Using Sex Differences to Improve Cardiovascular Care in Women

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Disclosure:
I have no Industry Relationships relevant to this presentation.

Full listing can be found at: http://www.dcri.duke.edu/research/coi.jsp

Leading Causes of Death in the US 2004

World Wide, CVD Is Increasing Faster in Women 1990→2020

Are Women Different? CVD Mortality Trends 1979-2004

Using Sex Differences to Improve Cardiovascular Care in Women: What’s the Problem?

- Quality Cycle
- Evidence base
  - Basic science, clinical science
  - Lumpers vs splitters
  - How to generate better data
- Physiology and pathophysiology
- Health care delivery/Sociology
Quality Cycle: CVD in Women
Improving Quality of Care for Women
DCRI Think Tank March 2007

Evidence Base
Prospective consideration of sex
Better representation of women in RCTs
Improved access to all data
Regulatory incentives

Clinical Practices
Proven sex specific diagnostic and therapeutic strategies
Facilitated by reimbursement policies

Outcomes
Improved processes of care
Reduced morbidity
Reduced mortality

Research Concepts
Sex-specific differences in pathophysiology, therapeutic response, adverse effects

Clinical Guidelines
Clarity regarding known differences and their impact
Focused statements regarding lack of data

IOM 2001: Does Sex Matter?
Even Macrophages Have A Sex
Ex vivo studies of male-donor MΦ
4x more androgen receptor mRNA
↑ Response of athero genes to androgens
27 genes upregulated 3-5x in male MΦ
Lipoprotein processing
LDL degradation, foam cells
Cell surface adhesion
Extracellular signaling
Coagulation and fibrosis
Transport protein genes
0 / 588 genes in female cells affected

Women in All NHLBI CV Trials
Excluding Single Sex Trials

What’s the Problem?
The Quality Cycle
- Basic science: Men and women are different
- Clinical science: Men and women are different
- Women are under represented in clinical trials
- Evidence base is limited
- Guidelines recommendations are not supported by evidence in women
- Outcomes are not tracked by sex
- The Quality Cycle isn’t operative to ensure quality of care for women

Under Representation of Women in Clinical Trials for Acute MI

Data in Elderly, Women are Missing From Clinical Guidelines Evidence Base
Can We Analyze the Data We Have?
Sex Differences: A Subgroups Problem

Lumper: Analyze men and women together, test for interactions

Splitter: Analyze effects on women and men separately

Sample Subgroups
Men vs Women
Adult vs Pediatric
Elderly vs Younger
African-American vs Caucasian (race, ethnic comparisons)
US vs Canada (eg international comparisons)

Special Thanks to Dan Mark, MD

Understanding Sex Effects:
The ‘Lumper’ Approach

- Lumping assumes that:
  - Subgroups are more similar than different
  - Information from one subgroup has utility for the other subgroup
- Analytic approach: pool data, test for interactions
- Main limitations:
  - Interaction tests have less statistical power
  - Does the analysis provide information about Men vs Women or the effect of drug vs placebo in women?

Understanding Sex Effects:
The ‘Splitter’ Approach

- Splitting assumes that:
  - Subgroups are more different than similar
  - Information from one subgroup unreliable for use in the other subgroup
- Analytic approach: separate subgroup analyses
- Main limitations:
  - Subgroups have smaller sample size; Smaller sample size means less power; Larger, more expensive trials
  - Double # tests → ↑ probability of False Positive result

Lumping Vs Splitting: A Cultural Issue?

- Lumping:
  - Favored by therapeutic studies (esp RCTs)
  - Use modeling to sort out subgroup issues
- Splitting/Subgroups:
  - Favored by clinicians, diagnostic studies
  - Feels closer to the empirical data
- This may reflect the relative involvement of statisticians in Dx studies (low) and RCTs (high)
- Statisticians are more comfortable w models and interaction terms

Lumpers vs Splitters: Final Thoughts

- Subgroups appear to offer more insights into underlying biology/pathophysiology
- Subgroups are required by US Law for NIH
- More realistic option is to select approach that is most useful to study at hand
- Use secondary data archives, web resources and meta-analyses to enhance power of female-only analyses

Recommendations to Improve the Evidence Base for CVD in Women- 1

1. Improve trial design to detect heterogeneity
   a. Power trials to test heterogeneity in outcomes by sex
   b. Further explore such heterogeneity when identified
   c. Develop alternative statistical methods for heterogeneity
2. Increase enrollment of women in trials
   a. Research on sex-related differences in recruitment and retention of subjects and how to overcome them
   b. Increase use of proven recruitment, retention strategies
   c. Employ regulatory and reimbursement strategies
   d. Better CMS coverage of trial expenses

Improving Quality of Care for Women
DCRI Think Tank March 2007
AHJ 2008; 156:816
Recommendations to Improve the Evidence Base for CVD in Women

3. Mandate reporting of 1º, 2º results in clinical trials by sex
   a. Journals require sex-specific reporting in all primary manuscripts
   b. Encourage 2º presentations and/or papers on results in women
   c. Enhance accessibility of new and existing data for review and for incorporation into meta-analyses

4. Create incentives for research in women
   a. More rigorous pre-market requirements regarding sex-based data
   b. Identify business incentives to create evidence in women
   c. Implement new FDA policies requiring discussion of the impact of sex before devices or drugs receive approval
   d. Consider extensions of patent duration for enhanced pre clinical testing of drugs and devices in women (similar to children)
   e. ↑ awareness among investigators, industry and regulators

Using Sex Differences to Improve Cardiovascular Care in Women: What’s the Problem?

- Quality Cycle
- Evidence base
- Physiology and pathophysiology
  - Risk assessment, 1º prevention
  - Diagnosis of chest pain
  - PCI
  - ACS
  - Antithrombotic therapy
- Health care delivery/Sociology

CV Risk Factors for MI are Similar in Men and Women: INTERHEART

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Value Men 50-59 yo</th>
<th>Value Women 50-59 yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90.9</td>
<td>90.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55.2</td>
<td>55.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>70.8</td>
<td>70.8</td>
</tr>
<tr>
<td>Obesity</td>
<td>44.6</td>
<td>44.6</td>
</tr>
<tr>
<td>HDL</td>
<td>46.8</td>
<td>46.8</td>
</tr>
<tr>
<td>LDL</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>58.0</td>
<td>58.0</td>
</tr>
<tr>
<td>Family history</td>
<td>52.0</td>
<td>52.0</td>
</tr>
<tr>
<td>CHD</td>
<td>30.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

FRS Underestimates Risk in Women: % Men, Women at > Intermediate Risk

MEN:
- 50-59 yo - 60%
- 60-69 yo - 92%

WOMEN:
- 50-59 yo - 1%
- 60-69 yo - 9%

Assessing Global CV Risk in Women: “Reynolds” Risk Score

- Framingham Risk Score
  - Poor predictive ability esp in women
  - Highly age dependent: 10 y risk low <65y
  - Ignores family history, DM, metabolic syndrome, inflammation, lifestyle (diet, exercise)

- Reynolds Score
  - AHA 2007 GL Lifetime risk score
  - High risk: CHD, PAD, DM, CRI or 10-yr FRS >20%
  - At risk: ≥ 1 RF (smoking, diet, inactivity, obesity, FHx, HTN, Lipids); Subclinical dz (CAC). Metabolic syndrome; OR Poor exercise capacity
  - Optimal risk: FRS <10%, healthy lifestyle, no RFs

What is the Best Way to Assess CV Risk in Women?

- Framingham Risk Score
  - Poor predictive ability esp in women
  - Highly age dependent: 10 y risk low <65y
  - Ignores family history, DM, metabolic syndrome, inflammation, lifestyle (diet, exercise)

- Reynolds Score
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  - High risk: CHD, PAD, DM, CRI or 10-yr FRS >20%
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  - Optimal risk: FRS <10%, healthy lifestyle, no RFs
What About Imaging? CAC Predicts CHD Deaths in Low-FRS Risk Women

- 3061 W, 45-84y in MESA study
- 90% low risk by FRS
- 32% of low risk had CAC >0; ↑ Risk of death
- Likelihood of death related to CAC score

<table>
<thead>
<tr>
<th>CAC</th>
<th>Prevalence</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>68%</td>
<td>1.0</td>
</tr>
<tr>
<td>1-99</td>
<td>22%</td>
<td>4.2</td>
</tr>
<tr>
<td>100-299</td>
<td>6%</td>
<td>5.7</td>
</tr>
<tr>
<td>&gt;300</td>
<td>4%</td>
<td>22.3</td>
</tr>
</tbody>
</table>

Should Statins be Used for 1° Prevention of CHD in Women?

<table>
<thead>
<tr>
<th>Outcome, group</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, men and women</td>
<td>0.95</td>
<td>0.89–1.01</td>
</tr>
<tr>
<td>CVD events, all</td>
<td>0.82</td>
<td>0.77–0.87</td>
</tr>
<tr>
<td>CVD events, women</td>
<td>0.96</td>
<td>0.85–1.12</td>
</tr>
<tr>
<td>CVD events, M&amp;W &gt; 69 yo</td>
<td>0.94</td>
<td>0.77–1.15</td>
</tr>
</tbody>
</table>

Statins and all-cause mortality

<table>
<thead>
<tr>
<th>LDL (mg/dL)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-29.9</td>
<td>0.86</td>
<td>0.77–0.96</td>
</tr>
<tr>
<td>30-39.9</td>
<td>0.82</td>
<td>0.74–0.90</td>
</tr>
<tr>
<td>40-59.9</td>
<td>0.79</td>
<td>0.70–0.90</td>
</tr>
<tr>
<td>≥60</td>
<td>0.76</td>
<td>0.68–0.85</td>
</tr>
</tbody>
</table>

Relative Risk of Major Bleeding

ASA benefits

Aspirin, Sex and Non Fatal MI

- Meta analysis of 23 trials (n = 113,494)
- Aspirin: ↓ non-fatal MI (RR = 0.72, 0.64–0.81)
- Trials w/ Men: RR = 0.62; Women: RR = 0.87

Should Aspirin be Used in 1° Prevention of CHD in Women?

- Meta analysis of 23 trials (n = 113,494)
- Aspirin: ↓ non-fatal MI (RR = 0.72, 0.64–0.81)
- Trials w/ Men: RR = 0.62; Women: RR = 0.87

The Guidelines: Does Atherosclerosis Imaging add Value in Women?

- Current data indicate that CAD risk stratification is possible in women.
- Bayesian approach suggests target population is intermediate risk: CAC can refine the risk prediction of an intermediate risk patient.
**Should Aspirin be Used in 1° Prevention of CHD in Women?**

**AHA Primary Prevention GL for Women (2007)**

- **High risk:**
  - ASA (75-325 mg/d) in all high-risk women (I-A)
  - If ASA-intolerant, use clopidogrel (I-B).
- **Women >65 yo:**
  - ASA (81 mg/qd or 100 mg/qod) if BP controlled and appropriate risk-benefit ratio (IIb-B).
- **Women <65 yo:**
  - Not recommended to prevent MI (III-B).

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**FHS: Presentation of CHD Men vs Women (30-62 yo)**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>38%</td>
<td>61%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>Coronary insufficiency</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Coronary death</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sudden death</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

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**Angina is More Common in Women**

- Meta analysis of 74 healthy populations; 31 countries
- 12,331 women; 11,511 men
- OR women 1.2 (US 1.4)

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**Implications of CP Type for CHD: CASS Study**

- Men
- Women

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**Survival in 840 ETT+ Patients**

- Women-REV
- Men-REV
- Men-No REV
- Women-No REV

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**Etiology of Ischemia in Symptomatic Women: Angiographic Findings**

- WISE study: 7603 women
- 936 underwent Cath
  - 34% Normal coronaries
  - 24% Nonobstructive CAD
  - 42% Obstructive CAD
- Sex specific aspects of CAD
  - Hormonal state
  - Endothelial dysfunction
  - Microvascular disease
  - Inflammation
  - Arterial remodeling
### Symptoms, CAD and Events in Women

- Three groups of women
  - ASx, Sx w nl CORs, Sx + CAD <50%
  - 5 y events (death, MI, CV hosp, CVA)

### Using Sex Differences to Improve Cardiovascular Care in Women: What’s the Problem?

- Quality Cycle
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- Physiology and pathophysiology
  - Risk assessment, 1° prevention
  - Diagnosis of chest pain
  - PCI
  - ACS
  - Antithrombotic therapy
- Health care delivery/Sociology

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### PCI in Women: DES v BMS

- NCDR Cath PCI linked to CMS: 262,700 pts
- 43% female
- Adjustment: IPW model w 102 covariates
- Overall PCI outcomes W v M similar:
  - Death (13.8 v 14.1%; HR 0.98)
  - MI (4.5 v 4.3%)
  - Revascularization (19.3 v 20.9%)
- DES use less likely in women (HR 0.89)
- DES v BMS outcomes in women
  - Death (12.9% vs 18.1; OR 0.76 favoring DES)
  - Similar ↓ mortality in men receiving DES (p=0.4)

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### Women with ACS

- Older, smaller, lower BMI
- More diabetes, HTN
- Decreased creatinine clearance
- Less often have typical symptoms at presentation
- Multiple delays in care
  - At home, EMS, ER/triage
- Less likely to receive GL recommended care

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### Higher AMI Mortality In Women? Influence of Age

- 1460 pts w/ 1st MI, <80 y
- Mortality 18.5% v 8.3%

### Mechanisms of Acute MI: Sex-specific Phenotypes

- 298 MI autopsies
- Thrombus in 98%
- Distinct etiologies:
  - Plaque rupture
  - 82% M, 63% W
  - Plaque erosion
  - 18% M, 37% W
Women w ACS: Outcomes Similar After Adjusting for RF, Comorbidities, CAD
- 136,247 pts from 11 ACS RCTs; 28% F
- Overall 30 d mortality: 9.6% W vs 5.3% M
- OR 1.91 → 1.06 adjusting for clinical factors
  - STEMI OR 1.15, NSTEMI OR 0.77, UA OR 0.55
- 35,128 pt w angiographic data
  - No obstructive CAD: 15% W v 8% M
  - After adj for cath, little difference btwn M and W

CRUSADE: Under Use of Evidence-Based Medications (<24 h)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Male</th>
<th>Female</th>
<th>Adj. Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>91.6%</td>
<td>89.6%</td>
<td>0.93 (0.86–1.01)</td>
</tr>
<tr>
<td>Heparin</td>
<td>84.0%</td>
<td>80.0%</td>
<td>0.91 (0.86–0.97)</td>
</tr>
<tr>
<td>GP IIb-IIIa</td>
<td>38.6%</td>
<td>28.7%</td>
<td>0.86 (0.81–0.92)</td>
</tr>
<tr>
<td>Tn +</td>
<td>39.3%</td>
<td>30.5%</td>
<td>0.87 (0.81–0.92)</td>
</tr>
<tr>
<td>Tn -</td>
<td>29.0%</td>
<td>19.4%</td>
<td>0.81 (0.71–0.93)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>77.7%</td>
<td>75.8%</td>
<td>1.01 (0.95–1.06)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>41.0%</td>
<td>35.6%</td>
<td>0.97 (0.92–1.01)</td>
</tr>
</tbody>
</table>

Differential Benefit of GP IIb/IIIa in Men vs. Women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prevalence/Event Rate</th>
<th>Odds Ratio</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;60)</td>
<td>Men 45% / Women 39%</td>
<td>1.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Men 25% / Women 23%</td>
<td>1.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Men 10% / Women 8%</td>
<td>1.15</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

GP IIb/IIIa Inhibitors in NSTEMI
Troponin, Sex and Rx Effect (30-day death)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess Dose Rate</td>
<td>17.2%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Attributable Risk</td>
<td>7.4%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Major Bleeding: GP IIb/IIIa Dose, Sex
Summary: Women with ACS

Epidemiology of ACS:
- Women can present diagnostic challenges
- Women more likely to have ischemia w/o ‘CAD’
- ACS 30d mortality driven by RF, comorbidity, anatomy and may not be different
  ► Sex specific risk stratification essential

Guidelines for ACS are largely neutral by sex, but...
- Effectiveness of invasive strategy, IIb/IIIa different
  ► Assessing risk, biomarkers is critical (eg: +/- Tn)
- Women more likely to have bleeding complications
- Balance of ischemic benefit and bleeding risk is key
  ► Antithrombotic dosing by weight and CrCl is essential

Using Sex Differences to Improve Cardiovascular Care in Women: What’s the Problem?
- Quality Cycle
- Evidence base
- Physiology and pathophysiology
- Health care delivery/Sociology

Health Care Delivery and Disparities in Cardiovascular Care
- Women are less likely to:
  - Be referred to cardiovascular procedures
  - Receive Guideline recommended therapies
    - Aspirin, beta blockers upon admission or discharge
    - Anticoagulants, lipid lowering therapy
  - Receive disease management
    - Counseling to quit smoking
    - Cardiac rehabilitation
  - Receive anticoagulants, or in proper doses
  - Be adequately treated
    - HBP is controlled in 35% of women

Sociology: Increasing Awareness
- Still only 57% overall appreciate importance of risk
- Racial differences: White 68%, Black 31%, Hispanic 29%
Risk Underestimation Leads to Under Treatment of Women

![Bar chart showing the comparison between aware of guidelines and use guidelines in practice for different groups.]

No ‘Evidence Gap’ in Sociologic Issues in Quality of CV Care for Women

- Poorer access to care
  - Affordability, More un- or under-insured
  - Transportation needs
  - Caregiver role
- Lower SES, advancing age
- Lack of knowledge
  - Education and information/health literacy
  - Failure to seek care
  - Failure to act on prevention

Quality Cycle: CVD in Women

Improving Quality of Care for Women

DCRI Think Tank March 2007

- Research Concepts
  - Sex-specific, including sex, race, ethnicity, sociologic issues
- Evidence Base
  - Representation of women in RCTs
- Clinical Guidelines
  - Clarity regarding known differences and their impact
  - Focused statements regarding lack of data
- Clinical Practices
  - Proven key strategies, effectiveness
- Outcomes
  - Improved processes of care
  - Reduced morbidity
  - Reduced mortality

Current Opportunities to Improve Quality of Care in Women with CVD

- Risk stratification for primary prevention
  - Lifetime risk, Reynolds score instead of FRS
  - Use of CAC screening
- Primary prevention: ASA and lipid use
- Chest pain diagnosis: Symptoms, +Tests count
- Revascularization: DES underuse, lower mortality
- Acute Coronary Syndromes
  - Risk stratification with Troponin critical to Rx
  - Anticoagulation safety: Body size, Cr Cl adj
- Health care delivery/Sociology