Gender Differences in Valvular Heart Disease

Linda D. Gillam, MD FESC

Disclosure: Core Lab services Edwards Lifesciences
Obstacles

• Interest in gender differences is a relatively new phenomenon

• Registries/RCT for valvular heart disease are under-developed

Modest evidence base
Confounding Variables

- Size
- Longevity
- Treatment biases
- Prevalence of coronary disease
- Possibility that pre-menopausal women ≠ post-menopausal women
Gender Differences in Valvular Heart Disease

- Etiology
- Pathophysiology (Ventricular Adaptation)
- Natural History
- Treatment Outcomes (surgical)
Aortic Stenosis
Etiology

• Congenital
  – Bicuspid
  – Unicuspid

• Acquired
  – Degenerative
  – Other
Bicuspid Aortic Valve

- Most common congenital heart defect
- Prevalence 0.5 - 2%
- Male predominance 3:1
In patients with bicuspid aortic valve does gender influence outcome?
At Diagnosis
Baseline Characteristics of Patients With and Without Baseline Aortic Valve Dysfunction
Toronto Congenital Program Referral Population

<table>
<thead>
<tr>
<th>Table 2. Baseline Characteristics of Patients With and Without Baseline Aortic Valve Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%) of Patients</strong></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Family history of coronary artery disease (n = 225)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
</tr>
<tr>
<td>Prior diagnosis of aortic coarctation</td>
</tr>
<tr>
<td>Prior aortic valvuloplasty or valvotomy in childhood</td>
</tr>
<tr>
<td>Right-left leaflet orientation (n = 158)</td>
</tr>
<tr>
<td>Aortic root &gt;35 mm</td>
</tr>
</tbody>
</table>

*Tzemos, N. et al. JAMA 2008;300:1317-1325. (Toronto Series)*

*p* Unless otherwise indicated.

*b* Calculated as weight in kilograms divided by height in meters squared.
Baseline Characteristics of Patients With and Without Valve Degeneration at Diagnosis
Mayo Clinic (Olmstead County)

<table>
<thead>
<tr>
<th>Population Variable</th>
<th>Total (n=212)</th>
<th>Absent (n=184)</th>
<th>Present (n=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>32±20</td>
<td>28±19</td>
<td>52±16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>138 (65)</td>
<td>117 (64)</td>
<td>21 (75)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>43 (20)</td>
<td>31 (17)</td>
<td>12 (43)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>5 (2)</td>
<td>3 (2)</td>
<td>2 (7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>56 (26)</td>
<td>45 (24)</td>
<td>11 (39)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ejection click, n (%)</td>
<td>71 (33)</td>
<td>67 (36)</td>
<td>4 (14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic murmur, n (%)</td>
<td>162 (76)</td>
<td>139 (76)</td>
<td>23 (82)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diastolic murmur, n (%)</td>
<td>35 (17)</td>
<td>30 (17)</td>
<td>5 (19)</td>
<td>0.78</td>
</tr>
<tr>
<td>Typical BAV, n (%)</td>
<td>182 (86)</td>
<td>157 (85)</td>
<td>25 (89)</td>
<td>0.56</td>
</tr>
<tr>
<td>Visible raphe, n (%)</td>
<td>103 (49)</td>
<td>83 (45)</td>
<td>20 (71)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic doming, n (%)</td>
<td>108 (51)</td>
<td>96 (52)</td>
<td>12 (43)</td>
<td>0.42</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63±5</td>
<td>64±5</td>
<td>63±5</td>
<td>0.40</td>
</tr>
<tr>
<td>LVD, mm</td>
<td>48±9</td>
<td>48±9</td>
<td>50±5</td>
<td>0.42</td>
</tr>
<tr>
<td>Aortic regurgitation, n (%)</td>
<td>100 (47)</td>
<td>82 (45)</td>
<td>18 (64)</td>
<td>0.03</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.03±0.4</td>
<td>1.03±0.4</td>
<td>1.06±0.2</td>
<td>0.51</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>198±45</td>
<td>193±42</td>
<td>220±52</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Following Diagnosis
## Predictors of Primary Cardiac Events

### Table 4. Predictors of Primary Cardiac Events

<table>
<thead>
<tr>
<th>Candidate Variables</th>
<th>Univariate Analysis</th>
<th></th>
<th>Multivariate Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Baseline age &gt;30 y</td>
<td>2.11 (1.56-2.87)</td>
<td>&lt;.001</td>
<td>3.01 (2.15-4.19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.82 (1.27-2.62)</td>
<td>.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.65 (1.24-2.20)</td>
<td>.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2.66 (1.70-4.18)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.00 (0.35-2.84)</td>
<td>.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>5.36 (1.89-15.24)</td>
<td>.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>0.52 (0.21-1.29)</td>
<td>.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.00 (0.97-1.04)</td>
<td>.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior diagnosis of aortic coarctation</td>
<td>0.30 (0.19-0.48)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior aortic valvuloplasty or valvotomy</td>
<td>1.92 (1.29-2.85)</td>
<td>.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior pregnancy</td>
<td>0.38 (0.13-1.08)</td>
<td>.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-left leaflet orientation</td>
<td>1.57 (1.11-2.21)</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe aortic stenosis</td>
<td>5.31 (3.98-7.09)</td>
<td>&lt;.001</td>
<td>5.67 (4.16-7.80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Moderate or severe aortic regurgitation</td>
<td>2.61 (1.96-3.48)</td>
<td>&lt;.001</td>
<td>2.68 (1.93-3.76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;55%</td>
<td>3.22 (1.98-5.24)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic sinus &gt;35 mm</td>
<td>1.93 (1.45-2.58)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.

Independent Predictors of Primary Cardiac Events

Gender is not predictive

Table 2. Independent Predictors of Outcome After Diagnosis

<table>
<thead>
<tr>
<th>End Points</th>
<th>Independent Multivariate Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predictor</td>
</tr>
<tr>
<td>Medical CV events</td>
<td>Cardiac death, CHF, new CV symptoms, stroke, endocarditis</td>
</tr>
<tr>
<td></td>
<td>Age ≥50 y</td>
</tr>
<tr>
<td></td>
<td>Valve degeneration</td>
</tr>
<tr>
<td>Surgical CV events</td>
<td>Aortic valve surgery, thoracic aorta surgery</td>
</tr>
<tr>
<td></td>
<td>Age ≥50 y</td>
</tr>
<tr>
<td></td>
<td>Valve degeneration</td>
</tr>
<tr>
<td>Aortic valve surgery</td>
<td>Valvotomy or valve replacement</td>
</tr>
<tr>
<td></td>
<td>Age ≥50 y</td>
</tr>
<tr>
<td></td>
<td>Valve degeneration</td>
</tr>
<tr>
<td>Aortic aneurysm surgery</td>
<td>Baseline aorta ≥40 mm</td>
</tr>
<tr>
<td>Total events</td>
<td>Medical or surgical events</td>
</tr>
<tr>
<td></td>
<td>Age ≥50 y</td>
</tr>
<tr>
<td></td>
<td>Valve degeneration</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CV, cardiovascular.
Conclusion

In patients with bicuspid valve

• For the same degree of valve dysfunction gender not predictive of outcome

• Controversy concerning impact of gender on development of dysfunction
  – Need natural history series
From another perspective: Surgical Series

- **N = 465 consecutive AS pts**
  - Bicuspid: ♂ vs. ♀ = 1.85:1
  - Tricuspid: ♂ vs. ♀ = 0.76:1
    (St George’s Hospital London)

- **N = 115 (65 men, 50 women)**
  - Men: 48% bicuspid
  - Women: 46% bicuspid
Pathophysiology of Aortic Stenosis
Ventricular Adaptation

• Women have thicker walls, smaller ventricles

  – Reduces wall tension and metabolic demand BUT predisposes to intraventricular and subaortic gradients

• Clinical significance uncertain
LVEF

• Women tend to have higher LVEF’s but likely not increased contractility
Long term outcomes?

- Rat model of aortic banding: males make earlier transition to ventricular dilatation, eccentric remodeling
Aortic Regurgitation

Inferential
At Surgery for AR

- Male predominance (4:1)
- Women
  - Older (median 68 vs 55 yrs)
  - More likely to have aortic pathology
  - More likely to have class III/IV HF (? Vs LV dimension indication)
  - Similar operative mortality
  - Worse long term outcomes  RR ≈ 4:1
    corrected for age, LVEF, symptoms, CABG, aortic aneurysm
In rats
(volume overload due to AV fistula)

• Despite same degree of hypertrophy, female rats less likely to decompensate
Surgery for Aortic Valve Disease
Short term
Surgical Outcomes

• In both STS and Euroscore risk calculators, female gender carries increased risk
  1.23 (CI 1.10-1.36) for AVR (STS)
  OR ≈ 1.4  cardiac surgery (Euroscore)
Outcomes (STS)

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Mort</th>
<th>CVA</th>
<th>RF</th>
<th>Vent</th>
<th>DSWI</th>
<th>Resp</th>
<th>Comp</th>
<th>PLOS</th>
<th>SLOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td>1.23 (1.10, 1.36)</td>
<td>1.25 (1.09, 1.43)</td>
<td>0.97 (0.88, 1.07)</td>
<td>1.29 (1.21, 1.38)</td>
<td>0.98 (0.72, 1.33)</td>
<td>0.86 (0.81, 0.93)</td>
<td>1.03 (0.98, 1.08)</td>
<td>1.25 (1.16, 1.35)</td>
<td>0.69 (0.66, 0.73)</td>
</tr>
<tr>
<td>CABG plus AVR</td>
<td>1.36 (1.26, 1.47)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.18 (1.10, 1.26)</td>
<td>1.52 (1.44, 1.61)</td>
<td>1.11 (0.88, 1.40)</td>
<td>0.92 (0.87, 0.97)</td>
<td>1.20 (1.15, 1.26)</td>
<td>1.31 (1.24, 1.38)</td>
<td>0.61 (0.87, 0.64)</td>
</tr>
</tbody>
</table>

*At body surface area of 1.8 m², adapted from *Ann Thorac Surg* 2009;88:S23–42 and *Ann Thorac Surg* 2009;88:43–62*

CHF - congestive heart failure; Comp - composite adverse event (any); CVA - cerebrovascular accident (stroke); CVD - cerebrovascular disease; DSWI - deep sternal wound infection; PLOS - prolonged length of stay; Resp - reoperation; RF - renal failure; SLOS - short length of stay; Vent - prolonged ventilation
Long term
Surgical Outcomes
Long-term
Kulik et al: Ottawa Heart 2009 95: 318-326

• Ottawa series of 2255 pts with AVR
  – Women older (68.3 ± 12.3 vs 64.3 ± 14.1)

• Equally likely to receive bioprosthesis vs. mechanical valve
Kulik et al: Ottawa *Heart* 2009 95: 318-326

![Graph showing freedom from reoperation for patients post-surgery. The graph compares male and female patients with mechanical and bioprosthetic AVR.](image)

- **Female vs male**
  - Mechanical AVR
    - Adjusted HR 0.8 p = 0.52
  - Bioprosthetic AVR
    - Adjusted HR 0.4 p = 0.04

<table>
<thead>
<tr>
<th>Patients at risk:</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>766</td>
<td>1489</td>
</tr>
<tr>
<td></td>
<td>386</td>
<td>812</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>260</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>57</td>
</tr>
</tbody>
</table>
Kulik et al: Ottawa Heart 2009

**Mechanical AVR**
- Adjusted HR 1.0 p = 0.79

**Bioprosthetic AVR**
- Adjusted HR 0.5 p < 0.0001

---

**Patients at risk:**
- **Female**:
  - 278 at 0 years
  - 166 at 5 years
  - 90 at 10 years
  - 20 at 15 years
- **Male**:
  - 674 at 0 years
  - 394 at 5 years
  - 161 at 10 years
  - 37 at 15 years

---

**Years postoperatively**
- 0
- 5
- 10
- 15

**Freedom from death (%)**
- 100
- 75
- 50
- 25
- 0
Surgical Outcomes
Long-term
Kulik et al: Ottawa Heart 2009 95: 318-326

• Women at increased risk of stroke post mechanical AVR for same degree of anticoagulation
  • adjusted HR 1.7; CI 1.1 – 2.7
Mitral Valve Disease
Rheumatic MS

- More common in women
  72% vs. 28% of cases
- Exaggerated immunologic response due to estrogen binding to receptors on CD4+ and CD8+ subsets of T lymphocytes capable of producing the mitral valve damage
- Male gender a predictor of successful valvuloplasty
Mitral Regurgitation
Mitral Regurgitation
Degenerative

- Overall prevalence 2-3% of population
  female to male ≈ 1.7 to 1
- Women more likely to have benign course
  less severe regurgitation
  less likely to require surgery

BUT

higher mortality if they develop severe mitral regurgitation
### Surgical Outcomes STS

Odds ratios (95% confidence intervals) for mortality and non-fatal outcomes of women vs men undergoing mitral valve surgery*

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Mort</th>
<th>CVA</th>
<th>RF</th>
<th>Vent</th>
<th>DSWI</th>
<th>Recor</th>
<th>Comp</th>
<th>PLOS</th>
<th>SLOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVR</td>
<td>1.11 (0.97, 1.27)</td>
<td>1.25 (1.09, 1.43)</td>
<td>0.97 (0.88, 1.07)</td>
<td>1.06 (0.98, 1.16)</td>
<td>0.98 (0.72, 1.33)</td>
<td>0.79 (0.72, 0.87)</td>
<td>0.79 (0.72, 0.87)</td>
<td>1.09 (0.99, 1.19)</td>
<td>0.69 (0.66, 0.73)</td>
</tr>
<tr>
<td>MVR Repair</td>
<td>0.97 (0.77, 1.21)</td>
<td>1.25 (1.09, 1.43)</td>
<td>0.97 (0.88, 1.07)</td>
<td>1.23 (1.10, 1.38)</td>
<td>0.98 (0.72, 1.33)</td>
<td>0.90 (0.80, 1.02)</td>
<td>1.03 (0.98, 1.08)</td>
<td>1.28 (1.12, 1.47)</td>
<td>0.69 (0.66, 0.73)</td>
</tr>
<tr>
<td>CABG plus MVR</td>
<td>1.36 (1.26, 1.47)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.18 (1.10, 1.26)</td>
<td>1.17 (1.08, 1.28)</td>
<td>1.11 (0.88, 1.40)</td>
<td>0.92 (0.87, 0.97)</td>
<td>1.20 (1.15, 1.39)</td>
<td>1.31 (1.24, 1.38)</td>
<td>0.66 (0.59, 0.74)</td>
</tr>
<tr>
<td>CABG plus MVR Repair</td>
<td>1.36 (1.26, 1.47)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.18 (1.10, 1.26)</td>
<td>1.25 (1.15, 1.36)</td>
<td>1.11 (0.88, 0.97)</td>
<td>0.92 (0.87, 0.97)</td>
<td>1.20 (1.15, 1.26)</td>
<td>1.31 (1.24, 1.38)</td>
<td>0.60 (0.55, 0.66)</td>
</tr>
</tbody>
</table>


CHF - congestive heart failure; Comp - composite adverse event (any); CVA - cerebrovascular accident (stroke); CVD - cerebrovascular disease; DSWI - deep sternal wound infection; PLOS - prolonged length of stay; Recor - reoperation; RF - renal failure; SLOS - short length of stay; Vent - prolonged ventilation.
Surgical Outcomes
STS

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Mort</th>
<th>CVA</th>
<th>RF</th>
<th>Vent</th>
<th>DSWI</th>
<th>RAOP</th>
<th>Comp</th>
<th>PLOS</th>
<th>SLOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVR</td>
<td>1.11 (0.97, 1.27)</td>
<td>1.25 (1.09, 1.43)</td>
<td>0.97 (0.88, 1.07)</td>
<td>1.06 (0.98, 1.16)</td>
<td>0.98 (0.72, 1.33)</td>
<td>0.79 (0.72, 0.87)</td>
<td>0.79 (0.72, 0.87)</td>
<td>1.09 (0.99, 1.19)</td>
<td>0.69 (0.66, 0.73)</td>
</tr>
<tr>
<td>MVRRepair</td>
<td>0.97 (0.77, 1.21)</td>
<td>1.25 (1.09, 1.43)</td>
<td>0.97 (0.88, 1.07)</td>
<td>1.23 (1.10, 1.38)</td>
<td>0.98 (0.72, 1.33)</td>
<td>0.90 (0.80, 1.02)</td>
<td>1.03 (0.98, 1.08)</td>
<td>1.28 (1.12, 1.47)</td>
<td>0.69 (0.66, 0.73)</td>
</tr>
<tr>
<td>CABG plus MVR</td>
<td>1.36 (1.26, 1.47)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.18 (1.10, 1.26)</td>
<td>1.17 (1.08, 1.28)</td>
<td>1.11 (0.88, 1.40)</td>
<td>0.92 (0.87, 0.97)</td>
<td>1.20 (1.15, 1.26)</td>
<td>1.31 (1.24, 1.38)</td>
<td>0.66 (0.59, 0.74)</td>
</tr>
<tr>
<td>CABG plus MVRRepair</td>
<td>1.36 (1.26, 1.47)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.18 (1.10, 1.26)</td>
<td>1.25 (1.15, 1.36)</td>
<td>1.11 (0.88, 1.40)</td>
<td>0.92 (0.87, 0.97)</td>
<td>1.20 (1.15, 1.26)</td>
<td>1.31 (1.24, 1.38)</td>
<td>0.60 (0.55, 0.66)</td>
</tr>
</tbody>
</table>


CHF - congestive heart failure; Comp - composite adverse event (any); CVA - cerebrovascular accident (stroke); CVD - cerebrovascular disease; DSWI - deep sternal wound infection; PLOS - prolonged length of stay; RAOP - reoperation; RF - renal failure; SLOS - short length of stay; Vent - prolonged ventilation.
Kulik et al: Ottawa *Heart* 2009 95: 318-326

- Female vs male
- Mechanical MVR
  - Adjusted HR 1.0 p = 0.95
- Bioprosthetic MVR
  - Adjusted HR 1.0 p = 0.86

Patients at risk:
- Female: 495, 334, 142, 37
- Male: 368, 204, 76, 16
A

Freedom from death (%)

Female vs male

Mechanical MVR
Adjusted HR 0.8 p = 0.15

Female expected
Male expected
Female actuarial
Male actuarial

Patients at risk:
Female 329 188 83 22
Male 231 115 46 11

Years postoperatively

B

Freedom from death (%)

Female vs male

Bioprosthetic MVR
Adjusted HR 0.6 p = 0.06

Female expected
Male expected
Female actuarial
Male actuarial

Patients at risk:
Female 164 72 34 23
Male 137 62 20 7

Years postoperatively
Valve Disease in Pregnancy

- In general regurgitant lesions well tolerated
- Stenotic lesions less well tolerated
Summary

• Important gender differences in valvular heart disease
  – Etiology
    • Bicuspid aortic valve more common in men
    • Rheumatic mitral (aortic?) disease
    • Degenerative mitral disease more common in women
Summary

• Ventricular response (aortic stenosis)
• Natural history (degenerative MR)
• Surgical outcomes
  – Women have poorer short term outcomes
  – Better outcomes longterm (bioprostheses)
Much to be learned

- Are ventricular size cutoffs that have been proposed (largely derived from studies of men) suitable for women?
- Are there interventions for rheumatic mitral disease?
- How can we improve short term surgical outcomes for women?
  - CVA
  - CAD