Women and Cardiovascular Disease: Is There Really a Sex Difference?

Martha Gulati MD MS FACF FAHA FASPC FESC
President, American Society for Preventive Cardiology
Professor of Cardiology, Cedars-Sinai Heart Institute
Anita Friedman Endowed Chair in Women’s Cardiovascular Medicine & Research
Director, Preventive Cardiology
Associate Director, Barbra Streisand Women’s Heart Center
Los Angeles, CA

Kevin Graham Prevention Lecture
Minneapolis Heart Institute
May 6, 2024

cedars-sinai.org
@drmarthagulati
www.drmarthagulati.com
Disclosures

Research funded by the Department of Defense (WARRIOR Trial) and the NIH-NHLBI (Mae WEST Study)

Dr Gulati serves on the advisory boards of Novartis, Esperion and Boehringer Ingelheim. She is on the Data Safety Monitoring Committee for an investigational drug by Merck. No products by any of these companies will be discussed here.

Understanding the “Other” Sex & Their Hearts

Women are NOT small men

Differences Due to Gender

Differences Due to Sex

Where Are the Women?

Thus humanity is male and man defines woman not in herself but as relative to him; she is not regarded as an autonomous being... She is defined and differentiated with reference to man and not he with reference to her; she is the incidental, the inessential as opposed to the essential. He is the subject, he is the Absolute - she is the other.

-Simone de Beauvoir
“... The medical 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 women’s health”

Nanette Wenger, MD
Emory University

How do we move beyond the bikini & protect a woman’s heart?

Cardiovascular Disease is Rising in the USA
Total Deaths in Women in USA 2021: 1,380,736

Cardiovascular Disease 439,729
Chronic Lung Disease 84,236
Lung Cancer 65,847
Breast Cancer 42,250

Prevalence of CVD in US Women:
• 60 Million

Prevalence of Breast Cancer in US Women:
• 4 Million

Martin, S. et al. Circulation. 2024
American Cancer Society 2024

Higher Mortality in Women With Acute Coronary Syndrome Persists

International Survey of Acute Coronary Syndromes–ARCHIVES (ISACS–ARCHIVES)

56,890 men and 30,922 women

Female patients had a higher 30-day mortality and acute heart failure risk, especially after STEMI

Worse Outcomes for Young Women with Acute MI

VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study:

Young women with AMI experience more adverse outcomes than men in the year after discharge.

Sex difference in coronary-related hospitalizations (SHR: 1.33; \( P = 0.02 \)) and noncardiac hospitalizations (SHR: 1.51; \( P = 0.01 \)).

Is it Sex or Is it Gender?

Gender influences

- Life style
- Access to care
- Employment
- Drug costs
- Ethnicity/culture
- Geographical location/Urbanization

ASCVD Diagnosis & Outcomes

Biological influences

- Sex
  - Race
  - Age
  - Hormonal status
  - Pregnancy history
  - Co-existing conditions

ASCVD Diagnosis & Outcomes

Humphries K, Pilote L. CJC 2018

Cedars Sinai Smidt Heart Institute

@drmarthagulati
www.drmarthagulati.com
Women Less Likely to Receive Guideline Recommended Medical Therapy After Acute Myocardial Infarction

- ↓ Cath/PCI
- ↑ DTB Time
- ↓ Thrombolytics
- ↑ DTN Time
- ↓ GDMT (24H or D/C)
- ↑ Mortality: STEMI
- ↑ Mortality in Young Women
- ↑ Readmissions in Women

Trends Persist over Time

Women with Chest Pain: Less Timely Care

National Hospital Ambulatory Medical Care Survey
2014-2018

- Represents ~ 29 million emergency department visits
- Young adults, ages 18 to 55, who presented to an emergency department with chest pain
- Women and people of color with CP waited longer to be seen by physicians, independent of clinical features
- Women were independently less likely to be admitted when presenting with CP
Secondary Preventive Care Underused in Women

**Central Illustration:** Statin Use in 601,934 Patients With Atherosclerotic Cardiovascular Disease on January 31, 2019

**Study Population**
- 601,934 patients with ASCVD
- Mean age: 67.5 ± 13.3 years
- Female: 54.2%
- CAD: 66.3%
- PAD: 10.2%
- Age 55 or younger: 66.3%

**Outcomes**
- Statin usage on January 31, 2019: ≤ 30 days
- Proportion of days covered

**Results**
- Proportion on high-intensity statin vs other statin vs no statin
- Odds of high (vs other) intensity statin use

Young Women after AMI: Less Likely to Receive GDMT

Arora S et al. Circulation 2019;139:1047-56

Sex Differences: Rehospitalization after AMI

- 31% rehosp ♂
- 25% rehosp ♀
- <55 Years: 28% greater risk ♂ ♀
- ≥55 Years: 8% greater risk ♂ ♀

Women of all age groups have a higher crude risk of rehospitalization, compared with men, over the 1st year post AMI
The Sickest Women Are Treated Less Aggressively Than Men

- Women were less likely to undergo invasive cardiac procedures, including revascularization and MCS
- Highest Mortality in Women, as well as Black and Hispanic

Central Illustration: Racial, Sex, and Ethnic Disparities in Outcomes of Patients With ST-Segment Elevation Myocardial Infarction and Cardiogenic Shock

- White
  - In-hospital Mortality: 33.3%
  - Revascularization: 82.4%
  - Mechanical Circulatory Support: 57.6%
  - Right Heart Catheterization: 16.7%
- Black
  - In-hospital Mortality: 33.6%
  - Revascularization: 77.1%
  - Mechanical Circulatory Support: 56.3%
  - Right Heart Catheterization: 16.9%
- Hispanic
  - In-hospital Mortality: 34.7%
  - Revascularization: 82.4%
  - Mechanical Circulatory Support: 61.4%
  - Right Heart Catheterization: 19.3%
- Other
  - In-hospital Mortality: 30.4%
  - Revascularization: 81.7%
  - Mechanical Circulatory Support: 62.9%
  - Right Heart Catheterization: 22.4%

ISACS-ARCHIVES: Women with STEMI are more likely to present with acute HF and this may explain sex differences in mortality

Cenco E et al. JACC Adv. 2023 May, 2 (3) 100294

Adding Insult to Infarct

Disparities in Acute Myocardial Infarction (AMI) in Women

Factors Contributing to Disparities
- Comorbidities
- Depression
- Socioeconomic Factors
- Symptom Awareness
- Delays in Presentations

Next Steps and Solutions
- Attention to Psychosocial Factors
- Focus on Health Literacy
- Electronic Medical Records (EMR) Prompts for GDMT
- Virtual Care-Team Guided Strategies
- Adequate Insurance for All Income Levels

GDMT in Heart Failure Underused in Women

<table>
<thead>
<tr>
<th></th>
<th>Women N=188</th>
<th>Men N=1970</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any GDMT Rx within 12M of Dx</td>
<td>40%</td>
<td>62%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any GDMT Rx within 90 days of Dx</td>
<td>30%</td>
<td>54%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any GDMT Rx within 30 days of Dx</td>
<td>22%</td>
<td>37%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

US Veteran Women with incident HF had a lower odds of receiving GDMT: OR=0.54 (95% CI, 0.37–0.79) for woman with incident HF receiving at least 1 HF medication vs men

Any of ACE inhibitor, ARB, bisoprolol, carvedilol, metoprolol, or mineralocorticoid receptor antagonist

Underutilization of Effective Cardiac Therapies in Women

- **TAVR**: have better outcomes vs
- **AFib**: 
  - Adequate Anticoagulation
  - NOAC
  - Rhythm control/ Ablation
- **ICD/CRT**: 
  - ICD/CRT use in vs
- **Heart Transplant**: Women: 25% of LVAD 25% of Transplant

Anu Lala/Martha Gulati. Journal of Cardiac Failure, 2022;28: 477-498
Dewidar et al. CJC 2022;4: 75-84
Thompson L et al. JAHA 2017; Law JACC 2018
Do Women Experience CVD Like Men?

Sex Differences in Presentation

Sex Differences in the Presentation of Myocardial Infarction

Acute Myocardial Infarction: 90% of Women & Men Reported Chest Pain
- Women report 3 or more accompanying symptoms
- Women who sought care prior to MI more likely to be told it was not cardiac

Kraaikampcaus et al. (Presented at ESC 2019)
Ferry A et al. JAMA 2019;8, DOI: (10.1161/JAMA.119.012307)

VIRGO Study
(Young Women & Men)

HERMES
(AI)

High-STEACS Trial

Myocardial Infarction
"Atypical" Chest Pain

Misused; often used to refer to communicate that pain is not cardiac rather than an atypical presentation. This fosters less intensive care.

90% of women and men with myocardial ischemia have “typical” symptoms.
What About the Sex Differences in CVD?

Prevalence of Non-Obstructive Coronary Artery Disease

<table>
<thead>
<tr>
<th></th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>UA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO IIb</td>
<td>10.2</td>
<td>9.1</td>
<td>13.9</td>
</tr>
<tr>
<td>Meta Analysis</td>
<td>6.8</td>
<td>4.2</td>
<td>13.5</td>
</tr>
<tr>
<td>n=102,004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.8</td>
<td>10.2</td>
<td>27.1</td>
</tr>
<tr>
<td></td>
<td>7.6</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>n=14,466</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% with non-obstructive CAD

STEMI

NSTEMI

UA

p<0.02 for all comparisons


ISCHEMIA Trial:
8518 patients with moderate or severe ischemia on stress testing
14% had no obstructive CAD
INOCA is Not a Benign Condition in Women

- WISE (n=540 women with INOCA, mean age 52 yrs)
- Compared to 1000 age and race-matched controls (St. James WTH)

Annualized Event Rate 2.5%/year

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI*</td>
<td>0.5%</td>
</tr>
<tr>
<td>Stroke**</td>
<td>1.0%</td>
</tr>
<tr>
<td>CHF**</td>
<td>1.5%</td>
</tr>
<tr>
<td>Death or any CV Outcome**</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

* Adjusted p = 0.03, ** Adjusted p = <0.0001

Obstructive CAD is Just One Phenotype of IHD!

Adapted from https://vitmby.com/the-ship-and-the-iceberg
Ischemia with No Obstructive Coronary Arteries (INOCA)

- Signs and symptoms of ischemia but no obstructive CAD (stenosis<50%)
- Estimated to affect at least 3-4 million women and men in the US
- Healthcare costs related to angina and heart failure hospitalizations and repeat testing/angiography

MINOCA/INOCA: Invisible to the Eye

Good News! It wasn’t a heart attack after all! Normal Coronary Arteries!
Takotsubo Syndrome (TTS)

- 90% Women
- No established Tx for TTS
- No specific treatment proven to reduce the risk of recurrent TTS
- 10% of TTS patients experience recurrent episodes of acute TTS
- Postmenopausal Women: 10% of all acute chest pain
- ~5% In-hospital Mortality in TTS
- ~20% left with persistent abnormalities in cardiac function
- Survivors: ↑MACE & Mortality

Do CVD Risk Factors affect Women in the same way as Men?

Sex Differences in Cardiac Risk Factors
Sex Differences in Traditional ASCVD Risk Factors

- Diabetes: ↑ CVD Risk for Women
- HTN: SBP Trajectory Differ by Sex
- Lipids: Lp(a): Women
- Tobacco: ↑ Risk for Women
- Exercise: ↓ Fitness in Women, ↑ Mortality Risk
- Inflammation: ↑ RA/SLE

Exercise Capacity in Women

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Percentage of Predicted Exercise Capacity for Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1: Hazard Ratios for Death from Any Cause and from Cardiovascular Causes among Women, According to the Deviation from the Expected Exercise Capacity for Age

<table>
<thead>
<tr>
<th>Exercise Capacity</th>
<th>Death from Any Cause</th>
<th>Death from Cardiovascular Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic Women</td>
<td>Symptomatic Women</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic Women</td>
<td>Symptomatic Women</td>
</tr>
<tr>
<td>Exercise capacity -85% of predicted value for age*</td>
<td>2.03 (1.31-3.17)</td>
<td>2.77 (1.90-3.97)</td>
</tr>
<tr>
<td>Exercise capacity -85% of predicted value for age*</td>
<td>2.64 (1.48-4.89)</td>
<td>3.02 (1.43-6.35)</td>
</tr>
</tbody>
</table>

* The reference group is women whose exercise capacity was at least 85 percent of that predicted for age.
† This group served as the reference group.
**Age-Predicted Heart Rate for Women: Not 220-Age!**

![Graph showing age-predicted heart rate for women]

- **Nomogram of percent peak heart rate for age**

![Graph showing nomogram]


---

**Sex Differences in Physical Activity & Mortality**

- **Greatest mortality benefit achieved at 300 min/wk MVPA - 18% lower all-cause mortality.**

- **Similar magnitude of benefit at 140 min/wk of MVPA, continued benefit with increasing min/wk of MVPA until 300 min/wk with 24% lower risk of death (HR: 0.76; 95% CI: 0.72-0.80)**

- **Greatest mortality benefit from 3 sessions/wk of muscle strengthening with a 14% lower hazard in all-cause mortality.**

- **Equivalent or greater benefit by engaging in only a single muscle strengthening/week.**

**Ji, H, Gulati, M et al. JACC 2024;83:783-793**

---
Pregnancy-Related Mortality Continues to Rise in USA


*Per 100,000 live births

Maternal Mortality Rates Continue to Rise

With persistent racial inequities
Pregnancy Mortality
23 Deaths/100,000 Live Births in USA (2020)

- Cardiovascular 15.5%
- Infection/Sepsis 12.7%
- Hemorrhage 11.4%
- Cardiomyopathy 11.0%
- Hypertensive Disorder 7.4%
- PE 9.2%

Identifying Preventable Maternal Deaths

OVERALL
- 33.5% Not Preventable
- 63.2% Preventable
- 3.2% Unable to Determine

CARDIOVASCULAR AND CORONARY CONDITIONS
- 27.3% Not Preventable
- 68.2% Preventable
- 4.6% Unable to Determine

WHILE PREGNANT
- 33.3% Not Preventable
- 63.2% Preventable
- 3.5% Unable to Determine

WITHIN 42 DAYS
- 29.0% Not Preventable
- 66.7% Preventable
- 4.4% Unable to Determine

43 DAYS TO 1 YEAR
- 41.7% Not Preventable
- 58.3% Preventable
- -- Unable to Determine

Report from Nine Maternal Mortality Review Committees 2018
Cdcfoundation.org

@drmarthagulati
www.drmarthagulati.com
CVD Assessment Algorithm For Peri- and Postpartum Women

Red Flags
- Shortness of breath at rest
- Severe orthopnea ≥ 4 pillows
- Resting HR ≥120 bpm
- Resting systolic BP ≥160 mm Hg
- Resting RR ≥30
- Oxygen saturations ≤94% with or without personal history of CVD

Personal History of CVD Without Red Flags

PROMPT EVALUATION and/or hospitalization for acute symptoms
plus
CONSULTATIONS with MFM and Primary Care/Cardiology

Countering Rising CVD in Pregnancy

Pre-pregnancy factors
- ↑ Cardiometabolic disorders (hypertension, obesity, diabetes)
- ↑ Maternal age
- ↑ Pregnancies in women with congenital and established CVD

CVD during pregnancy
- Ischemic heart disease
- Stroke
- Arrhythmia
- Heart failure
- Cardiomyopathy
- Pulmonary hypertension
- Hypertensive disorders of pregnancy

Strategies to mitigate rise in CVD
- Preventive efforts to reduce pregnancy cardiometabolic risk factors
- Pregnancy heart teams
- Standardized protocols to address maternal health emergencies
- Advocacy efforts to increase access to care and to lower societal barriers
Pregnancy = Nature’s Free Stress Test

Pregnancy complications = Effective CVD risk “stress tests”

Identify Women Who Would Benefit from Primary Prevention Efforts to Reduce ASCVD Risk

Originally published May 10, 2018

Future Risk of ASCVD by APOs

- 80% of women bear at least 1 child
- APOs: Occur in 10-20% pregnancies

Davis M et al JACC 2021;77:1763-1777
Potential Mechanisms for ASCVD with APOs

- Hypertension
- Obesity
- Dyslipidaemia
- Insulin resistance
- Small-for-Gestational-Age Infant
- Pre-eclampsia
- Miscarriage
- Preterm Birth
- High Parity
- Gestational Diabetes
  - Placental dysfunction
  - Cardiovacular maladaptation
  - Physiological glucose intolerance
  - Pre-existing risk
  - Endothelial dysfunction
  - Inflammation
  - Multifactorial
  - Lifestyle
- CVD
- CHD
- CVA

Wu P, Mamas M, Gulati M. Journal of Women’s Health 2019

The Fourth Trimester

1 week
2 weeks
6 weeks
12 weeks
Longitudinal

Assess

- Physical Exam
- Blood Pressure
- Cardiovascular Symptoms
- Mental Health
- Medication Adherence
- Lactation Support
- Family Planning
- Barriers to Care
- Social Support
- Establish Primary Care
- Longitudinal Assessment of CVD
- Risk Factors

Counsel

- Lactation
- Stress and Fatigue Management
- Family Planning
- Long-Term Risk of APOs
- Physical Activity
- Weight Management

Treat

- Hypertension
- Gestational Diabetes
- Chronic CVD Management
- Mental Health Disorders
- Referral to Social Services
- Referral to Primary Care or Subspecialty Care
- Screening for Diabetes,
  Hyperlipidemia, and CVD Risk Factors
- Contraception
- Referral to Nutritionist

Sex-Specific Risk Factors for ASCVD: Across the Lifespan

Young Women
- Age of Menarche
- PCOS
- OCP + Smoking

Reproductive Years
- Age of 1st Birth
- APOs
- Fertility Treatment
- Premature Menopause/ Ovarian Insufficiency/ FHA

Older Women
- Menopause
- HRT Use

Inclusion of Women in Cardiovascular Trials
“... overall strategic commitment of the NIH to make women’s health a priority, not just in the interest of women but for the well-being of the American people. And it is our hope that the bold and charming heroine Yentl will survive, but that her syndrome will slip back into history as a curiosity of times gone by.”

Dr. Bernadine Healy
Women Remain Underrepresented in Cardiovascular Trials

Globally:

↓ Enrollment esp Heart Failure, CAD Trials

↓ Enrollment in Device Trials

↓ Enrollment with Government Funding

Relatively Unstudied

---

Pharmacologic Therapies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Physiologic Differences</th>
<th>Pharmacokinetic Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal Transit Times</td>
<td>![Woman, Man, Arrow]</td>
<td>Slower Intestinal Transit in Women</td>
</tr>
<tr>
<td>Transdermal Absorption</td>
<td>![Woman, Man, Arrow]</td>
<td>↑ Transdermal Absorption in Women</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Body Water</td>
<td>![Man, Woman, Arrow]</td>
<td>↑ Total Body Water in Pregnant Women &amp; Men</td>
</tr>
<tr>
<td>Women Greater Adipose Tissue</td>
<td>![Woman, Man, Arrow]</td>
<td>↑ Adiposity in Women</td>
</tr>
<tr>
<td>Plasma proteins modulated by Estrogen</td>
<td>![Woman, Man, Arrow]</td>
<td>↑ Free Concentrations in Women (modulated by estrogen)</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>![Woman, Man, Arrow]</td>
<td>↑ Cardiac Output/ Rate of Distribution in Men vs Women</td>
</tr>
<tr>
<td>Body Fat</td>
<td>![Woman, Man, Arrow]</td>
<td>↑ Body Burden of Lipid Soluble Drugs in Women</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Excretion</td>
<td>![Woman, Man, Arrow]</td>
<td>↑ Glomerular Filtration Rate, Tubular Secretion &amp; Resorption in Men</td>
</tr>
<tr>
<td>Liver Metabolism</td>
<td>![Woman, Man, Arrow]</td>
<td>↓ Liver Enzyme Activity in presence of Estrogen: metabolism varies through pregnancy, menstrual cycle, use of contraceptives, after menopause in women</td>
</tr>
</tbody>
</table>

---

Anu Lala, Martha Gulati. Journal of Cardiac Failure, 2022;28:477-498
**Timeline of Requirements of Inclusion of Women: FDA, NIH, Congress**

- **1960s**: FDA: Requirement of specific subgroups exclude Race & Sex
- **1970s**: NIH: Recommended Women be included in studies
- **1980s**: FDA: Exclusion of Women of childbearing potential (Phase I/II)
- **1990s**: FDA: Removed restrictions for participation of women of childbearing potential
- **2000s**: FDA: Expectations for medical devices
- **2010s**: NIH mandates preclinical (cell/animal) studies include both sexes (2016)
- **2020s**: FDA: Framework to include sex/gender in device reporting
And Still Women Remain Understudied, While No One is Held Accountable….

FIGURE B-1 Average % of females in trials by year of FDA approval and therapeutic area (n = 287).

SOURCE: Analysis of FDA Drug Trials Snapshots as of May 2021.

Increase the Diversity in Trials to Understand Sex & Gender Differences

Continue to Follow Metrics Globally

Apply Guidelines Equally

Women Focused Centers

↓ Gender Bias in Care

Improving CVD Care for Women
Understanding Sex Differences in CVD

• Women remain underrecognized, underdiagnosed, undertreated & understudied in CVD

• Women Have Worse Outcomes after AMI: Women are Less likely to received Guideline Directed therapies

• How can we harness the power of EHR & AI to improve the care and remove the bias?

• Women Need to Be Studied; Sex-Differences Exist if We Look

Women’s Cardiovascular Health National Priority
Thank you!

@drmarthagulati
www.drmarthagulati.com