TREATMENT OF HYPERTROPHIC CARDIOMYOPATHY

SEPTEMBER 27, 2022
BEFORE WE BEGIN...

Important

- **All attendees are in listen only mode**
- **If you cannot hear, check the audio button on your personal computer to assure the sound is on.**
- **Please type your questions into the Q&A box at any time during the presentation. The moderator will read your questions during the question-and-answer period.**
- **The PDF version of the slides, as well as the recording of this presentation will be available on the Mended Hearts® website**
- **A Handout is available in the handout section of the website.**
Mended Hearts® mission is “to inspire hope and improve the quality of life of heart patients and their families through ongoing peer-to-peer support, education and advocacy.”
Dr. Florian Rader is the Medical Director of the Hypertension Center of Excellence, Co-Director of the Hypertrophic Cardiomyopathy Clinic and Associate Director of the Noninvasive Laboratory at Cedars-Sinai Smidt Heart Institute. He ranks as Associate Professor at Cedars-Sinai and UCLA. Dr. Rader graduated from medical school at the University of Vienna, Austria. He completed the Physician Scientist Program at Case Western Reserve University, MetroHealth Campus and Cleveland Clinic.
Treatment of Hypertrophic Cardiomyopathy: a new era?

Florian Rader, MD, MSc
Co-Director, Clinic for Hypertrophic Cardiomyopathies and Aortopathies

Disclosures: I am consultant for Bristoll-Myers-Squibb
Mavacamten is FDA approved for obstructive HCM (not non-obstructive HCM) under REMS program
Aficamten (or any other HCM treatments) is not FDA approved for HCM
Hypertrophic Cardiomyopathy (HCM)

- Usually inherited (or spontaneous) genetic mutation affecting the myocardial sarcomere-contractile elements of the heart muscle cell
- 1957: Brock subvalvular obstruction in patients suspected to have aortic stenosis
- 1958: Teare asymmetric left ventricular hypertrophy in 8 patients who died suddenly (autopsy)
- 1959+: Morrow and Braunwald described asymmetric hypertrophy, myocardial disarray and dynamic outflow obstruction
Definition

- Maximal left ventricular wall thickness:
  - $\geq 15$ mm
  - 13 to 14 mm with typical clinical presentation or family history of HCM
  - In children $\geq 2$ standard deviations of norm (Z-score of $\geq 2$)

$\rightarrow$ No aortic stenosis, or hypertension and infiltrative cardiomyopathies (although: HCM patients are not immune against these co-morbidities!)
Prevalence

General Population
1:500

700,000 people in U.S.

CARDIA
N=4,111;23-35 y
0.17%

Rural Minnesota
N=15,137;16-87 y
0.19%

Japan
N=3,354;20-77 y
0.17%

China
N=8,080;18-74 y
0.16%

Amer Indians
N=3,501;51-77 y
0.2%

Tanzania
N=6,680;22-91 y
0.2%

Barry Maron
Identifiable Gene Defect

<table>
<thead>
<tr>
<th>Sigmoid septum</th>
<th>Reverse septum</th>
<th>Neutral septum</th>
<th>Apical variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>181 (47%)</td>
<td>132 (32%)</td>
<td>32 (8%)</td>
<td>37 (10%)</td>
</tr>
<tr>
<td>Gene + (8%)</td>
<td>Gene + (79%)</td>
<td>Gene + (41%)</td>
<td>Gene + (32%)</td>
</tr>
</tbody>
</table>
Genetic testing-class I

• Genetic counseling for HCM patients/family
• Interpretation of genetic testing by experienced practitioner/counselor
• Genetic screening in first-degree relatives
• NOT class I:
  – Genetic testing for risk assessment
• Class III:
  – Genetic testing in relatives of affected without identified mutation
  – Clinical screening in genotype-negative relatives
Clinical Presentation

-Symptoms vary from shortness of breath to chest pain, palpitations, fatigue, lightheadedness, syncope but could be asymptomatic

-The majority of HCM patients will have at least mild HCM related symptoms from LVOT obstruction, diastolic dysfunction (abnormal filling due to stiffness of the heart muscle) or microvascular ischemia (abnormal small blood vessels that fail to deliver enough oxygen to the heart muscle during exercise)
AHA/ACC CLINICAL PRACTICE GUIDELINE

2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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Developed in collaboration with and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society for Cardiovascular Magnetic Resonance.
Endorsed by The Pediatric & Congenital Electrophysiology Society

ACCC/AHA Joint Committee Members, see page e608
Outflow tract obstruction

- Dyspnea
  - Outflow gradient ("obstruction")-high pressure in the heart
  - Mitral regurgitation Leaking valve with flow back towards lung circulation
Diastolic dysfunction

“stiff heart”, high filling pressure, high left ventricular end diastolic pressure (high pressure after filling of the heart before the next contraction) → high left atrial pressure → high lung-circulation pressure → shortness of breath

Heart can’t keep up with pumping all blood forward → Backup pressure causes shortness of breath
Diastolic dysfunction
Clinical Presentation

- HCM is a form of Heart failure with preserved ejection fraction (HFpEF)
- rarely progression heart failure with reduced ejection fraction (HFrEF)
→ Most commonly systolic function in HCM is hyperdynamic (LVEF >75%)
**Angina/Chest pain**

- **Mechanism:** Microvascular ischemia
  → “Supply demand mismatch” the thickened heart needs more oxygen, but gets less...
Treatment

“All that’s missing is the evidence”
Nonobstructive HCM

### 8.2. Management of Patients With Nonobstructive HCM With Preserved EF

#### Recommendations for Management of Patients With Nonobstructive HCM With Preserved EF

Referenced studies that support the recommendations are summarized in Online Data Supplement 15.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C-LD</td>
<td>1. In patients with nonobstructive HCM with preserved EF and symptoms of exertional angina or dyspnea, beta-blockers or non-dihydropyridine calcium channel blockers are recommended.¹⁻¹⁰</td>
</tr>
<tr>
<td>2a</td>
<td>C-EO</td>
<td>2. In patients with nonobstructive HCM with preserved EF, it is reasonable to add oral diuretics when exertional dyspnea persists despite the use of beta-blockers or non-dihydropyridine calcium channel blockers.</td>
</tr>
<tr>
<td>2b</td>
<td>C-LD</td>
<td>3. In patients with nonobstructive HCM with preserved EF, the usefulness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the treatment of symptoms (angina and dyspnea) is not well established.¹¹</td>
</tr>
<tr>
<td>2b</td>
<td>C-EO</td>
<td>4. In highly selected patients with apical HCM with severe dyspnea or angina (NYHA class III or class IV) despite maximal medical therapy, and with preserved EF and small LV cavity size (LV end-diastolic volume &lt;50 mL/m² and LV stroke volume &lt;30 mL/m²), apical myectomy by experienced surgeons at comprehensive centers may be considered to reduce symptoms.¹²</td>
</tr>
<tr>
<td>2b</td>
<td>C-EO</td>
<td>5. In asymptomatic patients with nonobstructive HCM, the benefit of beta-blockers or calcium channel blockers is not well established.</td>
</tr>
</tbody>
</table>
Treatment-Diastolic Dysfunction

Dyspnea from “diastolic heart failure”-abnormal filling of the left ventricle

Decrease heart rate to allow more time for filling:
- beta blockers—may worsen diastolic function??
- calcium channel blockers
- Mavacamten?
Treatment
Obstructive HCM

- Obstructive physiology?
  - See Figure 5

- Symptoms?
  - Repeat evaluation as per Figure 1, Box 2

- Avoid vasodilators and high-dose diuretics
  - Beta-blockade (1)
  - Verapamil or diltiazem (1)
  - If symptoms persist

- Disopyramide (1)
- Septal reduction therapy (1)

- Surgical candidate?
  - Septal ablation (1)
  - Other surgical indication or nonstandard indication?
    - Septal ablation (1)
    - Myectomy (1)
Dyspnea from “outflow gradient, i.e., HOCM”
Decrease heart rate to allow more time for filling which increases heart size and decreases obstruction; also: less forceful contraction
→ beta blockers (metoprolol, bisoprolol)
→ calcium channel blockers (verapamil, diltiazem)
→ Disopyramide
→ Mavacamten
→ Aficamten?
  → If medications fail surgical myectomy, catheter-based alcohol septal ablation (or maybe mitraclip?) are indicated
Treatment-beta blockers

- Atenolol, propranolol (Inderal), metoprolol (Toprol)
  - *Decrease cardiac contraction*
  - *Increase filling time*
  - *Decrease gradient (“obstruction”)*
  - *Decrease oxygen demand*
- Vasodilating BB – a “no-no” for HOCM but ok for nHCM without gradient: carvedilol (Coreg), nebivolol (Bystolic)
- *Problems:* Fatigue, depression, learning disabilities, slow heart rate, heart block (sometimes pacemaker required)
Metoprolol in HCM

Dybro et al. J Am Coll Cardiol 2021;78:2505–2517
Treatment—calcium channel blockers

Verapamil > diltiazem, NOT vasodilating CCB (amlodipine, nifedipine)

- *Decrease cardiac contraction*
- *Increase filling time*
- *Decrease gradient (“obstruction”) but sometimes not*
- *Decrease oxygen demand*

Contraindicated in patients with hypotension or severe dyspnea (class IV—at rest), especially in reduced ejection fraction

**Side effects:** Leg swelling, hypotension, constipation, heart block
• **Dr. Charles Pollick** did ground-braking work
• Titrate to symptoms (side effects) and gradient
• In the seminal study of 118 patients:
  – gradient was reduced from 75 to 40 mmHg
  – 66% did not need septal reduction Rx
  – mortality was reduced 1.4% versus 2.6%/year (p = 0.07)
  – Sudden cardiac death was reduced 1.0%/year versus 1.8%/year (p = 0.08)
• Some recommend use with beta blocker or calcium channel blocker (AV conduction)
• **Side effects:** dry mouth, urinary retention, constipation (mestinon-pyridostigmin helps)

Pollick NEJM 1982;307:997-999
Treatment - ranolazine

- **Ranexa**: Sodium-channel blocker approved for symptom-reduction in chronic CAD-angina

- Use in HCM based on preclinical studies and case reports (<20 patients)

- **1 RCT** showed no effect on peak VO2, BNP or QoL, only reduced PVCs - not a good treatment target!

- **Side effects**: minimal, sometimes dizziness, constipation, dry mouth

Case Rep Cardiol. 2018; 2018: 5142572
Olivotto I et al. Circ Heart Fail. 2018 2018;11:e004124
Myosin inhibitors

**Mavacamten, Aficamten:** oral, selective, small molecule targeting myocyte protein to decrease hypercontractility - first specifically targeted therapy for HCM

Myosin inhibitors

Contractile elements of the heart muscle contraction is usually hyperdynamic/too forceful with poor relaxation between contractions

Excessive myosin – actin connections cause this hyperdynamic contraction, hypertrophy, outflow obstruction and poor relaxation

Daniels MJ et al Circulation 2021 Sep 7;144(10):759-762
Mavacamten

• Preclinical: HCM mouse model
  – Prevented hypertrophy, myocyte disarray and fibrosis

Green et al. Science 2016;351:617
Mavacamten

- Preclinical: HCM cat model
  - Markedly reduced gradient

EXPLORER-HCM: obstructive HCM

• Phase 3 1:1 randomized trial; 75 sites, 220 patients

• Primary objective: 30 week effect on exercise capacity (peak VO2), and NYHA class

• Secondary: LVOT gradient reduction, safety, PK, BNP, Quality of life assessment, accelerometer (steps), effect on LV mass and structure (MRI) in 80 patients
EXPLORER-HCM: obstructive HCM

<table>
<thead>
<tr>
<th></th>
<th>Mavacamten group (n=123)</th>
<th>Placebo group (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>58.5 (12.2)</td>
<td>58.5 (11.8)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>57 (46%)</td>
<td>45 (35%)</td>
</tr>
<tr>
<td>Men</td>
<td>66 (54%)</td>
<td>83 (65%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>115 (93%)</td>
<td>114 (90%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (1%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Native American or Alaskan Native</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>53 (43%)</td>
<td>55 (43%)</td>
</tr>
<tr>
<td>Spain</td>
<td>17 (14%)</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>Poland</td>
<td>16 (13%)</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>Other*</td>
<td>37 (30%)</td>
<td>41 (32%)</td>
</tr>
<tr>
<td><strong>Hypertrophic cardiomyopathy genetic testing performed</strong></td>
<td>90 (73%)</td>
<td>100 (78%)</td>
</tr>
<tr>
<td>Pathogenic or likely pathogenic hypertrophic cardiomyopathy gene variant</td>
<td>23/90 (31%)</td>
<td>22/100 (22%)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of hypertrophic cardiomyopathy</td>
<td>33 (27%)</td>
<td>36 (28%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (10%)</td>
<td>23 (18%)</td>
</tr>
<tr>
<td>Septal reduction therapy</td>
<td>11 (9%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57 (46%)</td>
<td>53 (41%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>27 (22%)</td>
<td>39 (30%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>12 (10%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>15 (12%)</td>
<td>14 (11%)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>6 (5%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>17 (14%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2 (2%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td><strong>Background hypertrophic cardiomyopathy therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β blocker</td>
<td>94 (76%)</td>
<td>95 (74%)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>25 (20%)</td>
<td>27 (13%)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>27 (22%)</td>
<td>29 (23%)</td>
</tr>
<tr>
<td>Body-mass index, kg/m²</td>
<td>29.7 (4.9)</td>
<td>29.2 (5.6)</td>
</tr>
<tr>
<td>Heart rate, beats per min</td>
<td>63 (10.1)</td>
<td>62 (10.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128 (16.2)</td>
<td>128 (14.5)</td>
</tr>
</tbody>
</table>

Olivetti et al. Lancet 2020 Sep 12;396(10253):759-769
# EXPLORER-HCM: Results

<table>
<thead>
<tr>
<th>Primary endpoint†</th>
<th>Mavacamten group (n=123)</th>
<th>Placebo group (n=128)</th>
<th>Difference* (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either ≥1.5 mL/kg per min increase in pVO, with ≥1 NYHA class improvement or ≥3.0 mL/kg per min increase in pVO, with no worsening of NYHA class</td>
<td>45 (37%)</td>
<td>22 (17%)</td>
<td>19.4 (8.7 to 30.1; p=0.0005)</td>
</tr>
<tr>
<td>≥1.5 mL/kg per min increase in pVO, with ≥1 NYHA class improvement</td>
<td>41 (33%)</td>
<td>18 (14%)</td>
<td>19.3 (9.0 to 29.6)</td>
</tr>
<tr>
<td>≥3.0 mL/kg per min increase in pVO, with no worsening of NYHA class</td>
<td>29 (24%)</td>
<td>14 (11%)</td>
<td>12.6 (3.4 to 21.9)</td>
</tr>
<tr>
<td>Both ≥3.0 mL/kg per min increase in pVO, and ≥1 NYHA class improvement</td>
<td>25 (20%)</td>
<td>10 (8%)</td>
<td>12.5 (4.0 to 21.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints‡</th>
<th>Mavacamten group (n=123)</th>
<th>Placebo group (n=128)</th>
<th>Difference* (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-exercise LVOT gradient change from baseline to week 30, mm Hg</td>
<td>-47 (40), n=117</td>
<td>-10 (30), n=122</td>
<td>-35.6 (−43.2 to −28.1; p&lt;0.0001)</td>
</tr>
<tr>
<td>pVO, change from baseline to week 30, mL/kg per min</td>
<td>1.4 (3.1), n=120</td>
<td>-0.1 (3.0), n=125</td>
<td>1.4 (0.6 to 2.1; p=0.0006)</td>
</tr>
<tr>
<td>≥1 NYHA class improvement from baseline to week 30§</td>
<td>80 (65%)</td>
<td>40 (31%)</td>
<td>34% (22 to 45; p&lt;0.0001)</td>
</tr>
<tr>
<td>Change from baseline to week 30 in KCCQ-CSS§</td>
<td>13.6 (14.4), n=92</td>
<td>4.2 (13.7), n=88</td>
<td>9.1 (5.5 to 12.7; p&lt;0.0001)</td>
</tr>
<tr>
<td>Change from baseline to week 30 in HCMSS-SoB§</td>
<td>-2.8 (2.7), n=85</td>
<td>-0.9 (2.4), n=86</td>
<td>-1.8 (−2.4 to −1.2; p&lt;0.0001)</td>
</tr>
</tbody>
</table>

Olivetti et al. Lancet 2020 Sep 12;396(10253):759-769
EXPLORER-HCM: Results

Olivetti et al. Lancet 2020 Sep 12;396(10253):759-769
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EXPLORER-HCM: Results

NYHA class 1: no significant symptoms with exercise
NYHA class 2: mild exertional symptoms with vigorous exercise
NYHA class 3: Exertional symptoms with minimal exercise
NYHA class 4: resting symptoms

Olivetti et al. Lancet 2020 Sep 12;396(10253):759-769
Introduction and trial design

Mavacamten is a selective inhibitor of cardiac myosin that targets the underlying pathophysiology – excessive number of myosin-actin cross-bridges – of HCM\(^1\)\(^-\)\(^3\)

Mavacamten significantly reduced LVOT gradient and improved symptoms, functional capacity, and health status versus placebo over 30 weeks in patients with symptomatic obstructive HCM, and demonstrated a similar safety profile to placebo\(^4\),\(^5\)

### Preclinical

**EXPLORER-HCM** (Phase 3 study)

Mavacamten is a selective inhibitor of cardiac myosin that targets the underlying pathophysiology – excessive number of myosin-actin cross-bridges – of HCM\(^1\)\(^-\)\(^3\)

**MAVA-LTE**

Ongoing, dose-blinded, 5-year study of mavacamten (NCT03723655)

**EXPLORER-LTE**

Patients with symptomatic obstructive HCM who completed the EXPLORER-HCM study\(^6\)

**Patients with symptomatic obstructive HCM who completed the EXPLORER-HCM study**

- April 2019
- End of treatment

**EXPLORER-HCM** (n = 244)

Time (weeks)

-4 0 4 8 12 16 24 36 48 60 72 84 252

**Mavacamten 5 mg initiated**

- Dose adjustments were based on site-read echocardiography measures of Valsalva LVOT gradient and LVEF only.

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HCM, hypertrophic cardiomyopathy; LTE, long-term extension; LVOT, left-ventricular outflow tract.
## Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EXPLORER-LTE cohort (n = 231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>60.0 ± 11.9</td>
</tr>
<tr>
<td>Female sex, n (%</td>
<td>91 (39.4)</td>
</tr>
<tr>
<td>Background HCM therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>175 (75.8)</td>
</tr>
<tr>
<td>Calcium channel blocker*</td>
<td>38 (16.5)</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>14 (6.1)</td>
</tr>
<tr>
<td>II</td>
<td>152 (65.8)</td>
</tr>
<tr>
<td>III</td>
<td>65 (28.1)</td>
</tr>
<tr>
<td>NT-proBNP, ng/L, median (IQR)</td>
<td>783 (326, 1593) (n = 230)</td>
</tr>
<tr>
<td>Echocardiographic parameters, mean ± SD</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>74.0 ± 5.9 (n = 230)</td>
</tr>
<tr>
<td>LVOT gradient resting, mmHg</td>
<td>48.3 ± 31.9 (n = 231)</td>
</tr>
<tr>
<td>LVOT gradient Valsalva, mmHg</td>
<td>69.5 ± 33.3 (n = 228)</td>
</tr>
<tr>
<td>Time on study, weeks (median, range)</td>
<td>62.3 (0.3 – 123.9)</td>
</tr>
</tbody>
</table>

- At Weeks 48 and 84, 83% and 85% of patients, respectively, were receiving 10 mg daily mavacamten dose or less

*Includes verapamil or diltiazem.

HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LTE, long-term extension; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, standard deviation.
Results after 62.3 weeks (median) mavacamten treatment

Reduction in LVOT gradient

Expected reduction in LVEF

Reduction in NTproBNP

Improvement in NYHA functional class

Note: Data from EXPLORER-HCM are not shown. Baseline values represent those from the beginning of MAVA-LTE, not the beginning of the parent study. *Change from baseline are only summarized for patients with a value at both baseline visit and specific post-baseline visits. BL, baseline; LVOT, left ventricular outflow tract; SD, standard deviation.
Safety (Cumulative AEs)

<p>| EXPLORER-LTE cohort (n = 231) |  |</p>
<table>
<thead>
<tr>
<th>No. of patients (%)</th>
<th>Total no. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>201 (87.0)</td>
</tr>
<tr>
<td>Mild</td>
<td>87 (37.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>89 (38.5)</td>
</tr>
<tr>
<td>Severe</td>
<td>21 (9.1)</td>
</tr>
<tr>
<td>Drug-related TEAEs</td>
<td>40 (17.3)</td>
</tr>
<tr>
<td>CV ECI drug-related TEAEs</td>
<td>19 (8.2)</td>
</tr>
<tr>
<td>SAEs (drug-related and unrelated)</td>
<td>34 (14.7)</td>
</tr>
<tr>
<td>CV ECI SAEs</td>
<td>15 (6.5)</td>
</tr>
<tr>
<td>Drug-related SAEs</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>3 (1.3)</td>
</tr>
</tbody>
</table>

- The most common TEAEs of any grade occurring in ≥8% of patients were fatigue (10.4%), dizziness (10.0%), hypertension (10.0%), headache (8.2%), nasopharyngitis (8.2%), atrial fibrillation (9.1%),

- Exposure-adjusted incidence rate for drug-related CV SAEs were 2.52 per 100PY for cardiac failure and 2.53 per 100PY for decreased LVEF

<table>
<thead>
<tr>
<th>TEAEs leading to permanent treatment discontinuation</th>
<th>EXPLORER-LTE cohort (n = 231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>TEAEs</td>
<td>10 (4.3)*</td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>2‡</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1²į</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1#</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>1</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged QTCF</td>
<td>1</td>
</tr>
</tbody>
</table>

- Temporary treatment discontinuations per protocol due to meeting ≥1 qualifying event:
  - 7 (3.0%) increase in QTcF interval >15%
  - 10 (4.3%) mavacamten concentration ≥1000 ng/mL
  - 12 (5.2%) LVEF <50% (includes 4 previously reported)*
    - 2 events of LVEF <50% were considered as a TEAE
    - 5 patients permanently discontinued from the study
    - 7 patients resumed mavacamten treatment

*Includes cardiac failure (3) and decreased LVEF (2).
†Due to bacterial endocarditis (1), cardiac arrest (1), and acute myocardial infarction (1), all unrelated to treatment.
AE, adverse event; CV, cardiovascular; ECI, event of clinical interest; LTE, long-term extension; LVEF, left ventricular ejection fraction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
EXPLORER: HOCM
Cardiac MRI substudy @ 30 weeks (Mavacamten n=17, placebo n=18)

Mavacamten: VALOR-HCM

152 Patients with HOCM, eligible for septal reduction therapy, 112 randomized

**Question:** Can Mavacamten obviate/delay need for SRT?

Desai M et al. J Am Coll Cardiol 2022;80:95–108
Mavacamten: VALOR-HCM

152 Patients with HOCM, eligible for septal reduction therapy, 112 randomized

**Question:** Can Mavacamten obviate/delay need for SRT?

**Figure:**
- Comparisons of HCM Sarcomere and HCM Sarcomere with Mavacamten.
- Diagram of patients who underwent SRT or remained guideline eligible for SRT.
- Graphs showing LVOT gradient improvements over weeks since randomization for both placebo and Mavacamten groups.

**Key Points:**
- Mavacamten reduces myosin-actin cross bridges and attenuates hypercontractility and improves compliance and energetics.
- Higher percentage of patients in the Mavacamten group improved by 0, ≥1, or ≥2 NYHA Class compared to placebo.

**Data:**
- LVOT gradient improvements over weeks since randomization for both placebo and Mavacamten groups.

**References:**
Mavacamten: VALOR-HCM

152 Patients with HOCM, eligible for septal reduction therapy, 112 randomized

**Question:** Can Mavacamten obviate/delay need for SRT?

<table>
<thead>
<tr>
<th>Safety endpoints</th>
<th>Mavacamten (n = 56)</th>
<th>Placebo (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ejection fraction &lt;50%</td>
<td>2 (3.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Permanent discontinuation for LV ejection fraction &lt;30%</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Death, myocardial infarction or stroke</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On-treatment adverse events</th>
<th>Mavacamten</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of on-treatment adverse events</td>
<td>123</td>
<td>93</td>
</tr>
<tr>
<td>Total number of subjects with at least one on-treatment adverse event</td>
<td>41 (73.2)</td>
<td>34 (61.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious on-treatment adverse events</th>
<th>Mavacamten</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of serious on-treatment adverse events</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Number of subjects with serious adverse events</td>
<td>3 (5.4)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (3.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Coronavirus disease-2019</td>
<td>1 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Alcohol poisoning</td>
<td>0 (0.0)</td>
<td>1 (1.8)</td>
</tr>
</tbody>
</table>

Desai M et al. J Am Coll Cardiol 2022;80:95–108
Aficamten

- Similar effect on cardiac muscle as compared to Mavacamten
- Shorter half-life
- Less interactions with concomitant medications
- Phase 2 and phase 3 trials are ongoing
Mavacamten use in practice

CAMZYOS reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction.

**Echocardiogram assessments of LVEF are required** prior to and during treatment with CAMZYOS. Initiation of CAMZYOS in patients with LVEF<55% is not recommended.

Interrupt CAMZYOS if LVEF is <50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status.

The CAMZYOS REMS (Risk Evaluation and Mitigation Strategy) program is required by the US Food and Drug Administration (FDA) to ensure that the benefits of CAMZYOS outweigh the risks.
**Mavacamten use**

Only prescribe Mavacamten in patients with LVEF >55%, make sure non-pregnant and good plan for contraception, screen concomitant medication list for drug interaction (CYP450)

---

**CAMZYOS™ Dosing and Administration: Initiation Phase**

![Diagram showing dosing and administration phases with specific instructions for Weeks 4, 8, and 12.]

*Interrupt treatment if LVEF <50% at any clinic visit; restart treatment after 4 weeks if LVEF ≥50%. See Treatment Interruption.*

ECHO=echocardiogram; LVEF=left ventricular ejection fraction; LVOT=left ventricular outflow tract.
**Mavacamten use**

**CAMZYOS™ Dosing and Administration: Maintenance Phase**

**Week 12 + every 12 weeks**

- **LVEF <50%**
  - Interrupt treatment. See **Treatment Interruption** on next page

- **LVEF 50-55%, regardless of Valsalva LVOT gradient or LVEF >55% and Valsalva LVOT gradient <30 mmHg**
  - Maintain on the same dose and follow up 12 weeks later

  1. Up-titration to next higher daily (mg) dose level: 2.5 → 5; 5 → 10; 10 → 15 mg
  2. Recheck clinical status and ECHO in 4 weeks and maintain the same dose for the next 8 weeks unless LVEF<50%
  3. Further up-titration is allowed after 12 weeks of treatment on the same dose level

---

**ECHO=echocardiogram; LVEF=left ventricular ejection fraction; LVOT=left ventricular outflow tract.**
Sudden cardiac death prevention

Figure 3. ICD patient selection.
Thank you!

florian.rader@cshs.org
Apical aneurysm and risk for SCD

- Apical hypertrophy $\rightarrow$ apical scarring
- Midventricular obstruction $\rightarrow$ apical ballooning from pressure overload

LVH and risk for SCD

Also:
- Maximal wall thickness $\geq 30$ mm
- Secondary prevention (prior sudden cardiac death)
- FH of SCD and HCM in 1$^{st}$ degree family member
- Unexplained syncope

Minor:
- BP drop with exercise (obstruction and autonomic dysfunction)
- NSVT (scar)

Borderline:
- $>15\%$ LGE on CMR
- ?Troponin, ?BNP

Sudden death/1,000 patient-years

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2.6</th>
<th>7.4</th>
<th>11.0</th>
<th>18.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\leq 15$</td>
<td>16-19</td>
<td>20-24</td>
<td>25-29</td>
<td>$\geq 30$</td>
</tr>
</tbody>
</table>

Spirito et al. NEJM 2000
Mavacamten: **MAVERICK-HCM: non-obstructive HCM**

- 2 dosing groups (I: ~200 ng/mL; II: ~500 ng/mL) vs. placebo
- On stable (2 week) treatment until week 24
- LVOT gradient (rest, provoked and post-exercise) <30 mmHg
- NT-proBNP >300
- NYHA class II or III

**Excluded:**
- Sustained VT or appropriate ICD shock within 6 months
- AFIB during screening
- Septal reduction <6 months
- QTc>480ms

Ho CY et al. JACC 2020 Jun 2;75(21):2649-2660
Mavacamten: **MAVERICK-HCM: non-obstructive HCM**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Mavacamten</th>
<th>Group 2 Mavacamten</th>
<th>Pooled Mavacamten</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>58.3 ± 13.7</td>
<td>50.0 ± 14.7</td>
<td>54.0 ± 14.6</td>
<td>53.8 ± 18.2</td>
</tr>
<tr>
<td>Female</td>
<td>9 (47.4)</td>
<td>12 (57.1)</td>
<td>21 (52.5)</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5.3)</td>
<td>0 (0.0)</td>
<td>1 (2.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (5.3)</td>
<td>1 (4.8)</td>
<td>2 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>White</td>
<td>17 (89.5)</td>
<td>18 (85.7)</td>
<td>35 (87.5)</td>
<td>17 (89.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td>2 (9.5)</td>
<td>2 (5.0)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.8 ± 4.1</td>
<td>29.8 ± 6.1</td>
<td>29.3 ± 5.2</td>
<td>31.0 ± 4.9</td>
</tr>
<tr>
<td>Consented to optional HCM genotyping</td>
<td>14 (73.7)</td>
<td>14 (66.7)</td>
<td>28 (70.0)</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Pathogenic or likely pathogenic HCM gene mutation of 40 with genetic testing</td>
<td>7 (50.0)</td>
<td>7 (50.0)</td>
<td>14 (50.0)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml) geometric mean</td>
<td>889 (747–1,575)</td>
<td>763 (606–1,261)</td>
<td>821 (790–1,293)</td>
<td>914 (770–1,558)</td>
</tr>
<tr>
<td>cTNI (ng/ml) geometric mean</td>
<td>0.024 (0–0.503)</td>
<td>0.023 (0.016–0.080)</td>
<td>0.023 (0–0.253)</td>
<td>0.020 (0.013–0.119)</td>
</tr>
<tr>
<td>cTNI &gt;0.03 ng/ml</td>
<td>6 (31.6)</td>
<td>7 (33.3)</td>
<td>13 (32.5)</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (78.9)</td>
<td>18 (85.7)</td>
<td>33 (82.5)</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>III</td>
<td>4 (21.1)</td>
<td>3 (14.3)</td>
<td>7 (17.5)</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>Peak VO₂, ml/kg/min</td>
<td>19.5 ± 5.2</td>
<td>21.0 ± 6.6</td>
<td>20.4 ± 6.0</td>
<td>17.9 ± 5.1</td>
</tr>
<tr>
<td>Maximal LV wall thickness, mm</td>
<td>20.9 ± 3.0</td>
<td>20.4 ± 4.8</td>
<td>20.6 ± 4.0</td>
<td>18.8 ± 3.5</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>68.0 ± 5.2</td>
<td>69.4 ± 5.8</td>
<td>68.7 ± 5.5</td>
<td>66.4 ± 7.7</td>
</tr>
<tr>
<td>Lateral e', cm/s</td>
<td>8.5 ± 3.8</td>
<td>7.7 ± 2.6</td>
<td>8.1 ± 3.2</td>
<td>7.8 ± 3.6</td>
</tr>
<tr>
<td>Septal e', cm/s</td>
<td>5.3 ± 2.0</td>
<td>4.5 ± 1.6</td>
<td>4.9 ± 1.8</td>
<td>4.4 ± 1.7</td>
</tr>
<tr>
<td>E/e' average</td>
<td>13.9 ± 5.4</td>
<td>14.2 ± 7.7</td>
<td>14.1 ± 6.6</td>
<td>18.5 ± 9.9</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>59.5 ± 14.5</td>
<td>58.5 ± 18.6</td>
<td>58.9 ± 16.6</td>
<td>60.5 ± 21.6</td>
</tr>
<tr>
<td>LA volume index, ml/m²</td>
<td>40.3 ± 16.1</td>
<td>34.5 ± 8.9</td>
<td>37.3 ± 13.0</td>
<td>40.8 ± 15.2</td>
</tr>
<tr>
<td>Peak gradient, mm Hg</td>
<td>8.1 ± 3.3</td>
<td>9.4 ± 3.6</td>
<td>8.8 ± 3.5</td>
<td>7.8 ± 2.5</td>
</tr>
<tr>
<td>Background HCM therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>12 (63.2)</td>
<td>13 (61.9)</td>
<td>25 (62.5)</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>5 (26.3)</td>
<td>5 (23.8)</td>
<td>10 (25.0)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Neither</td>
<td>3 (15.8)</td>
<td>3 (14.3)</td>
<td>6 (15.0)</td>
<td>4 (21.1)</td>
</tr>
</tbody>
</table>
Mavacamten: MAVERICK-HCM: non-obstructive HCM

Ho CY et al. JACC 2020 Jun 2;75(21):2649-2660
Mavacamten: **MAVERICK-HCM: non-obstructive HCM**

**Summary:** MAVERICK was a small proof-of-concept study
Mavacamten improved biomarkers of heart failure (NTproBNP) and structural heart damage (troponin) but did not improve performance on cardiopulmonary exercise testing
Systolic dysfunction (EF<45%) occurred in 5 patient and was reversible in all

Ho CY et al. JACC 2020 Jun 2;75(21):2649-2660
For additional questions, please email: Andrea.baer@mendedhearts.org

The Mended Hearts, Inc.

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