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 Cardiovascular Disease

ADA 63rd Annual Advanced Postgraduate Course
March 4, 2016
San Francisco, California

C. Noel Bairey Merz MD
Medical Director and
Women’s Guild Endowed Chair
Barbra Streisand Women’s Heart Center
Cedars-Sinai Heart Institute

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

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  - 2 to 4 times higher in diabetes patients than in those without diabetes

Rancho Bernardo Study: Angina and Mortality by Diabetes Status

CHD Death in Women and Men With Angina

Men (n=822) and women (n=1184) 50-59 years of age at study entry. Average follow-up 13.2 years.

*P < 0.05.

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

Overarching Working Model of Ischemic Heart Disease Pathophysiology in Women
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

- Structural Features (macro- and microvessels)
  - Smaller size
  - Increased stiffness (fibrosis, remodeling, etc)
  - More diffuse disease
  - More plaque erosion versus rupture
  - Microemboli, rarefaction (drop out), disarray, etc

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

Model of Microvascular Angina 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)

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<0.03 for equivalence) 53% versus 62%
- - No chest pain (P<0.10 for equivalence) 39% versus 44%
- Multivariate predictors of impaired CFR
  - Tobacco use (P<0.0001)
  - Low CFR carries adverse prognosis, even with normal perfusion and CAC=0

REACH Registry: 4-Year Incidence of Cardiovascular Death/MI/Stroke

- Adjusted HR

Women, Diabetes and CVD

- Epidemiologic considerations
- Cardiovascular impact of biologic and metabolic diabetic abnormalities
- Evaluation and risk stratification
- Clinical considerations for optimal management
**BARI 2D Study: Type 2 Diabetes and CAD by Gender**

- **Baseline Characteristics**

<table>
<thead>
<tr>
<th>Female (n=702)</th>
<th>Male (n=1668)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>34.2 ± 6.0</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>73%</td>
</tr>
<tr>
<td>Current insulin use (%)</td>
<td>36%</td>
</tr>
<tr>
<td>NYHA ≥2 (%)</td>
<td>14%</td>
</tr>
<tr>
<td>History (%)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>22%</td>
</tr>
<tr>
<td>CHF</td>
<td>5%</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>45%</td>
</tr>
<tr>
<td>Proximal CAD disease (%)</td>
<td>11%</td>
</tr>
<tr>
<td>Totally occluded vessel (%)</td>
<td>16%</td>
</tr>
<tr>
<td>3 diseased regions (%)</td>
<td>23%</td>
</tr>
</tbody>
</table>

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

Look AHEAD: Study design

Look AHEAD: Patients meeting risk factor goals at 1 year

Look AHEAD: the first outcome RCT to achieve and maintain weight loss in at-risk CVD subjects

4 Statin Benefit Groups
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>Daily dose lowers LDL-C on average, by approximately 50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 35% to 50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;50%</td>
</tr>
<tr>
<td>Atorvastatin 20 (20) mg</td>
<td>Pravastatin 10 (10) mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td>Pravastatin 40 (40) mg</td>
<td>Fluvastatin 10-20 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td>Simvastatin 20-40 mg</td>
<td>Fluvastatin 20-40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.

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.

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

Controversies – Cholesterol

<table>
<thead>
<tr>
<th>Criticism</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why not continue to treat to target?</td>
<td>Unknown benefit for titration compared to known benefit:risk with fixed dose statin</td>
</tr>
<tr>
<td>What about HDL, non-HDL and TG?</td>
<td>Single and multi-drug trials do not support these targets or agents</td>
</tr>
<tr>
<td>What about uncertain risk (older asymptomatic, younger with family history)</td>
<td>LDL-C ≥160 mg/dL, lifetime risk, FH, hsCRP&gt;2, CAC&gt;300, ABI can be used</td>
</tr>
</tbody>
</table>

Number needed to harm (NNH) is lower for moderate intensity statins (simva, prava, lovastatin; more research needed) in low potency statins in primary prevention lower risk groups for longer term risk reduction vs harm of increased diabetes.
**ACCORD Trial: Intensive Blood Pressure Control in Type 2 Diabetes Mellitus**

- Prospective study
  - Type 2 diabetes patients at high risk for cardiovascular events (n=4733)
- 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>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>1.9 CV death/MI/Stroke</td>
</tr>
<tr>
<td>&lt;140</td>
<td>1.3 All-cause death</td>
</tr>
<tr>
<td></td>
<td>0.3 Sudden death</td>
</tr>
<tr>
<td></td>
<td>0.7 Heart failure</td>
</tr>
<tr>
<td></td>
<td>2.5 Renal failure or dialysis</td>
</tr>
<tr>
<td></td>
<td>3.3 Serious adverse events (%)</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: Gender-Based Outcomes**

**Death/MI/Stroke (Primary Outcome)**

- HR (95% CI)
  - Women Versus Men
  - Male (n=1666)
  - Female (n=702)

**Subsequent Revascularization (Secondary Outcome)**

- HR (95% CI)
  - Women Versus Men
  - Male (n=1666)
  - Female (n=702)


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

- Patients (n=2287)
- AHA/ACC Class I/II indications for PCI
- Suitable coronary artery anatomy
- 27% reduction in 2 proximal epicardial vessels
- Objective evidence of ischemia
  - >70% stenosis in >1 proximal epicardial vessel
  - CCS class III angina without provocation testing
- Randomization 1:1
- Follow-Up: 2.5 to 7 Years
- Primary Outcome: All-cause mortality, non-fatal MI
- Secondary Outcomes: Target MI, CHF, non-fatal MI, hospitalization
- Median follow-up: 4.6 years

COURAGE Study: Gender-Based Risk of Death or MI

**Relative Hazard Ratio for Death or Non-Fatal MI**

- Hazard Ratio
  - Overall
  - Men
  - Women

COURAGE Study: All-Cause Death by Diabetes Status

- All-Cause Death or MI at Year 4.5


FREEDOM Trial: Multivessel Revascularization in Type 2 Diabetes

- Randomized trial on PCI + DES versus CABG
  - Type 2 diabetes (HbA1c >7.8)
  - Multivessel CAD (>70% stenosis)
- Median follow-up 3.8 years
- All patients received guideline directed control of LDL, systolic BP, HbA1c
- Primary outcome
  - Composite of death of any cause, nonfatal MI, or nonfatal stroke

<table>
<thead>
<tr>
<th>Overall Baseline Characteristics</th>
<th>PCI (n=933)</th>
<th>CABG (n=947)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.2</td>
<td>63.1</td>
</tr>
<tr>
<td>Male (%)</td>
<td>73.2</td>
<td>69.5</td>
</tr>
<tr>
<td>History of (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>26.2</td>
<td>25.0</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>31.9</td>
<td>29.5</td>
</tr>
<tr>
<td>3-vessel disease (%)</td>
<td>62.1</td>
<td>64.0</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.7</td>
<td>66.6</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26.2</td>
<td>24.1</td>
</tr>
<tr>
<td>Low ≤32 (%)</td>
<td>34.7</td>
<td>36.2</td>
</tr>
<tr>
<td>Intermediate (%)</td>
<td>46.2</td>
<td>43.3</td>
</tr>
<tr>
<td>High ≥33 %</td>
<td>19.2</td>
<td>20.6</td>
</tr>
<tr>
<td>Lesions (number)</td>
<td>5.65</td>
<td>5.74</td>
</tr>
</tbody>
</table>

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
- Treatments effective for symptom and ischemia management in symptomatic women with evidence of ischemia and obstructive or nonobstructive CAD
- All patients with angina, aggressive risk factor modification and optimized medical management must be instituted