HYPERTENSION In Women

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*Disclosures: Consultant to Fresenius Medical Care, Pfizer, Celgene, Shire Human Genetics

More Women Die from Heart Disease than Men

Heart Disease Mortality in Women and Men
Absolute Number of Deaths, 1979-2004

64% of women vs. 50% of men had no previous symptoms

Calendar Years

Deaths in Thousands

Males
Females

Source: AHA 2007

Mortality Rates for CVD and CVD in 5yr Age Categories


Male & Female Mortality Rates for CVD (%)


Post-MI Risks Are Substantial for Women

38% of women will die within one year post-MI

Adapted from Thom T et al. Circulation. 2006;113:e85-e151.
Are women represented well in CVD clinical trials?

- In 2004, the AHA expanded its focus on female-specific clinical recommendations and sponsored the "Evidence-Based Guide- lines for Cardiovascular Disease Prevention in Women" and updated them in 2007.

- Initially, the guidelines challenged the conventional wisdom that women should be treated the same as men, primarily related to concerns about the lack of representation of women in clinical trials.


Prevalence of Hypertension by Age

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-34</td>
<td>51.5</td>
<td>56.8</td>
</tr>
<tr>
<td>35-44</td>
<td>25.1</td>
<td>29.2</td>
</tr>
<tr>
<td>45-54</td>
<td>37.6</td>
<td>42.3</td>
</tr>
<tr>
<td>55-64</td>
<td>54.3</td>
<td>60.3</td>
</tr>
<tr>
<td>65-74</td>
<td>64.7</td>
<td>70.2</td>
</tr>
<tr>
<td>75+</td>
<td>69.3</td>
<td>75.3</td>
</tr>
</tbody>
</table>

ET system is a physiologically important regulator of sodium balance and blood pressure.


Why the differential effect in later years?

Sex hormones influence systems that regulate blood pressure.

Are there other differences?
RAAS Activation Without the Protective Effect of Endogenous Estrogen

Loss of Estrogen Upregulates Components of the RAAS

Increased number of AT₁ receptors
Increased expression and activity of ACE
Elevated levels of circulating angiotensin II

Menopause activates the RAAS through up-regulation of both ACE activity and AT₁ receptor expression

Increased in Salt Intake Leads to Increases in Blood Pressure in Postmenopausal Women

Menopause Increases Salt-sensitivity

Estrogen Is a Potent Vasodilator

Abrupt Interruption of Estrogen Plays a Key Role in Postmenopausal Hypertension

Estrogen relaxes vascular smooth muscle by increasing PGII and NO levels; decreases vasoconstriction by acting as a calcium antagonist

Educate Patients About the Warning Symptoms of a Heart Attack

Women Receive Fewer Interventions to Prevent and Treat Heart Disease

- Less cholesterol screening
- Fewer lipid-lowering therapies
- Less use of heparin, beta-blockers and aspirin during myocardial infarction
- Less antiplatelet therapy for secondary prevention
- Fewer referrals to cardiac rehabilitation
- Fewer implantable cardioverter-defibrillators compared to men with the same recognized indications

Women and CVD: Are they Managed the same way?

- Chest pain, discomfort, pressure or squeezing are the most common symptoms for men and women
- Women are somewhat more likely than men to experience other heart attack symptoms, including:
  - Unusual upper body pain or discomfort in one or both arms, the back, shoulder, neck, jaw, or upper part of the stomach
  - Shortness of breath
  - Nausea/Vomiting
  - Unusual or unexplained fatigue (which may be present for days)
  - Breaking out in a cold sweat
  - Light-headedness or sudden dizziness


Sources: Mosca et al. 2010.
Encourage Patients To *Make The Call*.

- Only 53% of women said they would call 9-1-1 if experiencing the symptoms of a heart attack.
- However, 79% said they would call 9-1-1 if someone else was having a heart attack.
- For themselves, 46% of women would do something other than call 9-1-1—such as take an aspirin, go to the hospital, or call the doctor.

Source: Mosca et al. 2010.

Should We Treat HTN Intensively in Older Women (and men)?

- International (13 countries) multicenter (n=195) trial
- Ppts ≥80 yo with HTN
  - SBP 160 to 199 mm Hg
  - SBP after standing 2 minutes ≥140 mm Hg
- Randomized to indapamide 1.5 mg qd vs. placebo
  - Target BP <150/<80 mm Hg
  - Could receive perindopril (2 or 4 mg qd) or placebo
- Primary endpoint: Fatal or non-fatal stroke
  - Secondary endpoints of interest:
    - Total mortality, CVD death, cardiac death, stroke death, fatal/NF heart failure

Baseline HYVET

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Active Treatment (N = 1935)</th>
<th>Placebo (N = 1912)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>88.6±3.2</td>
<td>88.5±3.3</td>
</tr>
<tr>
<td>Female sex -- no. (%)</td>
<td>1174 (61.7)</td>
<td>1132 (60.3)</td>
</tr>
<tr>
<td>Blood pressure — mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>While sitting</td>
<td>173.0±8.9/90.8±6.6</td>
<td>173.0±8.9/90.8±6.6</td>
</tr>
<tr>
<td>While standing</td>
<td>164.0±11.5/87.7±6.3</td>
<td>167.0±11.1/90.8±6.3</td>
</tr>
</tbody>
</table>

- 3845 ppts randomized
  - Mean age 83 years (range 80-105 years)
  - 61% women; 12% with prior CVD
  - Baseline BP: 173/91 mmHg
  - Mean duration of F/U: 2 years (0 to 6.5 years)

HYVET Results

- Terminated early for significant reductions in primary endpoint and all-cause mortality
HYVET – Primary Endpoint

17.7/1000 p-y
12.4/1000 p-y
30% RRR; NNT 94 over 2 years

HYVET – Total Mortality

59.6/1000 p-y
47.2/1000 p-y
21% RRR; NNT 40 over 2 years

HYVET – Heart Failure

14.8/1000 p-y
5.3/1000 p-y
64% RRR; NNT 52 over 2 years

Conclusions:
Utility in treating Very Elderly (esp. Women) with HTN
Diuretic +/- ACEi appears to be safe in the Elderly

What do we know about risk factors for HTN in women?

Pregnancy as “Stress Test” for Cardiovascular Disease

15% of pregnancies are hypertensive

Opportunity for Prevention?

Adapted with permission from Sattar, BMJ, 2002
Hypertensive Disorders of Pregnancy

1. Chronic Hypertension
2. Transient Hypertension of Pregnancy
3. Chronic Hypertension with Preeclampsia
4. Preeclampsia

Chronic Hypertension

Neonatal outcome in women with proteinuria at baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term delivery</td>
<td>2.7</td>
</tr>
<tr>
<td>SGA</td>
<td>2.8</td>
</tr>
<tr>
<td>NICU adm</td>
<td>3.1</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>2.2</td>
</tr>
</tbody>
</table>

25% of Women with CH will develop Preeclampsia

Risk of preeclampsia among women with CH (Silai et al, NEJM 1998)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>hx of preeclampsia</td>
<td>1.6</td>
</tr>
<tr>
<td>long duration of htn</td>
<td>1.6</td>
</tr>
<tr>
<td>baseline DBP &gt; 100</td>
<td>2.2</td>
</tr>
<tr>
<td>proteinuria</td>
<td>1.1</td>
</tr>
</tbody>
</table>

MOMS FOLLOW-UP STUDY

N=23,223 Subjects/Pregnancies
(Only the first pregnancy within the study period was used)
(1998-2006)

Unadjusted OR (95% CI)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Unadjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>2.29 (1.92-2.73)</td>
</tr>
<tr>
<td>Essential HTN</td>
<td>5.26 (4.30-6.43)</td>
</tr>
<tr>
<td>All Neoplasms</td>
<td>1.14 (0.94-1.39)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>1.62 (0.76-3.46)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.29 (1.05-1.59)</td>
</tr>
<tr>
<td>Any Psychiatric Disorder</td>
<td>1.26 (1.05-1.50)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.42 (1.08-1.86)</td>
</tr>
</tbody>
</table>

Preeclampsia --- A Glimpse into the Future?
Kari Nyulbrant, MD, MPH, and Karen G. Tallman, MD, MPH.
Preeclampsia, a disorder of pregnancy characterized by increased blood pressure and proteinuria, complicates approximately 5% of pregnancies. Although several risk factors for this condition are well recognized, including obesity, previous preeclampsia, hyperemesis gravidarum, diabetes mellitus, young age, and previous miscarriage, its etiology remains unknown. Although several therapeutic approaches have been studied, no single intervention has been shown to prevent preeclampsia. The challenge of developing effective preventive strategies is particularly important as more women with preeclampsia develop chronic hypertension, heart disease, and diabetes mellitus later in life.

FUTURE RISK FOR...
- Chronic Hypertension
- CAD, Myocardial Ischemia
- Stroke
- Renal Biopsy and ESRD
Kaplan-Meier plot of cumulative probability of survival without admission to hospital for ischemic heart disease or death from ischemic heart disease comparing 19 years of follow-up in women with and without a history of preeclampsia. Smith et al, Lancet 2001; 357: 2002-2006.

Small-for-gestational-age, preterm, or hypertension during pregnancy predicts CVD in the mother ... and multiple conditions more predictive

Outcome of First Birth

Adjusted for age, height, SES, essential hypertension

Smith, Lancet 2001

Pre-eclampsia & Risk of HTN in Later Life

BMJ RESEARCH

Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis

JASN 2006

NEJM 2008

Pre-eclampsia & Risk of HTN in Later Life
Pre-eclampsia & Risk of Fatal and Non-fatal Ischaemic Heart Disease in Later Life

### Trials of Intermediate Duration

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no. of women</th>
<th>Total no. of men</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (60% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pre-eclampsia, 3-12 months</em></td>
<td>48,795</td>
<td>27,078</td>
<td>1.60 (1.24-2.06)</td>
<td>1.56 (1.21-2.01)</td>
</tr>
<tr>
<td><em>Pre-eclampsia, &gt;12 months</em></td>
<td>61,056</td>
<td>32,750</td>
<td>1.27 (1.00-1.63)</td>
<td>1.25 (1.00-1.59)</td>
</tr>
</tbody>
</table>

*Early and late pre-eclampsia combined; † Mild and severe pre-eclampsia combined*

Bellamy L, et al. ONLINE FIRST. BMJ. doi:10.1136/bmj.39335.385301.BE

2014 Hypertension Guidelines

- **Adult aged ≥18 years with hypertension**
  - Implement lifestyle interventions (cohort management).
  - Set blood pressure goal and discontinue blood pressure-lowering medication based on age, diabetes, and chronic kidney disease (CKD).

- **General population**
  - Use statins or ESC.

- **Diabetes or CKD present**
  - Use statins or ESC.

2014 Hypertension Guidelines

- **Blood pressure goal**
  - Systolic blood pressure <140 mm Hg in all but frail older (>80/>60 yo?) HTNsive pts (HYVET)
  - Possibly lower in CKD
  - Do not shoot for <120/<80 in diabetics (ACCORD)
  - Monitor for tolerance in all pts

- **Initial therapy**
  - Lifestyle remains important
  - In Blacks, CCB or thiazide (ALLHAT)
  - In Non-Blacks, ACEi, ARB, CCB or thiazide

Take-Home Points

- Shoot for <140/<90 mm Hg in all but frail older (>80/>60 yo?) HTNsive pts (HYVET)
- Possibly lower in CKD
- Do not shoot for <120/<80 in diabetics (ACCORD)
- Monitor for tolerance in all pts
- Initial therapy
- Lifestyle remains important
- In Blacks, CCB or thiazide (ALLHAT)
- In Non-Blacks, ACEi, ARB, CCB or thiazide

Do Men and Women Respond Differently to BP-Lowering Treatment?

Results of Prospectively Designed Overviews of Randomized Trials

- Overview analysis of 31 RCTs with CVD outcomes that included 103,268 men and 87,349 women.

- Achieved BP reductions were comparable for men and women in every comparison made.

Take-Home Points

- Use combination lower-dose therapy for higher BP/higher risk pts to maximize BP effects and minimize SEs/AEs
- Consider chlorthalidone for HTNsive CKD
- If treating HTN, ASA generally indicated (HOT trial)
  - And consider a statin for most (ASCOT-LLA)
- Engage pts and use systems of care

CONCLUSIONS

All BP-lowering regimens studied provided similar protection against major CV events in men and women. Differences in CV risks between sexes are unlikely to reflect differences in response to BP-lowering treatments.

AHA CVD Prevention Guidelines for Women: Clinical Recommendations for High Blood Pressure

- Encourage an optimal blood pressure of <120/80 mmHg through lifestyle approaches
- Pharmacotherapy is indicated when blood pressure is ≥140/90 mmHg
- Women generally respond to antihypertensive drugs similarly to men but there are special considerations:
  - ACEIs and ARBs are contraindicated for women who are or intend to become pregnant
  - Diuretics useful in some elderly patients at risk because of a decreased risk of hip fracture
  - However, women are more likely to develop diuretic-induced hyponatremia and hypokalemia
  - ACEI-induced cough is twice as common in women as in men
  - Women more likely to complain of CCB-related peripheral edema