. Continued

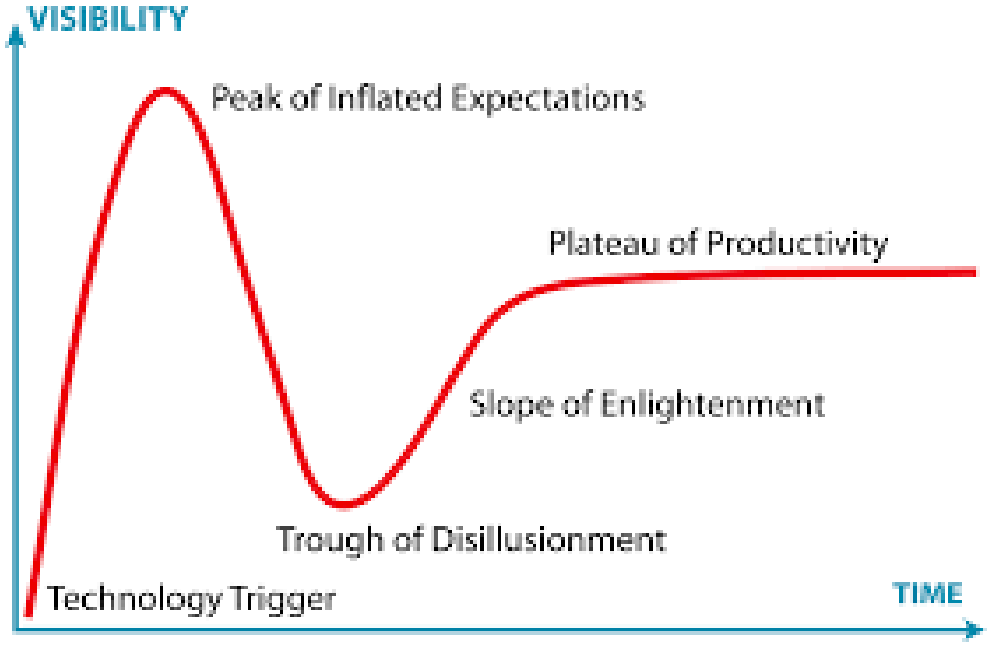
	Mavacamten[a]			Aficamten[b]
	EXPLORER-HCM	VALOR-HCM	EXPLORER-CN	SEQUOIA-HCM
Drug dosages	last dose at end of double-blind period: • 2.5 mg = 6% • 5 mg = 49% • 10 mg = 33% • 15 mg = 11%	last dose at end of double-blind period: • 2.5 mg = 21% • 5 mg = 23% • 10 mg = 34% • 15 mg = 21%	last dose at end of double-blind period: • 2.5 mg = 6% • 5 mg = 59% • 10 mg = 30% • 15 mg = 4%	dose at end of escalation phase: • 5 mg = 3% • 10 mg = 13% • 15 mg = 35% • 20 mg = 49%
Primary findings	37% of patients on mavacamten vs. 17% on placebo met the primary endpoint (difference +19.4%, 95% CI, 8.7 to 30.1; $p = 0.0005$)	76.8% of patients assigned to placebo and 17.9% assigned to mavacamten met guideline criteria or underwent SRT (difference 58.9%, 95% CI, 44.0 to 73.9; $p < 0.001$)	LSM difference in post-Valsalva LVOT gradient between mavacamten and placebo was −70.3 mm Hg (95% CI, −89.6 to −50.9 mm Hg; one-sided $p < 0.001$)	LSM difference in pVO_2 between aficamten and placebo was 1.7 mL/kg/min (95% CI, 1.0 to 2.4; $p < 0.001$)
Key secondary findings	all key secondary endpoints were significantly positive in favor of mavacamten vs. placebo			all key secondary endpoints were significantly positive in favor of aficamten vs. placebo
LVEF reduction during trial	−4.0%; 95% CI, −5.5 to −2.5		LSM change, 3.7% in mavacamten vs. 3.0% in placebo	−4.8%; 95% CI, −6.3 to −3.2
LVEF <50%	total of 9 patients through week 30 (5 during the study at week 26 [3 on mavacamten and 2 on placebo] and an additional 4 on mavacamten at week 30)	total of 2 patients on mavacamten through week 16	0 patients through week 30	total of 5 patients on aficamten through week 24 and 1 on placebo

CI, confidence interval; CPET, cardiopulmonary exercise testing; HCM, hypertrophic cardiomyopathy; HCMSQ, HCM Symptom Questionnaire; KCCQ-23 CSS, Kansas City Cardiomyopathy Questionnaire 23-point clinical summary score; LSM, least-squares mean; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SRT, septal reduction therapy.
[a]Data adapted from Desai et al.,[7] Olivotto et al.,[8] and Tian et al.[9]
[b]Data adapted from Maron et al.[11]

Desai & Braunwald, Med 5, 655–659, July 12, 2024 a 2024

Cardiac Myosin inhibitors: a reflexion





....the myosin inhibitor hysteria....

In transit from the **proof of concept hype zone** ➔ Precise clinical indications

b ny)

with its **inherent clinical, administrative, & financial burdens**

Not for all oHCM patients

Classical medical treatment

Refratory, intolerance

Classical approach

New approach

SRT

morbidity and mortality
related to center volume

ASA

✞ 0.6%- *2.3%*

Myectomy

✞ *3.8%-15.6%*

unmet need for better noninvasive alternatives to SRT

Myosin inhibitors

Efficacy
Safety
Cost- effectiviness???

Myectomy $ 42k
Mava $ 89.5k/year ➔ $ 1 million/12y

Institute of Clinical & Economic Review
health-benefit **price benchmark** for Mava
$12 -$15 K / year

Europa 1 k mês ?= 12k/ano=120 k em 10 anos

Miectomia 30 K? ASA?

In which patients?

1.Alternative to Medical treatment

Non responders
intolerants to first line therapy

. Alternative to SRT (ASA, Myectomy)

Frail/ high risk SRT (myectomy- ASA)
Refuse invasive SRT
non-expert centers
Bridge to septal reduction

3. Special subsets of more functional oHCM patients ?

Hypercontractile phenotypes
Severe obstruction and minimal LVH

Open questions

Sustained effectiveness & safety

LT extensions, multiple echos & genetic do not spoil a new fascinating group of drugs…

Clinical profiles

- oHCM➔ done
- Non obstructive HCM (HFpEF)➔ ?work in progress..**ODISSEY, ACACIA-HCM….& MAVERICK.**
- SCD➔? Direct vs Indirect Effect (LAVI, gradient, MWT…)…
- AF-Stroke➔ VALOR results … LA reverse remodeling
- HFrEF➔ No…? Remember BB ..

Natural history

- Early non-hypertophic phenotypes➔may be..
- Classical phenotypes➔oHCM
- Adverse Remodeling➔ No…? Remember BB ..
- Overt dysfunction➔ No…? Remember BB ..

- Placebo -Effect
- Non- responders
- AF?

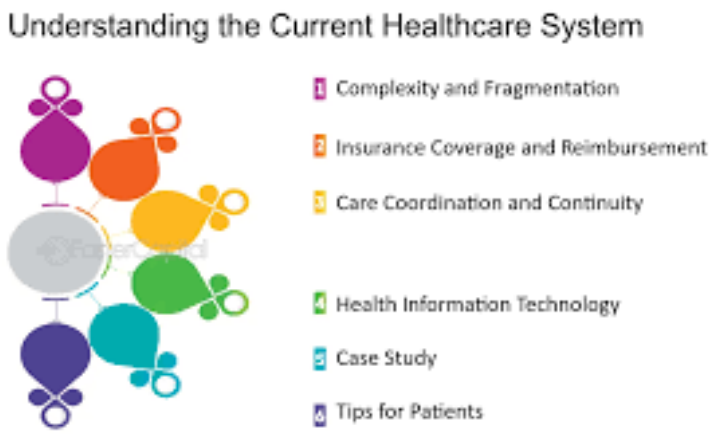
Pot-Pourri

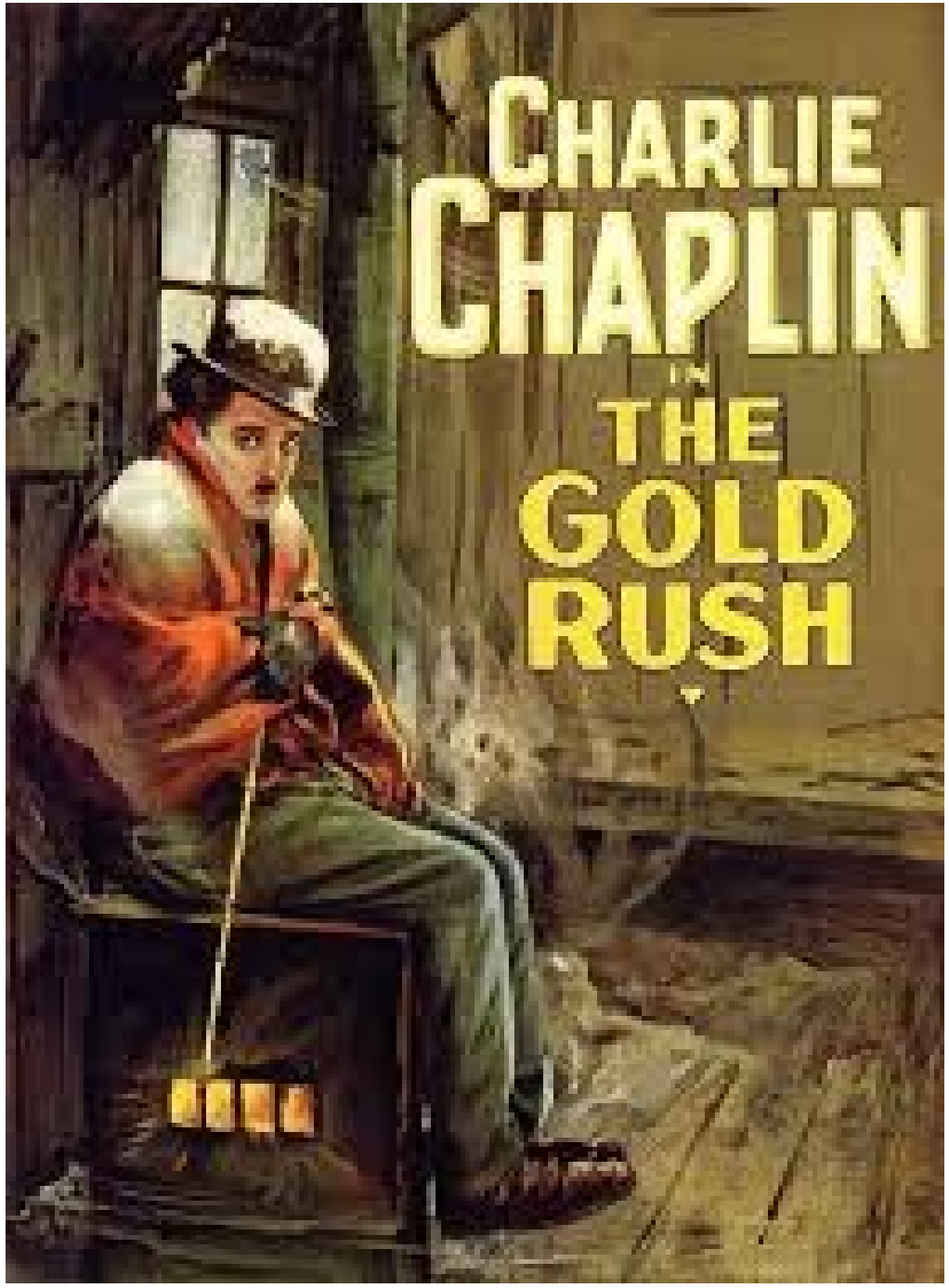
- Ethnic diversity in response?…black under represented..
- Pediatrics?
- Phenotyes? (Danon,Noonan,….)
- Genotype? No diferences G+ G- nor between genes/mutations..

Mava or Aficamten?*

Cost-effectiveness

hould doctors care about it in 2025?

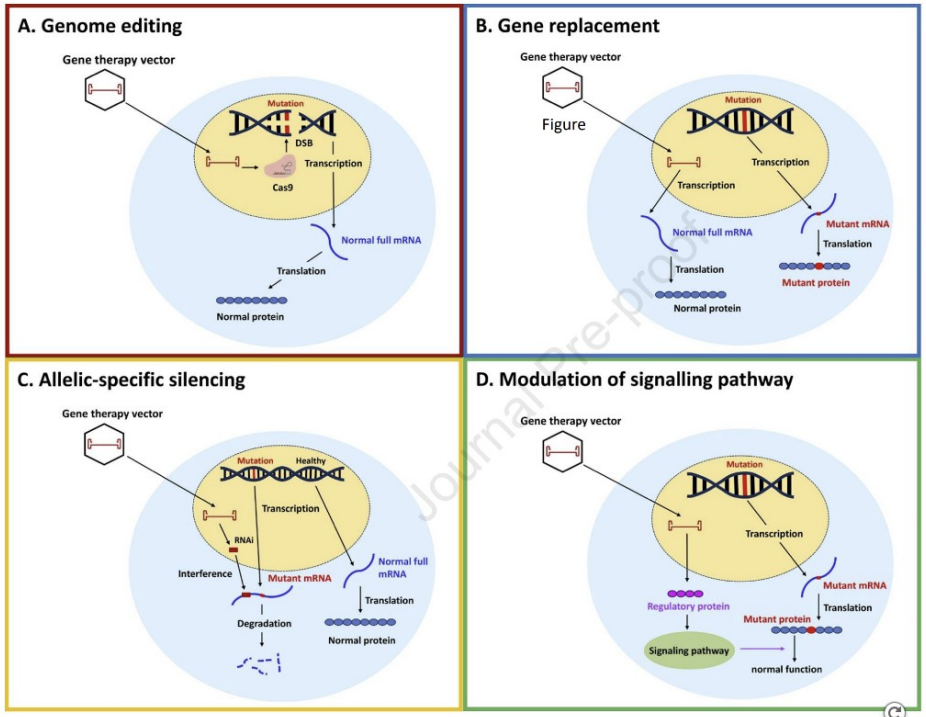


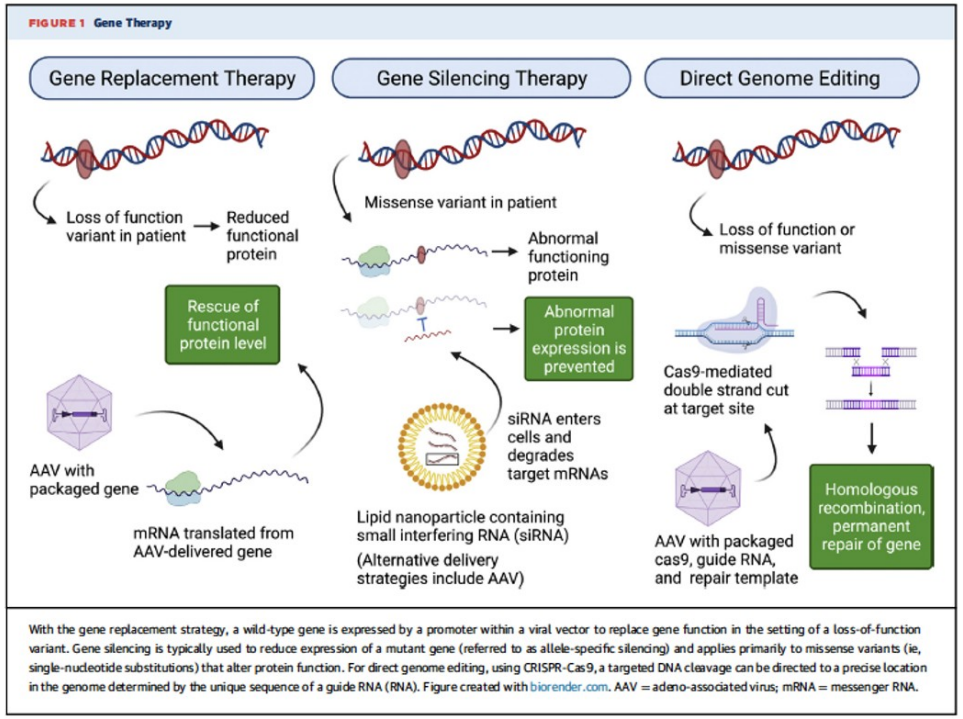

CHARLIE
CHAPLIN
IN
THE
GOLD
RUSH

Genetic therapy

Gene Therapy : the new frontier?

- HCM ➔ genetic treatment of a genetic disease, is logical➔ **cure** of the disease
- young HCM pts >> adverse events & worse prognosis than those presenting late in life
- **Editing, replacement, silencing**? All, one or none?

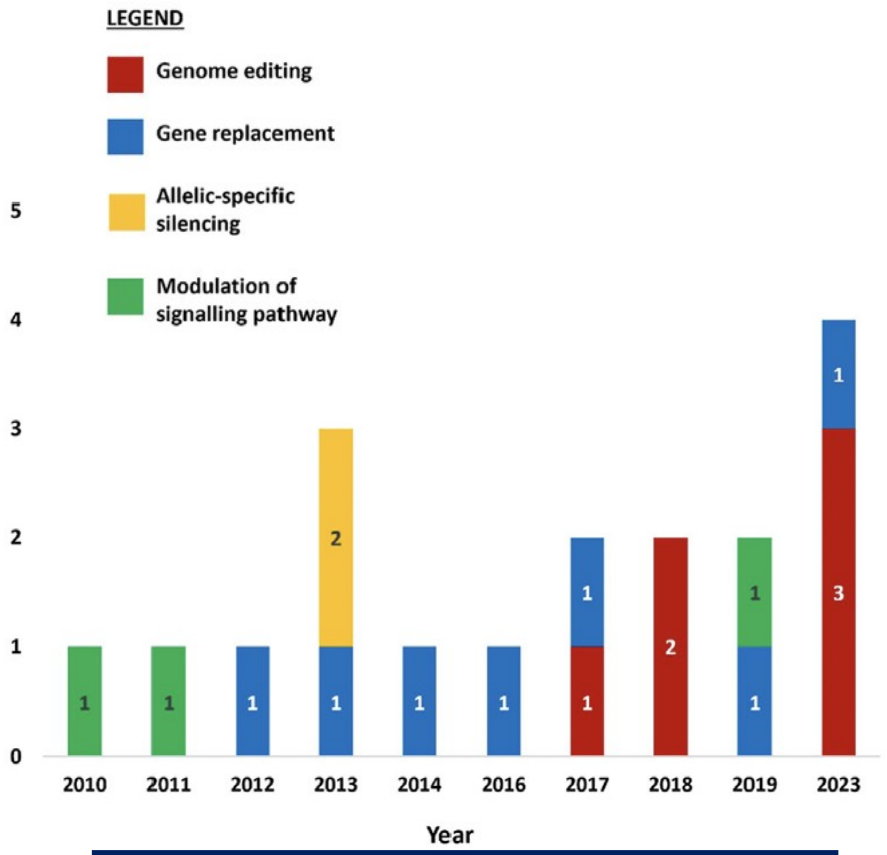




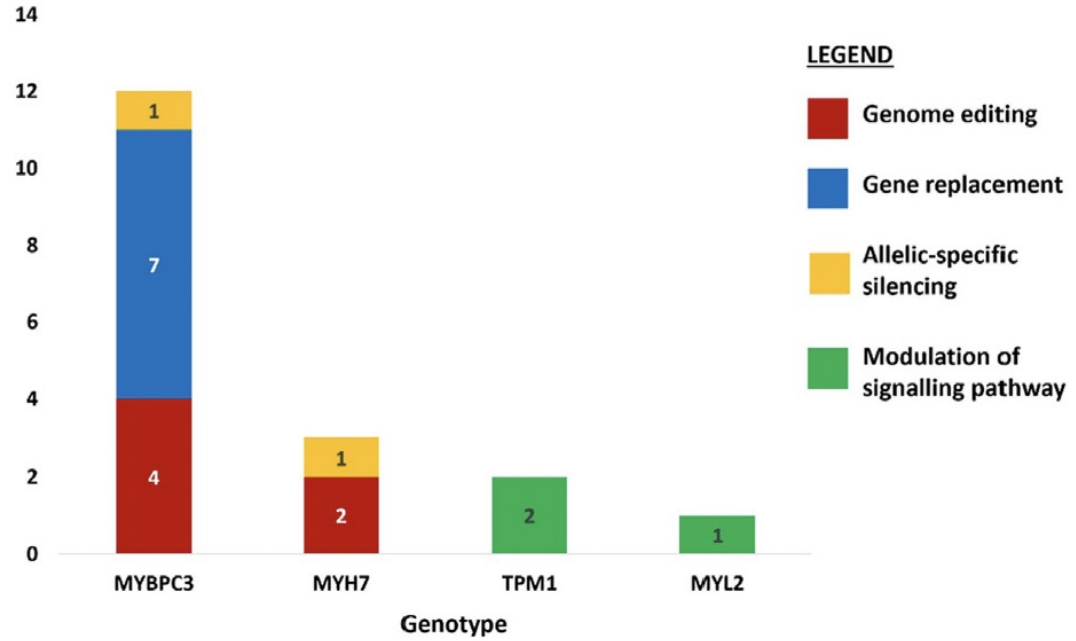
vehicle or method of delivery: AAV9, lipid nanoparticles (LNPs)

Helms A JACC 2022

Genetic therapy under investigation



Consistent but small increase



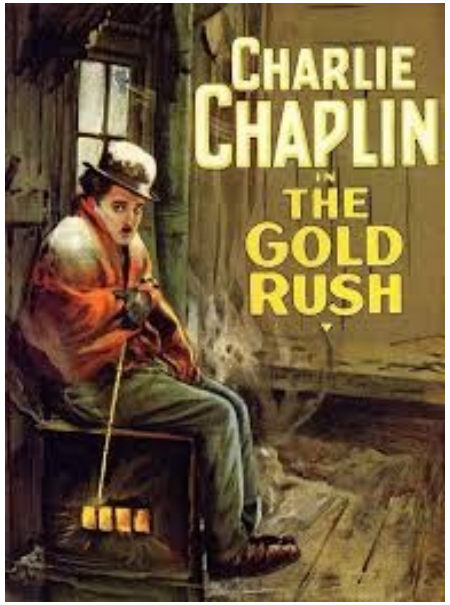
MYBPC (> frequent , missense/loss of function)

Paratz, Can J Cardiol 2024

Conclusions

Myosin inhibitors in HCM

- Efficacy
- Safety
- Real-world results
- Ready for prime time but..
- Cost-effectiveness, safety, dosage, CP450
- The case of Capropril and BB in HFrLVEF
- Do not spoil a fantastic new group of drugs



Genetic therapy in HCM

- Enormous potential, cure, but..
- Equity (costs)
- Safety (AAV inflamation + off-target effects)
- Eficacy (AAV antibodies, single dose problems)
- Minority (non monogenic disease+ severe & lethal refractory HCM in young pts ➔rare in HCM)

Thank you