Oral Contraceptives, Hormone Replacement Therapy, Migraine & Stroke Risk

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Grand Rapids, Michigan
(LGH Stroke Symposium, 10/18/14, 8 AM, 45 minutes)
Disclosure Relevant to This Lecture
(Past 12 Months)

Member of the Following Study Committees
1. Bayer (ARRIVE Steering Committee)
2. Takeda (MACE Adjudication Committee for Uloric)
3. Roche/Parexel (MACE Adjudication Committee for epogen)
4. Dendreon (MACE Adjudication Committee)
5. Brainsgate (IMPACT-24) (Steering Committees)
6. Cellceutix (DSMB)
7. AbbVie (MACE Adjudication Committee for SONAR)
8. Celgene (MACE Adjudication Committee)
9. Co-Director, US DIAS Clinical Coordinating Center

Consultancy
1. Norvartis (blood pressure lowering and cognitive impairment; NSAIDS & CV risk)

Speaker’s Bureau
1. Boehringer Ingelheim, Pfizer

Medical-Legal
1. Primarily defend physicians & hospitals in stroke litigation
2. Consultant to Boehringer Ingelheim

Major Stock Shareholder, Other Support (tangible or intangible)
1. None

MACE = major cardiovascular events
Learner Objectives

• You will be able to discuss stroke risk and preventive management in women in relation to the following factors:

1. Oral Contraceptive Pills
2. Hormone Replacement Therapy
3. Migraine
Abbreviations

AHA/ASA: American Heart Association/American Stroke Association
BP: blood pressure
CAD: coronary artery disease
CADASIL: Cerebral autosomal dominant arteriopathy and subcortical infarcts and leukoencephalopathy
CEE: conjugated equine estrogen
CI: confidence interval
HR: hazard ratio
HRT: hormone replacement therapy
LOE: level of evidence
MPA: medroxyprogesterone acetate
Mil: million
OCP: oral contraceptive pill
OR: odds ratio
RR: relative risk
TE: thromboembolic events
WHI: Women’s Health Initiative
Major References for Stroke in Women 2014

   Bushnell C et al. Stroke 2014: 45: 1545-1588

Stroke in Women

Brief Background Information & Striking Differences Between Men & Women
### Background Information-1

<table>
<thead>
<tr>
<th></th>
<th><strong>Women</strong></th>
<th><strong>Men</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Stroke prevalence:</strong></td>
<td>3.8 mil</td>
<td>3.0 mil</td>
</tr>
<tr>
<td>2. <strong>Stroke &amp; Disabled:</strong></td>
<td>&gt;200,000 more than men</td>
<td></td>
</tr>
<tr>
<td>3. <strong>Lifetime Stroke Risk</strong></td>
<td>Age 55-75 years: 20%</td>
<td>17%</td>
</tr>
<tr>
<td>4. <strong>More Likely to be Institutionalized:</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5. <strong>Stroke Deaths:</strong></td>
<td>~60%</td>
<td>~40%</td>
</tr>
<tr>
<td>6. <strong>Leading Mortalities:</strong></td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>5&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Why?

1. Women live longer
2. Women are older at time of stroke
3. Women are more likely to live alone
   *Worse premorbid status
   *Worse recovery & worse quality of life than men after stroke

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Background Information-3

Why?
1. **Menopause & Hormonal Changes**
   60% decline of estradiol that plateaus in 1-3 yrs. & a relative androgen excess

2. **Menopause Transition & Stroke Risk Factors**
   Increase in abdominal obesity, triglycerides, total & LDL cholesterol, BMI, fasting glucose, & decrease in HDL

3. **Age at Menopause & Duration of Estrogen Exposure**
   May or may not be predictive of stroke

Source: Lisabeth L, Bushnell C. Lancet Neurol 2011; 11: 82-91
**Hot Off the Press**
Population Attributable Risk (PAR) for CVD in Women & Men in the Late 1990s

<table>
<thead>
<tr>
<th>Risk</th>
<th>Prevalence</th>
<th>Adjusted HR</th>
<th>PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>46%</td>
<td>1.91</td>
<td>0.32</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13%</td>
<td>2.88</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>42%</td>
<td>1.54</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15%</td>
<td>2.13</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Source: Cheng S et al. Circulation 2014; DOI: 10.1161/CIRCULATIONAHA.113.008506
Oral Contraceptive Therapy
Which of the following means of contraception is associated with elevated stroke risk:

A. Low-dose OCPs
B. Vaginal ring contraception
C. Transdermal patch
D. All of the above
E. None of the above
OCPs: Background Information

• ~11 million OCP users in US
• Other forms of hormonal contraception (less known about stroke risk):
  A. Transdermal patch
  B. Vaginal ring
  C. Intra-uterine device

• **Risk of Stroke with OCP Low But Rises with Age**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19 yrs.</td>
<td>3.4/100,000</td>
</tr>
<tr>
<td>45-49 yrs.</td>
<td>64.4/100,000</td>
</tr>
</tbody>
</table>

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Low-Estrogen Oral Contraceptives

Contain <50 ug of estrogen
Estimates of Ischemic Stroke Risk

- **Meta-Analysis of Low-Dose Combined OCPs (2nd & 3rd generation only): 1980-2002**
  A. OR: 2.12 (95% CI 1.56, 2.86)

- **Progestogen-only pills**
  A. OR: 0.96 (95% CI 0.70, 1.31), p=NS

- **Danish population-based study**

  RR (ethinyl estradiol by dose)
  - 20 ug: 0.88 (95% CI .22, 3.53) to 1.53 (1.26, 1.87)
  - 30-40 ug: 1.40 (95 % CI .97, 2.03) to 2.20 (1.79, 2.69)

- **Progestin-only: no association**

  - **Transdermal patch: 3.15 (95% CI .79, 12.60)**
  - **Vaginal ring: 2.49 (95% CI 1.41, 4.41)**

Sources: Bushnell C et al. Stroke 2014; 45: 1545-1588
Relative and Absolute Risk of Ischemic Stroke for Low Estrogen OCPs Controlling for Hypertension & Smoking

RR= 1.93 (95% CI 1.35, 2.74)

Or

1 additional ischemic stroke/24,000 women

Gillum LA et al. JAMA 2000; 284: 72-78
Estimates of Hemorrhagic Stroke Risk

• Estimates less consistent
• Increased in developing countries but not in Europe
• In Asia, a number of single nucleotide polymorphisms that modulate various types of stroke risk, may place one at significant risk

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Additional Stroke Risk Factors & OCPs

- Older age
- Cigarette smoking
- Hypertension
- Migraine headache
- Obesity
- Hypercholesterolemia
- **Other/Coagulable Factors**
  - Heterozygous for Leiden Factor V, methyl tetrahydrofolate reductase or MTHFR 677TT mutation, Factor XIII mutation, B2 glycoprotein-1 antibodies, lupus anticoagulant, endothelial dysfunction (increase of von Willebrand factor levels & low ADAMTS13)

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Screening

- **Screen for modifiable risks** (hypertension, cigarette smoking, etc.)
- **Screen for thrombophilia or hypercoagulable disturbances**, if personal or family history of venous thromboembolism
- **Stroke Prevention in Young Women Study**
  - **Factor**
  - **Risk of Stroke**
  - A. Migraine w visual aura
    - OR = 1.5 (95% CI 1.1, 2.0)
  - B. Migraine w visual aura, OCP, smoke
    - OR = 7.0 (95% CI 1.3, 22.8)

MacClellan LR et al. Stroke 2007; 38: 2438-2445
Hormonal Contraception & Blood Pressure

- Limited data
- OCPs may marginally increase BP
- Infrequently leads to hypertension
  - Measurement of BP before OCP initiation may be an important preventive measure to detect women at risk for stroke

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Summary & Take-Home Messages

• Risk of stroke with low-dose OCPs is small (1.4-2.0 times)

• For 10,000 women treated with 20-ug dose of desogestrel with ethinyl estradiol for 1 year (Danish data):

  A. Arterial Thrombosis: 2/10,000 women
  B. Venous Thrombosis: ~7/10,000 women
  C. Vs. Risk of Stroke with Pregnancy: ~3/10,000 women

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
# AHA/ASA 2014 Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class/Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. OCPs may be harmful in women with additional risk factors (e.g., cigarette smoking, prior TE events)</td>
<td>Class III, LOE B</td>
</tr>
<tr>
<td>2. Among OCP users, aggressive therapy of stroke risk factors may be reasonable</td>
<td>Class IIb, LOE C</td>
</tr>
<tr>
<td>3. Routine screening for prothrombotic mutations before initiation of hormonal contraception is <strong>NOT</strong> useful</td>
<td>Class III, LOE A</td>
</tr>
<tr>
<td>4. Measurement of BP before initiation of hormonal OCP is recommended</td>
<td>Class I, LOE B</td>
</tr>
</tbody>
</table>

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Which of the following means of contraception is associated with elevated stroke risk:
A. Low-dose OCPs
B. Vaginal ring contraception
C. Transdermal patch
D. All of the above (but incidence is low)
E. None of the above
Menopausal Onset
&
Hormone Replacement Therapy (HRT)
Panacea

Or

Foe?

(Courtesy of Patricia Hurn, PhD Oregon Health Sciences Center)
Which of the following best characterizes HRT in relation to stroke & other risks:

A. Protects against dementia and cognitive decline and hip fracture
B. Is not associated with stroke, CHD, breast cancer & PE
C. Is safe in women 65 years and older
D. May be safe early on after menopause for short-term symptomatic use
Menopausal Onset and Stroke Risk

• Large body of evidence concerning age at menopause or premature or early menopause (e.g., includes hysterectomy & oophorectomy)

• Although the evidence is not entirely consistent, the data suggest increased stroke risk with earlier onset of menopause

• Few data on: lifetime estrogen exposure, duration of ovarian activity & time since menopause

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Postmenopausal Hormone Therapy
Main Results of WHI: Estrogen plus Progestin inHealthy Postmenopausal Women

<table>
<thead>
<tr>
<th>Factor (cases)</th>
<th>Outcome: HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD (n=286)</td>
<td>1.29 (1.02-1.63)</td>
</tr>
<tr>
<td>Breast Cancer (n=290)</td>
<td>1.26 (1.00-1.59)</td>
</tr>
<tr>
<td>Stroke (n=212)</td>
<td>1.41 (1.07-1.85)</td>
</tr>
<tr>
<td>PE (n=101)</td>
<td>2.13 (1.39-3.25)</td>
</tr>
<tr>
<td>Colorectal Cancer (n=112)</td>
<td>0.63 (0.43-0.92)</td>
</tr>
<tr>
<td>Endometrial Cancer (n=47)</td>
<td>0.83 (0.47-1.47)</td>
</tr>
<tr>
<td>Hip Fracture (n=106)</td>
<td>0.66 (0.45-0.98)</td>
</tr>
<tr>
<td>Other Cause of Death (n=331)</td>
<td>0.92 (0.74-1.14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probable Dementia</strong> (Modified Mini-Mental State Exam [MSE])</td>
<td><strong>HR= 2.05 (95% CI 1.21-3.48 or 45 vs 22/10,000 person-yrs; P=0.01)</strong> vs placebo for an additional 23 cases dementia/10,000 women person-yrs (mostly Alzheimer disease)</td>
</tr>
<tr>
<td><strong>Mild Cognitive Impairment (MCI)</strong> [3MSE]</td>
<td><strong>HR= 1.07 (95% CI 0.74,-1.55 or 63 vs 59/10,000 person-yrs; P=0.72)</strong></td>
</tr>
<tr>
<td><strong>Global Cognitive Function</strong> [3MSE]</td>
<td><strong>Smaller average increases in total scores vs. placebo (P=0.03)</strong></td>
</tr>
<tr>
<td><strong>Global Cognitive Function</strong> [3MSE]</td>
<td><strong>More clinically important decline (/&gt;=2SDs) on 3MSE vs. placebo (6.7% vs 4.8%; P=0.008)</strong></td>
</tr>
</tbody>
</table>

Source: Shumaker et al, JAMA 2003; 289: 2651; Rapp et al, JAMA 2003; 289: 2663
### WHI: Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy

*(overall p=NS)*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR and Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CHD Death</td>
<td>.94 (.54, 1.63)</td>
</tr>
<tr>
<td>2. Nonfatal MI</td>
<td>.89 (.63, 1.26)</td>
</tr>
<tr>
<td>3. Fatal Stroke</td>
<td>1.13 (.38, 3.36)</td>
</tr>
<tr>
<td>4. Nonfatal Stroke</td>
<td>1.39 (.91, 2.12)</td>
</tr>
<tr>
<td>5. DVT</td>
<td>1.47 (.87, 2.47)</td>
</tr>
<tr>
<td>6. PE</td>
<td>1.34 (.70, 2.55)</td>
</tr>
<tr>
<td>7. Total CVD</td>
<td>1.12 (.97, 1.30)</td>
</tr>
<tr>
<td>8. Invasive Breast Cancer</td>
<td>.77 (.57, 1.06)</td>
</tr>
<tr>
<td>9. Colorectal Cancer</td>
<td>1.08 (.63, 1.86)</td>
</tr>
<tr>
<td>10. Total Cancer</td>
<td>.93 (.75, 1.15)</td>
</tr>
<tr>
<td>11. Hip Fracture</td>
<td>.61 (.33, 1.11)</td>
</tr>
</tbody>
</table>

*(reduced in non-adjusted)*

WHI Steering Committee. *JAMA* 2004; 291: 1701-1712
WHI: Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years

“CONCLUSIONS AND RELEVANCE: CEE-based therapies produced no overall sustained benefit or risk to cognitive function when administered to postmenopausal women aged 50 to 55 years. We are not able to address whether initiating hormone therapy during menopause and maintaining therapy until any symptoms are passed affects cognitive function, either in the short or longer term.”

WHI 13-Year Follow-Up-1

Results

1. **CEE + MPA**
   A. **CHD**: HR = 1.18 (95% CI 0.95, 1.45)
   B. **Invasive Breast Cancer**: HR = 1.24 (95% CI 1.01, 1.53)
   C. **Other Risks**: increased risk of stroke, PE, dementia (age ≥ 65 yrs.), gallbladder disease, urinary incontinence
   D. **Benefits**: decreased hip fractures, diabetes, vasomotor symptoms
   E. Most risks/benefits dissipated post-intervention but some elevation in breast cancer persisted

Manson JE et al. JAMA 2013; 310: 1353-1368
Results

II. CEE Alone

A. CHD: HR = 0.94 (95% CI .78, 1.14)
B. Invasive Breast Cancer: HR = 0.79 (95% CI .61, 1.02)
C. Breast Cancer: HR = .79 (95% CI .65, .97)
D. Other Outcomes: similar to CEE + MPA
E. Younger Women (50-59 yrs.): more favorable all-cause mortality, MI, global index

Global Index/10,000/Yr. 50-59 Yrs. 70-79 Yrs.
A. CEE + MPA 12 excess 38 excess
B. CEE only 19 fewer 51 excess

Manson JE et al. JAMA 2013; 310: 1353-1368
Stroke Risk in RCTs of Perimenopausal & Postmenopausal Women

<table>
<thead>
<tr>
<th>Trial</th>
<th>No.</th>
<th>Avg. Age</th>
<th>Regimen</th>
<th>CVD Present?</th>
<th>Stroke, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERS</td>
<td>2763</td>
<td>66.7</td>
<td>CEE + MPA vs. Placebo</td>
<td>CAD</td>
<td>1.1 (.9, 1.7)</td>
</tr>
<tr>
<td>WEST</td>
<td>664</td>
<td>71</td>
<td>Estradiol vs. Placebo</td>
<td>Ischemic stroke/TIA</td>
<td>1.1 (.8, 1.6)</td>
</tr>
<tr>
<td>HERS II</td>
<td>2321</td>
<td>66.7</td>
<td>CEE + MPA vs. Placebo</td>
<td>CAD</td>
<td>1.09 (.75, 1.6)</td>
</tr>
<tr>
<td>WHI</td>
<td>16,608</td>
<td>63</td>
<td>CEE + MPA</td>
<td>No</td>
<td>1.3 (1.0, 1.7)</td>
</tr>
<tr>
<td>WHI</td>
<td>10,739</td>
<td>63</td>
<td>CEE</td>
<td>No</td>
<td>1.4 (1.1, 1.7)</td>
</tr>
<tr>
<td>DOPS</td>
<td>2012</td>
<td>49.7</td>
<td>17B estradiol +</td>
<td>No</td>
<td>.89 (.48, 1.65)</td>
</tr>
</tbody>
</table>

CEE: conjugated equine estrogen (0.625 mg)  MPA: medroxyprogesterone acetate (2.5 mg)
DOPS: Danish Osteoporosis Prevention for Stroke Trial (dosing depended on uterine status)
HERS: Heart Estrogen/Progestin Replacement Study
What About Selective Estrogen Receptor Modulators (SERMs)?

• **Raloxifene (60 mg) vs. placebo**

  Non-fatal Stroke: HR = 1.10
  (95% CI .92, 1.32)

  Fatal Strokes: HR = 1.49
  (95% CI 1.00, 1.24)

Timing of HRT

• There is interest in administration of HRT closer to the time of menopause as a possible safe strategy to reduce key menopausal symptoms

• Transdermal estradiol may be a safe alternative that does not increase the risk of venous thromboembolism and stroke & may reduce the risk of myocardial infarction

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
2012 Hormone Therapy Position Statement of The North American Menopause Society (NAMS)

• **Recommendation**

• Initiation of hormone therapy around the time of menopause to treat menopause-related symptoms & to prevent osteoporosis in women at high risk of fracture

• Estrogen therapy has a more favorable benefit-risk ratio allowing for more flexibility in extending duration of use compared to estrogen + progestogen therapy (breast cancer risk) for 3-5 years

Source: Menopause 2012; 19: 257-271
US Preventive Services Task Force Recommendation Statement on Hormone Replacement Therapy (HRT)

- **Recommendation Against Use of** (does not apply to women considering HRT for management of menopausal symptoms or women younger than 50 years who have had surgical menopause):

  1. Combined estrogen & progestin for prevention of chronic conditions in postmenopausal women (grade D)
  2. Estrogen for prevention of chronic conditions in postmenopausal women who have had a hysterectomy (grade D)

**Editorial:** regarding “timing hypothesis”, more definitive evidence needed

**KEEPS: Kronos Early Estrogen Prevention Study**  
**Arterial & CVD Risks in Recently Menopausal Women**

**Subjects:** 42-58 yr. olds, last menses 6-36 months ago & no prior CVD; n=727

**Intervention:** oral-CE E 0.45mg/d or transdermal 17-B estradiol, 50 mcg/d, plus 200 mg oral progesterone for 12 d/month vs. placebo for 48 months

**Results:**
1. Carotid artery intima-media thickness: \( p=NS \)
2. Coronary calcium score IL-6: \( p=NS \)
3. LDL & HDL cholesterol, CRP sex hormone binding globulin: improved

**Conclusion:** no affect on progression of atherosclerosis but some markers of CVD improved

Summary & Take-Home Messages

• Increase risk of stroke with HRT CEE/medroxyprogesterone formulations
• Insufficient data to assess the long-term risk of HRT in perimenopausal women <50 yrs. of age
• No benefit of raloxifene or tamoxifen for stroke prevention; both raloxifene and tibolone are associated with increased risk of stroke
• More data needed on timing, route, type, and duration of HRT

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Postmenopausal Hormone Recommendations

- CEE with or without medroxyprogesterone **should NOT** be used for first or recurrent stroke prevention in postmenopausal women (Class III, LOE A)

- SERMs such as raloxifene, tamoxifen or tibolone **should NOT** be use for first stroke prevention (Class III, LOE A)

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Best Answer to Audience Engagement Question: HRT

Which of the following best characterizes HRT in relation to stroke risk:

A. Protects against dementia and cognitive decline and hip fracture
B. Is not associated with stroke, CHD, breast cancer & PE
C. Is safe in women 65 years and older
D. May be safe early on after menopause for short-term symptomatic use
Migraine
Audience Engagement Question: Migraine

- Which of the following best characterizes migraine and stroke risk:
  - A. Risk is restricted to migraine without aura
  - B. Risk is restricted to men
  - C. Risk is not enhanced when there are other cardiovascular risk factors
  - D. Risk is restricted to migraine with aura
  - E. Risk is differential in that ischemic stroke is heightened but hemorrhagic stroke is not
Migraine: Background Information

- **Population prevalence** of migraine: ~18.5%
- **Prevalence of migraine with aura**: ~4.4%
- Women 4-fold more likely to have migraine
- **Migraine with aura** = migraine headache plus the following that typically precede headache:
  - Homonymous visual disturbance
  - Unilateral paresthesias or numbness
  - Unilateral weakness
  - Aphasia or speech difficulty

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Migraine as a Risk for Stroke
Women’s Health Study

• 27,840 US women >/= 45 years and free of CVD and angina at entry
• 5125 or 18.4% had history of migraine and 1434 or 39.7% had aura
• After 10 years of f/u, 580 major CVD events and multivariable HRs show for active migraine with aura v. no migraine:
  1. Major CVD: 2.15 (95% CI 1.58, 2.92; P<.001)
  2. Ischemic Stroke: 1.91 (95% CI 1.17, 3.10; P=.01)
  3. TIA: RR= 1.56 (95% CI 1.03, 2.36)
  4. Non-disabling stroke: RR= 2.33 (95% CI 1.37, 3.97)
  5. MI: 2.08 (95% CI 1.30, 3.31; P=.002)
  6. Coronary Revasc: 1.74 (95% CI 1.23, 2.46; P=.002)
  7. Ischemic CV Death: 2.33 (95% CI 1.21, 4.51; P=.01)
  8. 18 additional major CVD events attributable to migraine w aura/10,000 women/year; 4 additional strokes
  9. Women with active migraine w/o aura not at increased risk

Source: Kurth et al. JAMA 2006; 296: 283-291
Migraine & Stroke Risk

- Meta-Analyses & Stroke Risk
- Ischemic stroke & migraine with aura:
  \( OR = 2.51 \ (95\% \ CI \ 1.52, \ 4.14) \)
  \( (women > men) \)
- Ischemic stroke, migraine with aura in women &:
  \( OCPs: \ OR = 7.02 \ (95\% \ CI \ 1.51, \ 32.68) \)
  \( Cigarettes: \ OR = 9.03 \ (95\% \ CI \ 4.22, \ 19.34) \)

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Migraine/Aura, OCPs, Smoking and Stroke Risk

• Estimates of Stroke Risk for patient under 35 yrs with migraine with aura:
  1. 19/100,000 per yr.
  2. 30/100,000 per yr. (same pt. who uses OCPs)
  3. 44/100,000 per yr. (same pt. who smokes)
  4. 102/100,000 per yr. (same pt. who smokes and uses OCPs)

Estimate of Stroke Risk in Pregnant Women:
  1. 22/100,000 deliveries in nonsmokers
  2. 44/100,000 deliveries in smokers

Migraine & Hemorrhagic Stroke Risk

- Women’s Health Study: strongest in subset of women with fatal hemorrhagic stroke & in women <55 years of age
- Pregnant women, migraine & hemorrhagic stroke: OR= 9.1 (95% CI 3.0, 27.8) but closely associated with pre-eclampsia/eclampsia

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Migraine as a Risk for Hemorrhagic Stroke
Women’s Health Study

- Adjusted Hazard Ratios for Hemorrhagic Stroke in Migraine Patients (based on study of 5125 women who reported any history of migraine):

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>Migraine Aura</th>
<th>Any Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic</td>
<td>2.28</td>
<td>1.03</td>
</tr>
<tr>
<td>ICH</td>
<td>2.04</td>
<td>1.05</td>
</tr>
<tr>
<td>SAH</td>
<td>2.04</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Source: Kurth et al reported in Clinical Neurology News, March 2007
Was the Stroke a Result of Migraine or Some Other Condition?
Disorders Associated with Stroke & Migraine with Aura

Disorders with Brain Vessel Wall Abnormalities
- CADASIL
- Brain AVM
- Sturge-Weber (leptomeningeal angiomatosis)
- Moyamoya syndrome
- Hereditary hemorrhagic telangiectasia
- Sneddon syndrome
- MELAS
- COL4A1 mutations

Cardiac disorders: PFO, cardiac myxoma

Blood disorders: SLE, polycythemia, essential thrombocythemia, antiphospholipid antibody syndrome

MRI Head and White Matter Disease
Migraine with Aura and Subclinical Brain Lesions

- Migraine with aura in midlife was associated with late-life prevalence of cerebellar infarct-like lesions on MRI
- The association was statistically significant only for women

Sources: Scher AI et al. JAMA 2009; 301: 2563-2670
Kruit MC et al. JAMA 2004; 291: 427-434
Mechanisms that May Link Migraine to Stroke

- **Results strongest for migraine with aura**: white matter abnormalities, infarct-like lesions & volumetric changes of gray and white matter
- **Reduced numbers of endothelial progenitor cells**
- **Cervical artery dissection**
- **Risk factors for CVD**: aortic stiffness, cardiovascular risk factors (obesity, etc.)
- **Vascular smooth muscle cell/endothelial dysfunction**

Summary/Take-Home Messages

• Migraine with aura (not migraine w/o aura) is a risk for ischemic & hemorrhagic stroke in women, especially those < 55 years
• Risk is low, prognosis usually good
• Insufficient data to inform any benefit of treatment of migraine on stroke risk reduction
• Triptans are contraindicated in patients with a history of cerebral or coronary heart disease
• No data to guide administration of triptans in women with migraine with aura

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Migraine with Aura: Recommendations

• Because there is an association between higher migraine frequency and stroke risk, treatments to reduce migraine frequency might be reasonable although evidence is lacking that such treatment is
  (Class IIb, LOE C)

• Because women with migraine with aura & smoking have an increased stroke risk, it is reasonable to strongly recommend smoking cessation in this circumstance
  (Class IIa, LOE B)

Source: Bushnell C et al. Stroke 2014; 45: 1545-1588
Best Answer to Audience Engagement Question: Migraine

Which of the following best characterizes migraine and stroke risk:

- A. Risk is restricted to migraine without aura
- B. Risk is restricted to men
- C. Risk is not enhanced when there are other cardiovascular risk factors
- D. Risk is highest with migraine with aura
- E. Risk is differential in that ischemic stroke is heightened but hemorrhagic stroke is not
Thank You

Q & A