Calling for Nominations - *By Oct. 30*

**BENTDAHL DISTINGUISHED SERVICE AWARD**
Recognizes contributions to MHIF and accomplishments as an *outstanding leader, mentor, philanthropist, educator or researcher*.

2019 recipient: Dr. Elizabeth Grey

**ROBERT G. HAUSER LEADERSHIP AWARD**
Recognizes contribution to CVD prevention / treatment, advocacy for patients and profession, *visionary leadership and a strong commitment to excellence*.

2019 recipient: Dr. Kevin Harris

Submit to: jwagner@mhif.org

- **Who** you are nominating.
- For **What** award you want them considered.
- **How** they meet the criteria and **Why** you are nominating them.
MHIF FEATURED STUDY:
Proact Xa

DESCRIPTION:
A prospective, randomized, active (warfarin) controlled, parallel-arm clinical trial to determine if patients with an On-X aortic valve can be maintained safely and effectively on the factor Xa inhibitor apixaban.

There is an unmet need for an alternative anticoagulant drug (such as apixaban) to use instead of warfarin in participants with an aortic mechanical prosthetic valve. Patients will be randomized 1:1 apixaban versus warfarin 90 days or greater s/p surgery.

CRITERIA LIST/QUALIFICATIONS:

**Inclusion:**
1. 18 years or greater
2. Able to receive warfarin with a target INR of 2.0-3.0
3. Implantation of an On-X mechanical valve in the aortic position at least 90 days prior to enrollment

**Exclusion:**
1. Mechanical valve in any other position other than aortic
2. Any cardiac surgery 90 days prior to enrollment
3. Need to be on aspirin > 100 mg daily or a P2Y12 inhibitor
4. On dialysis or creatinine clearance of < 25 mL/min
5. Stroke within 3 months of enrollment

Providing an alternative to warfarin may lead younger patients to choose a mechanical valve with greater durability and better clinical outcomes.
Mitral valve prolapse – when does it stop being benign?

Iulia Tulai MD, Cardiology Fellow
Minneapolis Heart Institute

10/12/2020
Mitral valve prolapse...

Definition:
- superior displacement of mitral valve leaflet(s) ≥2 mm in systole above the annular plane in PLAX / apical view

- **Classic** (myxomatous degeneration) - thickening of the leaflets ≥5 mm
- **Non-Classic** – thickening of the leaflets <5 mm
MVP prevalence in US 2-3%  
- 7.8 million individuals in US  
- 176 million people worldwide

1997

2020

Freed et al (Framingham Heart Study, 3,941 participants) – MVP prevalence 2.4%

Important / Prognosis?

- Heterogenous prognosis – LVEF, degree of MR, LA enlargement etc.
- One of the less recognized and yet devastating outcomes can be sudden cardiac death.
The prognosis

1966

MVP first described

1966 - 1968

Benign condition...

1985

Late Systolic Murmurs and Non-Ejection (“Mid-Late”) Systolic Clicks: An Analysis of 90 Patients

- Malignant arrhythmic MVP entity
- Prevalence / characteristic not fully defined

The syndrome associated with mitral systolic click and late systolic murmur

 subsets of MVP patients at high risk development of MR, cerebral embolic events, IE and...

SCD – 0.4%/year (6 years follow up)

Echocardiographically Documented Mitral-Valve Prolapse — Long-Term Follow-up of 237 Patients

2010s

Benign condition...

The Mitr al Valve Prolapse Syndrome: A Systematic Review and Meta-Analysis

Arhythmic Mitral Valve Prolapse: JACC Review Topic of the Week

Benefits, Mitral Valve Prolapse and Risk of Ventricular Tachycardia

Malignant Mitral Valve Prolapse and Risk of Sudden Death

Natural History of Asymptomatic Mitral Valve Prolapse in the Community

Rheumatic Mitral Valve Disease and Risk of Death From Ventricular Tachycardia

Diffuse myocardial fibrosis in patients with mitral valve prolapse and ventricular arrhythmia

Mitral Valve Prolapse and Sudden Cardiac Death

Mitral Valve Prolapse: A Systematic Review and Meta-Analysis

Familial Clustering of Mitral Valve Prolapse
SCD incidence

Reported incidence of SCD varied on:

• methods of evaluation: autopsy vs survival

• study population

• available clinical information

• forensic analysis performed

2010s

SCD incidence

Reported incidence of SCD varied on:

• **methods of evaluation: autopsy vs survival**

  ex: autopsy - rarely “unequivocally related”

• study population

• available clinical information

• forensic analysis performed

2010s
SCD incidence

- **2010s**
  - 0.2 – 0.4% (Nishimura, NEJM 1985)
  - 2% - 4% (athletes) (Narayan, Heart Rhythm 2016 & Finocchiaro JAMA Cardiol 2016)
  - 0.14% (Nalliah, Heart 2019)

- **2020**
  - JAMA Cardiology – Association Between MVP and SCD, Muthukumar 2020
The problem

- AHA / ESC guidelines - no specific recommendations yet on identification and risk stratification of SCD in MVP

The problem

How can we identify the high-risk patient from a large population of low-risk patients?
Studies on MVP and SCD

**Table: Risk Factors for Sudden Cardiac Death in Mitral Valve Prolapse**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Age, mean (SD)</th>
<th>Female sex</th>
<th>VT</th>
<th>T-wave inversion</th>
<th>Blood Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP No.</td>
<td>20-49</td>
<td>60%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Muthukumar et al, 2015</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Muthukumar et al, 2017</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bana et al, 2018</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

1. Patient characteristics

1) Physical exam
2) Sex
3) Age
1. Patient characteristics

1) **Physical exam**

2) **Sex**

3) **Age**

• For arrhythmic MVP (AMVP), there are no specific physical findings…
1. Patient characteristics

1) Physical exam ✗
2) Sex
3) Age
1. Patient characteristics - 2) Sex

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients With MVP</th>
<th>Age</th>
<th>Women (%)</th>
<th>LVVF (%)</th>
<th>Mitral Annulus Dissection (%)</th>
<th>VA on ECG (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buil et al., 2017 (25) Retrospective</td>
<td>41</td>
<td>50</td>
<td>3.0</td>
<td>63 ± 7</td>
<td>N/A</td>
<td>N/A</td>
<td>43.7 Myocardial fibrosis by CMR</td>
</tr>
<tr>
<td>Pensozalo et al., 2016 (30) Prospective</td>
<td>52</td>
<td>44</td>
<td>63.0</td>
<td>65</td>
<td>None</td>
<td>N/A</td>
<td>63 Mitral annulus dissection by CMR, mitral systolic click</td>
</tr>
<tr>
<td>Narayanan et al., 2016 (5) Prospective</td>
<td>17</td>
<td>60.9 ± 16.4</td>
<td>29.4</td>
<td>54.2 ± 14.7</td>
<td>58.8</td>
<td>N/A</td>
<td>29 Young age, fewer comorbid conditions</td>
</tr>
<tr>
<td>Nordhaus et al., 2016 (22) Retrospective</td>
<td>5.669 (4+MVP), 5.669 (single MVP)</td>
<td>63.5 ± 16.3</td>
<td>47.0</td>
<td>62.0 ± 7.3</td>
<td>46</td>
<td>N/A</td>
<td>37% Biv-MVP more VT than with single-leaflet MVP</td>
</tr>
<tr>
<td>Fulton et al., 2018 (26) Retrospective</td>
<td>15</td>
<td>48.5 ± 6.1</td>
<td>78.5</td>
<td>53 ± 8</td>
<td>6.6</td>
<td>33.3</td>
<td>60 Female, b-MVP and papillary muscle fibrosis by CMR</td>
</tr>
<tr>
<td>Mahaleo et al., 2017 (25) Retrospective</td>
<td>21</td>
<td>51.6 ± 7.1</td>
<td>71.0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>38 Systolic systolic lateral mitral annular velocities–Pickelhaue sign</td>
</tr>
<tr>
<td>Basso et al., 2015 (6) Retrospective</td>
<td>43</td>
<td>41</td>
<td>61.0</td>
<td>N/A</td>
<td>N/A</td>
<td>83</td>
<td>28 Female and papillary muscles LGE on CMR</td>
</tr>
<tr>
<td>Srinivas et al., 2013 (19) Retrospective</td>
<td>10 (b-MVP)</td>
<td>33 ± 9.6</td>
<td>90.0</td>
<td>60.5 ± 3.1</td>
<td>50</td>
<td>78</td>
<td>100 Female, interventricular T wave, complex ventricular tachy, and b-MVP</td>
</tr>
<tr>
<td>Turkier et al., 2010 (23) Retrospective</td>
<td>58</td>
<td>33.5 ± 12.6</td>
<td>56.0</td>
<td>69.7 ± 2.7</td>
<td>15.5</td>
<td>N/A</td>
<td>34 Moderate-severe MR</td>
</tr>
<tr>
<td>Cheddar et al., 2013 (14) Retrospective</td>
<td>14</td>
<td>27.8 ± 6.6</td>
<td>86.0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>42.8 Endocardial friction lesions</td>
</tr>
</tbody>
</table>

*Miller M et al., Arrhythmic Mitral Valve Prolapse, JACC 2016*g
1. Patient characteristics - 2) Sex

**TABLE 1 Baseline Characteristics**

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Overall Population (N = 595)</th>
<th>No Arrhythmia (n = 338)</th>
<th>Ventricular Arrhythmia (n = 257)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>65 ± 16</td>
<td>63 ± 17</td>
<td>68 ± 15</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>278 (47)</td>
<td>178 (53)</td>
<td>100 (39)</td>
<td>0.0006</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 ± 5</td>
<td>25 ± 5</td>
<td>26 ± 5</td>
<td>0.0008</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>68 ± 14</td>
<td>67 ± 14</td>
<td>68 ± 15</td>
<td>0.40</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>107 (18)</td>
<td>51 (16)</td>
<td>54 (21)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>227 (38)</td>
<td>119 (35)</td>
<td>108 (42)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43 (7)</td>
<td>23 (7)</td>
<td>20 (8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>245 (41)</td>
<td>133 (39)</td>
<td>109 (42)</td>
<td>0.50</td>
</tr>
<tr>
<td>CAD History</td>
<td>135 (23)</td>
<td>65 (19)</td>
<td>70 (27)</td>
<td>0.02</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>46 (8)</td>
<td>19 (6)</td>
<td>27 (11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Charlon Index</td>
<td>0.84 ± 1.10</td>
<td>0.78 ± 1.06</td>
<td>0.92 ± 1.14</td>
<td>0.10</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope history</td>
<td>66 (11)</td>
<td>43 (13)</td>
<td>23 (9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Chest pain</td>
<td>110 (18)</td>
<td>69 (20)</td>
<td>41 (16)</td>
<td>0.20</td>
</tr>
<tr>
<td>Palpitation</td>
<td>213 (36)</td>
<td>122 (35)</td>
<td>91 (35)</td>
<td>0.90</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>210 (35)</td>
<td>114 (34)</td>
<td>96 (37)</td>
<td>0.40</td>
</tr>
<tr>
<td>Edema</td>
<td>53 (9)</td>
<td>28 (8)</td>
<td>25 (10)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Essayagh, Enriquez-Sarano et al, Presentation and Outcome of Arrhythmic Mitral Valve Prolapse, JACC 2020; 76: 637-49

1. Patient characteristics

1) Physical exam ✗
2) Sex - Male ✗
3) Age
1. Patient characteristics

1) Physical exam

2) Sex - Male

3) Age

---

1. Patient characteristics - 3) Age

<table>
<thead>
<tr>
<th>Source</th>
<th>Risk factors</th>
<th>MVP, No.</th>
<th>Age (mean, SD), y</th>
<th>Female sex</th>
<th>VT</th>
<th>T-wave inversion</th>
<th>Bileaflet MVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishimura et al, 1985</td>
<td>Leaflet thickness ≥5 mm</td>
<td>237</td>
<td>10-50</td>
<td>60%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Avierinos et al, 2002</td>
<td>Moderate to severe MR; LVEF &lt;50% for increased mortality</td>
<td>833</td>
<td>50 (21)</td>
<td>64%</td>
<td>NA</td>
<td>NA</td>
<td>39%</td>
</tr>
<tr>
<td>Carne et al, 2010</td>
<td>MAD &gt;8.5 mm for NSVT</td>
<td>38</td>
<td>57 (15)</td>
<td>47%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Srinivasan et al, 2013</td>
<td>Female; VT and bigeminy; higher burden of PVCs (2%) on Holter monitor</td>
<td>10</td>
<td>33 (16)</td>
<td>90%</td>
<td>7 Patients</td>
<td>78%</td>
<td>100%</td>
</tr>
<tr>
<td>Basso et al, 2015</td>
<td>LGE fibrosis: SCD—papillary fibrosis in 100% and inferobasal wall in 88%; nonfocal complex VA—39% with LGE on CMR</td>
<td>44</td>
<td>19-40</td>
<td>SCD, 13%; Living MVP with VA, 70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muthukumar et al, 2017</td>
<td>Picklevbia sign</td>
<td>21</td>
<td>52 (12)</td>
<td>71%</td>
<td>8 Events</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Dejgaard et al, 2018</td>
<td>MAD</td>
<td>40; 90</td>
<td>49 (15)</td>
<td>60%</td>
<td>14 Patients</td>
<td>NA</td>
<td>55 (47%); VT, 5 (30%)</td>
</tr>
<tr>
<td>Ermakov et al, 2018</td>
<td>Mechanical dispersion: 59 ms in VA vs 43 ms in no arrhythmia</td>
<td>59</td>
<td>55 (15)</td>
<td>51%</td>
<td>32 Patients</td>
<td>VA, 34%; No VA, 39%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MAD, mitral annulus disjunction; MR, mitral regurgitation; MVP, mitral valve prolapse; NA, not available; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; SCD, sudden cardiac death; VA, ventricular arrhythmia; VT, ventricular tachycardia.
1. Patient characteristics

1) Physical exam
2) Sex - Male
3) Age

2. EKG

1) Repolarization abnormalities
2) Ventricular arrhythmias (VAs)
2. EKG

1) Repolarization abnormalities

2) Ventricular arrhythmias (VAs)

Abnormal contractility/tugging in MVP

Regional ischemia

Miller et al, MVP and Sudden Cardiac Death - JACC 2018
2. EKG – repolarization abnormalities

Table 1. Clinical and Pathological Features of 43 Patients Who Died Suddenly With Isolated MVP

<table>
<thead>
<tr>
<th>Variables</th>
<th>SCG Resulting From MVP (n=43)</th>
<th>Control Subjects (n=15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-Lead ECG available, n (%)</td>
<td>12 (28)</td>
<td>5 (33)</td>
<td>...</td>
</tr>
<tr>
<td>Inverted/ biphasic T-wave D2, D3, dVF, n (%)</td>
<td>10 (23)</td>
<td>0</td>
<td>...</td>
</tr>
</tbody>
</table>

Basso / Perazzolo et al, Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death, Circulation 2015, 132:556-566

2. EKG – 1) Repolarization abnormalities

Table 1. Demographics of OHCA Cohort (n = 24)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>OHCA Cohort</th>
<th>Bileaflet MVP</th>
<th>No MVP</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24/1200 2%</td>
<td>10/24 42%</td>
<td>14/24 58%</td>
<td></td>
</tr>
</tbody>
</table>
| ST-T repolarization changes# | 16/23 (70%) | 8/9 (89%) | 8/14 (57%) | 0.17 |}

Sriram et al, Malignant Bileaflet Mitral Valve Prolapse Syndrome in Patients with otherwise Idiopathic out-of-hospital Cardiac Arrest, JACC 2013, 62:222-30
2. EKG – 1) Repolarization abnormalities

- In up to 40% of patients with MVP without SCD / sustained VAs
- 33-80% of patients with MVP-related SCD have biphasic / inverted T waves in inferior leads
- Abnormal T waves in inferior leads is not risk factor by itself, but risk profile should be further investigated
2. EKG

- 1) Repolarization abnormalities
- 2) Ventricular arrhythmias (VAs)
2. EKG

**LABORATORY INVESTIGATION**

**ELEKTROPHYSIOLOGY**

Electrophysiologic effects of papillary muscle traction in the intact heart

CHARLES C. GORNICK, M.D., H. GARRETT TOUBER, M.D., MARC C. PRETSCHER, M.D., IJTAB C. TUNA, M.D., ABDUL ALHAMI, M.D., AND DAVID G. BISCHET, M.D.

*Circulation* 73, No. 5, 1013-1021, 1986.

![Mitrail prolapse - JACC Imaging, 2008](image_url)

**FIGURE 1.** Schematic representation of instrumentation used to produce posterior papillary muscle traction and determine its electrophysiologic (pacing and recording electrodes) and mechanical (ultrasonic crystals) sequelae. LA = left atrium; LV = left ventricle.

2. EKG

• “In normal myocardium in situ, regional abnormal wall motion may be associated with alterations of local ventricular activation and refractoriness, factors that in the diseased heart may lead to increased susceptibility to arrhythmias”

2. EKG – 2) VAs

• PVCs - Common in MVP, with or without SCD (~40-50%)

• Frequently from papillary muscle region and outflow tract
  ➢ Regional stretch? Abnormal Ca++ handling?

• PVCs (isolated / complex)
  ➢ Not enough by themselves to deem high risk
  ➢ Consider additional risk stratification

Electrophysiologic effects of papillary muscle traction in the intact heart

Charles C. Gorlick, M.D., H. Garth Tooller, M.D., Marc C. Prizker, M.D., Ikie C. Tena, M.D., Adrian Alamjir, M.D., and David G. Bennett, M.D.


MVP and Sudden Cardiac Death - JACC 2018

Mitral valve prolapse - JACC Imaging 2008
2. EKG – 2) VAs

- PVCs origin - marker of SCD?

- In patients with BiMVP and SCD, Purkinje system plays a central role in arrhythmogenesis

- Ablation of clinically dominant VE foci
  - improved symptoms
  - reduced appropriate ICD shocks

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Table 2. Localization of Dominant Ventricular Ectopy in Cardiac Arrest and Nonarrest Patients

<table>
<thead>
<tr>
<th></th>
<th>Cardiac Arrest (n=9)</th>
<th>Nonarrest (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ventricular ablation procedures-total (limits per patient)</td>
<td>8 (limits 1–2)</td>
<td>11 (1–2)</td>
</tr>
<tr>
<td>Anatomic location of dominant VE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV papillary muscle</td>
<td>4/6</td>
<td>5/6</td>
</tr>
<tr>
<td>LV fascicle (nonpapillary)</td>
<td>4/6</td>
<td>4/6</td>
</tr>
<tr>
<td>RVOT</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Purkinje target</td>
<td>6/5</td>
<td>5/8</td>
</tr>
<tr>
<td>Location of Purkinje target</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV papillary muscle</td>
<td>4/6</td>
<td>3/6</td>
</tr>
<tr>
<td>LV fascicle (nonpapillary)</td>
<td>4/6</td>
<td>5/6</td>
</tr>
<tr>
<td>Ablation-induced VF from target VE</td>
<td>4/6</td>
<td>2/8</td>
</tr>
</tbody>
</table>

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Essayagh / Enriquez-Sarano et al, Presentation and Outcome of Arrhythmic Mitral Valve Prolapse, JACC 2020;76:637–49

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MVP patients comprehensively characterized n=595

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2. EKG – 2) VAs

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Essayagh / Enriquez-Sarano et al, Presentation and Outcome of Arrhythmic Mitral Valve Prolapse, JACC 2020;76:637–49

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MHIF CV Grand Rounds - October 12, 2020

24 of 57
2. EKG

- 1) Repolarization abnormalities
- 2) Ventricular arrhythmias (VAs)
3. Echocardiographic findings

- 1) Leaflet characteristics
- 2) Mitral regurgitation
- 3) Lateral mitral annular velocities
- 4) Mitral annular disjunction (MAD)
- 5) Speckle-Tracking Doppler
3. Echo findings – 1) Leaflet characteristics

A. Bileaflet MVP (BiMVP)

- Proposed as high risk feature for SCD
- 42% out of 24 young patients with idiopathic SCD had BiMVP

<table>
<thead>
<tr>
<th>Demographics of OHCA Cohort (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographic</th>
<th>OHCA Cohort</th>
<th>Bileaflet MVP</th>
<th>Non MVP</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24/1,200 (2%)</td>
<td>10/24 (42%)</td>
<td>14/24 (58%)</td>
<td>—</td>
</tr>
<tr>
<td>Age at arrest (y)</td>
<td>32 ± 15 (median)</td>
<td>33 ± 15 (median 24; range 6-40)</td>
<td>32 ± 14 (median 29; range 14-56)</td>
<td>0.84</td>
</tr>
<tr>
<td>Women</td>
<td>16 (67%)</td>
<td>9/10 (90%)</td>
<td>7/14 (50%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Sriram et al, Malignant Bileaflet Mitral Valve Prolapse Syndrome in Patients with otherwise Idiopathic out-of-hospital Cardiac Arrest, JACC 2013, 62:222-30
3. Echo findings – 1) Leaflet characteristics

**A. Bileaflet MVP (BiMVP)**

- Proposed as high risk feature for SCD

**Essayagh** – more VAs in patients with BiMVP compared to SiMVP

---

**TABLE 1: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Overall Population (N = 595)</th>
<th>No Atrial Fibrillation (N = 380)</th>
<th>Ventricular arrhythmia (N = 215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bileaflet</td>
<td>201 (40)</td>
<td>14 (4)</td>
</tr>
<tr>
<td></td>
<td><strong>187 (36)</strong></td>
<td><strong>10 (2)</strong></td>
</tr>
<tr>
<td><em>p</em> Value</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>
3. Echo findings – 1) Leaflet characteristics

A. Bileaflet MVP

- Bileaflet involvement found in 70% of the patients ≤ 40 years old with SCD and MVP

Basso / Perazzolo et al, Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death, Circulation 2015, 132:556-566

| Table 1. Clinical and Pathological Features of 43 Patients Who Died Suddenly With Isolated MVP |
|-------------------------------------------------|---------------------------------|-------------------|
| Variables                                      | SCD Resulting From MVP (n=43)   | Control Subjects (n=15) |
| MP leaflet involvement                        |                                 | P Value            |
| Posterior, n (%)                               | 13 (30)                         | 0                  | ... |
| Bileaflet, n (%)                               | 30 (70)                         | 0                  | ... |
| Endocardial fibrous plaque, n (%)              | 25 (58)                         | 0                  | ... |

3. Echocardiographic findings

- 1) Leaflet characteristics – Bileaflet MVP
- 2) Mitral regurgitation
- 3) Lateral mitral annular velocities
- 4) Mitral annular disjunction (MAD)
- 5) Speckle-Tracking Doppler
3. Echocardiographic findings

- 1) Leaflet characteristics – Bileaflet MVP
- 2) Mitral regurgitation
- 3) Lateral mitral annular velocities
- 4) Mitral annular disjunction (MAD)
- 5) Speckle-Tracking Doppler

3. Echo findings – 2) MR

**Moderate-Severe MR**

- Until recently thought to be an independent predictor of SCD (relative risk 8.4) (Türker, 2010)
- Conclusion derived from studies showing MR as independent predictor of complex VAs, not mortality

**Predictors of ventricular arrhythmias in patients with mitral valve prolapse.**

Turkkan T. Shopin M. Arazi G. Cepk M. Husey Y. Vuruk E. Cepk S. Esdiger O. Yurd E. H. Author information

**Abstract**

Arrhythmias have been reported to occur frequently in symptomatic patients with mitral valve prolapse (MVP). The mechanisms causing ventricular arrhythmias in patients with MVP have not been fully investigated. The purpose of this study was to determine the clinical, electrocardiographic and heart rate variability parameters, and plasma concentrations of electrolytes and inflammatory markers in predicting ventricular arrhythmias in patients with MVP. A total of 58 consecutive patients with MVP were included in this study. We performed electrocardiography, echocardiography, Holter analysis, routine biochemical tests including plasma concentrations of electrolytes and inflammatory markers, and evaluated the clinical characteristics. Ventricular arrhythmia defined as occurrence of any of the following: ventricular premature contractions (VPCs), VPC couples, and ventricular tachycardia documented by Holter analysis, continuous monitoring by electrocardiography. Twenty patients (34%) had ventricular arrhythmias, and 38 (66%) patients had no ventricular arrhythmias. Seventeen patients had VPC, 2 patients had VPC couplets and 1 patient had ventricular tachycardia. Univariate predictors of ventricular arrhythmias included isovolumetric relaxation time and the occurrence of moderate to severe mitral regurgitation. Multivariate logistic regression analysis showed that occurrence of moderate to severe mitral regurgitation was the only independent predictor of ventricular arrhythmias (relative risk 4.42; 95% confidence interval: 1.49-14.64; p < 0.01). Present study showed that the only independent predictor of ventricular arrhythmias in patients with MVP is the occurrence of moderate to severe mitral regurgitation.
• Dollar - 1991: 14/15 patients who had MVP-related SCD did not have significant (at least moderate) MR

### Table 1. Clinical and Morphologic Features of Mitral Valve Prolapse at Necropsy Unassociated With Other Congenital Cardiovascular Anomalies (149 patients aged 16 to 70 years)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>10</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>19</td>
<td>149/15</td>
</tr>
<tr>
<td>SCD due to MVP</td>
<td>14/14</td>
<td>1(1)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
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<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>149/15</td>
</tr>
</tbody>
</table>

AML = anterior mitral leaflet; CA = coronary artery; CAD = fatal coronary artery disease; CSA = cross-sectional area; FO = fossa ovalis; LV = left ventricular; MR = severe mitral regurgitation; MV = mitral valve; MVP = mitral valve prolapse; PFO = patent foramen ovale; PM = posterior mitral leaflet; SCD = sudden cardiac death; TV = tricuspid valve; - = absent; + = present.
3. Echo findings – 2) MR

- Essayagh / Enriquez- Sarano, 2020: 595 consecutive MVP patients: “severe MR was not an independent predictor for VAs”

<table>
<thead>
<tr>
<th>TABLE 1 Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Population (N = 595)</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>MR</td>
</tr>
<tr>
<td>No/trace</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
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<tr>
<td>ERO, mm²</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2 Incidence of Ventricular Arrhythmia Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=257)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>36 (22)</td>
</tr>
<tr>
<td>12 (8)</td>
</tr>
<tr>
<td>57 (36)</td>
</tr>
<tr>
<td>54 (34)</td>
</tr>
</tbody>
</table>

HR for mortality was not significant for ID or VT. Incidence of MVP stratified by ventricular arrhythmia severity is in all cells. Note the mortality difference with ventricular arrhythmia severity, which was considered worse. Abbreviations as in Figure 1.
### 3. Echocardiographic findings

- **1) Leaflet characteristics** – Bileaflet MVP
- **2) Mitral regurgitation** – Significant MR
- **3) Lateral mitral annular velocities**
- **4) Mitral annular disjunction (MAD)**
- **5) Speckle-Tracking Doppler**

### 3. Echocardiographic findings

- **1) Leaflet characteristics** – Bileaflet MVP
- **2) Mitral regurgitation** – Significant MR
- **3) Lateral mitral annular velocities**
- **4) Mitral annular disjunction (MAD)**
- **5) Speckle-Tracking Doppler**
3. Echo findings – Pickelhaube sign

**Pickelhaube sign:**
- peak systolic mitral annulus velocity $\geq 16$ cm/sec
- Muthukumar et al: - BiMVP
  - Patients with this criteria were more likely to have malignant VAs (67% vs 22%, $p<0.08$)
  - LGE by MRI was only present in the group with + Pickelhaube sign (33%)
  - Novel echocardiographic risk marker for malignant MVP syndrome - BiMVP

3. Echocardiographic findings

- 1) Leaflet characteristics – Bileaflet MVP
- 2) Mitral regurgitation – Significant MR
- 3) *Lateral mitral annular velocities* - Pickelhaube sign (Bileaflet MVP)
- 4) Mitral annular disjunction (MAD)
- 5) Speckle-Tracking Doppler
3. Echocardiographic findings

- 1) Leaflet characteristics – Bileaflet MVP
- 2) Mitral regurgitation – Significant MR
- 3) Lateral mitral annular velocities - Pickelhaube sign (Bileaflet MVP)
- 4) Mitral annular disjunction (MAD)
- 5) Speckle-Tracking Doppler

3. Echo findings – 4) MAD

- Mitral annular disjunction (MAD):
  - Detachment of the roots of the annulus from the ventricular myocardium to which it would normally be attached
  - Allows for mitral annulus hypermobility
3. Echo findings – 4) MAD

Carmo, 2010:

- Severity of MAD is associated with VA burden
- A disjunction greater than 8.5 mm was a reasonable criterion to predict the risk of NSVT
  - Sensitivity of 67%
  - Specificity of 83%
  - Odds ratio = 10; 95% CI: 1.28 - 78.1
3. Echo findings – 4) MAD

Perazollo, 2016:

- Length of MAD in MVP-SCD patients is significantly higher than in controls
- MAD was significantly longer in patients with LGE on MRI compared to those without LGE on MRI
- MAD = constant feature of arrhythmic MVP with LV fibrosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>MVP With Midsystolic Click (32 Patients)</th>
<th>MVP Without Midsystolic Click (20 Patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of MAD, mm</td>
<td>4.8 (3 to 7)</td>
<td>3 (2.3 to 4.8)</td>
<td>0.089</td>
</tr>
<tr>
<td>Curling, n (%)</td>
<td>27 (84)</td>
<td>10 (50)</td>
<td>0.008</td>
</tr>
<tr>
<td>Curling, mm</td>
<td>4.8 (1.8 to 5.5)</td>
<td>1.2 (0 to 4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Severe curling (&gt;3.5 mm), n(%)</td>
<td>20 (63)</td>
<td>6 (30)</td>
<td>0.023</td>
</tr>
<tr>
<td>LGE, n(%)</td>
<td>26 (81)</td>
<td>10 (50)</td>
<td>0.018</td>
</tr>
</tbody>
</table>
### 3. Echocardiographic findings

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1)</td>
<td>Leaflet characteristics – Bileaflet MVP ✓</td>
</tr>
<tr>
<td>2)</td>
<td>Mitral regurgitation – Significant MR ? ❌</td>
</tr>
<tr>
<td>3)</td>
<td>Lateral mitral annular velocities - Pickelhaube sign (Bileaflet MVP) ✓</td>
</tr>
<tr>
<td>4)</td>
<td>Mitral annular disjunction (MAD) ✓</td>
</tr>
<tr>
<td>5)</td>
<td>Speckle-Tracking Doppler</td>
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</tbody>
</table>

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### 3. Echocardiographic findings

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<tr>
<td>3)</td>
<td>Lateral mitral annular velocities - Pickelhaube sign (Bileaflet MVP) ✓</td>
</tr>
<tr>
<td>4)</td>
<td>Mitral annular disjunction (MAD) ✓</td>
</tr>
<tr>
<td>5)</td>
<td>Speckle-Tracking Doppler</td>
</tr>
</tbody>
</table>
3. Echo findings – 5) Speckle Tracking

- Supranormal strain (>24%) is witnessed in the posterolateral LV trident

- Subnormal strain (<18%) is seen in the corresponding opposite basal septal wall segments

- Postsystolic contraction (postsystolic shortening, incoordinate contraction)

3. Echocardiographic findings

- 1) Leaflet characteristics – Bileaflet MVP

- 2) Mitral regurgitation – Significant MR

- 3) Lateral mitral annular velocities - Pickelhaube sign (Bileaflet MVP)

- 4) Mitral annular disjunction (MAD)

- 5) Speckle-Tracking Doppler
4. MRI findings

• 1) MAD

• 2) Curling

• 3) Fibrosis

Cardiac MRI, steady state free precession (SSFP) sequence demonstrates mitral annular disjunction (yellow line). This was measured at 2.1 cm.
4. MRI findings

• 1) MAD

• 2) Curling

• 3) Fibrosis

Dejgaard et al, Mitral Annular Disjunction, JACC 2018, 72:1600-9

Figure 3. Relationship between length of mitral annular disjunction and curling in vivo. A significant correlation (ρ=0.85) between the depth of curling and length of mitral annular disjunction (MAD, both expressed as mm) on cardiac magnetic resonance is observed. LCD indicates late gadolinium enhancement.
4. MRI findings

• 1) MAD ✔

• 2) Curling ✔

• 3) Fibrosis
4. MRI findings - 3) Fibrosis

Basso, 2015 - Papillary muscle and/or inferobasal wall fibrosis:

- In almost 100% of patients with MVP-related SCD
- Correlated with ventricular arrhythmias origin.
- Structural hallmark of high SCD risk

| Table 1. Clinical and Pathological Features of 43 Patients Who Died Suddenly With Isolated MVP |
|-----------------|------------------|-----------------|
| Variables       | SCD Resulting From MVP (n=43) | Control Subjects (n=15) | PValue |
| MV leaflet involvement | | | |
| Posterior, n (%) | 13 (30) | 0 | ... |
| Mitral, n (%) | 30 (70) | 0 | ... |
| Endocardial fibrous plaque, n (%) | 25 (58) | 0 | ... |
| LV scar, n (%) | 43 (100) | 0 | ... |
| Inferobasal wall, n (%) | 30 (69) | 0 | ... |
| Fibrous tissue hypertrophy, % area | | | |
| PM, mean±SD | 30.5±10.7 | 6.2±1.6 | <0.0001 |
| Infarct wall, mean±SD | 33.1±7.6 | 8.4±1.4 | <0.0001 |
| Cardiomyocyte diameter, mm±SD, μm | 51.2±9.0 | 12.8±5.4 | <0.0001 |
| 12-Lead ECG abnormal, n (%) | 12 (28) | 5 (33) | ... |
| Inverted/abnormal T wave, DIII, AVL F, n (%) | 10 (23) | 0 | ... |
| VAs, n (%) | 12 (28) | 0 | ... |
| VA morphology, n (%) | 12 (28) | 0 | ... |

Letter by Sheppard et al Regarding Article, “Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death”

- Independent cohort of 3680 autopsies → 62 MVP (1.7%)
- LV fibrosis in 74% of cases
  - 1 or both of PMs – predominantly postero-medial PM
  - Adjacent LV wall
4. MRI findings - 3) Fibrosis

**Myocardial Fibrosis in Patients With Primary Mitral Regurgitation With and Without Prolapse**

- MVP is associated with more LV fibrosis on MRI compared with non-MVP patients [in primary MR patients]

- Patients with MVP and replacement fibrosis have the highest arrhythmic events (VT, SCD)

**Kitkungvan et al, Myocardial fibrosis in patients with primary mitral regurgitation with and without prolapse, JACC, 2018, Vol 72, 823-34**

**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MVP (n = 35)</th>
<th>Non-MVP (n = 120)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EF, %</td>
<td>66.9 ± 8.4</td>
<td>67.2 ± 8.3</td>
<td>0.79</td>
</tr>
<tr>
<td>LV EDV index, m/L</td>
<td>89.8 ± 20.1</td>
<td>77.8 ± 20.5</td>
<td>0.001</td>
</tr>
<tr>
<td>LV ESV index, m/L</td>
<td>75.4 ± 20.8</td>
<td>66.1 ± 23.5</td>
<td>0.005</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>30.5 ± 14.6</td>
<td>24.4 ± 11.7</td>
<td>0.001</td>
</tr>
<tr>
<td>MRI, %</td>
<td>5.9 ± 13.5</td>
<td>3.3 ± 14.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Presence of replacement fibrosis</td>
<td>60 (36.7%)</td>
<td>11 (16.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figures**

- Kitkungvan, 2016 - MVP vs non-MVP patients
  - More frequent replacement fibrosis in the basal inferolateral wall (31.1%) vs non-MVP patients – basal anteroseptum 3.4%
  - More prevalent replacement fibrosis in the segments adjacent to the posteromedial papillary muscle than non-MVP patients.

- Bui, 2017
  - Diffuse nonfocal subclinical fibrosis – associated with complex VAs
4. MRI findings - 3) Fibrosis

MRI showing fibrosis (positive LGE) at the base of the posteromedial papillary muscle as well as minimal fibrosis on the anterolateral papillary muscle.

Dark blood late gadolinium enhancement sequence (LGE) demonstrating fibrosis at the level of the posterior mitral annulus.

Multifocal PVCs arising from:
- posteromedial papillary muscle
- mitral annulus
4. MRI findings

• 1) MAD ✓
• 2) Curling ✓
• 3) Fibrosis ✓
5. Hybrid PET-MRI

- Localization concordance:
  - FDG +: basal-mid infero-lateral and basal-mid anterolateral
  - MRI +: basal mid infero-lateral
- FDG+: minor VAs
- MRI +: complex VAs
- Inflammatory component prodromal to fibrosis?

<table>
<thead>
<tr>
<th></th>
<th>FDG +</th>
<th>FDG -</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI +</td>
<td>14 (70%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>MRI -</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

6. Familial clustering

6) Family clustering
6. Familial clustering

• Familial clustering described in case reports, pathological series, surgical series
  ➢ Syndromic
  ➢ Nonsyndromic – 3 loci described on chromosomes 11, 16, 13 with mutations in DCHS1 and PLP1 genes
• No systematic study of familial SCD in MVP

7. Circulating biomarkers

• 7) Circulating biomarkers
6. Circulating Biomarkers

- **Soluble suppression of tumorigenicity-2 (sST2) serum level**
  - Higher in patients with MAD and VAs (comp. to patients w/o VA)
  - Proposed as marker of myocardial stretch

- **TGFβ1**
  - Higher levels in patients with myocardial and papillary muscle fibrosis and larger MAD

7. “Classic” SCD Risk Factors

- **Resting electrocardiogram findings**
  - T-wave inversions in the inferior leads
  - QT prolongation
  - QT dispersion
  - PVCs originating in RVOT and papillary muscle
  - NSVT and/or VT

- **Imaging findings**
  - Echocardiogram
  - Valve-related abnormalities
    - Aortic stenosis >5 mm
    - Severe MR
    - Leaflets constraints
    - Dilatation of the basal and mid-segmental annulus
    - Abnormal diastolic function
    - Left ventricular hypertrophy detected by LGE
  - Cardiac arrhythmia

- **Clinical factors**
  - Young female
  - Palpitations, presyncope
  - FH of sudden cardiac death
  - Exercise-induced polymorphic VT

- **Biomarker**
  - Soluble suppression of tumorigenicity-2

*Muthukumar et al, Association Between MVP and SCD, JAMA Cardiology 2020*
7) **EP study**

**JACC REVIEW TOPIC OF THE WEEK**

**Arrhythmic Mitral Valve Prolapse**

*JACC Review Topic of the Week*

Marc A. Miller, MD,* Srinivas R. Dukkipati, MD,* Mohit Turagam, MD,* Steve L. Liao, MD,§ David H. Adams, MD,§ Vivek Y. Reddy, MD

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**Risk stratification – EP study**

**Miller et al, Mt. Sinai:**

- If + high risk features and + EPS → Consideration of ICD

- If + high risk features and – EPS → Loop recorder

**Positive EP study:**

- sustained monomorphic VT induced with up to 3 ventricular extrastimuli

  or

- polymorphic VT or VF induced with up to 2 ventricular extrastimuli
# Treatment

1. Noninvasive / Medical management
2. Catheter based ablation
3. ICD
4. Mitral valve surgery

## Treatment (continued)

1. **Noninvasive / Medical management**
   - Avoid stimulants (caffeine, alcohol, tobacco)
   - Beta-blockers
   - Calcium channel blockers
   - Anti-arrhythmic medication...
   - Improved survival...
Treatment

- 1) Noninvasive / Medical management
- 2) Catheter based ablation
- 3) ICD
- 4) Mitral valve surgery

Treatment – 2) Catheter based ablation

- 25 patients with MVP
- PVCs mapped to papillary muscles
- 4/9 patients +LGE on MRI
- 76% had complete resolution of PVC with ablation
- 8% had improvement in PVC burden with ablation
Treatment – 2) Catheter based ablation

- Acute success of predominant VE foci 17/19 procedures
- Repeat ablation 6/14 patients
- New site of ectopy 2/14 patients
- Symptoms reduced 12/14

⇒ Appropriate ablation of predominant VE foci decreased number of appropriate ICD shocks

- 14 patients with MVP
  - 6/14 w prior SCD (and ICD)
    - all 6 w Purkinje origin VFib (4/6 PM)
  - 8/14 w/o SCD but w symptomatic complex PVCs
    - 5/8 Purkinje origin (3/ PM)

- 43/617 patients with MVP and significant VA
- Patients had ICD (30%) or VE ablation (70%)
- Most common foci of VE was left PM
- Successful ablation in 65%
- At 2.6 years mean follow up, 26% had VT recurrence

⇒ While ablation was acutely successful in the majority of cases, there was still a moderate rate of VA recurrence.
Treatment

• 1) Noninvasive / Medical management
• 2) Catheter based ablation
• 3) ICD
• 4) Mitral valve surgery
Treatment – 4) Mitral valve surgery

- Relatively limited data...

8 pts with BiMVP and ICD both pre- and post-MVR

MVR reduced the number of appropriate ICD shocks
Treatment – 4) Mitral valve surgery

- 32 patients with MVP undergoing MV surgery for MR sec to BiMVP

- Pre- & post-op Holter
  - ≥10% VA burden decrease
  - <10% VA burden decrease

- Patients with significant decrease in VA burden were younger (~42 yo, <60 yo)
• There are some easily identifiable high risk SCD features in patients with MVP
  ➢ Bileaflet MVP
  ➢ Purkinje-origin VAs
  ➢ Severe VAs
  ➢ Pickelhaube sign
  ➢ MAD
  ➢ Speckle tracking (supra-normal contraction, incoordinate contraction)
  ➢ Specific areas of replacement fibrosis
• Designing a cost-effective risk stratification model to identify patients at risk still remains a challenge
• Optimum treatment (medical, interventional, ICD, surgical correction) and optimal timing of intervention still remains unclear
• Awareness of this condition and individualized patient treatment remains paramount

Thank you!

Special thanks to Dr. Kevin Harris and Dr. Quirino Orlandi.