Stable Ischemic Heart Disease in Women and the Yentl Syndrome

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“…The community has viewed women’s health almost with a “bikini” approach, looking essentially at the breast and reproductive system, and almost ignoring the rest of the woman as part of woman’s health…”

Nanette Wenger, MD
Internationally Renowned Women’s Health Expert
2001: PBS documentary “A Woman’s Heart”
Yentl Syndrome
Stable Ischemic Heart Disease in Women
Mechanisms of myocardial ischaemia

Epicardial coronary arteries
- Atherosclerotic disease
- Vasospastic disease

Coronary microcirculation
- Microvascular dysfunction
  - Impairs coronary physiology and myocardial blood flow in subjects with risk factors
  - airport coronary ischaemia in CAD and CMP

To Study Talmud

Yentl
- 19th-century heroine, Isaac Bashevis Singer’s short story
- Being "just like a man" has historically been a price women have had to pay for equality. Being different from men has meant being second-class and less than equal for most of recorded time and throughout most of the world. It may therefore be sad, but not surprising, that women have all too often been treated less than equally in social relations, political endeavors, business, education, research, and health care.

Healy, NEJM 1991
Yentl Syndrome

- Term coined by Dr. Bernadine Healy
- Noted discrepancy in inclusion of women in cardiovascular trials
- Many landmark clinical trials had very low representation of women, yet applied the study results to both men AND women
- Assumption that if women (and diseases) present like men, THEN they will be taken seriously

Gender Differences in CAD Symptoms

- 217 patients, 41% women
- 90% ischemia and 10% AMI

Milner AM J Cardiol 1999;84:396
Prevalence of Angina equal in both Genders, Stress test Angina more common in men


Younger Women face higher CVD death with Angina

### Euro Heart Survey of Stable Angina

42% women, diagnosed with CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>(n=3779) n With Data Available</th>
<th>%</th>
<th>(n=2197) %</th>
<th>(n=1582) %</th>
<th>P, Male vs Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of heart failure</td>
<td>3769</td>
<td>7.9</td>
<td>8.3</td>
<td>7.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Prior MI (&gt;1 y)</td>
<td>2901</td>
<td>4.5</td>
<td>5.4</td>
<td>3.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Prior CVA or TIA</td>
<td>3779</td>
<td>5.2</td>
<td>5.9</td>
<td>4.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3779</td>
<td>7.1</td>
<td>7.4</td>
<td>6.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3866</td>
<td>17.8</td>
<td>17.1</td>
<td>18.8</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3576</td>
<td>61.7</td>
<td>58.6</td>
<td>66.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking†</td>
<td>3583</td>
<td>53.0</td>
<td>69.1</td>
<td>30.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3174</td>
<td>58.1</td>
<td>57.2</td>
<td>59.3</td>
<td>0.24</td>
</tr>
</tbody>
</table>

### Euro Heart Survey of Stable Angina: Baseline

<table>
<thead>
<tr>
<th>Medication</th>
<th>Overall (n=3779)</th>
<th>Male (n=2197)</th>
<th>Female (n=1582)</th>
<th>P, Male vs Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>3058</td>
<td>1551</td>
<td>1207</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering drug</td>
<td>1182</td>
<td>1156</td>
<td>736</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>1630</td>
<td>1117</td>
<td>713</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blocker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of antianginal drugs, mean (SD)</td>
<td>1.6 (0.9)</td>
<td>1.7 (0.9)</td>
<td>1.0 (0.9)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Euro Heart Survey of Stable Angina

Less likely to have test  More likely to have test

<table>
<thead>
<tr>
<th>Test</th>
<th>Adjusted odds ratio for women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>0.59</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td>0.81</td>
</tr>
<tr>
<td>Stress imaging</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Caroline Daly et al. Circulation. 2006;113:490-498

Cumulative probability of death or MI in patients with confirmed coronary disease and stable angina according to gender.

1 year follow up:
Similar use of antiplatelet agents but significant differences in lipid therapy (81% vs 76%)

Women 2 x ↑ death, nonfatal MI
- Adjusted for age, DM, LV function, CAD severity, pharmacotherapy, revascularization

Caroline Daly et al. Circulation. 2006;113:490-498
WISE Study

- NHLBI sponsored observational study
- Four-centers
- 887 women undergoing clinically ordered coronary angiography
- Mean age of the study subjects was 58 years, and 25% had diabetes.
62% of Women Undergoing Diagnostic Angiography Have No or Minimal Stenosis

- **Severe** or \( \geq 50\% \) stenosis: 38%
- **None** or \(< 20\% \) stenosis: 37%
- **Minimal** or 20%-49% stenosis: 25%

N=887

Microvascular Disease

- Exertional angina
- Abnormal SPECT
- No obstructive CAD
- Abnormal CFR and increased LVEDP
- Diffuse Atherosclerosis by IVUS
**Diffuse Disease**

Blockage in male coronary artery

Blockage in female coronary artery


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**Model of Microvascular Angina in Women**

Leslie J. Shaw, Raffaella Bugiardini, C. Noel Bairey Merz

Cardiac MRI

WISE: Persistent chest pain in women predicts future CV events

n = 673 WISE participants with chest pain at baseline

Event-free survival (%)

Years from PChP diagnosis (at one year)

Without CAD
HR 1.89 (1.06–3.39)
P = 0.03

With CAD
HR 1.17 (0.76–1.80)
P = 0.49

Neither PChP No PChP No PChP CAD Both

PChP = persistent chest pain

Treatment algorithm for patients with microvascular angina

Risk factor control → Traditional anti-ischaemic drugs → Non-traditional anti-ischaemic drugs → Drugs effective on nociception → Interventions for refractory angina

- Beta-blockers
- Ca-antagonists
- Ranolazine
- Xanthines
- ACEi
- Ivabradine
- Nicorandil
- Xanthines
- Tricyclics
- SCS
- EEC

Continue ↓ Continue ↓ Continue ↓ Continue

Filippo Crea et al. Eur Heart J 2014;35:1101-1111

5-year cardiovascular costs of drug treatment, office visits, outpatient procedures, and hospitalization

Leslee J. Shaw et al. Circulation. 2006;114:894-904
Annual indirect costs: out-of-pocket expenses, home care costs, lost work, lost productivity, travel costs, medical equipment, vitamin and supplement costs, and copayment costs.

Leslee J. Shaw et al. Circulation. 2006;114:894-904

Estimated lifetime costs of drug treatment and hospitalization

Leslee J. Shaw et al. Circulation. 2006;114:894-904
Case

- 62 year old female
- Smoker
- Found down on way back from bathroom
- CPR-AED
Coronary Artery Spasm

- First described in 1959
- Multifocal spasm
- Risk Factors:
  - Smoking
  - Excess alcohol
  - Drugs
  - Inflammation
  - Oxidative stress
  - Ethnicity
Pathogenetic mechanisms in coronary artery spasm.

Vasomotor tone
Increased
Smooth muscle contraction
Abnormal
Vagal activity
Withdrawn
Sympathetic activity
Reduced?
Increased?
Endothelial dysfunction
Nitric oxide release
Decreased?
Unchanged?
Phospholipase C activity
Enhanced

Lanza G et al. Circulation 2011;124:1774-1782

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(Top) ST-segment elevation in anterior leads, with reciprocal mild ST-segment depression in inferior leads and V6, during an angina attack in a patient with variant angina.

Lanza G et al. Circulation 2011;124:1774-1782

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Treatment Options

- Cessation of smoking
  - Obligatory
- Calcium antagonists
  - The most commonly used drugs
- Long-acting nitrates
  - Alone, or in combination with calcium antagonists
- Magnesium
  - IV for acute therapy
  - Oral supplementation for possible prevention

- Statins
  - In addition to calcium antagonists
  - To inhibit the RhoA-associated kinase pathway

- Percutaneous interventions
  - If refractory to medical therapy, stent implantation may be successful

- Coronary bypass
  - Success rate disputed

- Implantable defibrillator
  - If life-threatening arrhythmias are documented

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Provocative Testing for Coronary Reactivity and Spasm

1. Chest pain
   - Obstructive CAD on angiography
     - No provocation testing
   - Normal coronary angiogram or non-obstructive CAD
     - Suspected variant angina
       - Low suspicion
       - Intermediate suspicion
       - High suspicion
         - Sudden cardiac arrest survivor (absence of other heart disease)
           - Titrated therapy to negative provocation test

2. Non-invasive testing
   - ECG, 12 lead ambulatory monitoring, exercise testing, hyperoxilation testing
   - Initiate/intensify medical therapy (nitrates/CCBs)

3. Invasive ER or ACH testing
   - Titrated therapy to negative provocation test

Journal of the American College of Cardiology, Volume 63, Issue 2, 2014, 103 - 109

Melody Zaya, Puja K. Mehta, C. Noel Bairey Merz

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER
Case 2 Follow UP

- Recurrent event with Vfib arrest
- AICD placed
- Event free for 3 years now

Yentl Syndrome is Still Alive in SIHD

Bairey Merz, EHJ 2011
Conclusion: Challenges for Women

- Delays in symptom recognition with increased atypical angina
- Misdiagnosis
- Lower use of medications
- Lower use of angiography and revascularization,

↑ Mortality

A double standard...