GENETICS OF CARDIOMYOPATHIES

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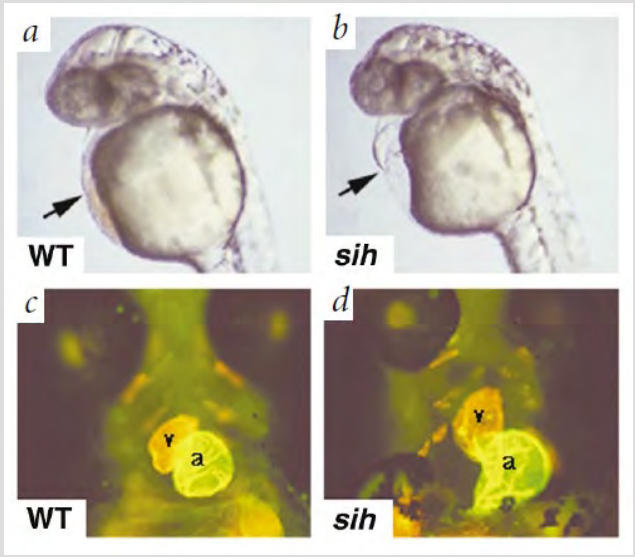
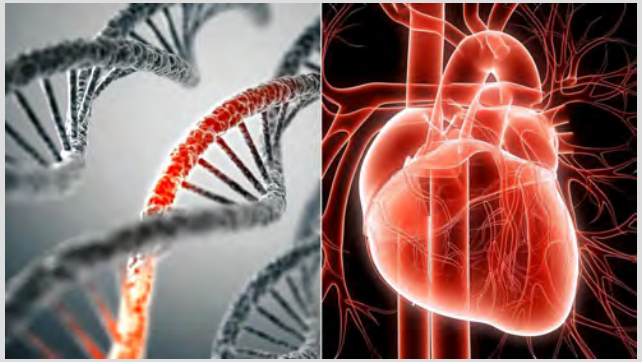
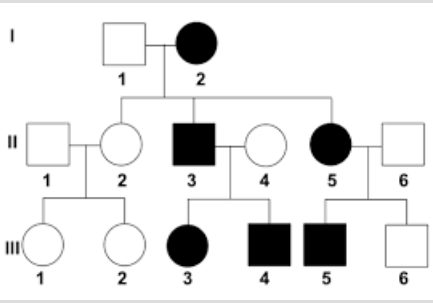






DISCLOSURES

- I am an employee of MyoKardia, Inc.
- Mavacamten is an investigational drug

PEDIATRIC CARDIOMYO

>50% of pediatric cardiomyopathies
Incidence
0.57 per 100K

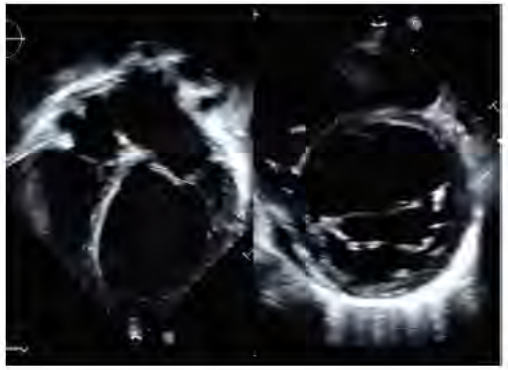
Many etiologies including mutations in genes encoding the sarcomere

DILATED CARDIOMYOPATHY

Definition: Depressed ventricular function secondary to subnormal myocardial systolic shortening
Incidence: 0.57 cases per 100000 children; over 50% of pediatric cardiomyopathies

Genetic Causes

- Sarcomere
- Costamere
- Z-band proteins
- Cytoskeletal
- Nucleoskeletal
- Desmosome
- Mitochondrial
- Calcium-handling
- Neuromuscular disorders
- Inborn errors of metabolism
- Genetic syndromes



Disease Associations

- Dominant mutations in the genes encoding the sarcomere
- Inflammation, either postinfectious or autoimmune
- Toxin exposure
- Neurohormonal abnormalities

Symptoms

- Presentation: Ranges from asymptomatic to acute decompensated heart failure and cardiogenic shock
- Arrhythmias: Especially increased with *LMNA*

Treatments

- Medical therapies to treat the symptoms of acute decompensated heart failure and to reverse the chronic effects of ventricular remodeling
- Mechanical support
- Heart transplantation

Outcomes

- Survival: Transplant-free survival ranges from 60% to 75% within 5 years after diagnosis with 20% to 45% of patients regaining normal cardiac function

Lee T, et al, *Circ Res, Sep* 2017

LESS COMMON PEDIATRIC CARDIOMYOPATHIES

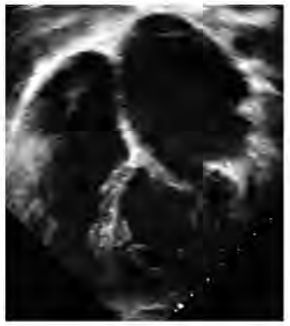
<5% each of pediatric CM

RESTRICTIVE CARDIOMYOPATHY

Definition: Noncompliant myocardium in the absence of ventricular hypertrophy
Incidence: Rarest form of pediatric cardiomyopathy with an incidence of 0.03 to 0.04 cases per 100000 children; 4.5% of pediatric cardiomyopathies

Genetic Causes

- Sarcomere
- Intermediate filament
- Calcium-handling
- Mitochondrial



Disease Associations

- Diastolic dysfunction from abnormalities affecting the contractile apparatus
- Altered calcium homeostasis
- Mitochondrial dysfunction

Symptoms

- Presentation: Ranges from no symptoms to overt heart failure, syncope, or sudden death
- Sudden death: Risk ≤28%
- Arrhythmias: Atrial/ventricular arrhythmias or heart block

Treatments

- Judicious use of diuretics
- Anticoagulation
- Antiarrhythmics
- Automatic implantable cardioverter-defibrillator
- Early consideration for heart transplantation

Outcomes

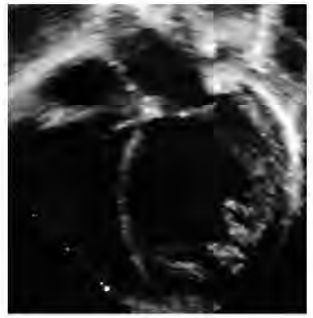
- Survival: 5-year survival from diagnosis of 68%

NONCOMPACTION CARDIOMYOPATHY

Definition: Presence of numerous and excessive ventricular trabeculations and deep intertrabecular recesses
Incidence: 0.12 per 100000 in 0 to 10 year olds, 0.81 per 100000 in infants; 4.8% of pediatric cardiomyopathies

Genetic Causes

- Similar to dilated cardiomyopathy
- Barth syndrome
- Notch signaling pathway



Disease Associations

- Premature arrest of myocardial development during embryogenesis
- As response to physiologic stresses

Symptoms

- Benign or severe course with progressive systolic or diastolic dysfunction, life threatening arrhythmias, or thromboembolism

Treatments

- Anticoagulation
- Dependent on if there is preserved systolic function or systolic dysfunction

Outcomes

- Survival: 18% died or underwent heart transplant

Lee T, et al, *Circ Res, Sep* 2017

HYPERTROPHIC CARD

42% of pediatric cardiomyopathies
Incidence
0.47 per 100K

Dominant mutations in genes encoding the sarcomere
Impaired energy use

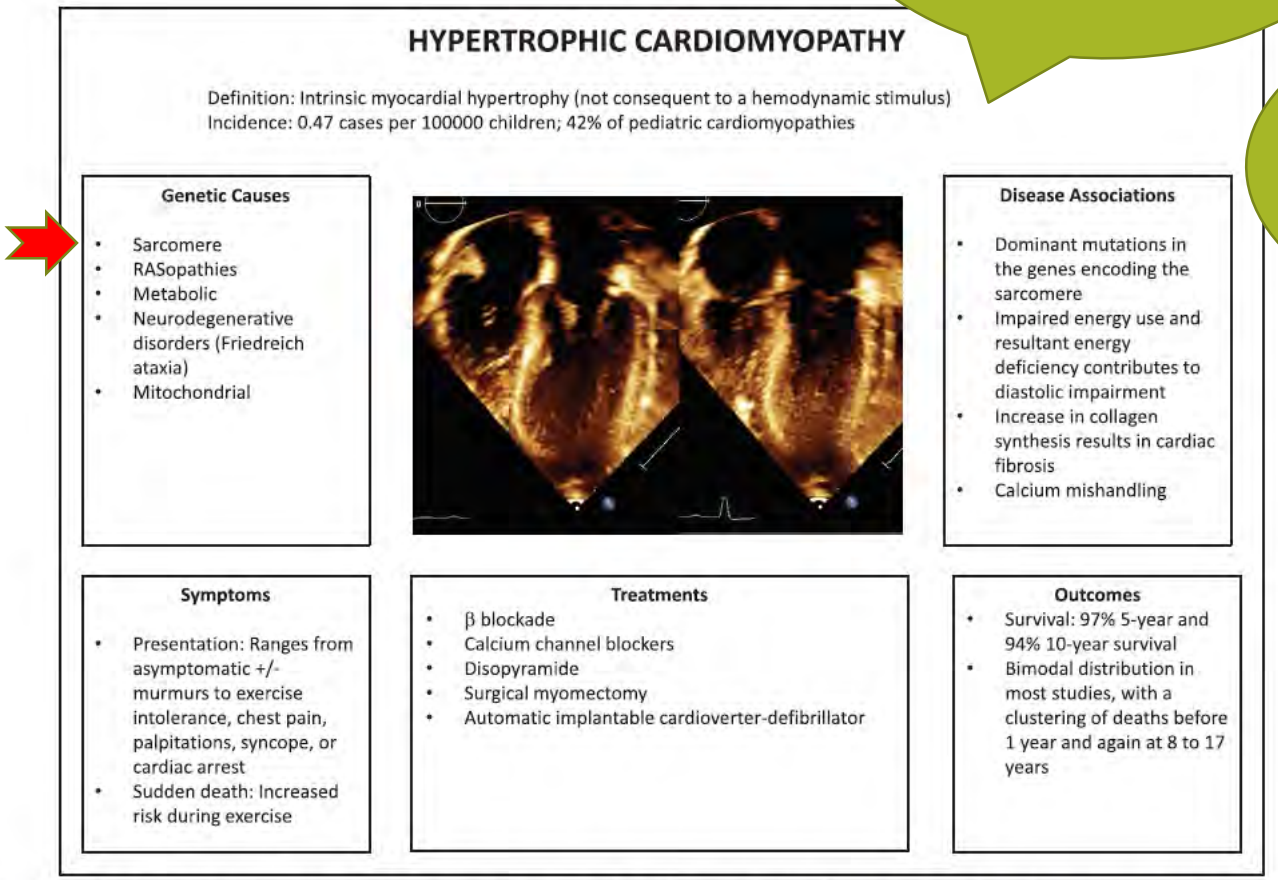


Figure 2. Hypertrophic cardiomyopathy. End-diastolic (**left**) and end-systolic (**right**) apical 4-chamber views of the left ventricle in a patient with severe hypertrophic cardiomyopathy. Regional left ventricular hypertrophy is most notable in the midseptum, lateral free wall, and lateral apex. The end-diastolic frame shows extension of the left ventricular cavity to the apex, and the end-systolic frame shows systolic apical obliteration.

Lee T, et al, *Circ Res, Sep* 2017

GENES ASSOCIATED WITH PEDIATRIC CARDIOMYOPATHIES

Table 1. Common Genes Associated With the Pediatric Cardiomyopathies

Gene Symbol	Inheritance	Associated Cardiac Phenotype(s)					Additional Phenotype(s)
		HCM	DCM	RCM	NCM	ARVC	
Sarcomere							
Thin filament							
ACTC1	AD	X	X	X	X		Atrial septal defect
TNNC1	AD	X	X				
TNNI3	AD, AR	X	X	X			
TNNT2	AD	X	X	X	X		
TPM1	AD	X	X		X		
Thick filament							
MYBPC3	AD	X	X	X	X		
MYH7	AD	X	X	X	X		Myopathies
MYL2	AD	X					
MYL3	AD, AR	X		X			

Many genetic testing laboratories today offer panel testing.
Delivery of genetic counseling services is evolving to support growing volume.

Lee, T, et al, *Circ Res*, Sep 2017

SYNDROMIC AND OTHER CARDIOMYOPATHIES

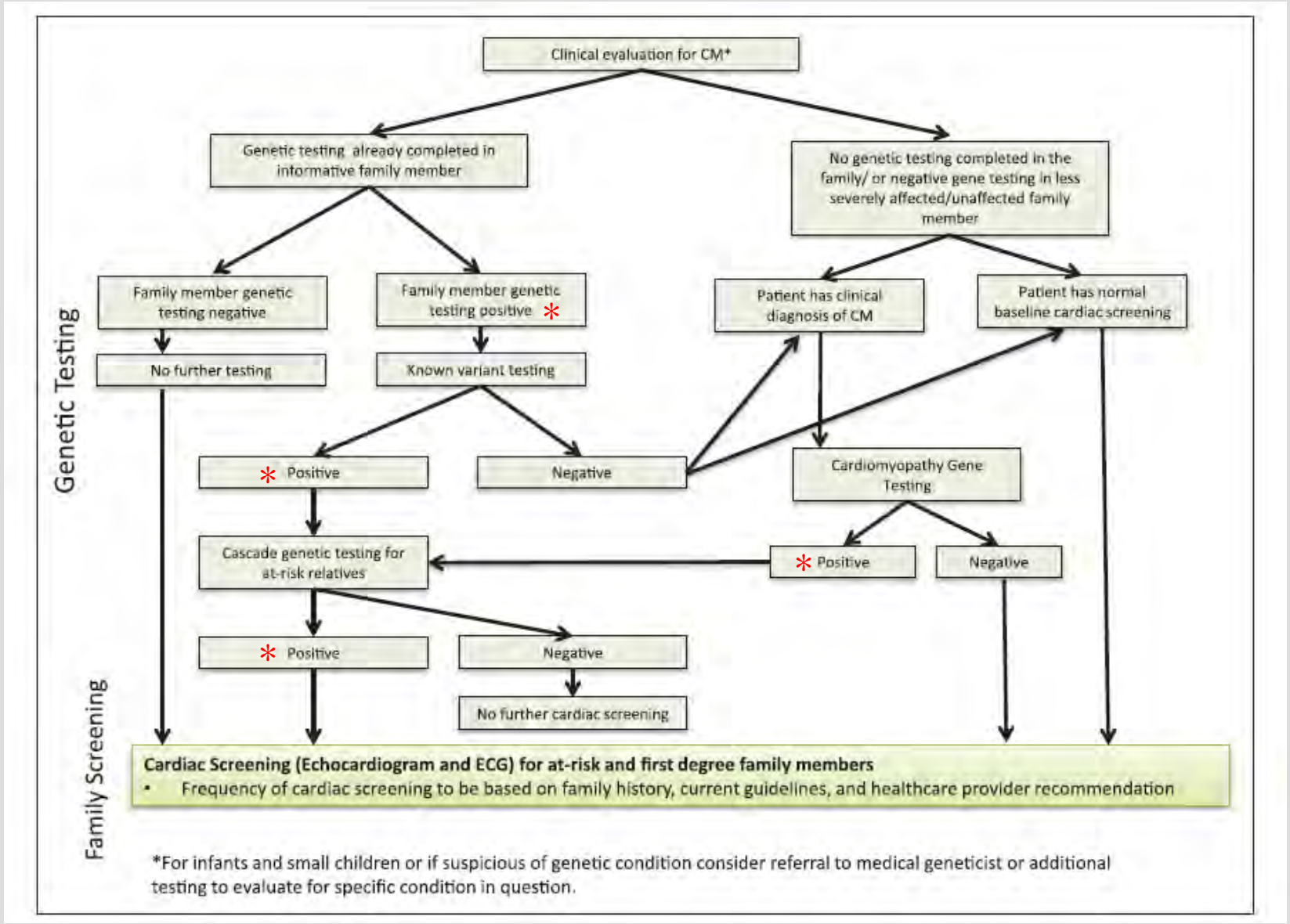
Syndromic cardiomyopathies		HCM					
BRAF	AD	X					Noonan/Costello/CFC syndrome
HRAS	AD	X					Noonan/Costello/CFC syndrome
KRAS	AD	X					Noonan/Costello/CFC syndrome
PTPN11	AD	X					Noonan/Costello/CFC syndrome
SOS1	AD	X					Noonan/Costello/CFC syndrome
SPRED1	AD	X					Noonan/Costello/CFC syndrome

Other Categories with Genetic Etiologies

Z-disc
Desmosome
Cytoskeletal
Intermediate filament
Nuclear membrane
Plasma membrane
Metabolic Disorders
Neuromuscular Disorders

Lee, T, et al, *Circ Res*, Sep 2017

GENETIC TESTING ALGORITHM FOR CARDIOMYOPATHY



*Positive testing defined as genetic testing that identifies a pathogenic mutation
In this algorithm, variants of uncertain significance (VUS) are treated as a negative result

Lee, TM, et al, Pediatric Cardiomyopathies, *Circ Res*, Sep 2017

ADDITIONAL TIPS

- Initiate genetic testing in the most clearly affected family member when possible
- Likely pathogenic variants should be handled on an individual basis
- Co-segregation studies should be performed if possible to improve interpretation
- Genetic testing result interpretation is probabilistic and may change over time; test results should be reviewed and updated every 2 – 3 yrs
- Consider referral to medical geneticist and/or utilize genetic counselors if possible
- All affected individuals should receive medical management for their specific diagnosis and symptoms

Lee, TM, et al, Pediatric Cardiomyopathies, *Circ Res*, Sep 2017

WHAT DO THE GUIDELINES SAY?

Table 3. Proposed Clinical Screening Strategies With Echocardiography (and 12-Lead ECG) for Detection of Hypertrophic Cardiomyopathy With Left Ventricular Hypertrophy in Families*

Age <12 y
Optional unless
Malignant family history of premature death from HCM or other adverse complications
Patient is a competitive athlete in an intense training program
Onset of symptoms
Other clinical suspicion of early LV hypertrophy
Age 12 to 18–21 y†
Every 12–18 mo
Age >18–21 y
At onset of symptoms or at least every 5 y. More frequent intervals are appropriate in families with a malignant clinical course or late-onset HCM.

*When pathologic mutations are not identified or genetic testing is either ambiguous or not performed.

†Age range takes into consideration individual variability in achieving physical maturity and in some patients may justify screening at an earlier age. Initial evaluation should occur no later than early pubescence.[125]

ECG indicates electrocardiogram; HCM, hypertrophic cardiomyopathy; and LV, left ventricular.

Adapted with permission from Maron et al.[126]

…pay attention to the hand-off here

Gersh B, et al, *Circulation*, 2011

OUTCOMES IN PEDI-ONSET HCM

- Maurizi, et al, *JAMA Cardiology*, June 2018
  - Long-term Outcomes of Pediatric-Onset HCM and Age-Specific Risk Factors for Lethal Arrhythmic Events.
    - 1644 consecutive patients with HCM, 100 diagnosed between ages 1 and 16 y (median 12.2)
    - 24 of 100 had CV events: 19 LAEs (14 SCD, 5 ICD shocks) and 5 HF events (2 transplant and 3 deaths)
    - No events in 15 patients with genotype neg results, 15 events experienced by 55 patients (27%) with genotype pos results
    - Multivariate analysis performed for predictors of LAEs
    - Disease causing mutations in Troponin I and T genes as age-specific risk factors carried 8-fold and 4-fold increases in the risk of an LAE, respectively
    - Children in this study showed a thin-filament genotype conveyed a distinctly worse prognosis associated with restrictive phenotypes, marked fibrosis and severe arrhythmic propensity, possibly mediated by microvascular ischemia

OUTCOMES IN HCM

- Ho, et al, *Circulation,* Oct 2, 2018
  - Genotype and Lifetime Burden of Disease in HCM: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe).
    - Data on 4591 HCM patients (2763 genotyped) followed for mean of 5.4 y; Median age of diagnosis 45.8 y
    - Analyzed for a composite outcome (cardiac arrest, transplant, appropriate ICD Rx, all-cause death, A Fib, stroke, NYHA III/IV symptoms and LVEF <35%)
    - Young patients (20-29 y) had a 4-fold higher mortality than the general US population at a similar age
    - Patients with pathogenic sarcomere mutations had two-fold greater risk for adverse outcomes compared to patients without mutations
    - Cumulative burden of disease was dominated by HF and atrial fibrillation many years following diagnosis
    - Young age of diagnosis and presence of a sarcomere mutation are powerful predictors of adverse outcomes

PRECISION THERAPY DEVELOPMENT FOR HCM

MYOKARDIA

Pioneering precision medicine for the treatment of cardiovascular disease

MISSION

Change the world for patients with serious cardiovascular disease through **bold and innovative science**

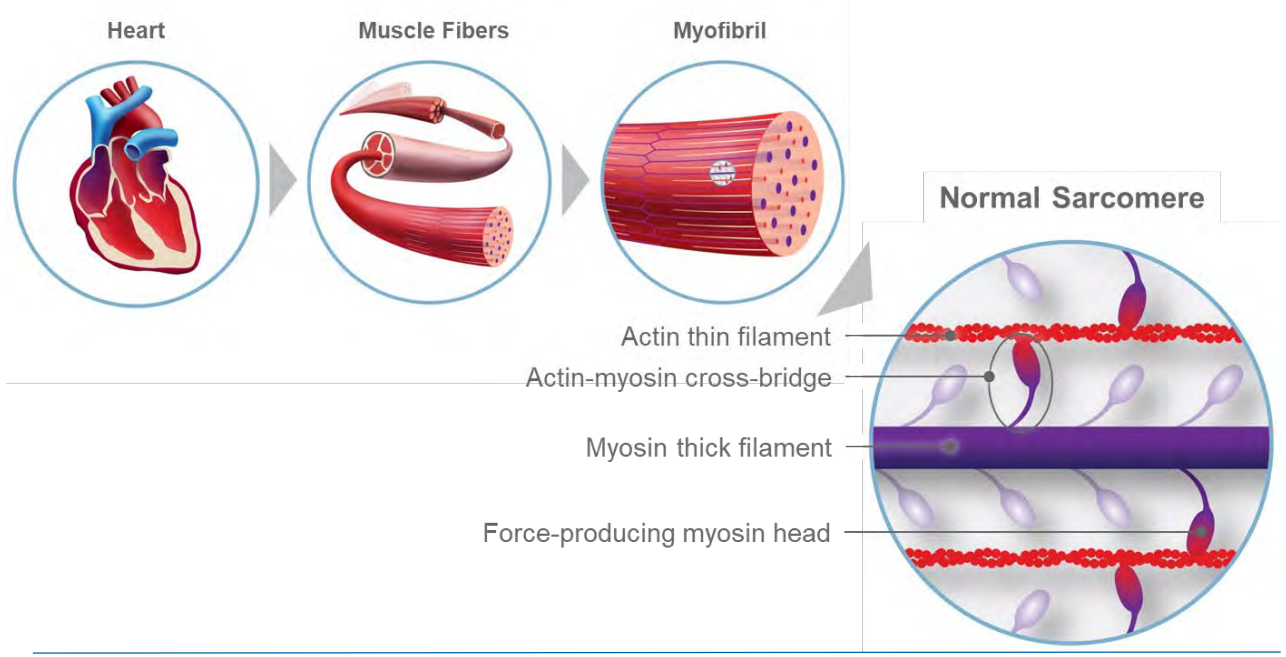
VALUES

- **Patients** First
- Passion for **Science**
- **Succeed** Together
- **Imagine** and **Innovate**
- Lifelong **Learning**

Ma a am e ar e s he er i a se o M

INTENDED TO REDUCE EXCESS CONTRACTILITY

- Oral small molecule
- Dosed once daily
- Studied in over 150 individuals across three Phase 1 trials and the **Phase 2 PIONEER-HCM trial**
- Orphan Drug Designation for the treatment of symptomatic, obstructive HCM



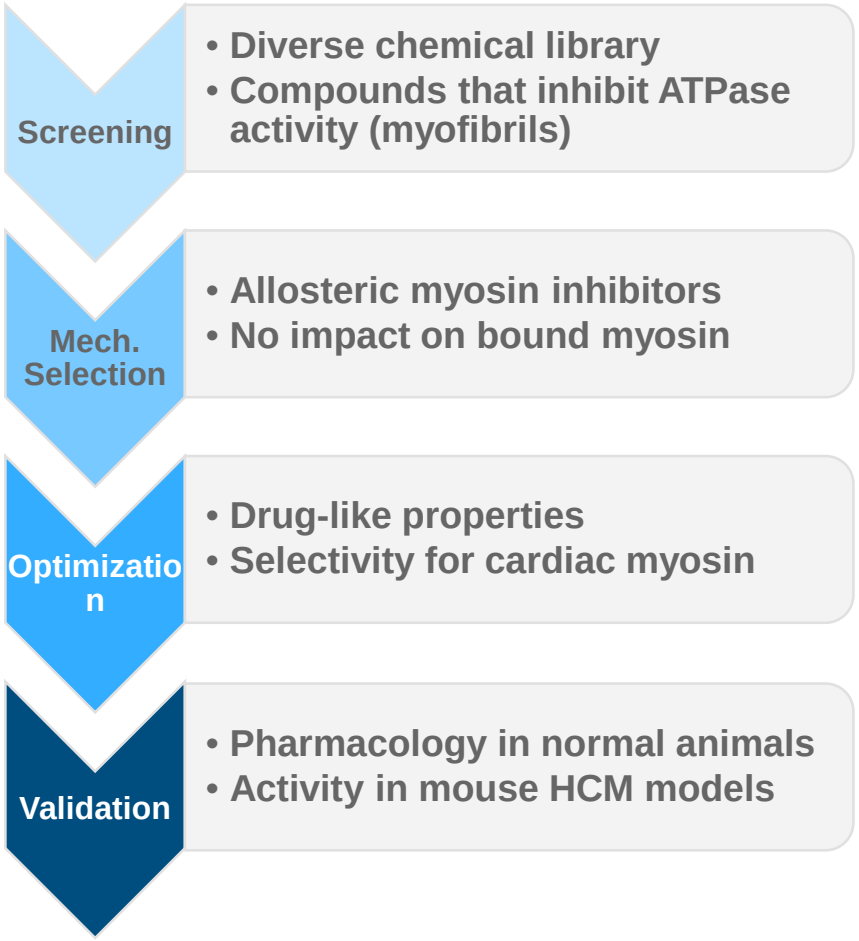
THERAPEUTIC HYPOTHESIS

- HCM is caused by an excess number of actin-myosin cross-bridges, leading to increased contractility and impaired relaxation
- Mavacamten restores the appropriate number of cross-bridges

HCM: hypertrophic cardiomyopathy

e i i a io o Ma a am e

Drug Discovery Process



What Mavacamten Does

- Locks myosin in an inactive state
  - Reduces the number of heads available for contraction
  - **Energy-sparing** (less ATP consumption)
- Does not affect myosin when bound to actin
  - Does not alter contraction kinetics
  - Low potential to impact diastole
- Does not affect calcium flux
  - Low arrhythmogenicity potential

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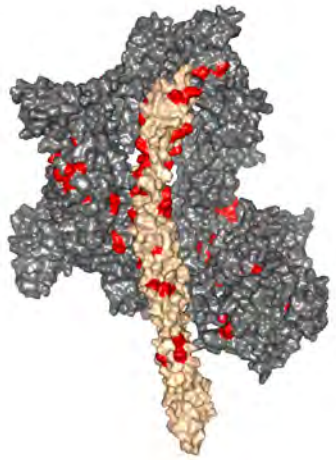

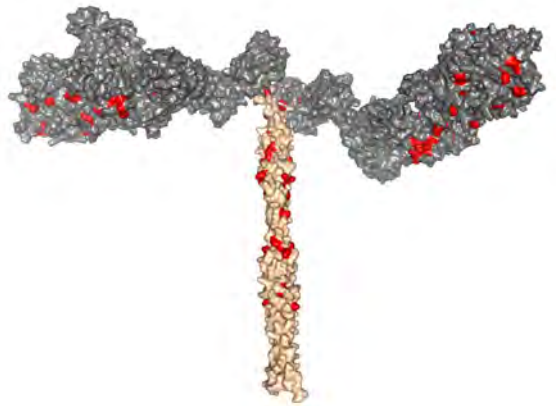

“Off” state
No contraction

“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. Alamo et al. eLife 6, e24634 (2017)
D. V. Trivedi et al. Biophysical Reviews 110, 27-48 (2018)

Ma a am e re o a es he o s a e o m osi

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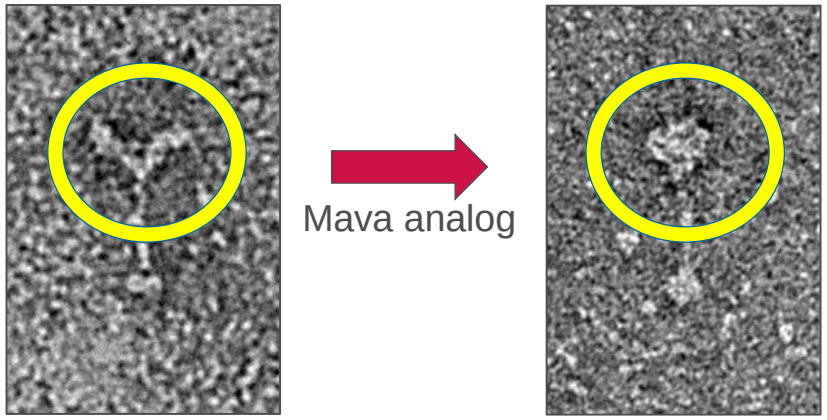
Electron microscopy images of myosin



"On" state consumes energy

"Off" state energy-sparing

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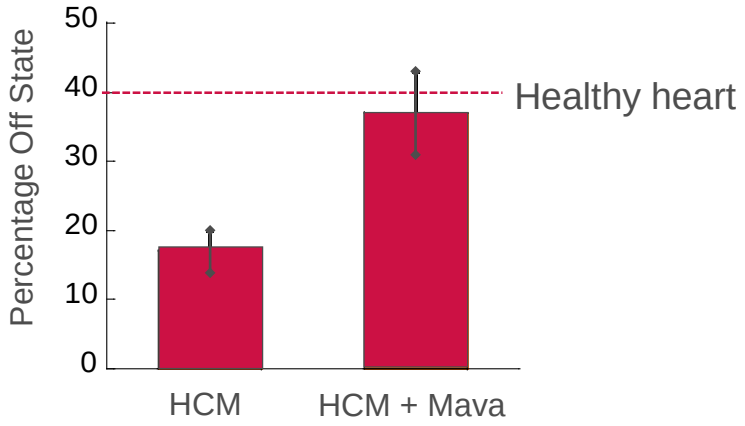
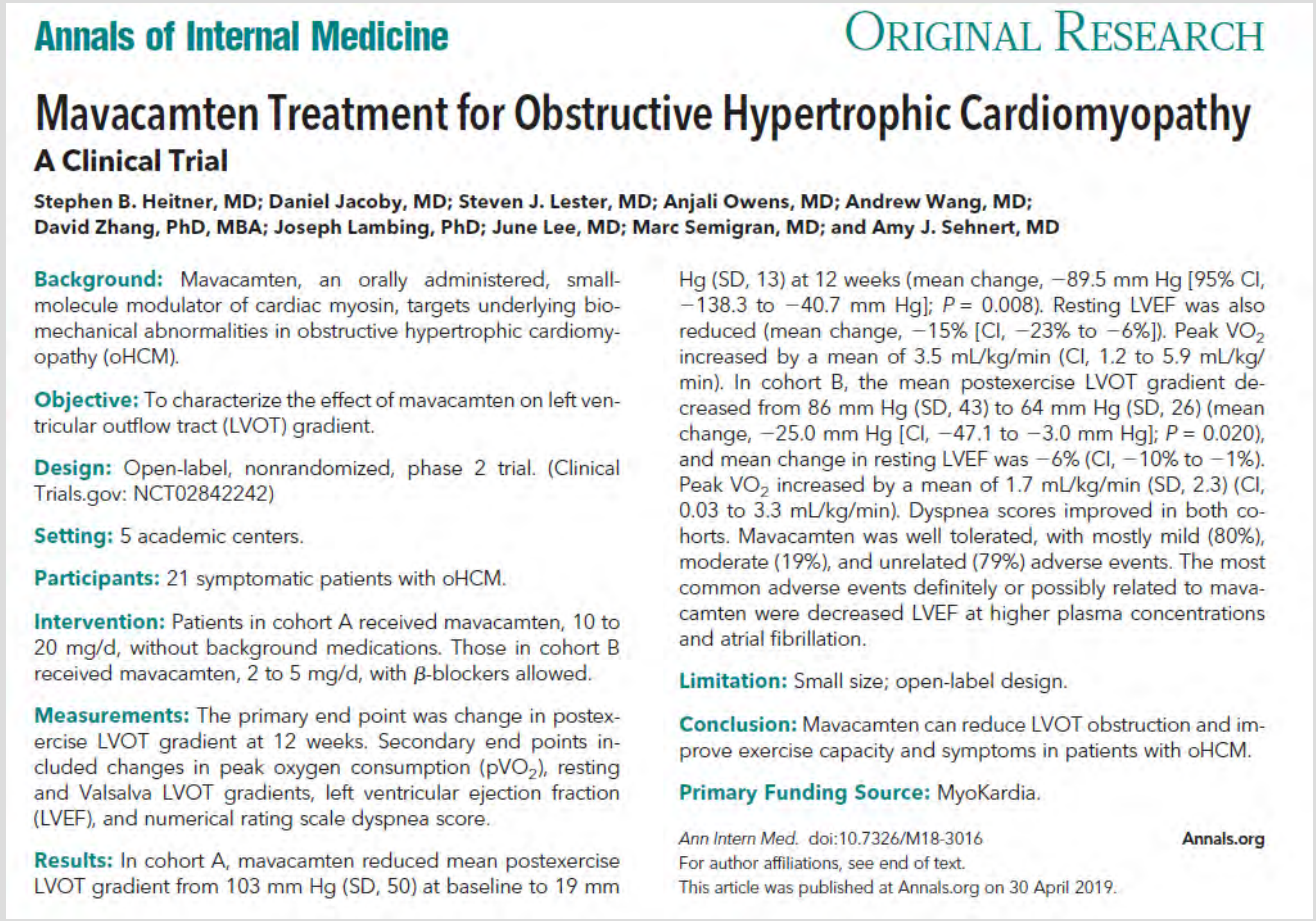
Percentage "off" state in HCM patients



Similar effects observed with other HCM mutations

R. L. Anderson et al. *Proc. Nat. Acad. Sci. USA*, 115, E8143-E8152 (2018)



Annals of Internal Medicine ORIGINAL RESEARCH

Mavacamten Treatment for Obstructive Hypertrophic Cardiomyopathy

A Clinical Trial

Stephen B. Heitner, MD; Daniel Jacoby, MD; Steven J. Lester, MD; Anjali Owens, MD; Andrew Wang, MD; David Zhang, PhD, MBA; Joseph Lambing, PhD; June Lee, MD; Marc Semigran, MD; and Amy J. Sehnert, MD

Background: Mavacamten, an orally administered, small-molecule modulator of cardiac myosin, targets underlying biomechanical abnormalities in obstructive hypertrophic cardiomyopathy (oHCM).

Objective: To characterize the effect of mavacamten on left ventricular outflow tract (LVOT) gradient.

Design: Open-label, nonrandomized, phase 2 trial. (Clinical Trials.gov: NCT02842242)

Setting: 5 academic centers.

Participants: 21 symptomatic patients with oHCM.

Intervention: Patients in cohort A received mavacamten, 10 to 20 mg/d, without background medications. Those in cohort B received mavacamten, 2 to 5 mg/d, with β-blockers allowed.

Measurements: The primary end point was change in postexercise LVOT gradient at 12 weeks. Secondary end points included changes in peak oxygen consumption (pVO_2), resting and Valsalva LVOT gradients, left ventricular ejection fraction (LVEF), and numerical rating scale dyspnea score.

Results: In cohort A, mavacamten reduced mean postexercise LVOT gradient from 103 mm Hg (SD, 50) at baseline to 19 mm Hg (SD, 13) at 12 weeks (mean change, −89.5 mm Hg [95% CI, −138.3 to −40.7 mm Hg]; $P = 0.008$). Resting LVEF was also reduced (mean change, −15% [CI, −23% to −6%]). Peak VO_2 increased by a mean of 3.5 mL/kg/min (CI, 1.2 to 5.9 mL/kg/min). In cohort B, the mean postexercise LVOT gradient decreased from 86 mm Hg (SD, 43) to 64 mm Hg (SD, 26) (mean change, −25.0 mm Hg [CI, −47.1 to −3.0 mm Hg]; $P = 0.020$), and mean change in resting LVEF was −6% (CI, −10% to −1%). Peak VO_2 increased by a mean of 1.7 mL/kg/min (SD, 2.3) (CI, 0.03 to 3.3 mL/kg/min). Dyspnea scores improved in both cohorts. Mavacamten was well tolerated, with mostly mild (80%), moderate (19%), and unrelated (79%) adverse events. The most common adverse events definitely or possibly related to mavacamten were decreased LVEF at higher plasma concentrations and atrial fibrillation.

Limitation: Small size; open-label design.

Conclusion: Mavacamten can reduce LVOT obstruction and improve exercise capacity and symptoms in patients with oHCM.

Primary Funding Source: MyoKardia.

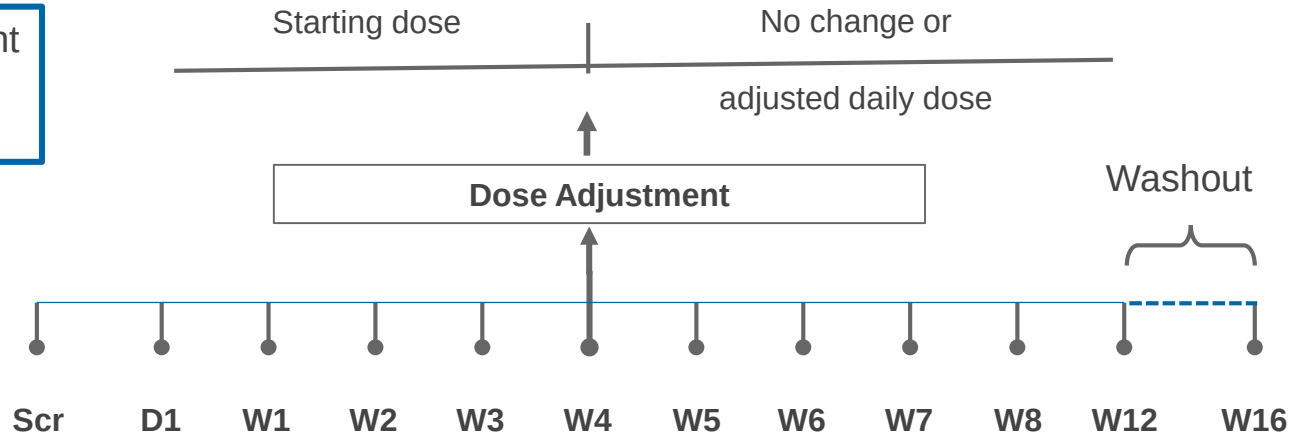
Ann Intern Med. doi:10.7326/M18-3016 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 30 April 2019.

Heitner, SB, MD, et al, *Ann Intern Med,* Apr 30, 2019

"Despite management with beta-blockers or nondihydropyridine calcium channel blockers, symptoms and disease burden persist for many patients with oHCM and therapeutic options are limited."

M ria Desi

- 12 Weeks Treatment
- Two Cohorts
- Different Doses



Stress echo	x					x					x	x
CPET		x									x	
Rest echo	x	x	x	x	x	x	x	x	x	x	x	x

	Starting Dose	Dose Adjustment Algorithm	Doses in Study
Cohort A (n=11)	10 mg ≤ 60 kg 15 mg >60 kg	Based on % decrease from baseline in LVEF	10 mg, 15 mg, 20 mg
Cohort B (n=10)	2 mg	Based on % decrease from baseline in resting LVOT peak gradient	2 mg, 5 mg

Heitner, S, et al, *Ann Intern Med*, April 30, 2019

D = day; Scr = screening; W = week

M ria oi s

Primary Endpoint

Change in post-exercise peak LVOT gradient from baseline to Week 12

Key Secondary and Exploratory Endpoints

- Change in Resting and Valsalva LVOT gradients from baseline to Week 12
- Change from Week 12 to Week 16 in post-exercise peak LVOT gradient
- Change in LVEF from baseline to Week 12
- Change in peak VO_2 and VE/VCO_2 from baseline to Week 12
- Change in dyspnea symptom score from baseline to Week 12
- Change in NYHA Functional Class from baseline to Week 12
- Change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) from baseline to Week 12

Heitner, S, et al, *Ann Intern Med*, April 30, 2019

M Base i e hara eris i s

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Cohort A (n = 11)	Cohort B (n = 10)
Mean age (range), *y*	56 (22-70)	58 (26-67)
Sex, *n (%)*		
Male	7 (64)	5 (50)
Female	4 (36)	5 (50)
Mean body mass index (SD), *kg/m²*	29.7 (4.1)	32.3 (5.4)
Mean heart rate (SD), *beats/min*	76 (10)	62 (8)
Mean blood pressure (SD), *mm Hg*		
Systolic	136 (13)	132 (14)
Diastolic	75 (8)	77 (15)
NYHA functional class, %		
II	64	50
III	36	50
Background HCM therapy, *n (%)**		
β-Blocker	9 (82)	9 (90)
Calcium-channel blocker	1 (9)	0 (0)
Disopyramide	5 (45)	0 (0)
Echocardiography parameters		
Mean interventricular septum thickness (SD), *cm*	1.7 (0.2)	1.5 (0.2)
Systolic anterior motion of mitral valve, *n (%)*	11 (100)	9 (90)
Mean left atrial volume index (SD), *mL/m²*	30 (10)	41 (20)
Mitral regurgitation present, *n (%)*	11 (100)	10 (100)

HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association.
* Patients in cohort A discontinued background HCM therapy ≥14 d before starting use of mavacamten.

Heitner, S, et al, *Ann Intern Med*, April 30, 2019

M es s ross a a e o Doses

Table 2. Primary, Secondary, and Exploratory End Points

End Point	Cohort A (n = 11)		Cohort B (n = 10)	
	Mean Baseline Value (SD)	Change at Week 12 (95% CI)	Mean Baseline Value (SD)	Change at Week 12 (95% CI)
Primary end point				
Postexercise LVOT gradient, *mm Hg**	103 (50) (n = 9)	−89.5 (−138.3 to −40.7) (n = 8)	86 (43) (n = 9)	−25.0 (−47.1 to −3.0) (n = 9)
Secondary end points				
Resting LVOT gradient, *mm Hg*	60 (28) (n = 11)	−47.8 (−72.2 to −23.4) (n = 10)	86 (63) (n = 10)	−48.5 (−82.8 to −14.1) (n = 10)
Valsalva LVOT gradient, *mm Hg*	97 (32) (n = 11)	−84.7 (−113.8 to −55.7) (n = 10)	100 (65) (n = 10)	−47.1 (−82.1 to −12.1) (n = 10)
Resting LVEF, %	70 (7) (n = 11)	−14.6 (−23.1 to −6.2) (n = 10)	75 (5) (n = 10)	−5.5 (−9.8 to −1.2) (n = 10)
pVO_2, *mL/kg/min*	20.7 (7.4) (n = 11)	3.5 (1.2 to 5.9) (n = 10)	19.4 (4.6) (n = 10)	1.7 (0.03 to 3.3) (n = 10)
VE/VCO_2	32.2 (5.4) (n = 11)	−2.2 (−6.1 to 1.7) (n = 10)	32.3 (4.4) (n = 10)	−2.5 (−4.3 to −0.7) (n = 10)
NRS dyspnea score†	4.9 (1.6) (n = 11)	−3.1 (−4.1 to −2.1) (n = 10)	4.0 (2.6) (n = 10)	−3.0 (−5.0 to −1.0) (n = 10)
Exploratory end points				
NYHA functional class	2.4 (0.5) (n = 11)	−0.9 (−1.4 to −0.4) (n = 10)	2.5 (0.5) (n = 10)	−1.0 (−1.3 to −0.7) (n = 10)
KCCQ OSS‡	65 (16) (n = 11)	14.4 (7.3 to 21.5) (n = 10)	61 (26) (n = 10)	16.0 (0.3 to 31.6) (n = 10)
Median change in NT-proBNP level (IQR), *pg/mL*	930 (647) (n = 11)	−425 (−748 to −68) (n = 10)	1834 (3209) (n = 9)	−81 (−637 to −16) (n = 9)
Systolic blood pressure, *mm Hg*	136 (13) (n = 11)	−6.5 (−16.8 to 3.8) (n = 10)	132 (14) (n = 10)	−9.2 (−19.7 to 1.3) (n = 10)
Diastolic blood pressure, *mm Hg*	75 (8) (n = 11)	8.8 (−0.1 to 17.7) (n = 10)	77 (15) (n = 10)	1.2 (−7.5 to 9.9) (n = 10)

IQR = interquartile range; KCCQ OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NRS = numerical rating scale; NT-proBNP = *N*-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; pVO_2 = peak oxygen consumption; VE/VCO_2 = volume expired/carbon dioxide production slope.

* In cohort A, 2 patients did not have postexercise measures (1 was unable to exercise at baseline and 1 had an image that was technically difficult to interpret), and 1 who discontinued because of an adverse event did not have a 12-wk measurement. In cohort B, 1 patient did not have postexercise measures because of technical issues related to imaging.

† Indicates perception of severity. Scores range from 1 to 10, with 10 being the most severe. A clinically significant change is defined as ≥1.

‡ Measures perception of overall health. Scores range from 0 to 100, with higher scores reflecting better health status. A clinically significant change is defined as ≥6.

Heitner, S, et al, *Ann Intern Med*, April 30, 2019

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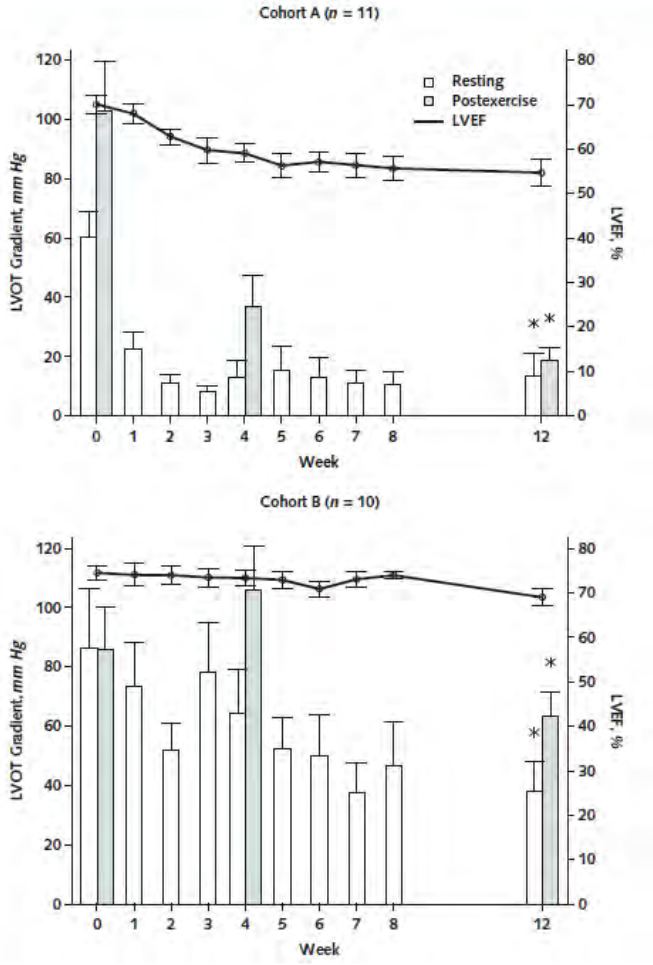
Figure 1. Effect of mavacamten on LVOT obstruction and LVEF.



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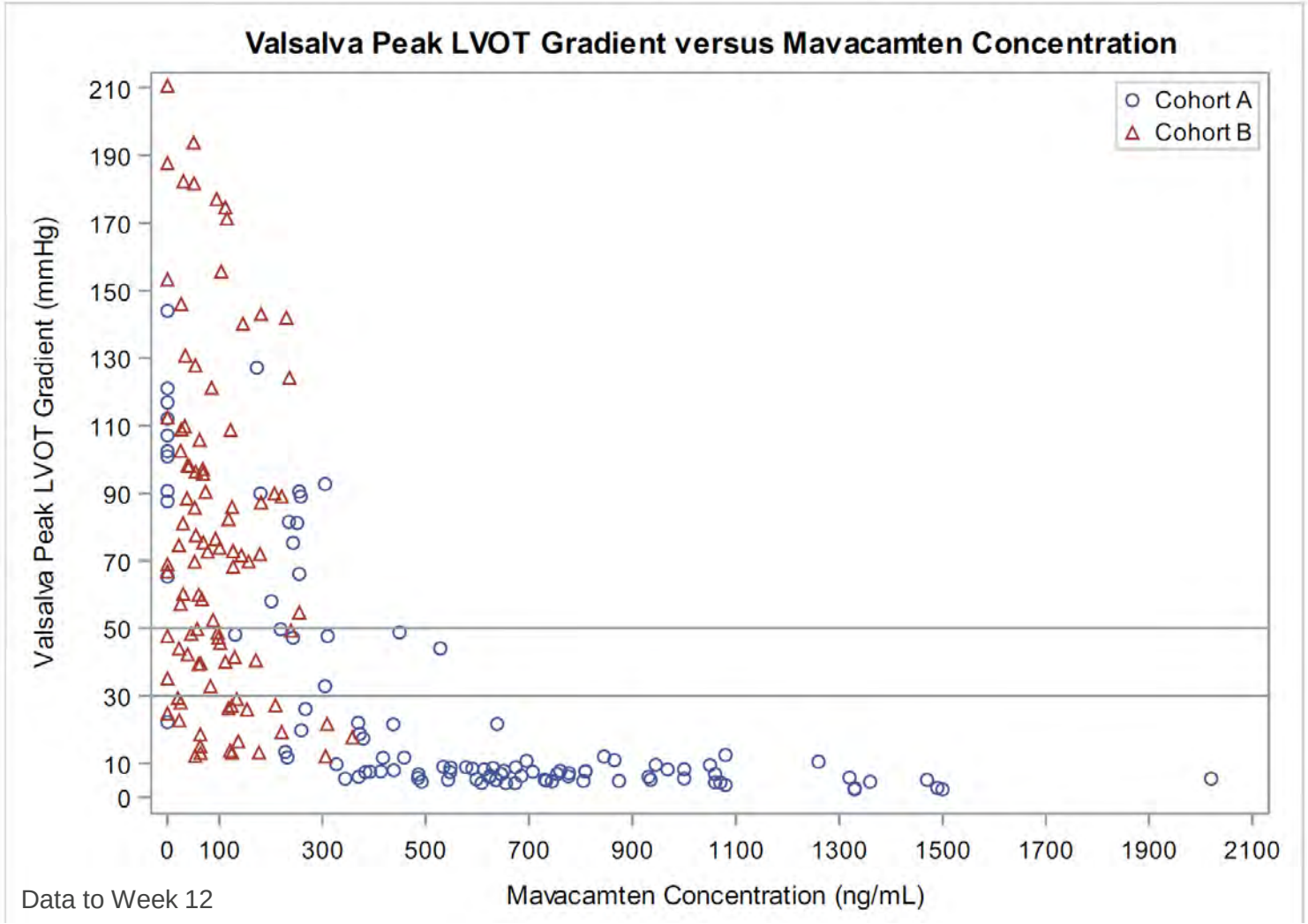

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Table 3. Adverse Events During Treatment

Adverse Events	Cohort A (*n* = 11)*	Cohort B (*n* = 10)*	Extension Study (*n* = 12)†
Total, *n*	62	59	17
Mild, *n (%)*	47 (76)	50 (85)	15 (88)
Moderate, *n (%)*	14 (23)	9 (15)	2 (12)
Serious, *n (%)*	1 (2)	0	0
Led to treatment discontinuation, *n (%)*	1 (2)	0	0

- Most AEs were mild (80%) to moderate (19%)
- Most AEs were unrelated to mavacamten
- One serious AE in Cohort A
  - History of paroxysmal atrial fibrillation who had recurrent AF and cardioverted
  - Patient elected to stop study drug at Week 4
- Independent data monitoring committee found no safety concerns

Heitner, S, et al, *Ann Intern Med*, April 30, 2019

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12-week treatment with mavacamten resulted in **statistically significant reductions in LVOT gradient**

Improvements in pVO_2 and NYHA functional classification were also observed

Generally well-tolerated in Cohort A & B

One SAE (Cohort A) resulting in study withdrawal

Independent data monitoring committee found no safety concerns

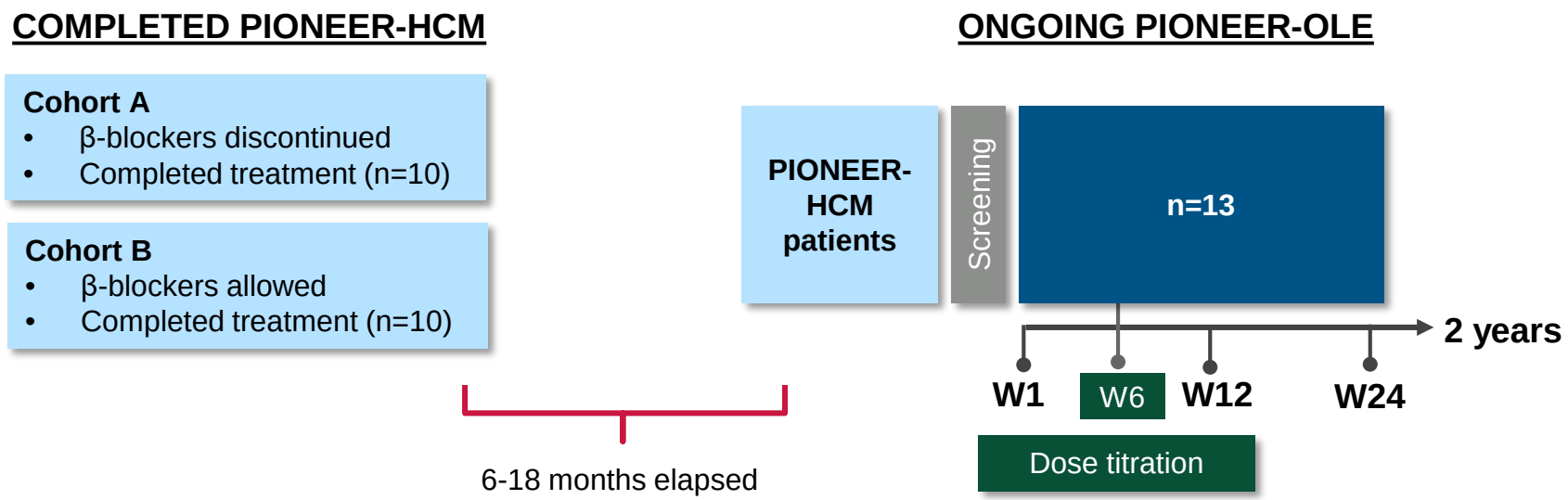
Informed Phase 3 starting dose and dose adjustment algorithm

Long-term Safety and Effectiveness of Mavacamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy Patients, PIONEER-Open Label Extension Study (PIONEER-OLE)

Stephen B. Heitner, MD; Daniel Jacoby, MD; Steven Lester, MD; Andrew Wang, MD; Liang Fang, PhD; Amy J. Sehnert, MD

Presentation ACC 2019 New Orleans

PIONEER-OLE: Study design



Mavacamten PIONEER-OLE Overview	
Patients enrolled	• n=13* • From PIONEER-HCM cohort A (n=5) and cohort B (n=8)
Outcomes	• Safety, tolerability, and select measures of efficacy using individualized dosing • Key measurements include LVOT gradient, LVEF, NT-proBNP

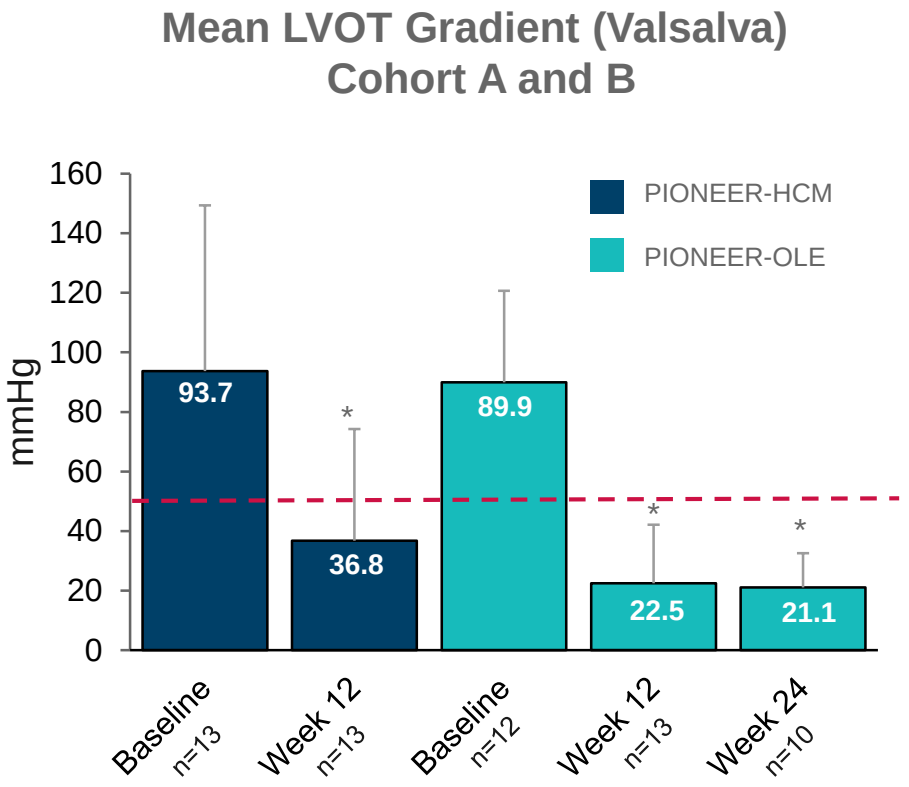
* One patient discontinued study after Week 24 following unrelated diagnosis of cholangiocarcinoma.

Demographics and Baseline Characteristics

Characteristic	PIONEER-HCM n=13	PIONEER-OLE n=13
Age, year, mean (SD)	56.5 (13.2)	57.8 (13.3)
Sex, n (%)		
Male	9 (69.2)	
Female	4 (30.8)	
NYHA functional class, n (%)		
Class II	9 (69.2)	12 (92.3)
Class III	4 (30.8)	1 (7.7)
Background HCM therapy while on study drug, n		
Metoprolol	7	11
Bisoprolol	0	1
Echocardiography parameters		
Resting LVEF (%), mean (SD)	73.0 (5.6)	72.0 (4.9)
LVOT gradient (mm Hg), mean (SD)		
Resting	69.7 (53.9)	67.3 (42.8)
Valsalva	93.7 (55.6)	89.9 (30.7)
Post-exercise	94.5 (45.0)	127.5 (33.4)
NT-pro BNP (pg/mL), mean (SD)	1601 (2702)	1836 (2886)

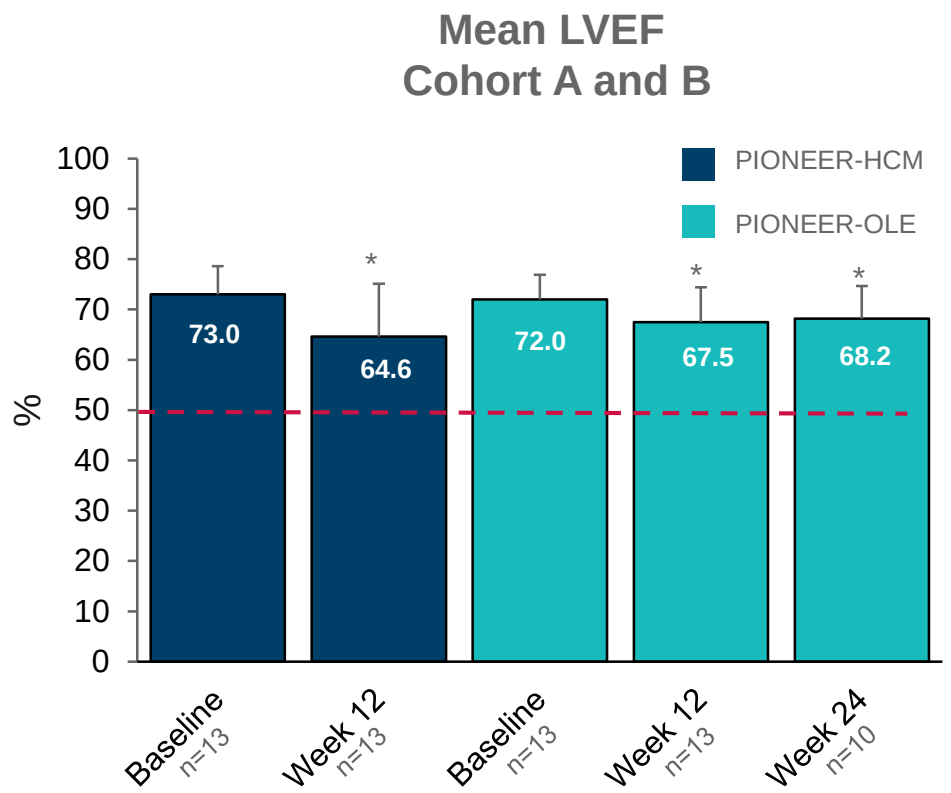
HCM, hypertrophic cardiomyopathy;- NYHA, New York Heart Association; SD, standard deviation

LVOT Valsalva Gradient and LVEF in PIONEER-HCM and PIONEER-OLE



*p<0.05 change from baseline

Threshold for guideline-based invasive intervention

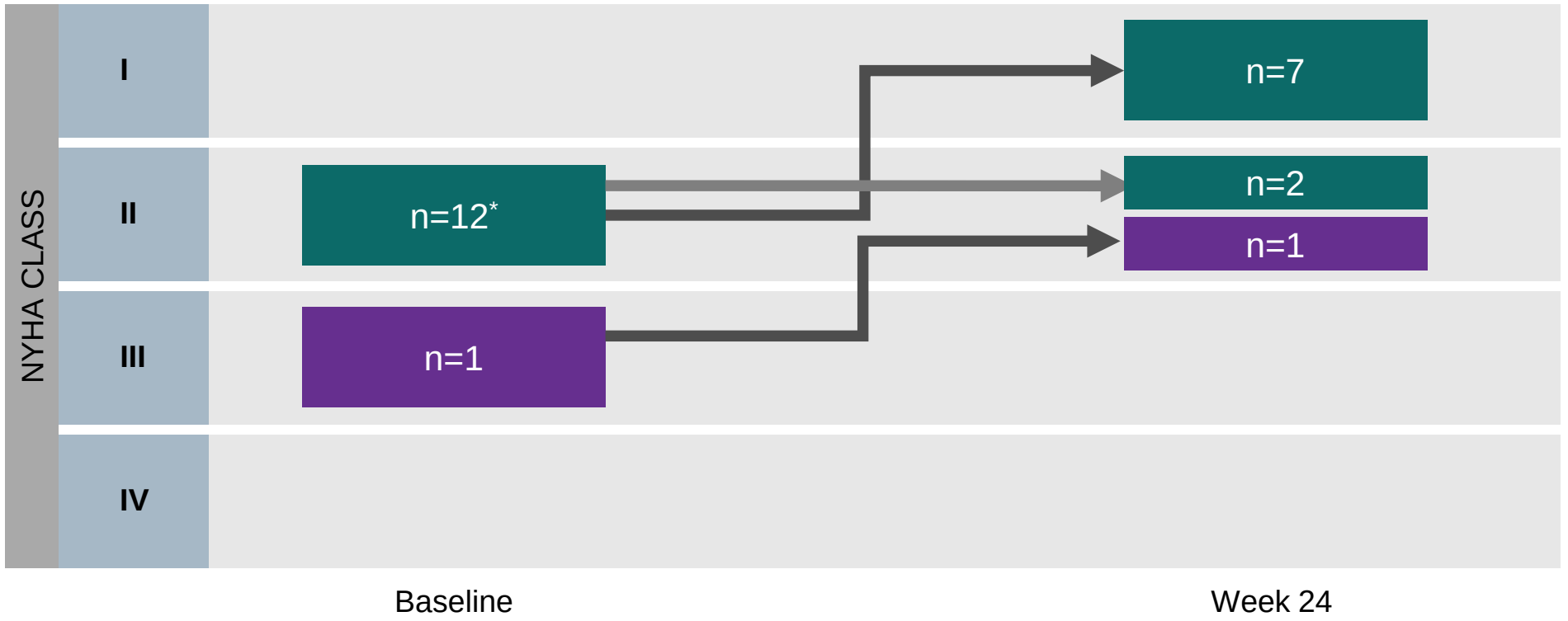


*p<0.05 change from baseline

Threshold for normal ejection fraction

Improvements in NYHA Functional Class

- NYHA Class improved in 8 out of 10 evaluable patients* at Week 24



*Three patients did not reach evaluation timepoint

Improvement in Levels of NT-proBNP

- Levels of NT-proBNP were significantly reduced at Weeks 12 and 24

Mean(SD)	PIONEER-HCM			PIONEER-OLE				
	BL n=12	Week 12 n=13	Δ BL to Week 12	BL n=13	Week 12 n=13	Δ BL to Week 12	Week 24 n=10	Δ BL to Week 24
NT-proBNP	1601.3 (2782)	684 (980)	-1070 (2409)*	**1836 (2886)**	**178 (202)**	**-1658 (-2695)***	**170 (225)**	**-2128 (3104)***

***P*<0.05**

Changes in Filling-related Parameters

- For exploratory assessments, mavacamten improved markers related to ventricular filling at Weeks 12 and 24 (Table 2):
  - There was a significant increase in mitral annular velocity during early diastole (e'lat) and concomitant reduction in E/e'_{lat}
  - There was a significant decrease in left atrial (LA) volume

Mean (SD)	PIONEER-HCM			PIONEER-OLE				
	BL n=13	Wk 12 n=13	Δ BL to Wk 12	BL n=13	Wk 12 n=13	Δ BL to Wk 12	Wk 24 n=10	Δ BL to Wk 24
e'_{lat} cm/s	6.2 (0.9)	7.2 (2.2)	0.9 (1.9)	6.4 (1.3)	8.4 (2.3)	2.0 (2.0)*	7.8 (2.2)	1.4 (2.0)*
E/e'_{lat}	13.1 (2.7)	10.5 (3.7)	-2.5 (3.4)*	12.8 (2.9)	9.8 (2.5)	-3.0 (3.4)*	10.3 (3.0)	-2.8 (3.1)*
LA vol index (mL/m^2)	39.0 (18.7)	35.1 (11.0)	-3.9 (11.8)	40.9 (16.4)	31.8 (8.4)	-9.2 (11.7)*	29.7 (8.0)	-13.6 (13.3)*

***P<0.05**. LA, left atrial.

Safety and tolerability

- There were no cardiovascular adverse events (AEs)
- There were no dose changes or dose interruptions due to AEs
- Of 34 AEs, most were mild (25) or moderate (5) and transient
  - 6 AEs were considered potentially related to study drug (fatigue, dyspnea, dizziness, lethargy, lightheadedness)

	PIONEER-OLE n=13
Number of patients with any AEs	12
Number of reported AEs[a]	34
Mild	25
Moderate	5
Severe[a]	3
Life-threatening and serious AEs[a]	1

[a]One patient had 3 severe AEs and 1 serious AE that were unrelated—male with history of ulcerative colitis presented 4 days after Week 24 visit with epigastric pain, elevated AST (>5X ULN), and biliary obstruction; subsequently diagnosed with Klatskin type cholangiocarcinoma at hepatic hilum (11/7) and underwent surgery; the patient discontinued study drug dosing and had an early study termination. AEs, adverse events; AST, aspartate aminotransferase; ULN, upper limit of normal

Conclusions

- Despite management with current therapies such as β-blockers, patients enrolled in PIONEER-OLE with similar levels of obstruction and hypercontractility after completing PIONEER-HCM 6-18 months prior.
- After 24 weeks of treatment patients experienced a significant reduction in LVOT peak instantaneous gradient, surrogate measures of left ventricular filling pressure, and improvement in clinical status:
    - There were significant reductions in LVOT gradient and levels of NT-proBNP, as well as in E/e'lat and LA volume.
    - Eight out of 10 evaluable patients reported significant improvements in NYHA.
- Ejection fraction was maintained above 50% in all patients.
- Dose titration to the target therapeutic range reduced gradient without compromising contractility below normal levels.
- During this approximately 10-month treatment period, mavacamten was well tolerated; the majority of AEs were mild and unrelated to the study drug.

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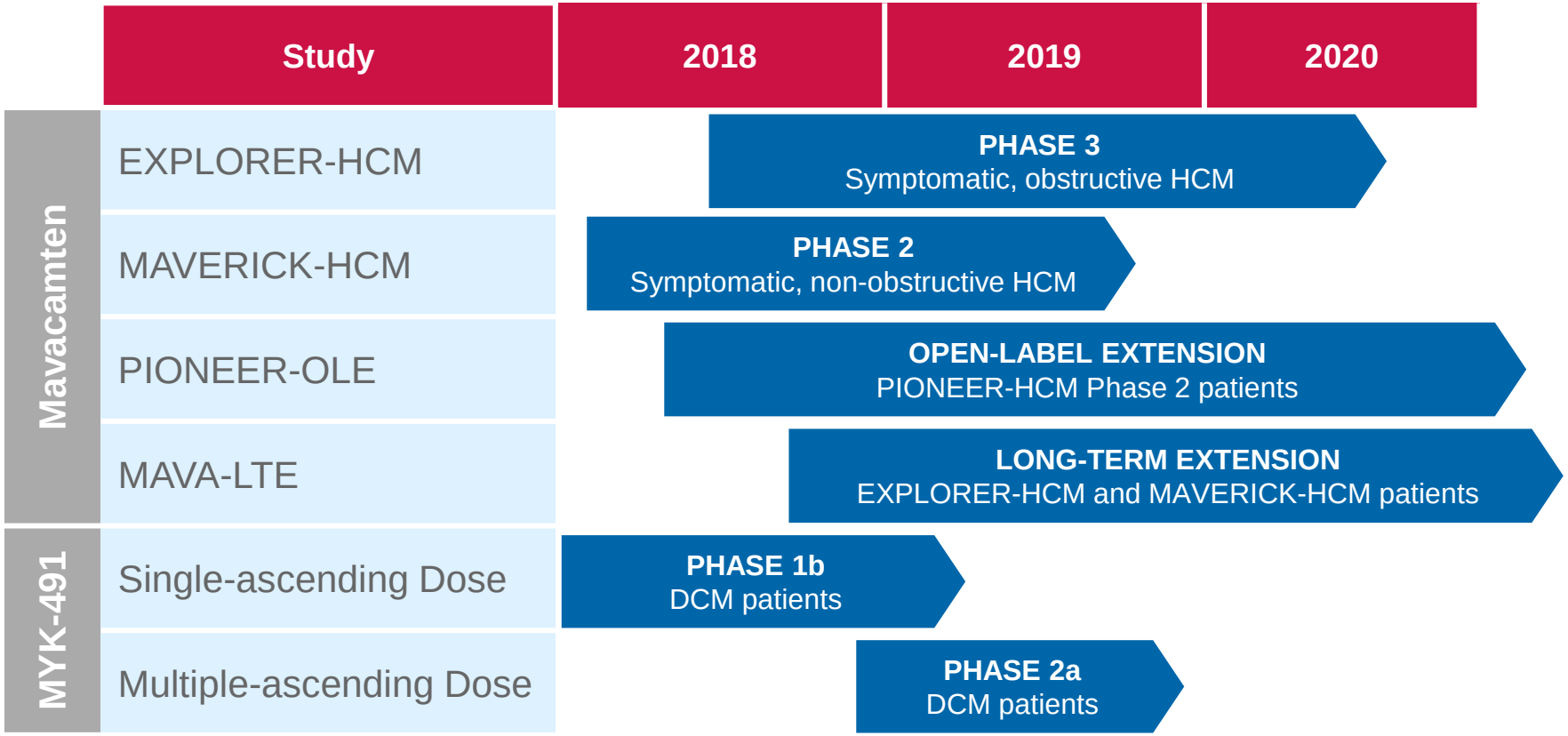
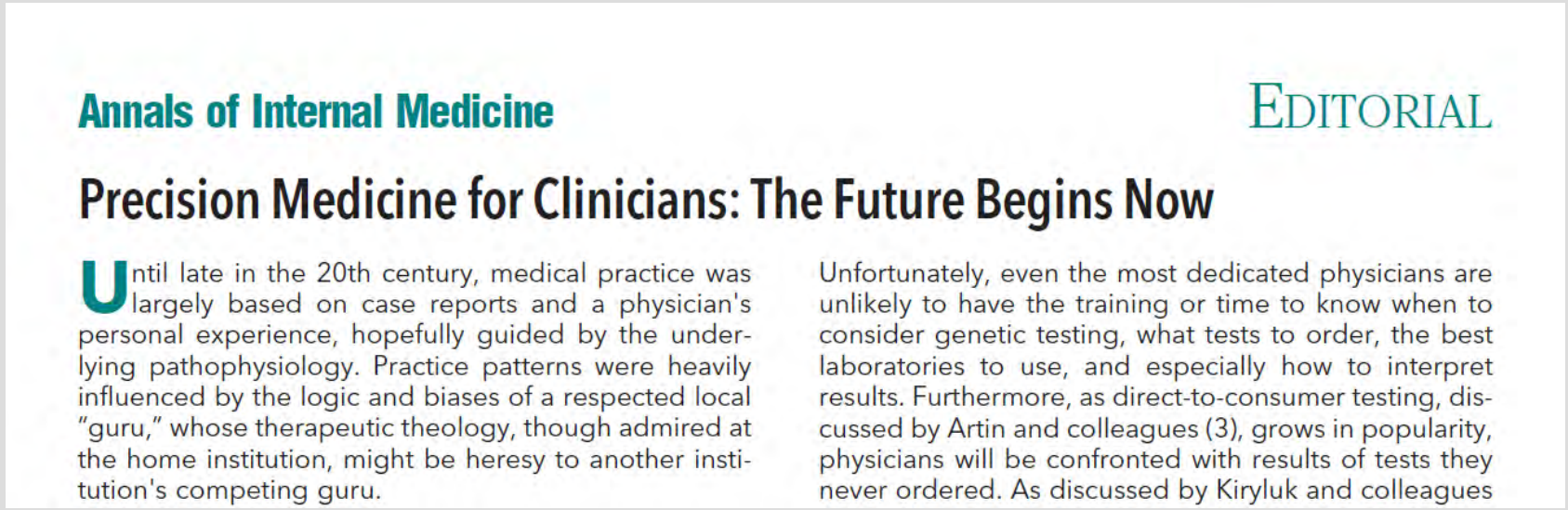




Annals of Internal Medicine

EDITORIAL

Precision Medicine for Clinicians: The Future Begins Now

Until late in the 20th century, medical practice was largely based on case reports and a physician's personal experience, hopefully guided by the underlying pathophysiology. Practice patterns were heavily influenced by the logic and biases of a respected local "guru," whose therapeutic theology, though admired at the home institution, might be heresy to another institution's competing guru.

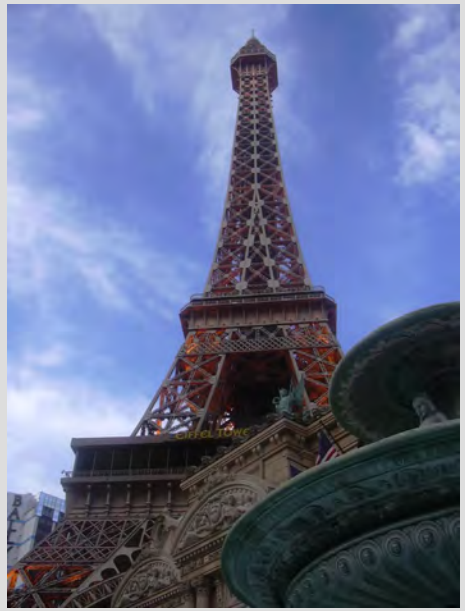
Unfortunately, even the most dedicated physicians are unlikely to have the training or time to know when to consider genetic testing, what tests to order, the best laboratories to use, and especially how to interpret results. Furthermore, as direct-to-consumer testing, discussed by Artin and colleagues (3), grows in popularity, physicians will be confronted with results of tests they never ordered. As discussed by Kiryluk and colleagues

Lee Goldman, MD, MPH and Jill S Goldman, MS, MPhil, *Ann Int Med,* Apr 30, 2019

"The explosion of genetic knowledge and the ready availability of genetic testing present amazing possibilities. For advances in genomics to improve health through precision medicine, however, we must educate current and future physicians, as well as the lay public."

ACKNOWLEDGEMENTS

- Patients who have and are currently participating in mavacamten clinical studies
- Global investigators specializing in HCM and their dedicated study staff
- MyoKardia team
- Bill Evans for the invitation to WSOPC 2019



THANK YOU!