GENDER DIFFERENCES IN CVD RISK MANAGEMENT: BIOLOGY, BIAS, OR BOTH?

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## Disclosure Statement

**Nanette Kass Wenger, M.D.**

<table>
<thead>
<tr>
<th>Name of Commitment</th>
<th>Name of Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Grants/Contracts/Trial</td>
<td>Abbott, Gilead Sciences, Merck, NHLBI, Pfizer</td>
</tr>
<tr>
<td>Steering Committee/Trial Adjudication</td>
<td></td>
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<tr>
<td>Committee/Trial Data Safety and Monitoring Board</td>
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<tr>
<td>Consultantship</td>
<td>Abbott Women's Advisory Board, Amgen, AstraZeneca, Gilead Sciences, Janssen Pharmaceuticals, Merck, Pfizer</td>
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</table>
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

CASE STUDY (1)

• A 45-year-old African American business woman, newly transferred to your community, presents at the office to establish care

• She reports well-controlled type 2 diabetes, diet-treated hypertension, and is asymptomatic

• Married, 3 children
  Moderate weight gain since birth of last child
  Recent increased smoking to control weight
  No regular physical activity

• Medication: metformin 500 mg BID
  ASA 81 mg QD
CASE STUDY (2)

- P.E. BP 160/90 mmHg, HR = 75/min
  BMI = 30 kg/m², waist circumference = 42 in
  No JVD, chest clear
  Normal S1, S2, + S4; sustained apex impulse
  Normal abdominal, extremity examination

- Laboratory data:
  Normal hemogram
  Hgh A1c = 6.5, FBS = 100 mg/dl
  Cr = 0.9 mg/dl
  LDL-C = 130/ mg/dl, HDL-C = 30 mg/dl, TG = 75 mg/dl
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

WHY IS HER HISTORY OF DIABETES SO IMPORTANT?
Increased CV Mortality Risk for Diabetic Women

  - Nondiabetic men ↓ 36.4%
  - Nondiabetic women ↓ 13.1%
  - Diabetic men ↓ 27%
  - Diabetic women ↑ 23%

- NHANES ischemic heart disease mortality
  - Nondiabetic men ↓ 43.8%
  - Nondiabetic women ↓ 20.4%
  - Diabetic men ↓ 16.6%
  - Diabetic women ↑ 10.7%
    - Black diabetic women ↑ 23%

Gu, JAMA 281:1291, 1999
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

Worse Outcomes: Diabetic Women vs Diabetic Men

- Excess CHD risk women > men with diabetes
  - 4- to 6-fold ↑ women
  - 2- to 3-fold ↑ men

- Relative risk fatal CHD 50% higher diabetic women vs diabetic men

- With initial MI, diabetes in women > men
  - 25.5% women
  - 16.2% men

- MI mortality with diabetes women > men
  - HR 9.4 women
  - HR 6.4 men

Manson, Arch Intern Med 151:1141, 1991
Juutilainen, Diabetes Care 27:2898, 2004
Hu, Diabetologia 48:856, 2005
Huxley, BMJ 332:73, 2006
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

Why Does Cardiovascular Disease Disparately Affect Women with Diabetes?

- Why paradoxic ↑ CV deaths in diabetic women
- Differential application RF control strategies, CHD therapies
- Differential effects of RF control strategies, CHD therapies
- Is it biology, bias, or both?
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

**Should Women Have Different Risk Assessment for Primary Prevention? (1)**

- 2 of 3 US women have at least 1 major coronary risk factor
  - Percentage increases with older age

- CHD death rates in younger adults, women > men, likely related to obesity epidemic

- Different gender values NCEP-ATP III

Wenger, J Women’s Health 8:465, 1999
Ford, JACC 50:2128, 2007
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

**Should Women Have Different Risk Assessment for Primary Prevention? (2)**

- **NCEP-ATP III**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at risk</td>
<td>≥55</td>
<td>≥45</td>
</tr>
<tr>
<td>Premature CHD</td>
<td>&lt;65</td>
<td>&lt;55</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>&lt;50 mg/dL</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Increased waist circumference</td>
<td>&gt;35 in</td>
<td>&gt;40 in</td>
</tr>
</tbody>
</table>

*NCEP-ATP III, Circulation 106:3143, 2002*
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

WHY IS SMOKING CESSATION SO IMPORTANT FOR WOMEN?
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

**Coronary Risk Factors: Smoking**

- CHD risk 25% higher in women than men smokers
- Cigarette smoking triples MI risk for women
- ↓ smoking cessation among women
- Goal for our patient: smoking cessation

*Prescott, BMJ 316:1043, 1998*
*Huxley, Lancet 378:1297, 2011*
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

WHY IS BLOOD PRESSURE CONTROL SO IMPORTANT FOR OUR PATIENT?

ANY PREFERRED MEDICATION?


**Gender Differences in CVD Risk Management: Biology, Bias, or Both?**

**Coronary Risk Factors: Hypertension**

- Hypertension a stronger risk factor for women than men
  - O.R. hypertension for first MI – 2.95 for women, 2.32 for men

- Higher percentage of older women than men have hypertension

- Disparities in cardiovascular health
  - ↑ hypertension African American women
  - Highest CHD, CVD mortality in African American women

- Our patient: ACE inhibitor preferred drug for hypertension in diabetic patients – goal BP 140 mmHg

*Rich-Edwards, NEJM 332:1758, 1995*
*Yusuf, Lancet 364:937, 2004*
*Wenger, J Women Health 8:465, 1999*
*Ford, JACC 50:2128, 2007*
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

WHY IS MANAGEMENT OF OVERWEIGHT, SEDENTARY LIFESTYLE SO IMPORTANT?
Coronary Risk Factors: Overweight, Sedentary Lifestyle

- Almost 2 of 3 U.S. women overweight or obese
- Physical inactivity most prevalent risk factor for women
- Weight management, physical activity favorably affect diabetes
- Goals our patient
  - BMI < 25 kg/m²
  - Physical activity – aerobic activity 30 min daily, minimum 150 min/wk
  - resistance training 2x/wk

Diabetes Care, 36:Supplement, 2013
WHAT ABOUT LIPID CONTROL? GOALS? DRUGS?
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

Coronary Risk Factors: Lipids

- ↓ HDL-C, ↑ TG better predicts CHD in women than men.

- Goals diabetic women
  - LDL-C: < 100 mg/dl
  - HDL-C: > 50 mg/dl
  - TG: < 150 mg/dl

- Initial therapy: statin

Diabetes Care, 36: Supplement, 2013
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

WHY SHOULD A PREGNANCY HISTORY HAVE BEEN PREVIOUSLY ADDRESSED IN THIS PATIENT?
Coronary Risk Factors: Pregnancy

- Patient reports pre-eclampsia with first pregnancy, gestational diabetes with third pregnancy

- Pregnancy complications and CHD risk
  - Pregnancy a cardiovascular, metabolic stress
  - Preeclampsia, gestational hypertension ↑ CHD risk
    - 2.6 x ↑ fatal myocardial ischemic events
    - 3-6 x ↑ risk subsequent hypertension
    - 3 x ↑ risk subsequent diabetes
  - Gestational diabetes → 7 x ↑ risk type 2 DM

Bellamy, BMJ 335:974, 2007
Roberts, Women’s Health Issues 20:304, 2010
Lykke, Hypertension 53:944:2009
Risk Stratification: Hypertensive Disorders of Pregnancy

- Detailed history pregnancy complications - routine component of CV risk assessment for women
  - Enable earlier intervention to prevent CVD risk

- Metabolic stress of pregnancy → potential for early prediction of future CV risk
  - ? shared RF preeclampsia, CVD

- Preeclampsia → CVD risk
  - 3-4 x ↑ hypertension
  - 2 x ↑ ischemic heart disease, stroke
  - Residual endothelial dysfunction, association with ↑ CAC

Mosca, Circulation 123:1243, 2011
Bellamy, BMJ 335:974, 2007
McDonald, Am Heart J 156:918, 2008
Magnussen, Obstet Gynecol 114:961, 2009
Roberts, Womens Health Issues 20:304, 2010
Fraser, Circulation, published online February 17, 2012
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

- Should I begin menopausal hormone therapy? My menopausal symptoms are minimal.
- Will hormones improve my coronary risk?
**Gender Differences in CVD Risk Management: Biology, Bias, or Both?**

### WHI Results

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>Decreased Risk</th>
<th>No Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen plus progestin - July 2002</td>
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<td></td>
</tr>
</tbody>
</table>

- Heart attack 29%
- Breast cancer 26%
- Blood clots 2x
- Strokes 41%
- Dementia
- Ovarian Cancer

- Hip fractures 34%
- Colorectal cancer 37%
- Cancer of uterine lining

- Quality of life

<table>
<thead>
<tr>
<th>Estrogen alone – March 2004</th>
</tr>
</thead>
</table>

- Strokes
- Probable dementia or memory loss

- Hip fractures

- Breast cancer
- Heart disease

WHI, Women’s Health Initiative National Institutes of Health

Anderson, *JAMA* 291:1701, 2004
Menopausal Hormone Therapy

- Menopausal hormone therapy not recommended for the primary or secondary prevention of cardiovascular disease.

*Mosca, Circulation 123:1243, 2011*
*USPSTF, Ann Intern Med 158:47, 2013*
### Special Contributors to CVD Risk in Women

- Depression and other psychosocial risk factors
- Autoimmune disease
  - Lupus erythematosus
  - Rheumatoid arthritis
- Consider as “at risk” women and screen for CVD risk factors

*Salmon, Am J Med 121(10 suppl 1):S3, 2008*
*Mosca, Circulation 123:1243, 2011*
Aspirin for Primary Prevention

- Aspirin routinely recommended for primary prevention CHD in men but not women
- Women’s Health Study
  - 39,876 healthy low risk women > age 45
  - Prevents stroke (not MI or CV death) < age 65
    - potential for GI bleeding
  - Prevents stroke, MI, CV death > age 65 but ↑ risk GI bleeding
    - individualize
- Men – Physicians’ Health Study
  - Benefit MI, not stroke
- Our patient: aspirin reasonable; diabetes and other coronary risk factors

Ridker, NEJM 352:1293, 2009
Diabetes Care 36:Supplement, 2013
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

Why Does Cardiovascular Disease Disparately Affect Women with Diabetes?

EVIDENCE FOR BIOLOGY
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

**Effect of Interventions, Comorbidities: Diabetic Women**

- Modest weight gain ↑ RR diabetes in women almost 3 fold
  - Small amount of weight loss (>5 kg) ↓ diabetes risk

- ↓ Age at diagnosis of diabetes in women in recent years
  - ? Related to obesity epidemic

- Moderate physical activity →↓ risk CHD, stroke in diabetic women

- Metabolic syndrome
  - ↑ in women with PCOS
  - ↑ in menopausal women

- Diabetic women →↑ PCOS risk
  PCOS women →↑ diabetic risk
  - Complicating metabolic syndrome

Colditz, Ann Intern Med 122:481, 1995
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

↑ Adverse CV Risk Profile Diabetic Women

• Obese diabetic women (but not men) have impaired endothelial-dependent vasodilation

• Diabetic women have prothrombotic coagulation profile

• Diabetic women > diabetic men
  • ↓ HDL-C
  • Small particle size LDL-C
  • ↑ TG
  • Consequences of this dyslipidemia diabetic women > nondiabetic women

• Abdominal obesity diabetic women > diabetic men, 24.4% vs 15.6%
  • Obesity →↑ hypertension, dyslipidemia, insulin resistance, CRP

Steinberg, Circulation 101:2040, 2000
Grundy, Circulation 105:2231, 2002
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

*Why Does Cardiovascular Disease Disparately Affect Women with Diabetes?*

**EVIDENCE FOR BIAS**
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

Gender Disparity in Intensity of CV Risk Reduction

- Coronary RF present in diabetic women before diabetes diagnosed
  - Nurses’ Health Study
  - RR CHD with diabetes 2.82

- Diabetic women < men treatment of cardiac risk factors
  - ↓ HbA\textsubscript{1c} control
  - ↓ lipid lowering medication
    - ↓ LDL-C levels < 100 mg/dl
  - ↓ aspirin (with and without CHD)
  - ↓ BP at goal < 130/80 mmHg

Hu, Diabetes Care 25:1129, 2002
Wexler, Diabetes Care 28:514, 2005
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

Are Women with CHD and Diabetes Less Likely to Receive Appropriate Care? (1)

- 2005 Health Effectiveness Data and Information Set (HEDIS) CVD and diabetes measures
  - Gender disparities for ambulatory preventive care

- Suboptimal cholesterol control common after acute cardiac events, both diabetic and nondiabetic women
  - 2 commercial managed care plan measures
  - 5 Medicare managed care plan measures

- Uninsured patients - ? More vulnerable – not analyzed

- Eliminating gender disparities in cholesterol control may potentially ↓ 4800-10,000 cardiac events annually

Chou, Women’s Health Issues 17:139, 2007
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

Are Women with CHD and Diabetes Less Likely to Receive Appropriate Care? (2)

- Quality of CV and diabetes care in managed care enrollees
  - 11 HEDIS measures

- LDL control in diabetic persons
  - 19% less likely Medicare women vs men
  - 16% less likely commercial plan women vs men

- Relevance
  - Elderly women represent fastest-growing population segment
  - β-blocker prescription after MI and ACE inhibitor prescription for heart failure also lower in women vs men

Bird, Women's Health Issues 17:131, 2007
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

**Gender Disparities in Office-Based Care**

- Commercial managed care settings
  - HEDIS quality measures
  - ↓ Lipid control in women
    - 5-9% disparities in women with diabetes, CV disease, or both
  - Minority ethnicity, ↓ SES also adversely affected care

- Disparities in Medicare managed care
  - HEDIS quality measures
  - ↓ Cholesterol control women vs men
  - African-American diabetic patients ↑ gaps in care, ↓ health outcomes vs white diabetic patients
  - African-American diabetic women most disadvantaged

*Chou, Women’s Health Issues 17:120, 2007*
*Chou, Women’s Health Issues 17:150, 2007*
Gender Differences in CVD Risk Management: Biology, Bias, or Both?

Worse Outcomes Diabetic Women: Biology, Bias, or Both

- Prevalence diabetes equal for U.S. women and men, 10.2% vs 11.2%
- BUT
  - More adverse CV risk profiles diabetic women vs diabetic men
    - Obesity
    - Hypertension
    - Atherogenic dyslipidemia
  - ↑ Severity CV risk factors diabetic women vs diabetic men
  - ↑ Clustering comorbidities diabetic women
  - ↓ Risk factor treatment/control diabetic women vs diabetic men
  - ↓ Prescription statins, aspirin for CV prevention in diabetic women
- Likely reflects BOTH biology and bias

Wexler, Diabetes Care 28:514, 2005
Huxley, BMJ 332:73, 2006
Gender Differences in Cardiovascular Disease