Women with diabetes face a higher risk of CVD compared to diabetic men. Women with ischemic heart disease are less likely to have obstructive CAD yet face a higher adverse event risk compared to men. The American College of Cardiology/American Heart Association (ACC/AHA) released a clinical practice guideline in November 2013 to optimize risk assessment and optimal medical treatment of women and men with and without diabetes to reduce cardiovascular risk in adults. The ACC/AHA Guidelines for management of cholesterol will be specifically addressed for women. Revascularization will be also be addressed specially for women.

References:

Women, Diabetes and CVD

- Epidemiologic considerations
- Cardiovascular impact of biologic and metabolic diabetic abnormalities
- Evaluation and risk stratification
- Clinical considerations for optimal management

New female majority Yentl and Yentl Syndrome

WISE
NHLBI
AHA

Begin

1984-1996: 12 years to recognize/take action

Coronary Heart Disease Mortality Among Young Adults in the US: 1980-2002 (Ford et al JACC 2007, 50:2128)

- Included women and men aged 35 and older using ICD-9 codes in US Census data
- Mortality from CHD fell 52% in men and 49% in women
- Improved mortality each decade from 1980s, 1990s until the 2000s
- Age analysis demonstrates:
  - Leveling off of mortality decline in men 35-54 yrs in the 2000s
  - Actual increase in mortality in women 35-54 yrs, and specifically among women 35-44 yrs (p<0.05)
- Results are consistent with a UK study (O’Flaherty et al Heart 2007;10:1136).
- Concomitant with increased use of thrombolysis, PCI, statins and antithrombotics (ASA), yet adverse nutrition, physical activity, obesity, diabetes and smoking trends.
Diabetes and CVD

- 24 million Americans have diabetes
  - 18 million diagnosed
  - 6 million undiagnosed
- At least 65% of patients with diabetes die of heart disease or stroke
- Heart disease death rates
  - 2 to 4 times higher in diabetes patients than in those without diabetes

Rancho Bernardo Study: Angina and Mortality by Diabetes Status

![Graph showing CHD Death in Women and Men With Angina](image)

- Multivariate Hazard Ratio for Heart Disease Mortality in CHD Death in Women and Men With Angina
  - Normal Glucose (n=66/33)
  - Impaired Glucose Tolerance (n=54/18)
  - Type 2 Diabetes (n=22/10)

- 1.91
- 1.07
- 1.65
- 3.55

Gender Differences in Obstructive CAD on Elective Diagnostic Angiography

![Graph showing Gender Differences in Obstructive CAD on Elective Diagnostic Angiography](image)

- Incidence (per 1000 person-years)
- Age (years)
- 45-54, 55-64, 65-74, 75-84, 85-94

- Women
  - 4.0
  - 3.1
  - 5.3
  - 5.8
  - 4.2
- Men
  - 6.9
  - 5.6
  - 10.1
  - 10.5
  - 7.6

Mechanisms and Manifestations of Ischemia: Impact on CVD Risk in Women

- Endothelial dysfunction
- Smooth muscle dysfunction (Raynaud’s, migraine, coronary artery spasm)
- Inflammation
  - Plasma markers
  - Vasculitis (Takayasu’s, rheumatoid, SLE, CNSV, giant cell, etc)

Women, Diabetes and CVD

- Epidemiologic considerations
- Cardiovascular impact of biologic and metabolic diabetic abnormalities
- Evaluation and risk stratification
- Clinical considerations for optimal management

Gender Differences in Ischemic Heart Disease in Women

<table>
<thead>
<tr>
<th>Structural Features (macro- and micro-vessels)</th>
<th>Functional Features (macro- and micro-vessels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smaller size</td>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Increased stiffness (fibrosis, remodeling, etc)</td>
<td>Smooth muscle dysfunction (Raynaud’s, migraine, coronary artery spasm)</td>
</tr>
<tr>
<td>More diffuse disease</td>
<td>Inflammation</td>
</tr>
<tr>
<td>More plaque erosion versus rupture</td>
<td>Plasma markers</td>
</tr>
<tr>
<td>Microemboli, rarefaction (drop out), disarray, etc</td>
<td>Vasculitis (Takayasu’s, rheumatoid, SLE, CNSV, giant cell, etc)</td>
</tr>
</tbody>
</table>
Overarching Working Model of Ischemic Heart Disease Pathophysiology in Women

Shaw LJ, et al.
J Am Coll Cardiol.

Model of Microvascular Angina in Women

Shaw LJ, et al.
J Am Coll Cardiol.

Gender Effects on Coronary Flow Reserve

- Impaired CFR (<2.0) common in women and men regardless of symptoms (52% versus 56%; \( P = 0.002 \) for equivalence)
  - Chest pain (\( P = 0.02 \) for equivalence)
  - No chest pain (\( P = 0.10 \) for equivalence)
- Multivariate predictors of impaired CFR
- Tobacco use (\( P = 0.001 \))
- Low CFR carries adverse prognosis, even with normal perfusion and CAC=0

Citation: Murthy V, et al.
J Am Coll Cardiol.

CFR: coronary flow reserve; MBF: myocardial blood flow.

Women, Diabetes and CVD

- Epidemiologic considerations
- Cardiovascular impact of biologic and metabolic diabetic abnormalities
- Evaluation and risk stratification
- Clinical considerations for optimal management

Diagnostic Evaluation Algorithm for Symptomatic Women Presenting With Suspected IHD

Initial Exercise Treadmill Testing Strategy

No Resting ST Segment Abnormalities

Assess Routine ADL or DASI

Abnormal or Indeterminate ECG

Limited

Initial Imaging Strategy

Stress Imaging

Intermediate-High IHD Risk

Low Risk

Intermediate-High Risk

High Risk

Standardized Reporting of Low-to-High Risk Abnormalities

Women Study 2-Year MACE Rate: ETT Versus Exercise MPI

- No incremental benefit of an initial diagnostic strategy of exercise MPI versus ETT
  - Relative hazard for MACE
    - 1.3 (95% CI 0.5-3.5) for the exercise MPI versus ETT (\( P = 0.59 \))
  - Index testing costs were higher for exercise MPI versus ETT (\( P = 0.001 \))
  - Overall cumulative diagnostic cost savings
    - 48% with ETT versus exercise MPI (\( P < 0.001 \))

Shaw LJ, et al.
Circulation.
2011;124;11239-11249.

ETT: exercise treadmill test.
MPI: myocardial perfusion imaging.
**DIAD Study: Screening and Cardiac Outcomes in Asymptomatic Diabetics With CAD**

- Randomized, controlled trial
  - Type 2 diabetes with no symptoms of CAD (n=1123)
- Randomized groups
  - Screened (adenosine-stress radionuclide MPI)
  - Not screened
- Cardiac event rates over 4.8 years
  - Low overall rate
  - Not significantly reduced by MPI screening for myocardial ischemia

**Implications**
- Routine screening of asymptomatic patients with diabetes is not justified

**Gender Differences in Obstructive CAD on Elective Diagnostic Angiography**

- Women had a higher risk profile at baseline compared with men
- Women tended to have less severe or less extensive disease on coronary angiography despite a longer duration of diabetes

**Diabetes and SIHD**

- Epidemiologic considerations
- Cardiovascular impact of biologic and metabolic diabetic abnormalities
- Evaluation and risk stratification
- Clinical considerations for optimal management
  - Optimal Medical Therapy (OMT): ASA, statin, ACE/ARB, BB
  - Therapeutic Lifestyle Change (TLC): Nutrition, Physical Activity, Weight Management
  - HTN, DM and Chol – treat to goal???
Proportional Effects of Treatment Strategies on Mortality

- Antiplatelet
- Beta Blocker
- Calcium
- Statin
- Fibrinolytics
- tPA vs. SK
- Thrombolytic
- ACE Inhibitors

Women vs. Men

Favors Treatment vs. Control

OR (95% CI)

0 0.5 1 1.5 2

NHANES: Trends in Goal Attainment in Adults With Type 2 Diabetes

- HbA1c (<7%)
- BMI (<25 kg/m²)
- LDL-C (<100 mg/dL)
- Waist Circumference (<102-cm; <88-F)

Overall

Non-CVD

With CVD

Δ Weight >7%

Good risk factor reduction
Associated with weight loss

Look AHEAD: Study design

- Usual medical care + lifestyle intervention* for 4 years, with maintenance counseling thereafter
  - * ≥ 7% mean weight loss with hypocaloric diet + pharmacologic therapy ± exercise ± moderate physical activity
  - DIET: 1200-1500 kcal/day (<250 lbs) or (500-1800 kcal/day (≥250 lbs)
  - MI = myocardial infarction

Primary endpoint: CV death, nonfatal MI, nonfatal stroke

Changes in Weight, Physical Fitness, Waist Circumference, and Glycated Hemoglobin Levels during 10 Years of Follow-up.

Look AHEAD: Patients meeting risk factor goals at 1 year

Usual medical care

+ diabetes support and education for 4 years

Total follow-up 11.5 years

Look AHEAD Research Group


Look AHEAD Research Group.


Look AHEAD: the first outcome RCT to achieve and maintain weight loss in at-risk CVD subjects
Look AHEAD: No CVD outcome benefit with weight loss – why?

Cumulative Hazard Curves for the Primary Composite End Point.

### Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (40-80 mg)</td>
<td>Atorvastatin 10-20 mg</td>
<td>Atorvastatin 5 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Pravastatin 40 mg</td>
<td>Pravastatin 10 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>PPARs 2-4 mg</td>
<td>PPARs 1 mg</td>
</tr>
</tbody>
</table>

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

### New Perspective on LDL–C & Non-HDL–C Goals

- Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL–C goals
- Unknown net benefit from treat-to-target strategy
  - Non-statin drugs added to statin to reach goal
  - Unknown magnitude of additional benefit (IMPROVE-IT results suggest it is small)
  - Known rates of additional adverse effects and cost
- May result in suboptimal statin therapy
  - 2nd prevention LDL 95 on pravastatin 10 mg
  - Safety concerns: Reduce dose of atorvastatin from 80 to 20 mg to add ezetimibe, niacin or fibrates

### Now That HPS2-THRIVE and IMPROVE-IT are Out (and PCSK9 coming), Don’t We Have to Change the Guidelines? - NO

- “Clinicians treating high risk patients who have a less than anticipated response to statins, who are unable to tolerate a less than recommended intensity of a statin or who are completely statin intolerant, may consider the addition of non-statin cholesterol lowering therapy…”
- “In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug-drug interactions and consider patient preferences.”
- Nothing informative on LDL goals
**ACCORD Trial: Intensive Blood Pressure Control in Type 2 Diabetes Mellitus**

- Prospective study
  - Type 2 diabetes patients at high risk for cardiovascular events (n=7233)
- Randomized groups
  - Intensive systolic BP reduction (<120 mm Hg)
  - Standard systolic BP reduction (<140 mm Hg)
- Mean follow-up: 4.7 years
- Intensive BP control
  - No evidence this strategy reduces the rate of composite outcomes of major cardiovascular events

**Outcomes After 1 Year**

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Events (%/Year)</th>
<th>All-cause death</th>
<th>Stroke</th>
<th>Heart failure</th>
<th>Renal failure or dialysis</th>
<th>Serious adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>1.9</td>
<td>1.3</td>
<td>0.3</td>
<td>0.7</td>
<td>2.5</td>
<td>3.3</td>
</tr>
<tr>
<td>&lt;140</td>
<td>2.1</td>
<td>1.2</td>
<td>0.5</td>
<td>0.8</td>
<td>2.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**BARI 2D Study**

- Randomized controlled trial
  - 2 treatment strategies tested in a 2 x 2 factorial design
  - Patients in whom angina symptoms were controlled (82%) or asymptomatic (18%)
- Comparisons
  - Prompt coronary revascularization versus intensive medical therapy, with intensive medical therapy alone with later revascularization only for clinical indications
  - Choice of the intended PCI or CABG procedure was selected by the treating physicians before randomization
- Insulin sensitizing strategy to an insulin provision strategy for glycemic management with target HbA1c of <7.0%

**BARI 2D Study: Medical Therapy Versus Revascularization**

**Moderate & high intensity statins**

Similar benefit (RRR) and harm (NNH) in women and men

Number needed to harm (NNH) is lower for moderate intensity statins (simva, prav, lovastatin; more research needed in low potency statins in primary prevention who risk groups for longer term risk reduction vs harm of increased diabetes.
BARI 2D Study: Death/MI/Stroke Among Medical Therapy Assigned Patients

<table>
<thead>
<tr>
<th>Baseline Characteristics by Stratum</th>
<th>PCI (n=1605)</th>
<th>CABG (n=763)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.0</td>
<td>63.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>67.8</td>
<td>75.8</td>
</tr>
<tr>
<td>Proximal LAD disease (%)</td>
<td>10.3</td>
<td>19.4</td>
</tr>
<tr>
<td>3-vessel disease (%)</td>
<td>20.3</td>
<td>52.4</td>
</tr>
<tr>
<td>Total occlusions (%)</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td>Myocardial jeopardy index (%)</td>
<td>37.2</td>
<td>59.7</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50% (%)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Prior revascularization (%)</td>
<td>28.6</td>
<td>13.0</td>
</tr>
</tbody>
</table>


COURAGE Trial: Optimal Medical Therapy + PCI for Stable Coronary Disease

Follow-Up: 2.5 to 7 Years

Follow-Up: 2.5 to 7 Years

COURAGE Study: Gender-Based Risk of Death or MI

Relative Hazard Ratio for Death or Non-Fatal MI

Overall Baseline Characteristics

Randomized trial on PCI + DES versus CABG

Overall Baseline Characteristics

Optimal medical therapy

Optimal medical therapy + PCI

Primary outcome

Composite of death of any cause, nonfatal MI, or nonfatal stroke

No Diabetes (n=1468)

Diabetes (n=766)

COURAGE Trial: All-Cause Death by Diabetes Status

FREEDOM Trial: Multivessel Revascularization in Type 2 Diabetes

Lesions (number) 5.65 5.74


Favors OMT Better

Favors OMT+PCI Better

Favorability

Hazard Ratio

Hazard Ratio

Hazard Ratio

Favorability

Hazard Ratio

Hazard Ratio

Favorability

Hazard Ratio

Hazard Ratio

Favorability

Hazard Ratio

Hazard Ratio
FREEDOM Trial: Multivessel Revascularization in Type 2 Diabetes

5-Years After Randomization

Women, Diabetes and CVD: Summary

- Cardiovascular disease is the leading cause of death in women
  - Diabetes is the double whammy for women (4-fold increase)
  - Angina is a more common manifestation
- Microvascular angina: angina and ischemia without epicardial CAD in women is prevalent and significant
- Treatments effective for symptom and ischemia management in symptomatic women with evidence of ischemia and obstructive or non-obstructive CAD
- All patients with angina, aggressive risk factor modification and optimized medical management must be instituted
- CABG is preferred in women and men with DM for revascularization for mortality benefit