RISKS AND GENDER-SPECIFIC DIFFERENCES OF WOMEN'S HEART HEALTH

American Heart Association
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OBJECTIVES

• Understand disparities of diagnosis and management of cardiovascular disease in women

• Raise awareness of unique risk of cardiovascular disease effecting women

• Identify potential social barriers, biochemical and physiological differences

• Identify emerging treatment and therapeutic options
• Designed to spread awareness cardiovascular (CV) disease impact on women
  • Only 55% of women realize heart disease is most likely cause for death
  • CV disease claims 1 in 3 deaths
• Encourages involvement in outreach through education and research
• Cardiovascular disease claims 1 in 3 women in the United States
• More deaths from cardiovascular disease than all cancers combined
• Historically, women under represented in cardiovascular research and drug trials
• Unique factors contribute to healthcare disparity
  • Biochemical/anatomical
  • Socioeconomic
• Different health/disease states
FIGURE 2
Relative Risk of Cardiovascular Events in Men and Women With Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CVD Event</td>
<td>4.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>1.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Coronary Mortality</td>
<td>3.6</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Age-Adjusted Risk Ratio

[Image of bar chart showing relative risk for men and women with diabetes for various cardiovascular events]
**CENTRAL ILLUSTRATION:** Women-to-Men Hazard Ratios for Myocardial Infarction, Coronary Heart Disease, Heart Failure, and All-Cause Mortality Among Beneficiaries Without a History of Coronary Heart Disease and Among Beneficiaries With a Previous Myocardial Infarction

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
</tr>
<tr>
<td>No history of CHD</td>
<td>0.64 (0.62 to 0.67)</td>
</tr>
<tr>
<td>History of MI</td>
<td>0.94 (0.92 to 0.96)</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
</tr>
<tr>
<td>No history of CHD</td>
<td>0.53 (0.51 to 0.54)</td>
</tr>
<tr>
<td>History of MI</td>
<td>0.87 (0.85 to 0.89)</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
</tr>
<tr>
<td>No history of CHD</td>
<td>0.93 (0.90 to 0.96)</td>
</tr>
<tr>
<td>History of MI</td>
<td>1.02 (1.00 to 1.04)</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
</tr>
<tr>
<td>No history of CHD</td>
<td>0.72 (0.71 to 0.73)</td>
</tr>
<tr>
<td>History of MI</td>
<td>0.90 (0.89 to 0.92)</td>
</tr>
</tbody>
</table>

CVD Mortality Trends for Males and Females
(United States 1979-2015)

INITIATIVES AFFECTING WOMEN AND CARDIOVASCULAR DISEASE

• (1948: Framingham Heart Study commissioned by Congress)

• 1986: NHLBI publishes proceedings of Coronary Heart Disease in Women: Reviewing the Evidence, Identifying the Needs

• 1992: American Heart Association publishes the first scientific statement on women and CVD

• 1994: NIH guidelines state that women are to be included in all human subject research and that valid analyses of differences in intervention effects are to be conducted; cost is not an allowable reason for exclusion, and recruitment outreach programs are initiated and supported


• 2004: AHA publishes first evidence-based guidelines for preventing CVD in women

source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3362050/
NHLBI Heart Research: Fiscal Year 2013

The NHLBI's research portfolio supports a range of research on women’s health and ensures that women are represented in clinical trials.

Percent of Men and Women Enrolled in NHLBI Cardiovascular Trials

Including the Women's Health Initiative
- 68.2% Women
- 31.8% Men

Excluding the Women's Health Initiative
- 45.9% Women
- 54.1% Men
Central Illustration: Participation of Women of CVD Clinical Trial: Prevalence-Corrected Estimate

CVD Mortality Trends for Males and Females (United States 1979-2015)

CASE 1: 68 YEAR OLD F

• 65 YEAR OLD FEMALE WITHOUT PRIOR KNOWN HISTORY OF CORONARY DISEASE PRESENTS TO ED AFTER MVA FOR EVALUATION

• DENIED ACUTE SYMPTOMS ASIDE FROM BEING “SHOOK UP” AFTER ACCIDENT

• NAGGING HEARTBURN, NO NAUSEA, NO CHEST PAIN. “BURNING QUALITY” TO EPIGASTRIUM

• INSISTENT ON DISMISSAL FROM ED TO CARE FOR HUSBAND

• REPORTS BEING TREATED WITH PANTOPRAZOLE BY PCP IN LAST 2 WEEKS FOR INTERMITTENT REFLUX WITH SIMILAR QUALITY DISCOMFORT
CASE 1: 68 YEAR OLD F
• Through more inclusive research studies and promotion of cardiovascular event risk, women’s heart disease process better represented

• “Unique” physiological differences

• Allows for alternate symptom identification during acute coronary syndrome and stroke

• Results in better treatment, outcomes, and recognition of disparity in disease management
GENDER DIFFERENCES: PRESENTATION

- Chest pain ("classic angina") less likely in women
  - More common: shoulder or jaw pain, arm or back pain, nausea, or breathlessness
- Stroke
  - Nonfocal symptoms
- Result
  - Delayed diagnosis
  - Increased morbidity and mortality

NHLBI. Heart Disease in Women external icon, Accessed October 2, 2018.
Symptom Presentation

Heart Attack
Signs and Symptoms

- Heavy chest pain
- Cold and sweaty
- Pain in neck or left arm
- Nausea
- Sudden onset of symptoms
- Short of breath
- More tired than usual

Men and Women

- Flu-like symptoms
- Feelings of indigestion or heartburn
- Symptoms for a number of days
- Heartburn
STROKE SYMPTOMS: WOMEN VS. MEN

Men and women share a common set of stroke symptoms. But women also can experience more subtle warning signs.

**WOMEN**
- Face drooping
- Arm weakness
- Speech difficulty
- Vision problems
- Trouble walking or lack of coordination
- Severe headache without a known cause
- General weakness
- Disorientation & confusion or memory problems
- Fatigue
- Nausea or vomiting

**MEN**
- Face drooping
- Arm weakness
- Speech difficulty
- Vision problems
- Trouble walking or lack of coordination
- Severe headache without a known cause

American Heart Association.
<table>
<thead>
<tr>
<th>Source</th>
<th>Study Description</th>
<th>Patient Population</th>
<th>Study Years</th>
<th>Sample Size</th>
<th>Mean Age, y</th>
<th>Age Adjusted</th>
<th>Race Adjusted</th>
<th>Proportion Without Chest Pain, %</th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brieger et al, 2004</td>
<td>GRACE Registry</td>
<td>ACS</td>
<td>1999-2002</td>
<td>20,881</td>
<td>65.8</td>
<td>Yes</td>
<td>No</td>
<td>7.3 (10.6)</td>
<td>7.3</td>
<td>10.6</td>
<td>8.4</td>
</tr>
<tr>
<td>Canto et al, 2000</td>
<td>National MI Registry</td>
<td>MI</td>
<td>1994-1998</td>
<td>434,877</td>
<td>69.3</td>
<td>Yes</td>
<td>Yes</td>
<td>28.6 (38.6)</td>
<td>28.6</td>
<td>38.6</td>
<td>32.7</td>
</tr>
<tr>
<td>Canto et al, 2002</td>
<td>Alabama UA Registry</td>
<td>UA</td>
<td>1993-1999</td>
<td>4167</td>
<td>72.3</td>
<td>Yes</td>
<td>Yes</td>
<td>50.2 (53.0)</td>
<td>50.2</td>
<td>53.0</td>
<td>51.7</td>
</tr>
<tr>
<td>Culi et al, 2002</td>
<td>CCUs Croatia</td>
<td>MI</td>
<td>1990-1995</td>
<td>1996</td>
<td>58.8</td>
<td>Yes</td>
<td>No</td>
<td>12.4 (20.3)</td>
<td>12.4</td>
<td>20.3</td>
<td>14.8</td>
</tr>
<tr>
<td>Dorsch et al, 2001</td>
<td>United Kingdom</td>
<td>MI</td>
<td>1995</td>
<td>2096</td>
<td>70.6</td>
<td>Yes</td>
<td>No</td>
<td>17.6 (24.6)</td>
<td>17.6</td>
<td>24.6</td>
<td>20.1</td>
</tr>
<tr>
<td>Goldberg et al, 1998</td>
<td>Worcester MI Study</td>
<td>MI</td>
<td>1986-1988</td>
<td>1360</td>
<td>67.7</td>
<td>Yes</td>
<td>No</td>
<td>18.0 (23.0)</td>
<td>18.0</td>
<td>23.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Milner et al, 2004</td>
<td>Worcester MI Study</td>
<td>MI</td>
<td>1997-1999</td>
<td>2073</td>
<td>70.2</td>
<td>Yes</td>
<td>No</td>
<td>30.9 (45.8)</td>
<td>30.9</td>
<td>45.8</td>
<td>37.3</td>
</tr>
<tr>
<td>Roger et al, 2000</td>
<td>Olmsted County, Minnesota</td>
<td>UA</td>
<td>1985-1992</td>
<td>2271</td>
<td>63.0</td>
<td>Yes</td>
<td>No</td>
<td>25.0 (19.0)</td>
<td>25.0</td>
<td>19.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Stern et al, 2004</td>
<td>26 Hospitals, CCU, Israel</td>
<td>ACS</td>
<td>2000</td>
<td>2113</td>
<td>64.9</td>
<td>Yes</td>
<td>No</td>
<td>18.7 (29.7)</td>
<td>18.7</td>
<td>29.7</td>
<td>21.7</td>
</tr>
</tbody>
</table>

**Table 1. Acute Coronary Syndrome Presentation Without Chest Pain or Discomfort According to Sex—Summary of Studies From Large Cohorts**

Abbreviations: ACS, acute coronary syndrome; CCU, coronary care unit; MI, myocardial infarction; UA, unstable angina.
DIFFERENCES: MYOCARDIAL INFARCTION

- Women with STEMI have significant delays in presentation and revascularization with a higher 30-day mortality compared with men
  - Symptom to door time was 4x higher in women
  - Door to balloon time was longer in women
  - 30 day mortality was higher for women

DIFFERENCES: MYOCARDIAL INFARCTION

- Post-ACS (NSTEMI, STEMI) observational studies show consistent underuse of guideline-recommended therapies among women compared with men.

- Women with nonobstructive CAD and MI are less likely to be prescribed medications for secondary prevention of MI.

- Results in increased rates of readmission, reinfarction, and death in the first year after MI.

DIFFERENCES: MYOCARDIAL INFARCTION

• Although referral to CARDIAC REHAB is designated as a performance measure of healthcare quality after AMI, CR has failed to reach >80% of eligible women in the last 3 decades!

• Eligible women more likely to include uninsured, unmarried, socioeconomically disadvantaged, smokers, depressed, obese, sedentary, elderly, and nonwhite, less educated, less social support, and competing family obligations

• Depressive symptoms are linked to suboptimal CR attendance

• Evidence suggests that CR exercise training improves depression in women

Mosca et al, Circulation. 2011;123
Smith, et al, Circulation. 2015;131
Balady et al, Circulation. 2007; 115
Fihn et al, Circulation. 2014;129
DIFFERENCES: STROKE

• Increased stroke severity and mortality in women

• Poorer functional outcome after acute ischemic stroke (22.7% of women are fully recovered by 6 months vs. 26.7% of men)

• Women are less likely than men to be discharged home after a stroke admission (40.9 vs. 50.6%)

• Women 10% less likely to be admitted to the hospital within the first 3 h of stroke onset than men

• Women 13% less likely to receive tPA

DIFFERENCES: HEART FAILURE

- Meta-analysis of 10 years, 43 studies
- Women less likely to undergo invasive procedures like heart catheterization
- Less use of aspirin, statins, and ACE-inhibitors
- More likely to undergo therapy or testing for secondary prevention

Zhao M, et al. JAMA 9:11
### Heart failure trials: number and percent of women enrolled in each and LVEF for entry

<table>
<thead>
<tr>
<th>Study</th>
<th>% Women</th>
<th>No. of Women</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-HeFT</td>
<td>40</td>
<td>420</td>
<td>≤35%</td>
</tr>
<tr>
<td>CHARM–Overall</td>
<td>32</td>
<td>2400</td>
<td>Any</td>
</tr>
<tr>
<td>CHARM–Preserved</td>
<td>40</td>
<td>1212</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>19</td>
<td>515</td>
<td>≤35%</td>
</tr>
<tr>
<td>COMPANION</td>
<td>32</td>
<td>493</td>
<td>≤35%</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>30</td>
<td>75</td>
<td>Unknown</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>20</td>
<td>469</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>DIG</td>
<td>22</td>
<td>1520</td>
<td>≤45%</td>
</tr>
<tr>
<td>ELITE-I</td>
<td>33</td>
<td>240</td>
<td>≤40%</td>
</tr>
<tr>
<td>ELITE-II</td>
<td>31</td>
<td>966</td>
<td>≤40%</td>
</tr>
<tr>
<td>MADIT-II</td>
<td>16</td>
<td>192</td>
<td>≤30%</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>23</td>
<td>898</td>
<td>≤40%</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>32</td>
<td>145</td>
<td>≤35%</td>
</tr>
<tr>
<td>PARADIGM</td>
<td>22</td>
<td>1832</td>
<td>≤40%</td>
</tr>
<tr>
<td>RALES</td>
<td>27</td>
<td>446</td>
<td>≤35%</td>
</tr>
<tr>
<td>SCD HeFT</td>
<td>23</td>
<td>588</td>
<td>≤35%</td>
</tr>
<tr>
<td>SOLVD-Prevention</td>
<td>11</td>
<td>484</td>
<td>≤35%</td>
</tr>
</tbody>
</table>
DIFFERENCES: HEART FAILURE

• Women account for 40% of all patients with HFrEF

• Women 60% less likely to undergo left ventricular assist device (LVAD) implantation for severe heart failure

• Women higher risk of mortality and adverse events after LVAD
  • Younger women undergoing LVAD as bridge to transplant
  • Men more likely to receive transplant

Gruen J. et al, JACC: Heart Failure 8:9
HORMONAL DIFFERENCES

- Women believed to have “protective” benefit of estrogen
- Not seen with replacement therapy
- After age 65, risk of CV event accelerates, comparable to men
• HRT (estrogen + progestin or estrogen alone) should not be started in postmenopausal women after AMI for secondary prevention of coronary events

• Women who are already taking HRT at the time of their MI should discontinue taking these agents

HORMONE REPLACEMENT

- Estrogen imparts anti-inflammatory effect in healthy vessels before contributing to pro-inflammatory changes after atherosclerotic changes.
Back to MESA CAC

Input your age, select your gender and race/ethnicity, input (optionally) your observed calcium score and click "Calculate".

Age (45-84): 70

Gender: female

Race/Ethnicity: white

Observed Agatston Calcium Score (optional): 50

Calculate

The estimated probability of a non-zero calcium score for a white female of age 70 is 59%.
HORMONAL DIFFERENCES

Incidence of Cardiovascular Disease Relation to Menopause Status

Central Illustration: Testosterone/Estradiol Ratio and the Risk of Incident CVD, CHD, and HF in Post-Menopausal Women: MESA

Incidence (per 1,000 women)

Age (years)

<40 40-44 45-49 50-54

0.8 2.2 3.6 4.0 3.6 6.5


• Post-menopausal women exhibit an exponential increase in the incidence of HFpEF
CENTRAL ILLUSTRATION: The Role of Estrogen in Regulation of Titin Isoform Switch

Estrogen improves Ca++ homeostasis via:
- L-type Ca++ channel
- RyR
- PKA
- SERCA

Estrogen inhibits hypertrophic gene program:
- ↓ Ang II and AT-1
- ↓ Calcinurin
- ↑ ANP

Estrogen modulates titin subunit ratio by:
- ↓ PKC signaling
- ↑ NO – PKG axis

Estrogen improves cardiac energy balance:
- ↑ mitochondrial ATP production
- ↓ mitochondrial oxidative stress

Impaired early relaxation

LVH

Impaired energy metabolism

Myocyte death (apoptosis)

Myocardial fibrosis

Estrogen inhibits apoptosis by regulating:
- Oxidative stress
- P38α, p38β and p53
- NFαB
- ASK1
- CRHR2

Estrogen inhibits fibrosis by:
- Cardiac fibroblast transformation
- ↓ Chymase expression
- ↑ ANP

CASE 2

- 39 year old female presents one week after c-section delivery for twin infants
  - Post-delivery course was unremarkable
  - Prenatal course notable for pregnancy induced hypertension
    - Managed successfully with oral nifedipine until time of delivery
  - Prior to delivery, noted persistent mild pitting edema to feet (“shoes were tight”)
    - Moderate dyspnea on exertion- more restful periods needed
  - Symptoms worsened after returning home
PREGNANCY

• Emerging evidence identifies unique factors during or as result of pregnancy
  • Peripartum cardiomyopathy
  • Preeclampsia/Eclampsia
  • Vascular complications and latent cardiovascular risk
PERIPARTUM CARDIOMYOPATHY

• Cause uncertain

• Incidence (in US): 1 in 1500 to 1 in 4000
  • Worldwide: 1 in 100 (Nigeria) to 1 in 20,000 (Japan)

• Tendency to effect older mothers or multiparid patients

• Potentially related to history of pregnancy related hypertension or preeclampsia
PERIPARTUM CARDIOMYOPATHY

• Prognosis variable
  • Most studies show variability in tendency for recovery
• Risk of recurrence with future pregnancies
• Duration of treatment uncertain
  • Risk of future pregnancy and fetal complications
HYPERTENSION IN PREGNANCY

Hypertension in pregnancy

<20 weeks of gestation
  - Proteinuria
    - Chronic hypertension with superimposed preeclampsia

>20 weeks of gestation
  - New or increased proteinuria
    - Chronic hypertension
  - Proteinuria
    - Preeclampsia
  - No proteinuria
    - Gestational hypertension
CENTRAL ILLUSTRATION: Pathogenesis of Preeclampsia

HYPERTENSION IN PREGNANCY

- Latent effects can last decades
- Increases risk for stroke, essential hypertension, renal disease and other end-organ damage

HYPERTENSION IN PREGNANCY

- Incidence of hypertensive disorder during pregnancy influences long term cardiovascular health
**CENTRAL ILLUSTRATION:** Hypertensive Disorders of Pregnancy Are Associated With Long-Term Risk of Diverse Cardiovascular Diseases

- Coronary Artery Disease
- Heart Failure
- Aortic Stenosis
- Mitral Regurgitation

CASE 3

- 68 year old female, previously seen for risk management and history of heart murmur returns in follow up after completing chemotherapy

- Diagnosed one year ago with undifferentiated lymphoma
  - treated with radiation, RCHOP chemotherapy
    - rituximab, cyclophoshamide, doxorubicin, vincristine prednisolone
  - After completing chemotherapy, feels persistently weak, short of breath, two episodes of near syncope during yard work.
Lossy compression - not intended for diagnosis
Rates of cardiovascular disease and breast cancer in women
Leading causes of death
World, 2016

Cardiovascular diseases
Cancers
Respiratory diseases
Diabetes
Lower respiratory infections
Dementia
Neonatal deaths
Diarrhoeal diseases
Road injuries
Liver disease

Cardiovascular Disease
- Autoimmune Diseases
- Depression
- Diabetes Mellitus
- Gestational Diabetes Mellitus
- Dyslipidemia
- Hypertension
- Inflammation
- Personal history of Cardiovascular Disease
- Preeclampsia
- Pregnancy-Associated Hypertension
- Sleep Apnea

Breast Cancer
- Age
- Diet
- Family History
- Alcohol Intake
- Hormone Replacement
- Obesity/Overweight
- Physical Activity
- Tobacco Use

BRCA Genes
- Dense Breasts
- Diethylstilbestrol Exposure
- Early Menstrual Period
- High Dose Chest Radiation
- Late or No Pregnancy
- Oral Contraception Pills
- Personal History of Breast Cancer
- Starting Menopause After Age 55

Source: IHME, Global Burden of Disease, Our World in Data
<table>
<thead>
<tr>
<th></th>
<th>Risk of CVD</th>
<th>Risk of Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Diet</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Western Diet</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Light-Moderate Alcohol Intake</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Red/Processed Meat</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sedentary Lifestyle</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Premenopausal Obesity</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Smoking</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Early Menarche</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Early Menopause</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Hormone Replacement Therapy</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
BREAST/GYNECOLOGICAL CANCER

• Strong correlation between diagnosis of breast or ovarian/uterine cancer and subsequent risk of major adverse cardiovascular events

<table>
<thead>
<tr>
<th>Survival status</th>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>938 (80.6)</td>
<td>214 (68.6)</td>
<td>2 (33.3)</td>
<td>1,154 (77.9)</td>
</tr>
<tr>
<td>Dead</td>
<td>226 (19.4)</td>
<td>98 (31.4)</td>
<td>4 (66.7)</td>
<td>328 (22.1)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>1,164 (78.5)</td>
<td>312 (21.1)</td>
<td>6 (0.4)</td>
<td>1,482 (100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>39 (17.3)</td>
<td>43 (43.9)</td>
<td>4 (100)</td>
<td>86 (26.2)</td>
</tr>
<tr>
<td>Other Major Cancers (^a)</td>
<td>14 (6.2)</td>
<td>8 (8.2)</td>
<td>0 (0.0)</td>
<td>22 (6.7)</td>
</tr>
<tr>
<td>Other Cancer Death</td>
<td>26 (11.5)</td>
<td>5 (5.1)</td>
<td>0 (0.0)</td>
<td>31 (9.5)</td>
</tr>
<tr>
<td>Total CVD</td>
<td>49 (21.7)</td>
<td>14 (14.3)</td>
<td>0 (0.0)</td>
<td>63 (19.2)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>21 (9.3)</td>
<td>9 (9.2)</td>
<td>0 (0.0)</td>
<td>30 (9.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9 (4.0)</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>11 (3.4)</td>
</tr>
<tr>
<td>Other CVD</td>
<td>19 (8.4)</td>
<td>3 (3.1)</td>
<td>0 (0.0)</td>
<td>22 (6.7)</td>
</tr>
<tr>
<td>Others (^b)</td>
<td>98 (43.4)</td>
<td>28 (28.6)</td>
<td>0 (0.0)</td>
<td>126 (38.4)</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease.

\(^a\) Major cancers include lung, ovarian, and colon cancers.

\(^b\) Other causes of death include COPD, pneumonia, sepsis, accident, Alzheimer’s disease, etc. For more details, see S5 Table.
BREAST/GYNECOLOGICAL CANCER

- Treatment: chemotherapy
  - Anthracyclines (ex, doxorubicin): heart failure
    - Risk occurs at 240 mg/m2
  - Taxanes (paclitaxel): arrhythmias
    - Bradycardia, non sustained VT
  - Monoclonal antibodies (trastuzumab): heart failure
    - 5% monotherapy, up to 27% when used with anthracyclines
Anthracycline cohort
p-value 0.01

Trastuzumab cohort
p-value 0.02
BREAST/GYNECOLOGICAL CANCER

- Adjuvant radiation therapy
- Pericarditis
- Valvular disease
- Coronary disease
  - More commonly involves LAD
- Dose dependent effect
- Independent of side/location

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

- Case control study of 963 women with major coronary events compared to 1205 controls
- 44% of coronary events occurred less than 10 years after breast cancer was diagnosed
  - 33% occurred 10-19 years afterward, 23% occurred 20+ years afterward.
- 54% of case patients were known to have died from ischemic heart disease
- Higher mortality with history of left sided radiation

PHARMACOLOGICAL TREATMENT

- Unique variables
- Breastfeeding/pregnancy
- Potential for childbearing, risk of fetal development or demise
  - Existing treatment, potential needs, anticoagulation
- Pharmacokinetics
## Variations in PK properties of drugs in women

<table>
<thead>
<tr>
<th>PK Property</th>
<th>Effect in Women</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Less oral drug absorption</td>
<td>Less gastric acid secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slower GI motility and transit time</td>
</tr>
<tr>
<td>Distribution</td>
<td>Larger for lipophilic drugs</td>
<td>Greater body fat</td>
</tr>
<tr>
<td></td>
<td>Smaller for hydrophilic drugs</td>
<td>Lower total body water</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Phase I</td>
<td>Variations in enzyme activity due to pregnancy, menopause, OC use and menstruation</td>
</tr>
<tr>
<td></td>
<td>Increased activity of CYP2B6, CYP2D6, CYP3A4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased activity of CYP1A2, CYP2E1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased activity of xanthine-oxidases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased activity of N-acetyltransferases, sulfoxidases, methyltransferases</td>
<td></td>
</tr>
<tr>
<td>Excretion</td>
<td>Lower but marginal difference when normalized for body weight</td>
<td>Decreased renal blood flow, GFR, and tubular secretion and reabsorption</td>
</tr>
</tbody>
</table>
• Increasing awareness of disease presentations, risk, and physical attributes in women have improved female cardiovascular management.

• Greatest progress through inclusion of women in medical studies and research.

• Promotion through sources such as AHA have been paramount.

• Identifiable gaps in care have improved outcomes in women.
THANK YOU!

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