Mavacamten for Hypertrophic Cardiomyopathy: Effectiveness and Value

Public Meeting — October 22, 2021

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INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Patient and Clinical Experts

Gwen Mayes, JD, MMSC, Patient Advocate; Founder, GwenCo Health

- Gwen Mayes serves as a consultant to the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia. She also consults for cardiac device companies including Edwards Lifesciences and Paragonix.

Lisa Salberg, Founder and CEO, Hypertrophic Cardiomyopathy Association

- The Hypertrophic Cardiomyopathy Association receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.

Milind Desai, MD, MBA, Director of Clinical Operations; Director, Hypertrophic Cardiomyopathy Center, Department of Cardiovascular Medicine; Heart, Vascular & Thoracic Institute, Cleveland Clinic

- Dr. Desai serves as an investigator for the VALOR study of mavacamten.

Martin S. Maron, MD, Director, Hypertrophic Cardiomyopathy Center, Tufts Medical Center; Co-Director, Chanin T. Mast Hypertrophic Cardiomyopathy Center Morristown Medical Center, Atlantic Health System

- Dr. Maron served as a site investigator for a Phase I mavacamten study and serves as a steering committee member for a Phase II Cytokinetics study of a second-generation myosin inhibitor.

Why Are We Here Today?

“HCM has a huge impact on my life, and it affects my job. I can’t walk more than 10 minutes without stopping to catch my breath, I can’t workout like I used to, I am gaining weight, I can only walk up one flight of stairs at a time, I am embarrassed to be around people who may see me struggling to breathe – it keeps me secluded in my home. And what is most depressing is seeing how I am getting worse and can’t stop it.”

Patient with HCM

Why Are We Here Today?

- What happens the day these treatments are approved by the FDA?
- Patients can have difficulty accessing drugs
  - Coverage eligibility
  - Costs (out-of-pocket and insurance premiums)
- What happens to patients and others in the health care “system”?

The Impact of Rising Health Care Costs

Leonard Edloe
Richmond, Virginia

The Whitman family
Bird City, Alaska

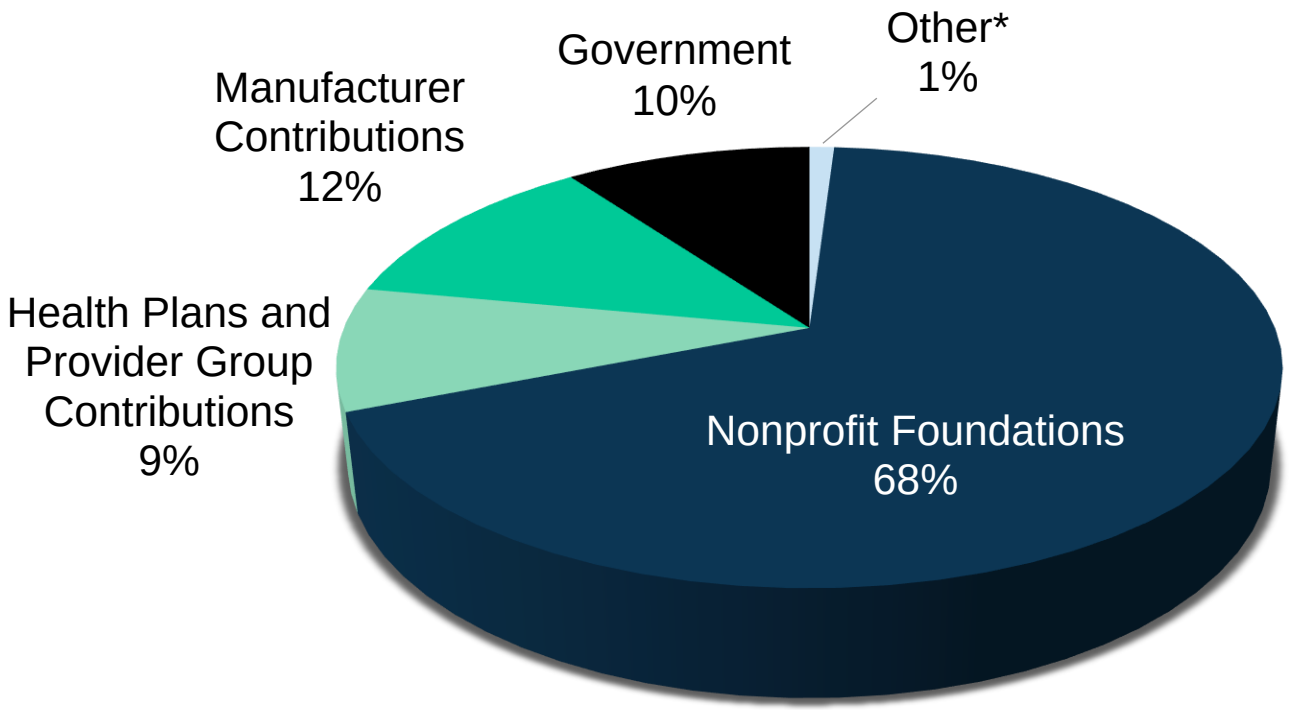
The Maccoux family
Brooklyn Park, Minnesota

Organizational Overview

- California Technology Assessment Forum Public Advisory Council
- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2021

https://icer.org/who-we-are/independent-funding/



*Individual / matching contributions and speech stipends

How Was the ICER Report Developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Illinois at Chicago cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
  - **Milind Desai, MD, MBA**, Director of Clinical Operations; Director, Hypertrophic Cardiomyopathy Center, Department of Cardiovascular Medicine; Heart, Vascular & Thoracic Institute, Cleveland Clinic
  - **Martin S. Maron, MD**, Director, Hypertrophic Cardiomyopathy Center, Tufts Medical Center; Co-Director, Chanin T. Mast Hypertrophic Cardiomyopathy Center Morristown Medical Center, Atlantic Health System
  - **Steve R. Ommen, MD**, Medical Director, Mayo Hypertrophic Cardiomyopathy Clinic, Mayo Clinic
  - **Lisa Salberg**, Founder and CEO, Hypertrophic Cardiomyopathy Association
- How is the evidence report structured to support CTAF voting and policy discussion?

Value Assessment Framework: Long-Term Value for Money

Agenda

Time (PT)	Activity
9:00 am – 9:20 am	**Meeting Convened and Opening Remarks** Steven D. Pearson, MD, MSc, President, ICER
9:20 am – 10:00 am	**Presentation of the Clinical Evidence** Jason H. Wasfy, MD, MPhil, Associate Professor, Harvard Medical School, Massachusetts General Hospital
10:00 am – 10:40 am	**Presentation of the Economic Model** Surrey M. Walton, PhD, Associate Professor, University of Illinois at Chicago College of Pharmacy
10:40 am – 11:15 am	**Public Comments and Discussion**
11:15 am – 11:25 am	**Break**
11:25 am – 12:15 pm	**CTAF Vote on Clinical Effectiveness and Value**
12:15 pm – 1:00 pm	**Lunch Break**
1:00 pm – 2:30 pm	**Policy Roundtable**
2:30 pm – 3:00 pm	**Reflections from CTAF**
3:00 pm	**Meeting Adjourned**

Presentation of the Clinical Evidence

Jason H. Wasfy, MD, MPhil

Associate Professor, Harvard Medical School

Medical Director, Massachusetts General Physicians Organization

Director of Outcomes Research, Massachusetts General Hospital Heart Center

Massachusetts General Hospital

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Key Collaborators

- Molly Beinfeld, MPH, Senior Research Lead, Evidence Synthesis, ICER
- Emily Nhan, Research Assistant, ICER

Disclosures:

We have no conflicts of interest defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

Dr. Wasfy does not have conflicts of interest defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

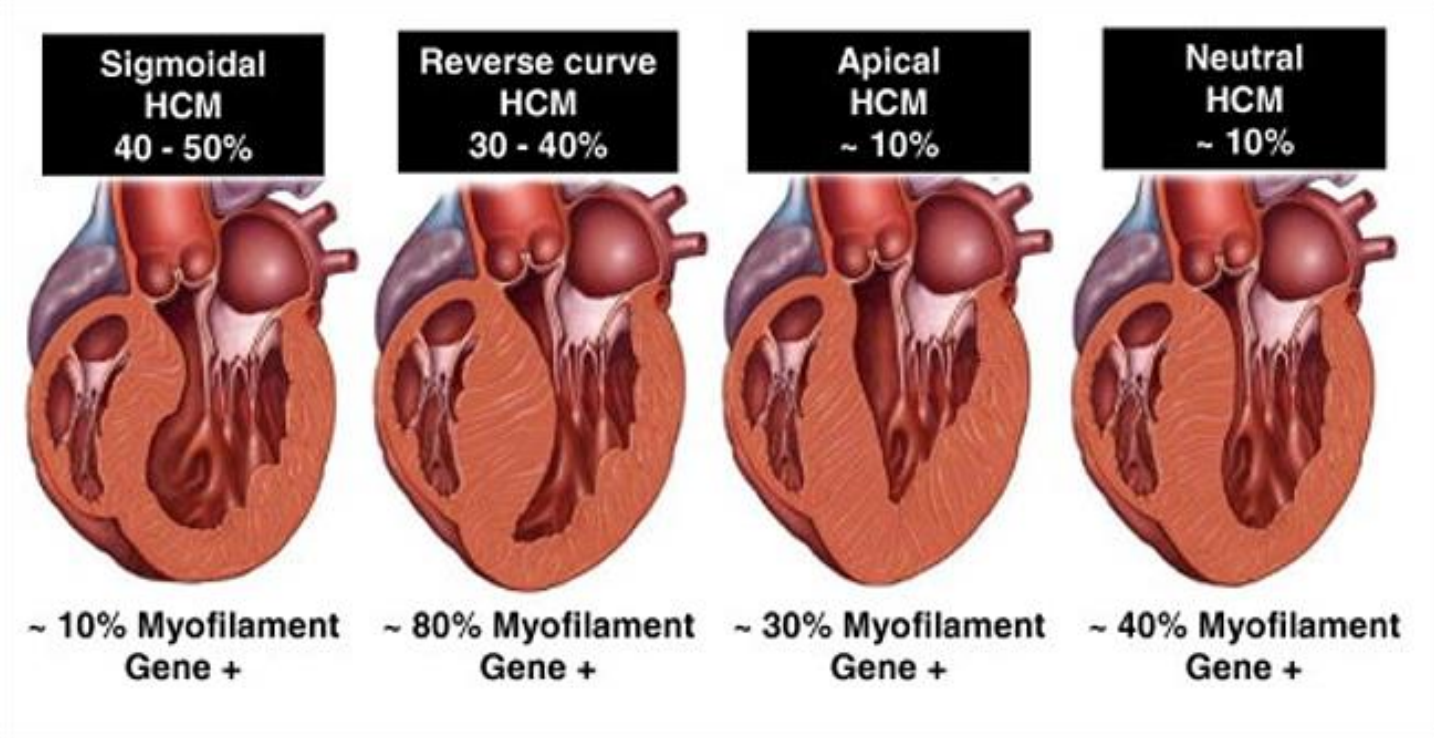
Background

- Hypertrophic cardiomyopathy (HCM) is a genetic disorder involving heart muscle that causes dysfunction and thickening
- Hypertrophic obstructive cardiomyopathy (HOCM) is a subtype of HCM in which the thickening leads to narrowing/obstruction in the left ventricular outflow tract
- Narrowing causes pressure drop, leading to symptoms with shortness of breath and chest discomfort with exertion. Reducing gradient is a core goal of therapy
- Palpitations, dizziness, syncope also prominent. Atrial fibrillation poorly tolerated
- Symptoms can be also be related to diastolic dysfunction, microvascular angina

Background

- HCM must be distinguished from other types of hypertrophy (hypertensive heart disease, athlete's heart, amyloidosis)
- True prevalence unknown due to screening differences with imaging modalities (1 in 500 by echo but 1 in 70 by cMRI)
- With appropriate use of implantable cardioverter-defibrillators, rate of SCD has decreased to 0.5% per patient-year

Left Ventricular Outflow Tract Obstruction is Related to Cardiac Morphology



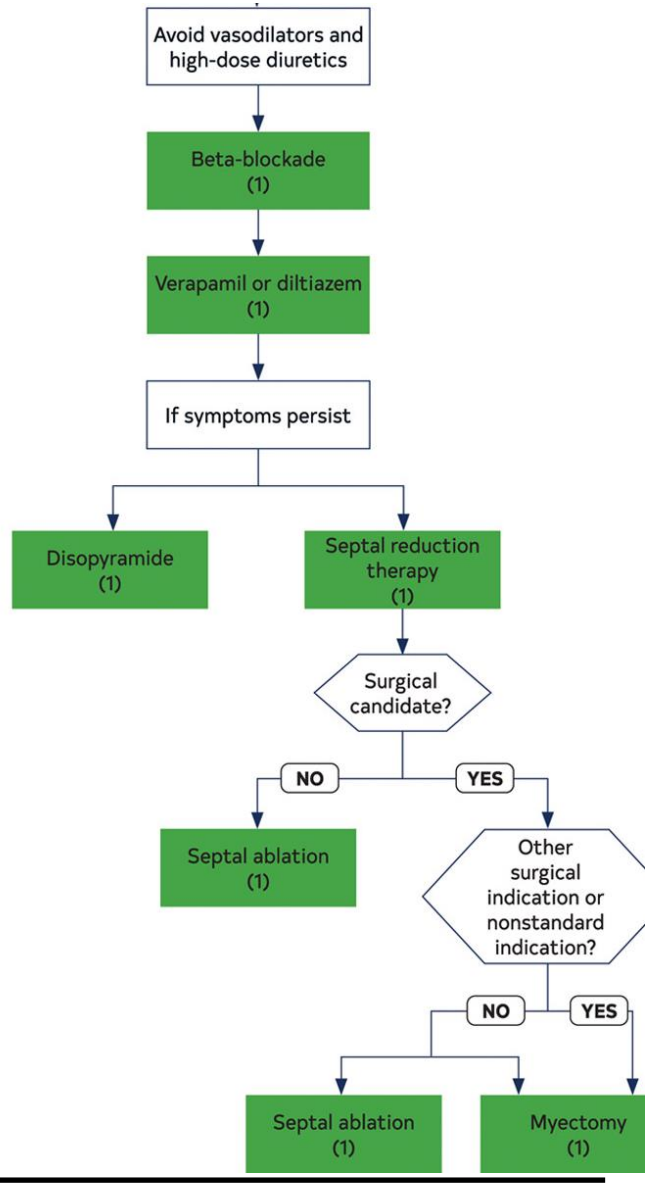
Naidu et al. ACC 2015
Bos et al. JACC 2009

Standard of Care and Management

- For patients with exertional symptoms attributable to LVOT obstruction:

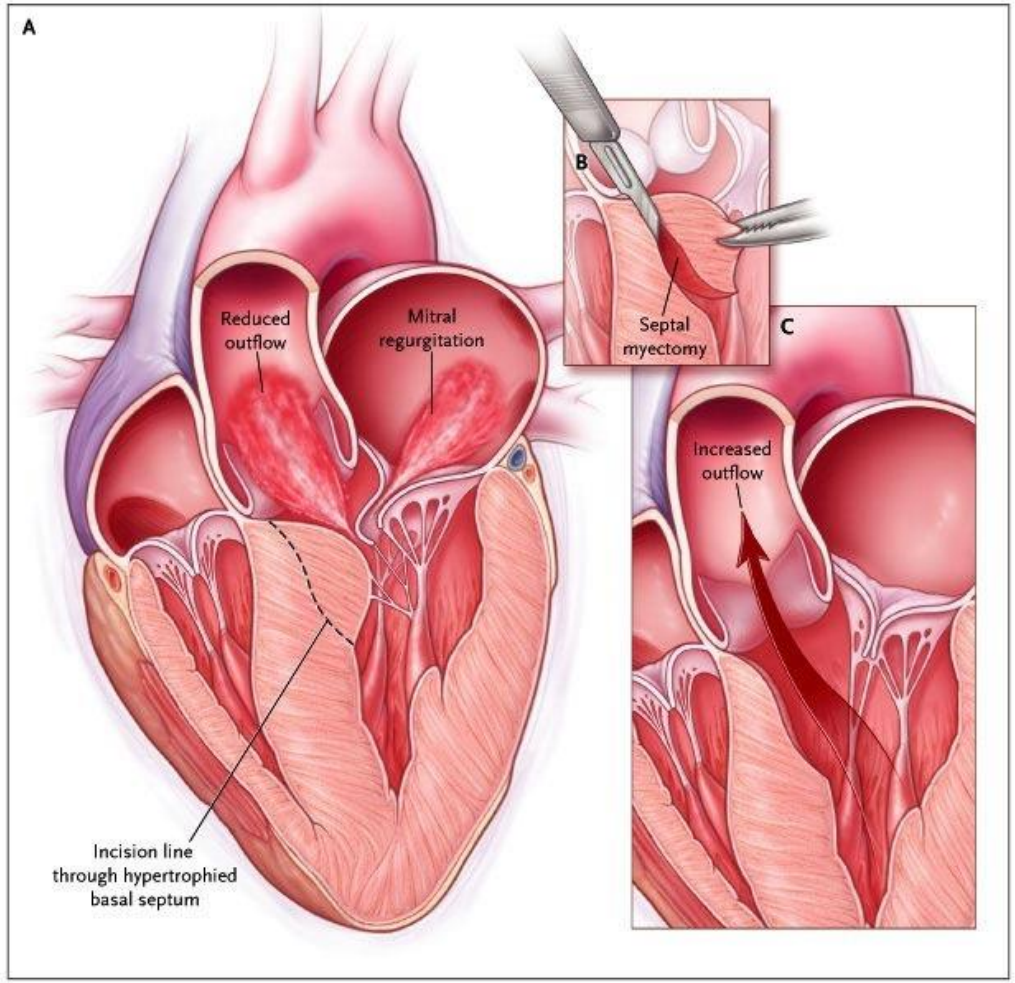
First line: Negative inotropic agents (beta blockers and calcium channel blockers) are first line

Then: Disopyramide or septal reduction procedures



Ommen et al. *Circulation* 2020

Septal Reduction Procedures



Nishimura *NEJM* 2004

Therapies Under Review

- Interventions
  - Mavacamten is an oral, first-in-class modulator of cardiac myosin
  - PDUFA date: January 28, 2022
- Comparators
  - Usual care
  - Disopyramide
  - Percutaneous septal ablation
  - Surgical myectomy
- Comparisons are informed by input from patients, ACC/AHA guidelines, and feedback from clinical experts and public commentary

Scope of Review

- Patients with symptomatic HOCM
- Outcomes included functional status, health-related quality of life, echocardiographic parameters, peak oxygen consumption (peak VO_2), serum cardiac biomarkers

Insights from Discussions with Patients

- In initial discussions with the Hypertrophic Cardiomyopathy Association, they sent out questions to patients
- We are grateful for these detailed responses! 641 responses from patients, caregivers, patient advocates
- Common themes:
  - Side effects of beta blockers
  - Difficulty accessing treatment (centers of excellence/knowledgeable specialists and drug shortage of disopyramide)
  - Impacts of both symptoms and drug side effects on work, education, family, relationships
  - Only 50% of patients say treatments “work well”

Clinical Evidence

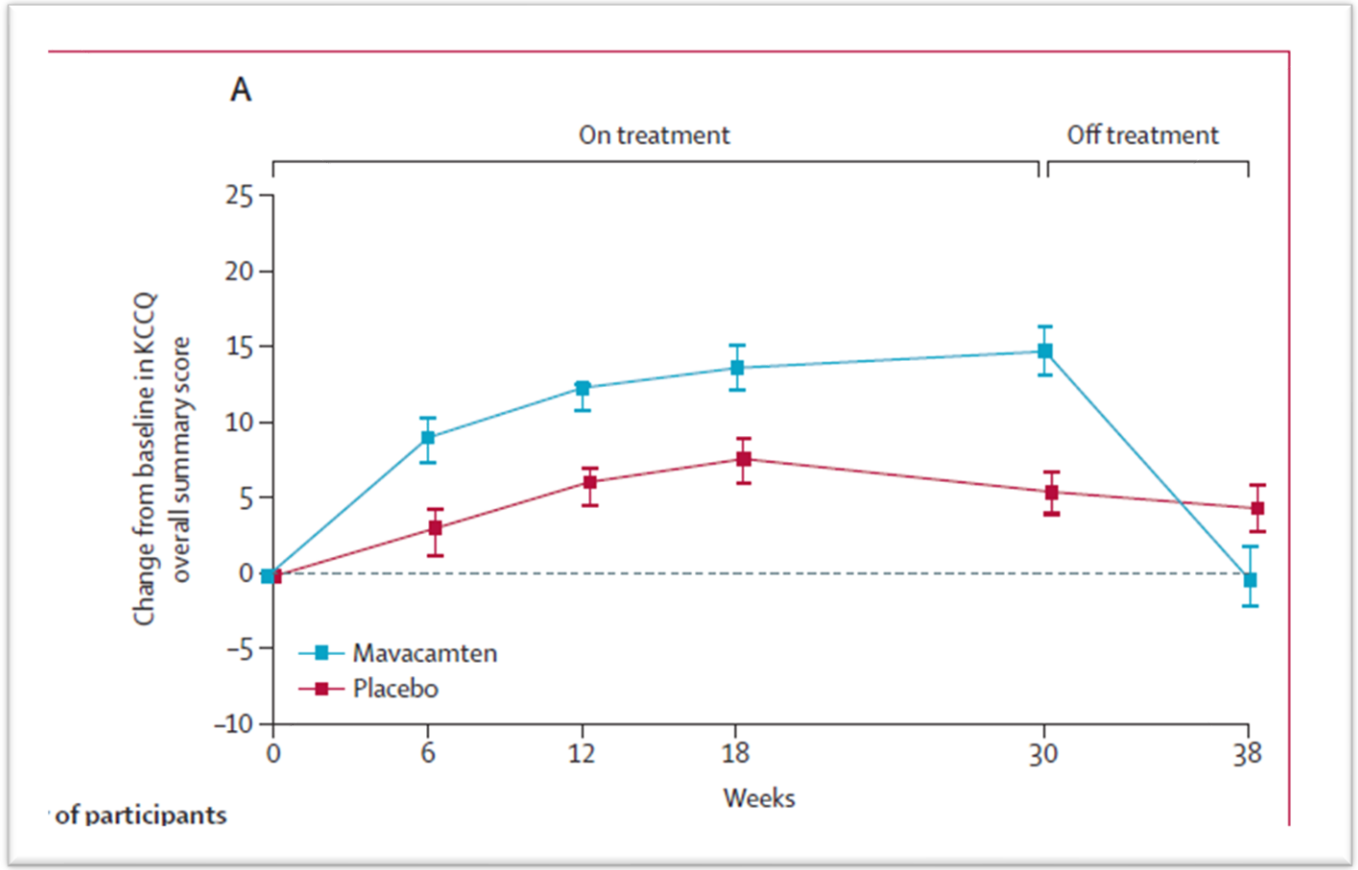
Mavacamten: EXPLORER RCT (n=251)

- At 30 weeks, composite outcome of improvement in a physiological parameter (+1.5 mL/kg improvement in pVO_2) and clinician-defined symptom improvement (at least 1 NYHA class) or +3.0 mL/kg improvement with no NYHA worsening
    - Achieved by 37% of patients in the mavacamten arm at 30 weeks compared to 17% in the placebo arm (p=0.0005)
- Nearly 50% of patients on mavacamten achieved NYHA class I at 30 weeks compared to 21% of patients on placebo (p<0.0001)

	Mavacamten (n=123)		Placebo (n=128)	
	Baseline	30 Weeks	Baseline	30 Weeks
NYHA Class I (%)	0	49.6	0	21.1
NYHA Class II (%)	71.5	42.3	74.2	57.8
NYHA Class III (%)	28.5	6.5	25.8	19.5
Missing (%)	0	1.6	0	1.6

EXPLORER RCT Patient-Reported Outcomes

- Kansas City Cardiomyopathy Questionnaire (KCCQ) is a measure of health status in heart failure
- Change in KCCQ-OS at 30 weeks greater with mavacamten than placebo (+14.9 vs. +5.4, p<0.0001)
- MCID: 4-6 points
- Reverted to baseline after 8-week washout period



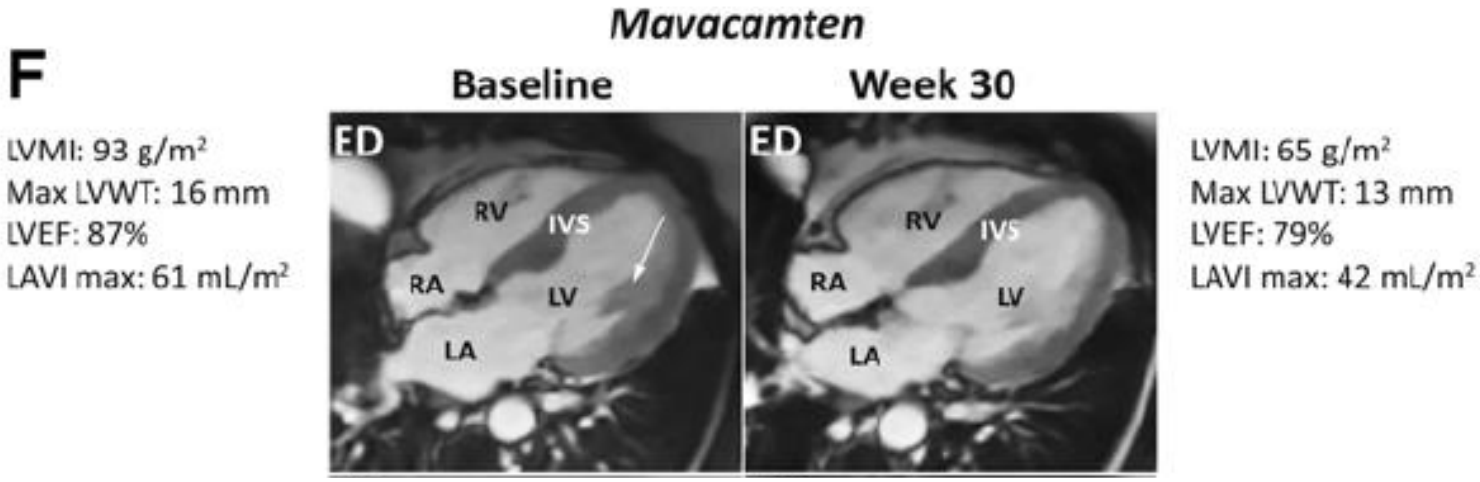
Spertus et al *Lancet* 2021
Olivotto et al *Lancet* 2020
Ho et al *Circ HF* 2020
Butler et al *Eur J HF* 2020

EXPLORER: Secondary Endpoints

- Greater reduction in post-exercise LVOT gradient with mavacamten (-43.2 mm Hg vs. -28.1 mm Hg, $p<0.0001$)
- Greater increase in peak VO_2 with mavacamten (+1.4 mL/kg/min, $p=0.0006$)
- Primary endpoint concordant with patient-reported outcomes, objective physiological endpoint, and purported mechanism
- Also concordant with large drops in LVOT gradient seen in PIONEER Phase II trial

Mavacamten: Longer Term Effects

- Of patients in EXPLORER that received cMRI, mavacamten patients had greater reduction in LV mass index and left atrial volumes
- Symptoms as reported by KCCQ return to baseline after stopping mavacamten
- Discordance of imaging and patient-reported outcomes?



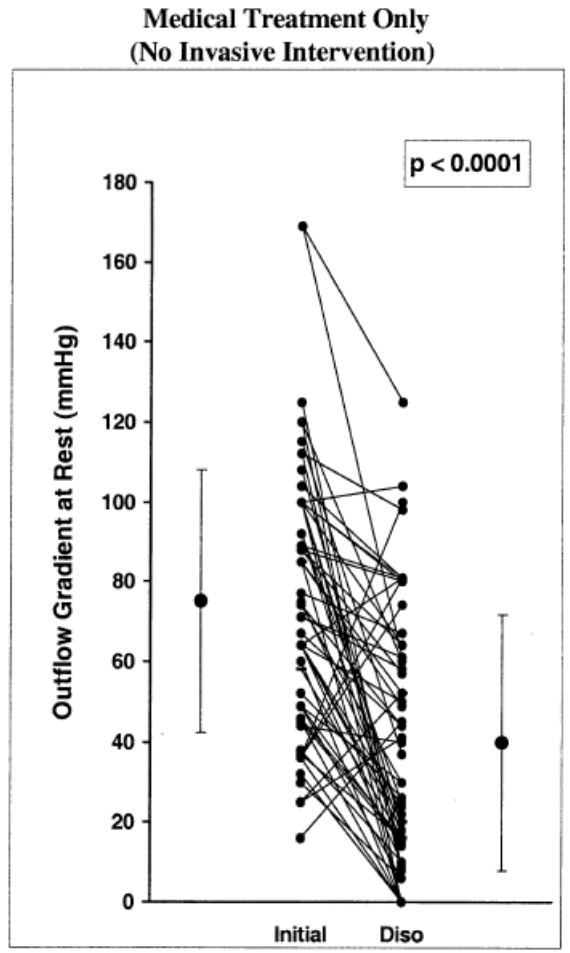
Saberi et al. *Circulation* 2021
Spertus et al. *Lancet* 2021

Mavacamten: Uncertainties

- EXPLORER protocol required temporary treatment discontinuation for clinical endpoints including LVEF <50%
- 3 patients on mavacamten and 2 on placebo discontinued due to LVEF decreases during the study period
- In addition, 4 patients receiving mavacamten had LVEF <50% at week 30
- 3 patients recovered, 1 had persistent low LVEF after AF ablation with complications
- Clinical experts disagree about the relevance/importance of these findings

Disopyramide: Sherrid 2005

- Evidence for disopyramide overall very limited
- Mostly short term, small, and physiologic observational studies
- Practical limitations – national shortage of the long-acting version
- No trials
- Among those who stayed on disopyramide, mean NYHA Class declined from 2.3 → 1.7 (p<0.0001)
- 40/134 (34%) required major interventions – among these patients, functional status did not improve
- Selection bias (patients who were doing worse were not maintained on disopyramide) and unclear external validity (only patients appropriate for disopyramide were started on it)



Septal Reduction Therapies: Liebregts 2015

- Systematic literature review and meta-analysis of 16 myectomy cohorts and 11 septal ablation cohorts
- Pooled mean improvement in NYHA class before and after treatment was:
  - -1.16 for septal ablation
  - -1.51 for myectomy
- Large reductions in median LVOT gradients were associated with both procedures
  - 71% for septal ablation
  - 77% for myectomy

Harms of Mavacamten and Disopyramide

Mavacamten

- Generally well tolerated
- ? Importance of decreasing LVEF
- Discontinuation 1.6%

Disopyramide

- Risk of arrythmia and prolonged QT interval
- Discontinuation due to side effects (7-23%)
- Side effects include anti-cholinergic effects – xerostomia (dry mouth), constipation, urinary hesitancy
- Contraindications include narrow angle glaucoma, difficult to treat hypertension, risk of BPH

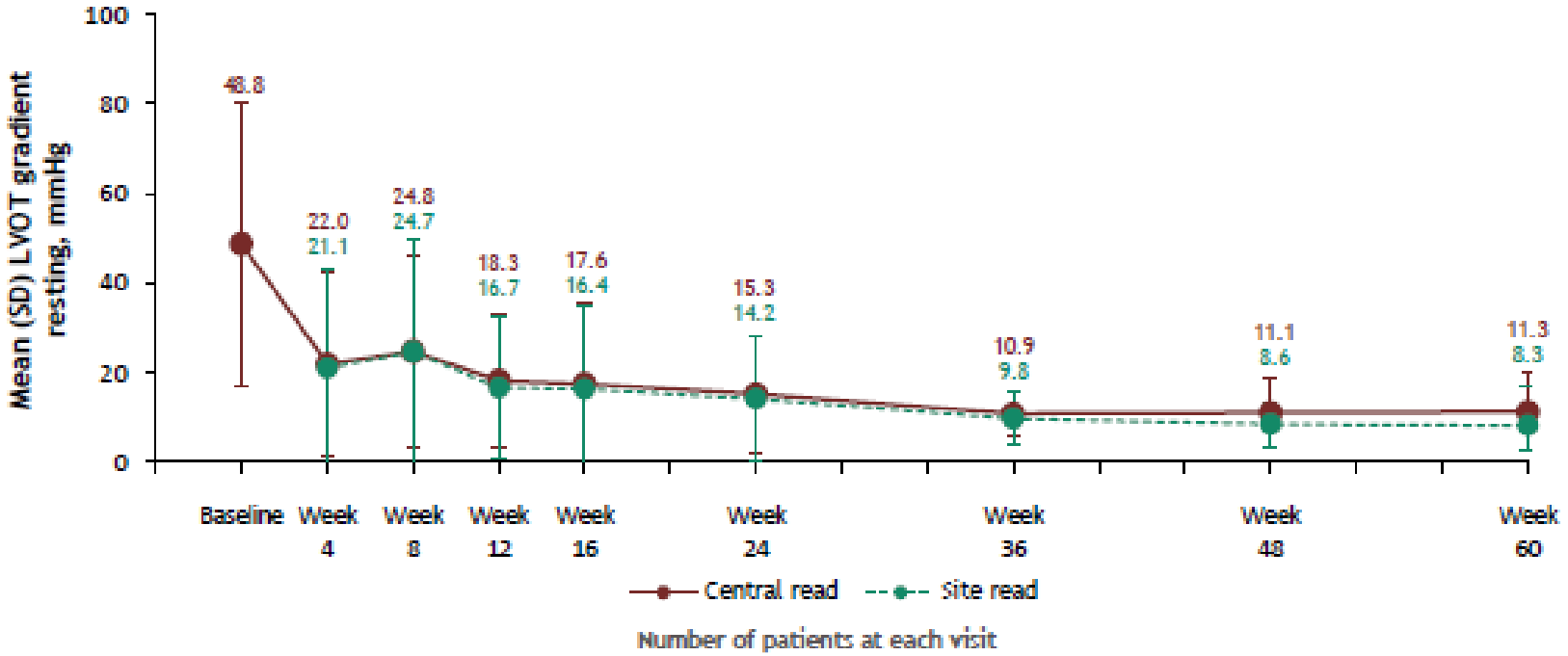
Harms of Septal Reduction Therapy

	Septal Ablation	Myectomy
Peri-Procedural Adverse Arrhythmic Events (VT and VF), %	2.2	1.0
Peri-Procedural Mortality (<30 Days), %, Weighted Mean (95% CI)	1.3 (0.7-1.8)	2.5 (1.4-3.6)

New pacemaker requirement – 4.4% for surgical myectomy and 10.0% for septal ablation
Reintervention – 1.6% for myectomy and 7.7% for septal ablation
Among studies after 2000, periprocedural mortality was no different for myectomy vs. septal ablation (1.1% vs. 1.3%, p=0.75)

Unpublished and Ongoing Trials

- 5-year long-term extension study (MAVA-LTE)
- Of 49 patients with a week 48 assessment, 71% improved by at least 1 NYHA class



Rader et al. ACC 2021

Controversies and Uncertainties

- Disagreements about importance of decreased LVEF – longer term follow-up data is likely to address this. One patient in REDWOOD-HCM (a trial of aficamten) had decreased LVEF – data presented a few weeks ago
- More than 90% of patients in EXPLORER were white – concerns about representativeness
- No trials in key comparisons with septal reduction or disopyramide
- Discordance between imaging data in EXPLORER and patient-reported outcomes – durability of treatment effect of mavacamten is unclear
- Likely strong patient preference dependence of therapy options (small risk of death with procedures a/w larger treatment benefit)

Potential Other Benefits and Contextual Considerations

- Patients with symptomatic HOCM are often at stage of lives when making decisions about families, careers, education
- Patient perspective about fear of death and unpredictability of symptoms – effects on relationships and career decisions
- Caregivers report needing to take time off from work, causing financial stress
- Mavacamten could provide more access to treatment options (although unclear if will be prescribed only at specialized centers)

Public Comments Received

- Gaps in data, particularly regarding comparisons of mavacamten to disopyramide and septal reduction procedures
- Importance of critical appraisal of data from trial populations
- Safety of initiation of disopyramide at home?

Summary

- Relative to usual care, mavacamten improves patient reported outcome (KCCQ), clinician-estimated functional status (NYHA), as well as objective physiological parameter (peak $V0_2$), concordant with mechanism (LVOT gradient)
- Trials have not been performed to compare mavacamten versus disopyramide, but evidence for disopyramide is relatively weak
- Trials have not been performed to compare mavacamten to septal reduction procedures – these decisions will likely be preference-sensitive

ICER Evidence Ratings

Treatment	Comparator	ICER Evidence Rating
Mavacamten Plus Usual Care	Usual care alone	P/I
Mavacamten Plus Usual Care	Disopyramide	P/I
Mavacamten Plus Usual Care	Septal reduction therapies	No rating

P/I: promising but inconclusive, moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit

Questions

Presentation of the Economic Model

Surrey M. Walton, PhD, MA

Professor, Pharmacy Systems, Outcomes, and Policy

Assistant Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research

University of Illinois at Chicago College of Pharmacy

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Key Review Team Members

- Jyotirmoy Sarker, MPharm, MBA, MBiotech, Graduate Student, Pharmacy Systems, Outcomes, and Policy, University of Illinois at Chicago
- Melanie D. Whittington, PhD, Associate Director of Health Economics, ICER

Disclosures:

Financial support was provided to the University of Illinois at Chicago from ICER.

University of Illinois at Chicago researchers have no conflicts to disclose defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

Objective

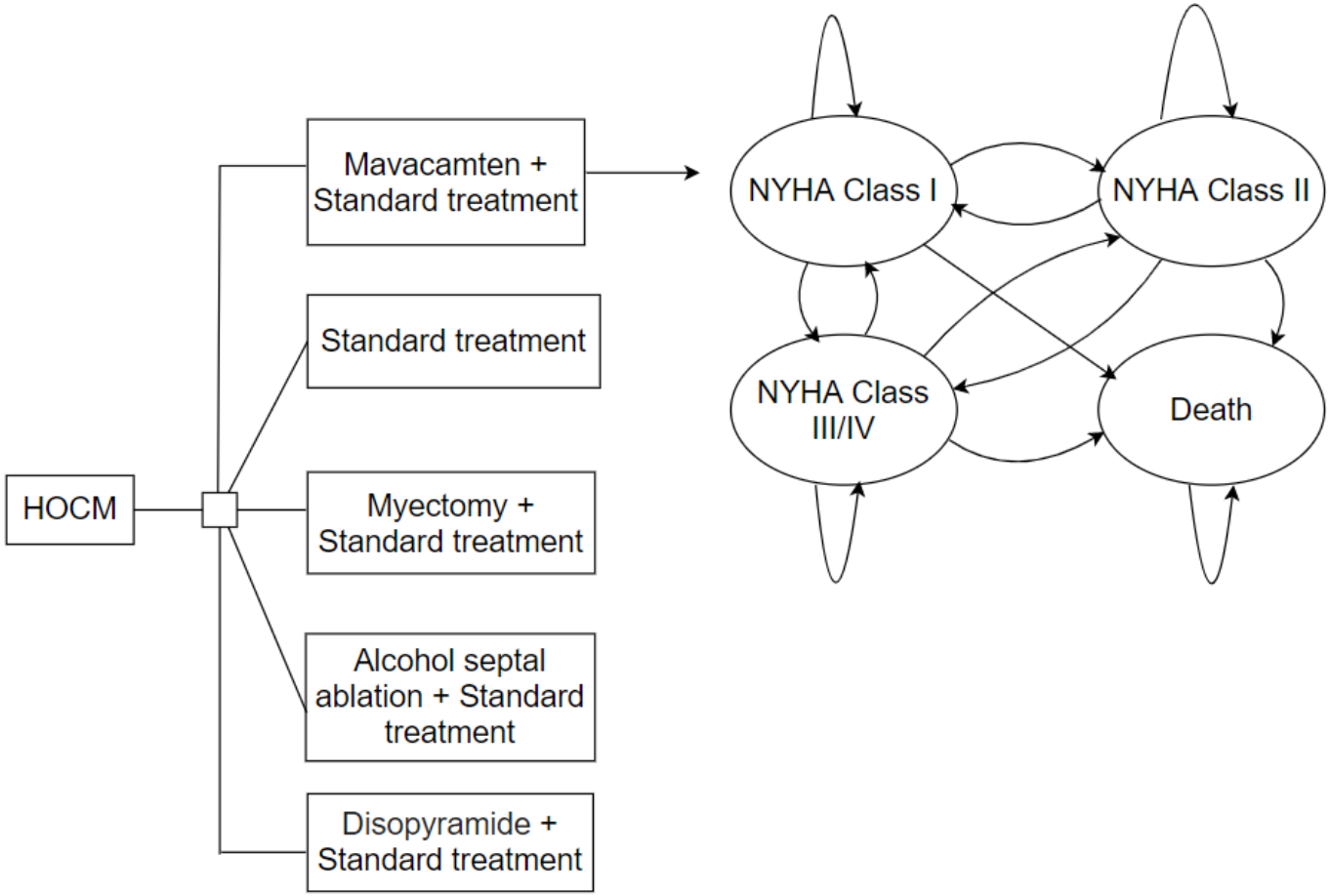
- Estimate the cost effectiveness of mavacamten and standard of care compared with standard of care as well as disopyramide, myectomy, and septal ablation each with standard of care

Methods in Brief

Methods Overview

- **Model**: Semi Markov model
- **Setting**: United States
- **Perspective**: Health care sector perspective
- **Time Horizon**: Patient lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: 4 weeks
- **Primary Outcomes**: Cost per QALY gained; cost per LY gained, cost per evLY gained, cost per NYHA I year gained

Model Schematic



Population Characteristics

- US patients with HOCM
  - Starting age: 58
  - 41% female

Key Model Assumptions

- Placeholder price of mavacamten: $75,000 per year
- Patient utilities are estimated via NYHA class
- Mortality is the same across all NYHA classes
- Discontinuation is not considered in the model
- For mavacamten and standard of care, treatment effect extrapolated for 8 cycles (32 weeks) based on EXPLORER trial data. After 8 cycles, proportion of live patients in different NYHA classes are held constant
- Proportion of patients in different NYHA classes in myectomy, septal ablation, and disopyramide arms held constant after applying a literature-based treatment effect in cycle 1

Key Model Inputs: Treatment Effects

Treatment Effect of Mavacamten

	NYHA I	NYHA II	NYHA III	NYHA IV	Missing
Baseline	0%	71.5%	28.5%	0%	0%
Week 14	31.7%	55.3%	3.3%	0%	9.8%
Week 30	49.6%	42.3%	6.5%	0%	1.6%

Model Input

	NYHA I	NYHA II	NYHA III/IV
Baseline	0%	71.5%	28.5%
Cycle 4 (Week 16)	36.85%	59.28%	3.87%
Cycle 8 (Week 32)	52.11%	40.78%	7.11%

Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2020;396(10253):759-769.

Key Model Inputs: Treatment Effects

Treatment Effect of Standard of Care

	NYHA I	NYHA II	NYHA III	NYHA IV	Missing
Baseline	0%	74.2%	25.8%	0%	0%
Week 14	16.4%	64.1%	14.8%	0%	4.7%
Week 30	21.1%	57.8%	19.5%	0%	1.6%

Model Input

	NYHA I	NYHA II	NYHA III/IV
Baseline	0%	74.2%	25.8%
Cycle 4 (Week 16)	18.22%	66.28%	15.50%
Cycle 8 (Week 32)	20.31%	57.96%	21.73%

Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2020;396(10253):759-769.

Key Model Inputs: Treatment Effects

Treatment Effect of Septal Ablation and Myectomy

Procedure	NYHA Reduction (%)
Septal ablation	45
Myectomy	45

Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AF, Michels M, ten Berg JM. A Systematic Review and Meta-Analysis of Long-Term Outcomes After Septal Reduction Therapy in Patients With Hypertrophic Cardiomyopathy. JACC Heart Fail. 2015 Nov;3(11):896-905. doi: 10.1016/j.jchf.2015.06.011. Epub 2015 Oct 7. PMID: 26454847.

Model Input

	Myectomy			Septal Ablation		
	NYHA I	NYHA II	NYHA III/IV	NYHA I	NYHA II	NYHA III/IV
Baseline	0.00	0.72	0.29	0.00	0.72	0.29
Cycle 1	0.76	0.21	0.02	0.76	0.21	0.02

Key Model Inputs: Mortality from Procedure

Procedure	Mortality
Myectomy	1.3%
Septal Ablation	1.1%

Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AF, Michels M, ten Berg JM. A Systematic Review and Meta-Analysis of Long-Term Outcomes After Septal Reduction Therapy in Patients With Hypertrophic Cardiomyopathy. JACC Heart Fail. 2015 Nov;3(11):896-905. doi: 10.1016/j.jchf.2015.06.011. Epub 2015 Oct 7. PMID: 26454847.

Key Model Inputs: Treatment Effects

Treatment Effect of Disopyramide

	NYHA I	NYHA II	NYHA III/IV
Initial Evaluation	9	40	29
Follow-Up Evaluation	29	42	7

Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005 Apr 19;45(8):1251-8. doi: 10.1016/j.jacc.2005.01.012. PMID: 15837258.

Model Input

	Mavacamten		
	NYHA I	NYHA II	NYHA III/IV
Baseline	0.12	0.51	0.37
Cycle 1	0.28	0.53	0.19

Key Model Inputs: Costs

Treatment and Health States Costs	Costs	Source
Per Year Cost of Mavacamten	$75,000	Placeholder price
Per Year Cost of Metoprolol	$834	Red Book
Per Year Cost of Verapamil	$730	
Per Year Cost of Disopyramide	$5,384	
Disopyramide Hospitalization	$8,559	http://www.hcupnet.ahrq.gov/
Myectomy Procedure Cost	$122,759	M Butzner PS, M Maron, E Rowin, CC Teng, E Stanek, H Tan, L Robertson. PCV35 Costs of Septal Reduction Therapy for Obstructive Hypertrophic Cardiomyopathy: A US Claims Analysis. Value in Health. 2021;24:S73.
Septal Ablation Procedure Cost	$55,706	
Echocardiogram Cost	$101	http://www.cms.gov/
NYHA I Health State Cost (Per Cycle)	$751	EXPLORER trial Zueger PM, Kumar VM, Harrington RL, Rigoni GC, Atwood A, DiDomenico RJ, Touchette DR. Cost-Effectiveness Analysis of Sacubitril/Valsartan for the Treatment of Heart Failure with Reduced Ejection Fraction in the United States. Pharmacotherapy. 2018 May;38(5):520-530. doi: 10.1002/phar.2108. Epub 2018 Apr 25. PMID: 29601093.
NYHA II Health State Cost (Per Cycle)	$2,045	
NYHA III Health State Cost (Per Cycle)	$2,826	

Key Model Inputs: Utilities

Quality of Life (QOL) Parameters for Mavacamten and Standard of Care

QOL	Utility for Mavacamten	Utility for Standard of Care	Average Used for Comparators
NYHA Class I	0.950	0.952	0.951
NYHA Class II	0.866	0.850	0.858
NYHA Class III/IV	0.708	0.704	0.706

An average disutility by age of 0.0007 per year was applied, which reflects average utility decrement in the US

Xie J, Wang Y, Xu Y, Garrison LP. Health utilities among patients with obstructive hypertrophic cardiomyopathy (oHCM): an analysis of patient health-related quality of life in the EXPLORER-HCM trial. ISPOR; May 17-20, 2021; Virtual.

Key Model Inputs: Utilities

Disutility from Procedure

Source of Disutility	Disutility
Disutility of Pacemaker (Both Septal Ablation and Myectomy Arm)—Lifetime	0.045[1]
Disutility of Septal Ablation Procedure—One Cycle	0.041*[2]
Disutility of Myectomy Procedure—Six Cycles	0.086†[3]

*Disutility of MI
†Disutility of coronary artery bypass graft (CABG)

1. Beller JP, Tyerman Z, Mehaffey JH, Hawkins RB, Charles EJ, Yarboro LT, Teman NR, Wancheck T, Ailawadi G, Mehta NK. Early Versus Delayed Pacemaker for Heart Block After Valve Surgery: A Cost-Effectiveness Analysis. J Surg Res. 2021 Mar;259:154-162. doi: 10.1016/j.jss.2020.11.038. Epub 2020 Dec 3. PMID: 33279841; PMCID: PMC7897291.

2. Jiang M, You JHS. Cost-effectiveness analysis of 30-month vs 12-month dual antiplatelet therapy with clopidogrel and aspirin after drug-eluting stents in patients with acute coronary syndrome. Clin Cardiol. 2017 Oct;40(10):789-796. doi: 10.1002/clc.22756. Epub 2017 Jul 6. PMID: 28683175; PMCID: PMC6490524.

3. Cohen DJ, Osnabrugge RL, Magnuson EA, Wang K, Li H, Chinnakondepalli K, Pinto D, Abdallah MS, Vilain KA, Morice MC, Dawkins KD, Kappetein AP, Mohr FW, Serruys PW; SYNTAX Trial Investigators. Cost-effectiveness of percutaneous coronary intervention with drug-eluting stents versus bypass surgery for patients with 3-vessel or left main coronary artery disease: final results from the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation. 2014 Sep 30;130(14):1146-57. doi: 10.1161/CIRCULATIONAHA.114.009985. Epub 2014 Aug 1. PMID: 25085960.

Results

Base-Case Results

Treatment	Total Drug Cost	Total Cost	QALYs	Life Years	NYHA I Years	evLY
Mavacamten*†	$1,258,000	$1,568,000	14.75	16.58	8.50	14.75‡
Standard Treatment	$12,600	$434,000	13.78	16.58	3.33	13.78
Disopyramide*	$116,000	$509,000	14.06	16.58	4.69	14.06
Septal Ablation*	$67,800	$297,000	14.97	16.40	12.49	N/A
Myectomy*	$135,000	$364,000	14.97	16.37	12.47	N/A

*Each of these treatments includes use of standard first-line therapy
†Cost estimates for mavacamten were based on a placeholder price of $75,000 per year
‡evLY for mavacamten is calculated as compared to standard treatment

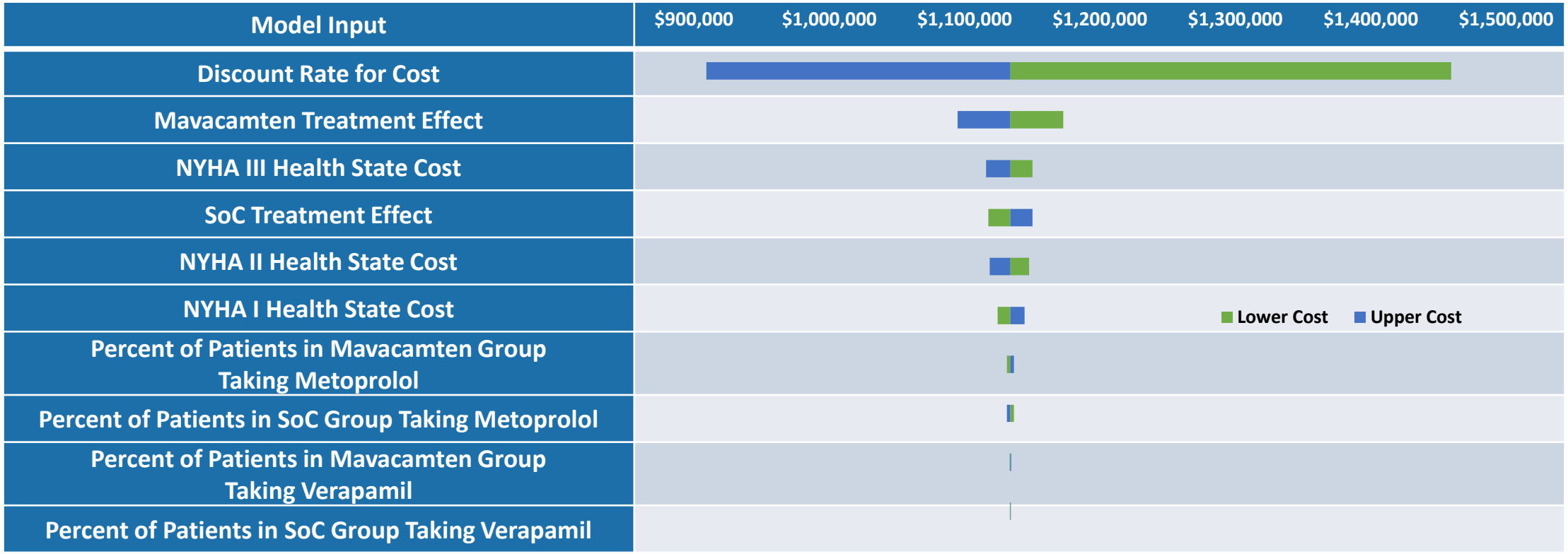
Base-Case Incremental Results

Drug	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Additional NYHA I Year
Mavacamten	Standard treatment	$1,200,000	Undefined	$1,200,000	$219,000
	Disopyramide	$1,500,000	Undefined	$1,500,000	$278,000
	Myectomy	Dominated	$5,600,000	N/A†	Dominated
	Septal ablation	Dominated	$7,000,000	N/A†	Dominated

*Incremental cost ratios are based on a placeholder price of $75,000 per year for mavacamten
†Incremental cost per evLY gained not applicable due to fewer lifetime QALYs for mavacamten as compared to myectomy and septal ablation

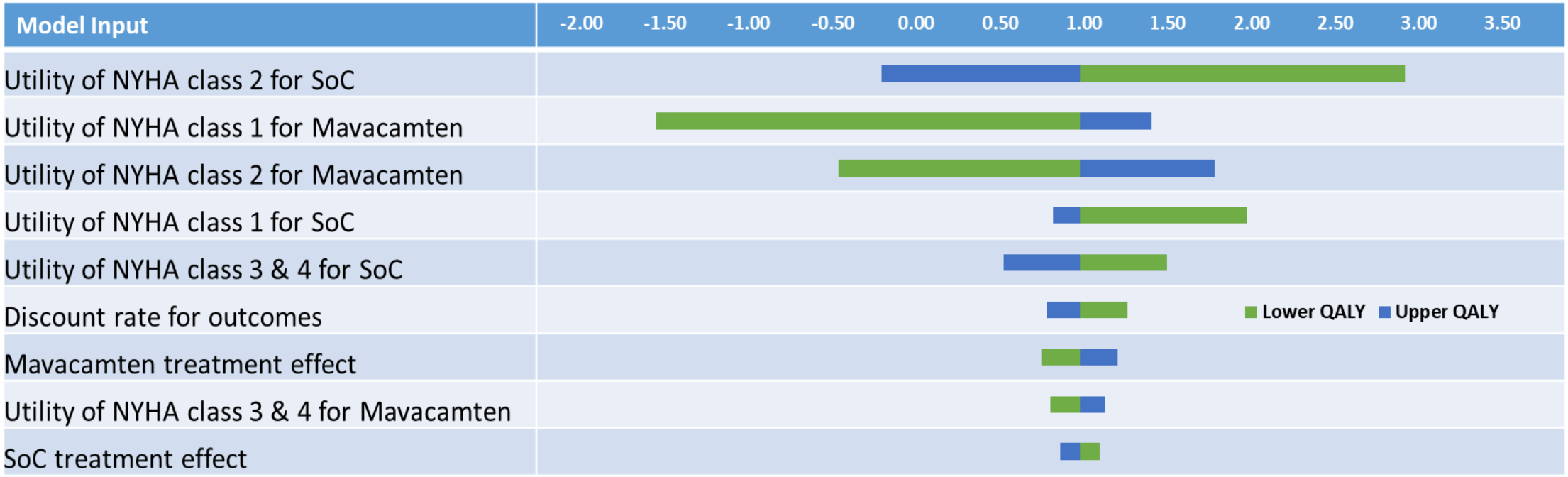
One Way Sensitivity Analyses

Mavacamten vs. Standard of Care Incremental Cost



One Way Sensitivity Analyses

Mavacamten vs. Standard of Care Incremental QALY



Probabilistic Sensitivity Analysis

Drug	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Mavacamten vs. Standard of Care	0.00%	0.00%	0.00%

Scenario Analyses

Incremental Cost-Effectiveness Ratios for Mavacamten in Scenario with Higher Mortality for NYHA Class III/IV

Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Additional NYHA I Year
Standard Treatment	$893,000	$2,600,000	$693,000	$219,000
Disopyramide	$1,100,000	$3,100,000	$874,000	$279,000
Myectomy	Dominated	$15,800,000	N/A	Dominated
Septal Ablation	Dominated	$29,900,000	N/A	Dominated

Scenario Analyses

Scenario Analysis with Employability Gain Assumptions

Scenario	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Additional NYHA I Year
Full Employment for NYHA I and Not for Class II and III/IV (Both Mavacamten and Standard Treatment Group)	$876,000	N/A	$876,000	$165,000
Full Employment for All Patients in Mavacamten Group and Not for Standard Treatment Group	$242,000	N/A	$242,000	$46,000

Limitations

- Model results are based on a placeholder price for mavacamten
- Absence of long-term data on treatment efficacy (30 weeks trial length)
- Lack of evidence from direct comparison with myectomy, septal ablation, and disopyramide (also, insufficient data to conduct NMA)
- The utility scores are from the EXPLORER trial
- The evidence for myectomy, septal ablation, and disopyramide comes from observational studies
- Absence of data on actual societal costs of HOCM (the modified societal perspective scenarios are based on assumptions of productivity gain)
- Heterogeneity in HOCM patients not addressed in the model

Comments Received

- NYHA classes do not capture day to day utility adequately
- A societal perspective should have been used
- NYHA classes are related to mortality
- There is variability by gender and race in patient outcomes
- The model does not include discontinuation and adverse events

Conclusions

- Actual cost effectiveness of mavacamten will depend on its price
- At placeholder price, incremental cost per QALY of mavacamten and standard of care vs. standard of care is well beyond standard threshold levels
- When compared with disopyramide, the incremental cost per QALY is even higher
- At the placeholder price, mavacamten is dominated by myectomy and septal ablation
- Sensitivity and scenario analysis suggests findings are robust at the placeholder price

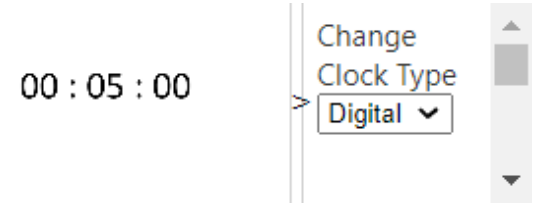
Questions

Manufacturer Public Comment and Discussion

John Whang, MD, FACC
Vice President, US Medical, Bristol Myers Squibb

Conflicts of Interest:

- *Dr. Whang is a full-time employee of Bristol Myers Squibb.*

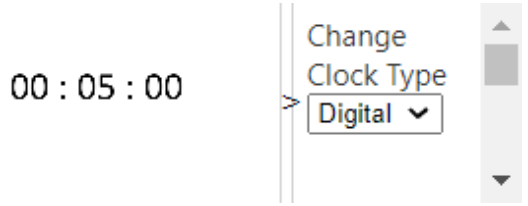


Public Comment and Discussion

Billur Ternar Dowse, MSc
Patient/Advocate

Conflicts of Interest:

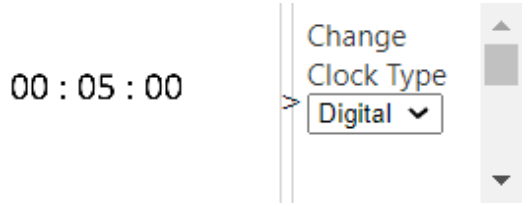
- *Billur T. Dowse has collaborated with the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.*



Gwen Mayes, JD, MMSc
Patient Advocate, Founder and Chief Concept Officer, GwenCo Health

Conflicts of Interest:

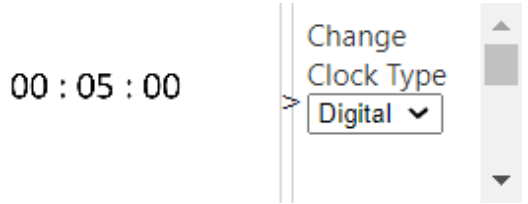
- *Gwen Mayes serves as a consultant to the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia. She also consults for Edwards Lifesciences, Paragonix, and Natural Cycles.*



Pastor Kent Sperry, MDiv
Patient/Advocate

Conflicts of Interest:

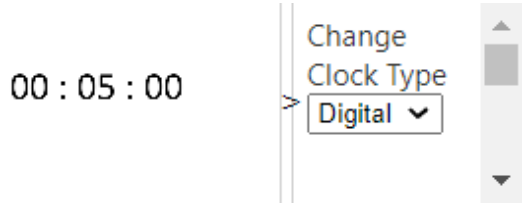
- *No financial conflicts of interest to disclose.*



Nikora Groomes, JD
Patient/Advocate

Conflicts of Interest:

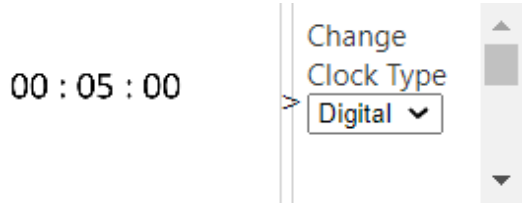
- *No financial conflicts of interest to disclose.*



Lisa Salberg
Founder & CEO, Hypertrophic Cardiomyopathy Association

Conflicts of Interest:

- *The Hypertrophic Cardiomyopathy Association receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.*



Break

Meeting will resume at 11:25 am

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Voting Questions

<u>Patient Population for all questions:</u> Adults with symptomatic hypertrophic obstructive cardiomyopathy (HOCM) on background therapy with beta blockers and/or calcium channel blockers.

Clinical Evidence

1. Is the currently available evidence adequate to demonstrate that the net health benefit of mavacamten added to background therapy is superior to that provided by background therapy alone?

A. Yes

B. No

2. Is the currently available evidence adequate to demonstrate that the net health benefit of mavacamten is superior to that provided by disopyramide?

A. Yes

B. No

Contextual Considerations and Potential Other Benefits or Disadvantages

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for HOCM on the basis of the following contextual considerations:

3. Acuity of need for treatment of individual patients based on the short-term risk of death or progression to permanent disability

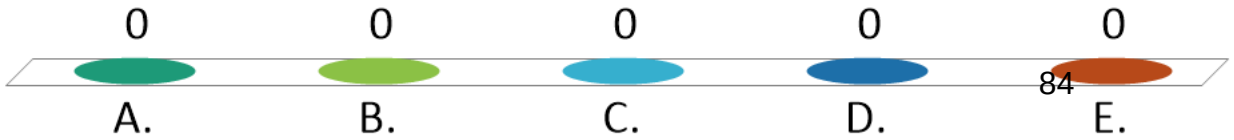
A. Very low priority

B. Low priority

C. Average priority

D. High priority

E. Very high priority



4. Magnitude of the lifetime impact on individual patients of the condition being treated

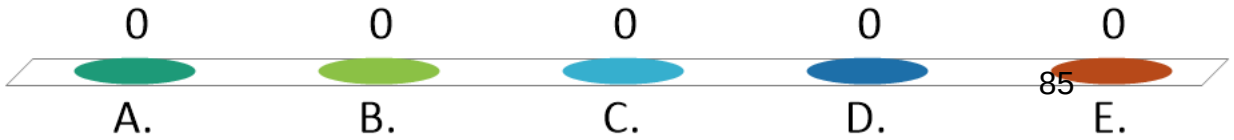
A. Very low priority

B. Low priority

C. Average priority

D. High priority

E. Very high priority



5. Other (as relevant)

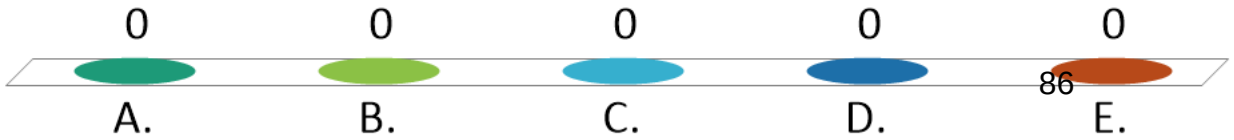
A. Very low priority

B. Low priority

C. Average priority

D. High priority

E. Very high priority



What are the effects of mavacamten on the following outcomes that inform judgment of the overall long-term value for money of mavacamten?

6. Patients' ability to achieve major life goals related to education, work, or family life

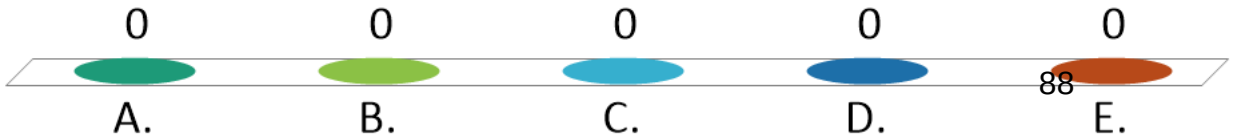
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



7. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life

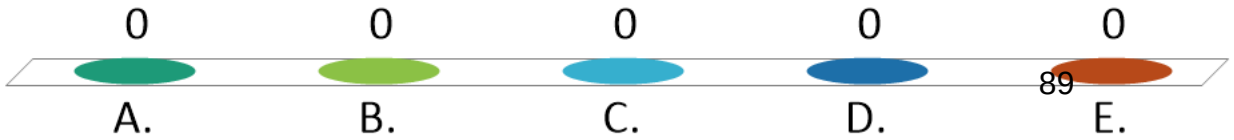
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



8. Patients' ability to manage and sustain treatment given the complexity of regimen

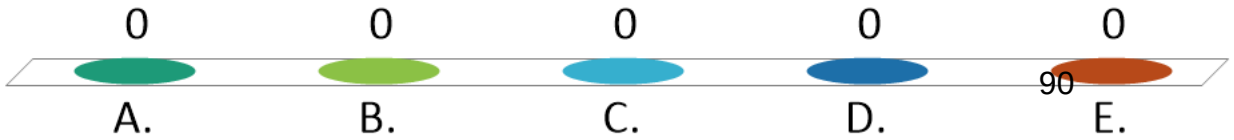
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



9. Society's goal of reducing health inequities

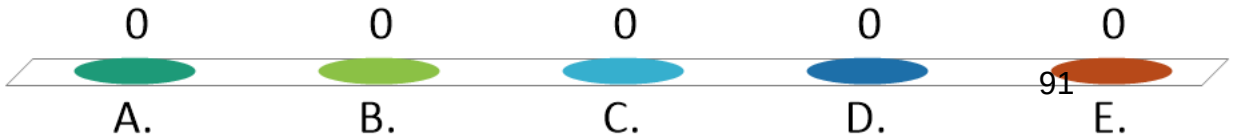
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



10. Opportunity to improve access to treatment

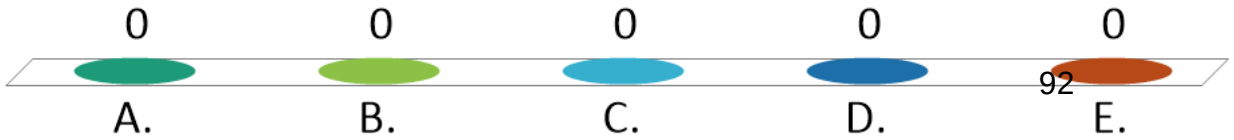
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



11. Availability of a treatment with different timing and types of risks and benefits, relative to existing procedural and surgical options

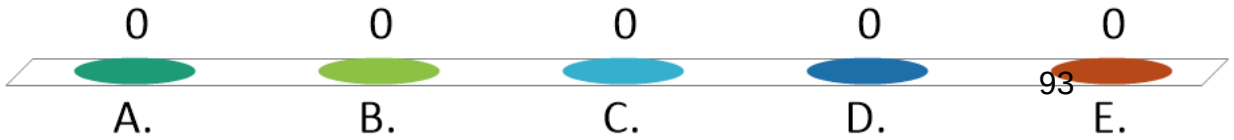
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



12. Other (as relevant)

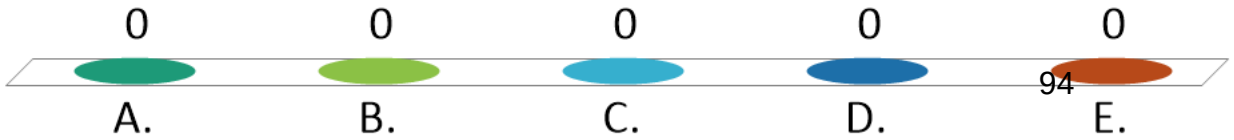
A. Major negative effect

B. Minor negative effect

C. No difference

D. Minor positive effect

E. Major positive effect



Lunch

Meeting will resume at 1:00pm

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Policy Roundtable

Policy Roundtable

Policy Roundtable Participant	Conflict of Interest
Milind Desai, MD, MBA, Director of Clinical Operations, Hypertrophic Cardiomyopathy Center, Cleveland Clinic	Dr. Desai serves as an investigator for the VALOR study of mavacamten sponsored by Bristol Myers Squibb/MyoKardia.
Martin Maron, MD, Director, Hypertrophic Cardiomyopathy Center and Research Institute, Tufts Medical Center	Dr. Maron served as a site investigator for a Phase I study of mavacamten and currently serves as a steering committee member for a Phase II study of a second-generation myosin inhibitor sponsored by Cytokinetics.
Gwendolyn Mayes, JD, MMSc, Founder and Chief Concept Officer, GwenCo Health	Gwendolyn Mayes serves as a consultant to the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia. She also consults for cardiac device companies, including Edwards Lifesciences and Paragonix.
Carla McSpadden, RPh, BCGP, MBA, Director, Clinical Formulary Strategies, Humana	Carla McSpadden is a full-time employee of Humana.
Lisa Salberg, Founder and CEO, Hypertrophic Cardiomyopathy Association	The Hypertrophic Cardiomyopathy Association receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.
John Watkins, PharmD, MPH, BCPS, Residency Program Director, Premera Blue Cross	John Watkins is a full-time employee of Premera Blue Cross.

CTAF Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around November 16, 2021
  - Includes description of CTAF votes, deliberation, policy roundtable discussion
- Materials available at: https://icer.org/hypertrophic-cardiomyopathy-2021/#overview

Adjourn

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