Update in Women’s Health 2011

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Conflicts of Interest: None

Our Systematic Review
• Reviewed all titles published in top journals
  — March 1, 2010 to March 1, 2011
• Evaluated potential impact on internists’ clinical practice
• Top third of abstracts reviewed by all 4 of us
• Consensus reached about those most worthy of your time today

Sources Reviewed
• New England Journal of Medicine
• Journal of the American Medical Association
• Annals of Internal Medicine
• Archives of Internal Medicine
• British Medical Journal
• Lancet
• Obstetrics and Gynecology
• American Journal of Obstetrics and Gynecology
• Journal of General Internal Medicine
• PLoS Medicine
• American Journal of Public Health
• Circulation
• Diabetes
• Diabetes Care
• Cochrane database of systematic reviews
• Guideline Clearing House
• ACP Journal Club
• Journal Watch Women’s Health
• Journal Watch
• AND a MEDLINE search using medical subject heading, “sex factors”

Plan for today
• Issues for Reproductive Aged Women
• Diseases of Early Adulthood into Mid-Life
• Management of the Menopausal Woman
• Osteoporosis and Bone Health

Issues for Reproductive Aged Women
Eleanor B. Schwarz, MD

Case
• Ms. Estie Dee, 26 year old woman
• Recently, noted a new vaginal discharge
• Tested positive for gonorrhea
• History of intimate partner violence
• Partner won’t use condoms
Q: Can I take the same pills as last time?
A. Yes, 500mg po Cipro should still work
B. No, you have to get a shot
C. You can either take:
   400mg po Cefixime x1
   or get 250mg IM Ceftriaxone x1
   (plus treatment for Chlamydia with
    Aztho 1gm po x1
    OR Doxy 100mg po BID x 7D)

A: Beware resistant gonorrhea

• Recommend Ceftriaxone 250mg IM rather than 125mg IM
• If Sx persist, culture and check sensitivities
• Test for reinfection 3 months after treating
• Rx her partner

The News

• Sexually transmitted diseases treatment guidelines, 2010.

Q: Is there some way I can protect myself from HIV?
Yes:
A. Use nonoxynl-9
B. Douche with coca-cola
C. Use a diaphragm
D. Use tenofovir

Expeditied Partner Therapy is permitted in most states

Recommended: 27 states
Potentially allowable: 15 more
Still prohibited in: Arkansas, Florida, Kentucky, Michigan, Ohio, Oklahoma, South Carolina, West Virginia

Refresher

• HIV is an epidemic
• Young women face the greatest risk of HIV infection
The News

- Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

- **AIM:** To assess whether insertion of gel within 12 hours before sex and a second dose of gel as soon as possible within 12 hours after sex reduced the incidence of HIV infection

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Tenofovir safety and efficacy

- Double blind RCT
- N=889, women who were HIV- in urban and rural South Africa
  - Monthly follow up for 30 months
  - 95% completed study (!!?)

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Results

Safety:
- NO less condom use
- Fewer urogenital symptoms (e.g. menorrhagia)
  - 47% vs. 54%, p=0.06
- More diarrhea and GI infections
  - 17% vs. 11%, p=0.02

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Impact for Practice

- FDA granted Fast Track approval for 1% gel in Oct 2010
- Likely late 2012 before gel is available

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Management of Menorrhagia
**Case**

- Ms. Annie May is a 40 year old woman
- s/p bariatric surgery, BMI=32, BP=142/102
- Significant menorrhagia, Hgb=10

**What do you tell her?**

A. Let's try a birth control pill
B. You should consider a copper IUD
C. Mirena® has been labeled for menorrhagia
D. Tranexamic acid (Lysteda®) is a new option in Europe

**Considering a birth control pill?**

- Advise on use of 10 contraceptives in 160+ conditions:
  - 1 No restriction
  - 2 Advantages generally > theoretical or proven risks
  - 3 Risks (theoretical or proven) usually > advantages
  - 4 Unacceptable health risk

**Considering Mirena?**

- Safely used by >150 million women
- FDA labeled treatment since Oct 2009
- Recommended by ACOG since Jan 2010
  - More effective than oral contraceptives
  - More effective than oral medroxyprogesterone
  - More cost-effective than hysterectomy
  - Reduces risk of endometrial cancer
  - Works with inherited bleeding disorders

**The News**

- Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial
  - Lukes AS et al. ObGyn 2010;116:865-75
- **AIM:** To assess the efficacy and safety of an oral formulation of tranexamic acid for the treatment of heavy menstrual bleeding

**Tranexamic Acid**

- Competitively inhibits activation of plasminogen to plasmin (ie, plasmin)
- Plasmin degrades fibrin (ie, fibrin)
- Fibrin forms clot (ie, clot)
- 8x the activity of aminocaproic acid
- Injectable form FDA approved in 1986
- Oral form used in Europe since the 1970’s
## Methods

- Double blind, placebo RCT (n=196)
  - Tranexamic acid 3.9 g/d x 5D per menses
  - Pre-Tx mean $\geq$ 80 mL per menses x2
  - Followed for 6 cycles
- Outcomes:
  - Mean reduction in blood loss from baseline
    1. $>$ placebo
    2. $>$ 50 mL
    3. $>$ woman’s personally meaningful threshold
      (predetermined & required to be $>$ 36 mL)
  - Health-related quality of life

## Results

**It Works!**

- Effects at 1 month, consistent to 6 months
- Blood loss $>$ 50 mL $\rightarrow$ 56% vs. 19%, $p < 0.001$
- Personally meaningful reduction in blood loss?
  - 69% vs. 29%, $p < 0.001$
- Limitations in social and physical activities and self-perceived blood loss, $p < 0.01$

## Results

**It seems safe…**

- Majority of adverse events mild to moderate
- GI symptoms similar to placebo
- One DVT in the placebo group
- NOT powered to look at VTE
- Do not use with estrogen
- Multiple generic products abroad since 1970’s
- Swedish study showed no increased thrombosis
  - Over 20 years of use
  - Used by thousands of women

Rybo G. Therapeutic Advances 1991; 4:1-8

## Impact for Practice

- Oral Lysteda® (FDA approved Nov 2009) is an option for acute bleeds
  - 2 x 650mg tab TID for up to 5 days
    - $5-$6/pill$\rightarrow$ $30/day
  - Requires renal dosing
- Mirena® for long term relief

## Case

Ms. Bristol Reagan, 19 year old woman
- Family Hx of depression
- Has a serious boyfriend and wants to start “the pill”
- “Having an abortion would make me really depressed”

## Refresher

- Half of US pregnancies are unintended
- Half of unintended pregnancies are aborted
- 16% sexually active 18-19yo get pregnant

Finer LB. J Adolesc Health. 2010. PMID: 20708573
The News

- Number of oral contraceptive pill packages dispensed and subsequent unintended pregnancies.

- **AIM**: To estimate how number of pill packages dispensed relates to subsequent pregnancies and abortions.

Methods

- 84,401 women who received OCPs from California’s Family PACT in January 2006

- Linked to Medi-Cal pregnancy events

Results

- 1-year supply → fewer pregnancies
  - 1.2% with 12 cycles
  - 3.3% with 3 cycles / 2.9% with 1 cycle

- 1-year supply → fewer abortions
  - 46% reduction in odds (95% CI 0.32-0.93), controlling for age, race/ethnicity, prior pill use

The News

- Induced first trimester abortion and risk of mental disorder

- **AIM**: To assess the risk of a first psychiatric contact
  - Before/after first-trimester induced abortion
  - Before/after first childbirth

Methods

- Danish Civil Registration
  - 954,702 women >15 years of age, born 1962-1993

- Danish Register of Patients & Psychiatric central register, 1995-2007

- Rates of 1st psychiatric treatment 9 months pre or 12 months post
  - n=84,620, 1st first trimester induced abortion
  - n=280,930, 1st childbirth

- Adjusted for maternal age, calendar month
Results

- Abortion did not affect rates of psychiatric contact (p=0.19)
- Childbirth did (p<0.001) for 6 to 9 months
  - psychiatric contact for affective disorder
    - RR=3.79 (2.86-5.02) 1 month postpartum
    - RR=1.69 (1.31-2.17) 7-9 months postpartum
  - neurotic, stress-related, or somatoform disorders
    - RR=3.60 (2.97-4.37) 1 month postpartum
    - RR=1.33 (1.11-1.60) 7-9 months postpartum

Impact for Practice

- Give her a year’s worth of OCPs today
  - Typical use failure rate 5% in 1st year use
- Encourage placement of an IUD or Implanon ASAP
  - Typical use failure rates 0.1%
- Caution her about risk of postpartum depression

Case

- Ms. Jones presents to your office for her physical. During the visit, she mentions that she is concerned about her oldest daughter. Normally a well-developed, straight-A, 16 year old girl, she has recently lost significant weight, yet is obsessed with her caloric intake. She has not had her menses in over 3 months. Ms. Jones has also noticed that her daughter has been spending hours on a certain eating disorder website – one that proposes to be a “support group” Should she be worried?

Background

- Society is obsessed with weight; 35% of adolescent girls feel they are overweight
- In women, lifetime prevalence of anorexia is 0.5-1.0%, and of bulimia is 1-3%; many more with ED-NOS
- Peak onset in adolescence and young adulthood

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prevalence</th>
<th>NIH Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating Disorders</td>
<td>10 million</td>
<td>$12,000,000</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>4.5 million</td>
<td>$647,000,000</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2.2 million</td>
<td>$350,000,000</td>
</tr>
</tbody>
</table>

The News: Pro-Eating Disorder Web Sites

- Aim: To examine the features of pro-eating disorder websites and analyze the messages to which users may be exposed.
Methods

- Systematic review of 180 active websites using Yahoo and Google
- Included other forums, journals, blogs
- 2 independent reviewers
- 64 coded variables in 6 themes:
  - Site logistics, site accessories, thinspiration material (tips and techniques), recovery, perceived themes, perceived harm

Results

- 91% open to the public; 79% were interactive
- 84% provided pro-anorexia content; 64% pro-bulimia content
- 85% offered “thinspiration” material
- 83% offered overt suggestions on engaging in eating-disordered behavior
- Only 38% included recovery information or links
- Perceived harm (Likert scale 1-5):
  - 89 sites were ranked “medium” harm (score of 2 or 3)
  - 39 sites ranked “high” harm (4 or 5): content could lead to immediate and life-threatening problems

Themes:
- Control, success, perfection, solidarity
- Reference to “wannabes” (1/3); not a lifestyle choice
  - If you want to lose weight, go on a diet fatty. One is either Anorexia or not. It is a gift and you cannot decide to have an eating disorder. So if you are looking for a way to lose weight, s-s-sorry junior! Move on, try Jenny Craig.

Examples of websites:
- www.proanamia.org
- www.prettythin.com
- www.houseofthin.com
- www.fadingobsession.xanda.com
- www.pro-ana-nation.com

Example: The Thin Commandments

1. If you aren’t thin, you aren’t attractive.
2. Being thin is more important that being healthy.
3. You must buy clothes, cut your hair, take laxatives, starve yourself, do anything to make yourself look thinner.
4. Thou shall not eat without feeling guilty.
5. Thou shall not eat fattening food without punishing oneself afterward.
6. Thou shall count calories and restrict intake accordingly.
7. What the scale says is the most important thing.
8. Losing weight is good; gaining weight is bad.
9. You can never be too thin.
10. Being thin and not eating are signs of true willpower and success.

Conclusions and Implications

- Pro-eating disorder websites are easily accessible, dynamic communities that often serve as a venue for expression
  - Often depict graphic material
  - Many are interactive (video, social networking)
- Many encourage and motivate continued eating-disordered behavior
- Awareness is key for clinical practice
- Further research needed to better understand the effect of such exposure on users
Case

• You are called by a funeral home to sign a death certificate for one of your patients. She was a 50 year old woman with hypertension, rheumatoid arthritis, and progressive lung disease on home oxygen. She was found unresponsive by her husband.

Which is most likely a true statement about her death?

A. Myocardial infarction is a reasonable explanation since no cause of death is obvious
B. You should not list rheumatoid arthritis as a contributing factor as it rarely results in death
C. Autoimmune disorders result in significantly greater mortality than previously recognized

Background

• Autoimmune disorders are a group of disease caused by pathological immune responses against host antigens
• Collective disease burden is difficult to assess
  – Disease classification systems (ICD, WHO mortality) based on pathogenesis, organ system, or etiology
  – "Autoimmune" often hidden under organ system
• Prior study1: Autoimmunity in top 10 causes of death in US woman < 65 years; many limitations

The News: Autoimmunity and Mortality

• Aim: To estimate the collective burden of mortality from autoimmune diseases in women in the United Kingdom

Methods

• Analyzed death certificate data between 1993 – 2003
• 3,150,267 females aged ≥ 1 year of age
• 35 autoimmune diseases as underlying or contributing cause
• ICD-9 used for 1993-2000; ICD-10 for 2001-2003

Results

• 283,236 deaths out of 26,658,346 women
• Autoimmunity listed in 9271 (3.3%) and as underlying cause in 4420 (1.6%)
• Most frequent conditions: RA, rheumatic heart disease, idiopathic fibrosing alveolitis, multiple sclerosis

<table>
<thead>
<tr>
<th>Mortality Rank by Underlying Cause</th>
<th>Age 1-14</th>
<th>Age 15-34</th>
<th>Age 35-54</th>
<th>Age 55-74</th>
</tr>
</thead>
<tbody>
<tr>
<td>7th</td>
<td>7th</td>
<td>7th</td>
<td>6th</td>
<td></td>
</tr>
</tbody>
</table>

• Similar results when both underlying and contributory causes of death were considered
• Proportion of females dying from autoimmune disease remained fairly constant from 1993-2003
Conclusions and Implications

- Autoimmune disorders are a leading cause of death in women
- Mortality burden is hidden in various mortality rankings
- Proportion of females dying with an autoimmune disease has remained constant over time
- Re-allocation of research/public health dollars deserves consideration
- In practice, early diagnosis and aggressive treatment of autoimmune disorders is indicated

Case

- Mrs. Monroe is a 62 year old healthy woman who presents to your office with a small breast lump. Mammography and subsequent biopsy confirm a diagnosis of ductal carcinoma. She undergoes lumpectomy and receives word that her sentinel lymph node is positive.

What is the next appropriate step?

A. She should pursue standard XRT and chemotherapy as further axillary node dissection will not improve her survival
B. She should undergo axillary lymph node dissection to better prognosticate and tailor her chemotherapeutic regimen
C. She should undergo axillary lymph node dissection; if other nodes are positive, she should pursue bone marrow transplant

The News: Value of Axillary Node Dissection

- Aim: To determine the effects of complete axillary lymph node dissection (ALND) on survival in patients with breast cancer and sentinel lymph node (SLN) metastasis

Methods

- 891 women with clinical T1-T2 invasive breast cancer and 1-2 SLNs containing metastasis treated with lumpectomy and XRT
- Randomized to ALND or no further axillary treatment; non-inferiority trial
- Systemic chemo at the discretion of the treating physician
- Primary endpoint: Overall survival

Results

- Median follow-up of 6.3 years
- No difference in rates of adjuvant systemic chemo between the groups (97% in SLND and 96% in ALND)
- Overall survival rates: 92.5% in SLND group and 91.8% in ALND group
  - Adjusted HR: 0.87 (90% CI, 0.62-1.23)
- Disease-free survival also not statistically significant (83.9% in SLND group and 82.2% in ALND group)
- Morbidities higher in ALND group: Lymphedema, paresthesias, wound infections, etc.
Figure 2. Survival of the ALND Group Compared With SLND-Alone Group

Conclusions

• No difference in overall survival or disease-free survival between breast cancer patients with SLN metastasis who received SLND only vs. ALND
• Short study follow-up, but axillary recurrence usually presents at 1-2 years
• Higher survival rates than prior studies – testament to more effective XRT and chemo?

Implications for Practice

• When Mrs. D. A. Thomas calls you, her internist of 10 years who “knows me better than anyone”, to confirm the opinion of her world-famous breast surgeon, you can reassure her that axillary dissection will not improve her survival despite a positive sentinel node
• You can also mention that she is less likely to suffer long-term complications such as lymphedema

Case

• A 55 year old woman undergoes routine mammography. She obtains her report through the new “patient portal” of your EMR – and asks you what she should do about “arterial calcifications”?

What do you tell her?

A. The calcifications are insignificant and should not have been put on the report
B. The calcifications may have predictive value for development of coronary heart disease; she should see you to discuss modification of her other cardiac risk factors
C. The calcifications are hugely worrisome; she needs to undergo stress testing right away

Background

• Coronary heart disease (CHD) is the leading cause of death in women
• 500,000 deaths per year
• Previous studies have shown an increased radiographic prevalence of intimal artery calcifications in patients with CHD (coronary artery, aorta)\(^1\)\(^-\)\(^2\)
• Concern about age as a confounding variable

\(^1\)Moore ET, et al. Radiology 1989;172:711-6
Benign Breast Arterial Calcification

- Often appear as parallel tracks
- Usually in the medial layer
- Prevalence of 9% of all mammograms
- Prevalence increases to 50% in women over age 65

From American Journal of Roentgenology

The News: Breast Arterial Calcification on Mammography

- Aim: To estimate whether mammography can be an early, valid tool for predicting the development of coronary heart disease in women.

Methods

- 5 year prospective cohort study
- 1995 women enrolled at 4 outpatient radiology facilities
- Baseline questionnaire: demographics, risk factors for CHD, personal history of CHD, menopausal status, HT use
- Repeat questionnaires at years 2, 4, and 5
- Blinded review of films for breast arterial calcification (BAC)
- Primary outcome: development of CHD

Results

- 1451 women included in analysis
  - Mean age 56.3 (± 12.1) years, 94.7% white, 60.9% post-menopausal
  - At baseline, 16.3% were BAC-positive
    - Were older (68.7 vs. 54.3 years)
    - Had a higher prevalence of 4 out of 6 CHD risk factors
  - Over the 5 year study:
    - Prevalence of CHD was 20.8% in BAC-positive group vs. 5.4% in the BAC-negative group (p<0.001)

- Among women with no CHD at baseline, BAC-positive women more likely to develop CHD than BAC-negative women (6.3% vs. 2.3 %, p=0.003)
- Forest plot of statistically-significant contributors to 5 year incidence of CHD (controlled for age and other variables):

Conclusions

- Presence of breast arterial calcification on mammography is a marker for development of CHD, independent of age
- Strength of association comparable to, if not stronger than, other cardiac risk factors
- BAC is currently under-reported as an incidental finding
Implications for Practice

- Consideration should be given to routine reporting of BAC on mammography
- May allow for earlier detection and prevention of CHD events through aggressive risk factor modification

Key Article

- Aim: To update the 2007 guidelines to include data on effectiveness (observed clinical risks and benefits) in addition to efficacy (controlled trials)

Key Points

- New risk classification scheme:
  - **High Risk**: CHD, PAD, CVD, CKD, DM, AAA, 10-year risk ≥ 10%
  - **At Risk**:
    - Major cardiac risk factors
    - Evidence of advanced subclinical atherosclerosis (coronary calcification, carotid plaque, or ↑ IMT),
    - Systemic collagen vascular disease
    - H/o preeclampsia, gestational DM, HTN in pregnancy
  - **Ideal Cardiovascular Health**: Good BP, cholesterol, physical activity, diet

Key Points

- Stronger physical activity recommendations:
  - Moderate ≥ 150 minutes/week, or
  - Vigorous ≥ 75 minutes/week
- More stringent diet recommendations:
  - DASH or DASH-like
  - May include omega-3 fatty acids (in fish or supplement) for women with ↑ cholesterol or triglycerides
- Variety of acceptable 10-year risk assessment tools: Framingham, Reynolds, etc.
- Aspirin may be useful in women ≥ 65 (81 mg daily or 100 mg every other day) if BP controlled and benefit outweighs bleeding risk

Management of the Menopausal Woman

Megan McNamara, MD

The Saga of Hormone Replacement Therapy Continues…

- Three types of women I now have in my practice:
  - Women who were previously treated with HRT but discontinued it
  - Women who are currently being treated with HRT
  - Women who never want to be treated with HRT

What is the most current evidence for counseling each of these women about the risks, benefits, and efficacy of treatment?
Women who were previously treated with HRT

Case
- Ms. M. is a 60 year old female who presents to your office for routine preventive care. At age 51 she started combined HRT for treatment of severe hot flashes, and continued therapy for about 3 years.
- A close friend is being treated for breast cancer.
- Ms. M. wonders if her HRT did “lasting damage.” What do you tell her?

What do you tell Ms. M.?
A. There is no evidence that combined HRT increases the risk of breast cancer, so she doesn’t have to worry
B. Combined HRT increases the incidence of breast cancer, but the cancers are more benign
C. Breast cancer patients treated with HRT actually had longer survival than those who weren’t on HRT
D. If the HRT is discontinued, the risk of invasive breast cancer goes away, so there is no “lasting damage”
E. None of the above

Refresher
- Observational studies: breast cancers diagnosed in HRT users were more favorable and lower stage than in non-HRT users
- WHI E+P RCT: increased risk of invasive breast cancers + delayed breast cancer diagnoses >>> more advanced-stage cancers
- Unknown:
  - 1) Breast cancer incidence declined after discontinuation of HRT in the WHI E+P study, but what is the long-term effect on incidence?
  - 2) Is breast cancer mortality affected by E+P use?

The News
- Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women
- Aim: To assess the long-term effect of combined E+P therapy on cumulative breast cancer incidence and breast cancer mortality

Methods
- Long-term follow-up of women included in the initial WHI E+P trial
- 678 cases of breast cancer identified through August, 2009 with mean follow-up of 11.0 years

<table>
<thead>
<tr>
<th>Phase of Trial</th>
<th>Dates</th>
<th>Number of Women in the E+P Group</th>
<th>Number of Women in the Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention Phase</td>
<td>November 1993-July 2002</td>
<td>8506</td>
<td>8102</td>
</tr>
<tr>
<td>Postintervention Phase</td>
<td>July 2002 - March 2005</td>
<td>8056</td>
<td>7682</td>
</tr>
<tr>
<td>Extension Phase</td>
<td>April 2005-August 2009</td>
<td>Consented: 6545</td>
<td>Consented: 6243</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analyzed: 8506</td>
<td>Analyzed: 8102</td>
</tr>
</tbody>
</table>
Methods

- Women who did not consent to the extension phase were censored March 31, 2005 (breast cancer incidence) and December 31, 2005 (breast cancer mortality), although they could continue to be followed up for vital status (overall mortality).
- Secondary analyses adjusted hazard ratios for reconsent rates according to baseline characteristics and randomization assignment.

Results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%) of Invasive Breast Cancers</th>
<th>Number (%) of Invasive Breast Cancers Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size &gt;2cm</td>
<td>77 (21.2)</td>
<td>48 (17.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Positive lymph nodes</td>
<td>81 (23.9)</td>
<td>43 (16.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of positive lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>258 (76.3)</td>
<td>218 (83.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>1-3</td>
<td>60 (17.8)</td>
<td>34 (13.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>20 (5.9)</td>
<td>8 (3.1)</td>
<td></td>
</tr>
<tr>
<td>SEER Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>288 (75.2)</td>
<td>238 (81.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Regional</td>
<td>86 (22.5)</td>
<td>46 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td>5 (1.3)</td>
<td>7 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- Combined E+P therapy increases the cumulative risk of invasive breast cancer, and diagnosed cancers are more likely to be node-positive.
- This risk becomes evident within about 4.7 years of randomization and is persistent through a total of 11 years of follow-up.
- There was a statistical trend for an increased risk of breast cancer deaths in the E+P group.

Impact for Practice

- Another study which suggests that there are significant harms associated with combined E+P therapy, and that risks may persist after discontinuation of therapy.
- Continued careful selection of patients for combined E+P therapy is warranted.
Key Supporting Article

• Lung Cancer Among Postmenopausal Women Treated with Estrogen Alone in the Women's Health Initiative Randomized Trial – Chlebowski et al. 2010
• What is known: combined E+P therapy in the WHI increased lung cancer mortality
• What is hypothesized: hormones (especially progestin) stimulate angiogenesis, which may increase lung and breast cancer metastases
• What is unknown: the effect of E therapy alone on lung cancer incidence and mortality

Key Supporting Article

• Post-hoc analysis of data from the WHI E-only trial
• Similar numbers of women in the estrogen-only and placebo group were diagnosed with lung cancer, and non-small cell cancers were of comparable number, stage, and grade
• There was no increased risk of lung cancer death associated with E therapy

Case

• Mrs. R. is a 52 year old healthy female presenting with severe hot flashes. She has no known medical problems, but her mother died of a stroke.
• She was given a prescription for oral 0.625 CEE/2.5 MPA by her gynecologist, but wants your opinion about whether this will increase her risk of stroke.
• Her best friend is on an “hormone patch.”
• What do you tell her?

Women who are currently being treated with HRT

All of the following are true EXCEPT...?

A. Her overall risk for stroke is low.
B. A lower dose of estrogen + progestin might minimize her risk for stroke.
C. The “hormone patch” is more likely to cause stroke than oral HRT.
D. Oral HRT increases the risk of stroke by 30%.

Refresher

• Several trials have shown that oral HRT increases the risk of stroke by 30% – Both estrogen or estrogen + progestin therapy
• Transdermal estrogen is as effective for relieving hot flashes as oral estrogen and avoids hepatic first-pass effect
• Hypothesis: transdermal HRT may have less effect on cardiovascular risk than oral therapy
The News

- Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study

**Aim:** To assess the risk of stroke associated with oral and transdermal hormone replacement therapy

### Methods

- Exposure information
  - Index date = date of first stroke
    - same date for both cases and controls
  - All prescriptions for HRT issued during the year preceding the index date
  - Oral vs. transdermal
  - Low dose vs. High dose
    - <0.625mg EE vs. >0.625 EE or
    - <2mg oral estradiol vs. >2mg oral estradiol or
    - <50µg transdermal vs. >50µg transdermal

### Results:

#### Risk of Stroke According to Drug Type and Route of Administration

<table>
<thead>
<tr>
<th>Type of HRT</th>
<th>Cases N=15,710</th>
<th>Controls N=59,958</th>
<th>Adjusted Rate Ratio‡</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>14,496</td>
<td>55,834</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen only</td>
<td>81</td>
<td>317</td>
<td>1.02</td>
<td>0.78-1.34</td>
</tr>
<tr>
<td>Estrogen + Progestin</td>
<td>22</td>
<td>124</td>
<td>0.70</td>
<td>0.47-1.22</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen only</td>
<td>262</td>
<td>802</td>
<td>1.35</td>
<td>1.16-1.58</td>
</tr>
<tr>
<td>Estrogen + Progestin</td>
<td>356</td>
<td>1233</td>
<td>1.24</td>
<td>1.08-1.41</td>
</tr>
</tbody>
</table>

‡Adjusted for: age, BMI, smoking, ET, DM, Htn, hyperlipidemia, HTN, dcb, CV disease, TIA, use/NSAID, use, history of hysterectomy or oophorectomy.

### Conclusions

- Transdermal hormone therapy was not associated with an increased risk of stroke
- Comparatively, oral estrogen therapy did increase the risk for stroke, and higher doses were associated with greater risk
- Taking it with a grain of salt:
  - Many fewer patients were using transdermal therapy as compared to oral therapy, so differences might be difficult to detect
  - Inherent biases present in any case-control study
Impact for Practice

• Results suggest that transdermal HRT may be safer
• It is just as effective as oral therapy for treating hot flashes
• There is biological plausibility for these results
• More research is needed, but for now, I will preferentially recommend transdermal HRT

Key Supporting Article

• Estrogen and Progestogen Use in Postmenopausal Women: 2010 Position Statement of The North American Menopause Society
• Harms of treatment:
  – No increased risk of CHD if HRT initiated in women aged 50-59 or within 10 years of menopause
  – Breast cancer risk greater among those with a shorter "gap time"
• Discontinuing HRT:
  – No benefit for tapering
  – DEXA scanning for some women

Case

• Ms. R.T. is a 48 year old African-American female with severe hot flashes and night sweats. She is a lawyer, and the hot flashes are affecting her work.
• She has tried dressing in layers, avoiding hot beverages, and even herbal supplements, but nothing seems to help.
• She is desperate for relief, but really wants to avoid HRT because of a strong family history of breast cancer.
• She has seen Lexapro™ (escitalopram) advertised on TV and wants to know if it would work for her.

Which of the following is true?

• A. Escitalopram is effective for treating hot flashes, but only works in women with anxiety or depression
• B. African-American women are less likely than Caucasian women to respond to escitalopram for hot flash treatment
• C. Dry mouth, increased sweating, and fatigue are all more common in women treated with escitalopram
• D. Fifty-five percent of women treated with escitalopram experienced a 50% reduction in hot flash frequency

Refresher

<table>
<thead>
<tr>
<th>Medication and Dose</th>
<th>% of Treated Patients with 50% Reduction in Hot Flash Frequency</th>
<th>% of Placebo Patients with 50% Reduction in Hot Flash Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine 37.5-150mg/d</td>
<td>54-70%</td>
<td>30%</td>
</tr>
<tr>
<td>Paroxetine 12.5-25mg/d</td>
<td>50-76%</td>
<td>33-57%</td>
</tr>
<tr>
<td>Sertraline 50-100mg/d</td>
<td>40-56%</td>
<td>21-41%</td>
</tr>
<tr>
<td>Gabapentin 300-2400mg/d</td>
<td>46-84%</td>
<td>27-47%</td>
</tr>
</tbody>
</table>

The News

- Efficacy of Escitalopram for Hot Flashes in Health Menopausal Women: A Randomized Trial
- Freeman EW et al. JAMA 2011; 305(3):267-274.
- AIM:
  - To determine the efficacy of escitalopram for reducing the frequency, severity, and bother of hot flashes
  - To determine if there is effect modification with regard to race, menopausal status, depressed mood, or anxiety

Results: Study Population

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>(% of Women Escitalopram Group)</th>
<th>(% of Women Placebo Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 50-54 years</td>
<td>46.2</td>
<td>46.9</td>
</tr>
<tr>
<td>African American</td>
<td>45.2</td>
<td>47.5</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>80.9</td>
<td>82.2</td>
</tr>
<tr>
<td>No hysterectomy or oophorectomy</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>Self-reported health is Excellent, Very Good, or Good</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>PHQ-9 Depression Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No depression</td>
<td>73.1</td>
<td>76.2</td>
</tr>
<tr>
<td>Mild depression</td>
<td>23.1</td>
<td>14.9</td>
</tr>
<tr>
<td>Moderate depression</td>
<td>3.8</td>
<td>7.9</td>
</tr>
<tr>
<td>GAD-7 Anxiety Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anxiety</td>
<td>76.9</td>
<td>81.2</td>
</tr>
<tr>
<td>Mild anxiety</td>
<td>18.3</td>
<td>14.9</td>
</tr>
<tr>
<td>Moderate anxiety</td>
<td>4.8</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Results

- Percent of women who experienced > 50% reduction in hot flash frequency
  - Escitalopram: 55%
  - Placebo: 36%
- No effect modification according to race, menopausal status, or depression and anxiety scores
- More adverse events reported in placebo than escitalopram group

Conclusions

- Escitalopram was effective in reducing hot flash severity and frequency
  - both African American and Caucasian women
- Therapy was well-tolerated
- Symptoms returned once escitalopram was discontinued
**Impact for Practice**

<table>
<thead>
<tr>
<th>Medication and Dose</th>
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</tr>
<tr>
<td>Escitalopram 10-20mg/d</td>
<td>56%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Another arrow in my quiver! Safe, well-tolerated, and useful even in patients who are not anxious or depressed.

**Bone Health, Calcium and Vitamin D**

- Calcium and myocardial infarction and cardiovascular events
- High dose Vitamin D and falls and fractures
- Bisphosphonates and atypical femoral fractures

**Case**

- 67 year old woman with hypertension and osteopenia comes in for an annual examination. As you review her medications with her, she tells you that she has stopped taking her calcium supplements because she heard that calcium might cause heart attacks. What do you tell her?

**Choices**

- 1. Keep taking your calcium- it’s good for your bones
- 2. As long as you are taking Vitamin D with it, it should be fine
- 3. Good decision. Stay off the calcium

**Background**

- Calcium supplements are widely recommended for bone health
- Previous studies have shown that calcium is necessary but not sufficient for reducing osteoporosis risk
- A 5 year randomized controlled trial in healthy older women, where CVD outcomes were prespecified showed possible increases in MI and cardiovascular events in women who took calcium

  = Roland MI et al. BMJ 2008;336:262-6
The News

- Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis
  - Bolland M et al. BMJ 2010;341:c3691
- AIM: To determine whether calcium supplements increase the risk of cardiovascular events

Methods

- Patient level and trial level meta-analysis
- Eligible articles were RCTs, at least 100 participants, age >40 and duration at least a year
- Lead authors provided data
- CV outcomes measured by self report, hospital admissions and death certificates

Results

- 15 eligible trials
  - 5 had patient level data
    - n= 8,151
    - Median follow-up 3.6 years
  - 11 had trial level data
    - n= 11,921
    - Mean of 4 years

- NNT with calcium for five years to cause one incident event
  - MI: 69
  - Stroke: 100
  - MI, stroke or sudden death: 61
  - Death: 77

Fig 2. Cumulative incidence of myocardial infarction, stroke, composite of myocardial infarction, stroke, or sudden death, and death by treatment allocation in five studies that contributed patient level data.

Fig 3. Random effects models of effect of calcium supplementation on cardiovascular events and death.
Conclusion

• Calcium supplements were associated with a 30% increase in myocardial infarction and smaller, non-significant increases in stroke and mortality
  – MI risk was higher in those with a dietary calcium intake above the mean
• Findings consistent across trials
• Did not include calcium co-administered with Vitamin D

Impact for Practice

• Calcium supplements without co-administered Vitamin D are associated with a small increased risk of MI
• Calcium supplements modestly increase BMD and have a modest protective effect against fracture
• Reassessment of the role of calcium alone for osteoporosis prevention

Key Article

• Background: Calcium and Vitamin D may act independently and interactively
• Analysis of Calcium supplementation, Vitamin D supplementation or both on CVD outcomes

Key Article

• Reduction in CVD risk with Vitamin D supplementation at moderate to high doses (100 IU per day)
• No impact on CVD with calcium supplements
• No impact on CVD with combined calcium and Vitamin D

CASE

• Vita Dee is a 65 year old woman with hypertension and osteopenia. She takes a calcium and Vitamin D supplement but worries that she should be getting more Vitamin D. What do you tell her about how much she needs?

Vitamin D

• 1. 1,000 IU per day
• 2. 2,000 IU per day
• 3. 50,000 IU once a week
• 4. 600 IU per day
Background

• The role of Vitamin D in human health has received widespread attention
• Vitamin D clearly has a role in bone health but association with other health outcomes has been less clear
• 25-OH Vitamin D levels are widely ordered and deficiency widely treated

THE NEWS

• Annual high-dose oral Vitamin D and falls and fractures in older women
• AIM: To determine whether a single annual dose of Vitamin D could reduce the risk of falls and fracture

Background

• The results of RCTs of the effect of Vitamin D on falls and fractures have been inconsistent
• Fracture risk reduction may be greater among adherent patients

Methods

• Single center, double blind RCT among 2,256 community dwelling, Australian women aged 70 and older
  – All at higher hip fracture risk
  – Past fracture, maternal history of fracture, self identified faller
• Single annual dose of cholecalciferol (500,000 IU) vs placebo for 3-5 years
  – Autumn or winter
• Falls and fractures measured by monthly calendar and telephone interviews
  – Radiologic confirmation of fractures in substudy

Results

• 155 women on Vitamin D had 171 fractures and 125 on placebo had 135 fractures
• RR for fracture in Vitamin D group
  – 1.26 (95% C.I. 1.00, 1.59) vs the placebo group
  – 4.9 vs 3.9 per 100 person years
• RR for falling in Vitamin D group
  – 1.31 (95% C.I. 1.12-1.54) in the first three months
  – 1.13 (95% C.I. 0.99, 1.29) in subsequent 9 months
  – (p<0.02 for homogeneity)

Conclusion

• Annual high dose Vitamin D was associated with an increased risk of falls and fractures
• Increase in falls was highest in the first 3 months after the Vitamin D
Impact for Practice
• High dose annual supplementation is not recommended
• The impact on fractures and falls of more frequent or lower doses of Vitamin D is less clear

Key Article
• Recent publication of new IOM guidelines for calcium and Vitamin D
  • www.iom.edu/reports/2010/Dietary-Reference-intakes-for-Calcium-and-Vitamin-D
• RDA
  – 600 IU for women aged 9-70
  – 800 IU for women over age 70
  – Upper limit 4,000 IU per day
• 25-OH Vitamin D level of 20 ng/ml is the goal

Follow-up
• Bonnie Bony is a patient who you started on a bisphosphonate last year because of a hip BMD t score of -3.0. She calls your office to inform you that she has stopped her bisphosphonate because she has been reading about an increased risk of fractures in women who take these medications. What are you going to advise her?

Case
• 1. Good idea. Stay off your alendronate
• 2. We need to restart it right away
• 3. Let’s check a bone density and decide
• 4. Let’s just switch to daily PTH injections

The News
• Black DM et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. NEJM 2010;362:1761-71
• AIM: To determine the incidence of femoral shaft fractures in patients in bisphosphonate RCTs

Background
• Several case series have described an increased risk of atypical femoral shaft fractures in bisphosphonate users
  – Subtrochanteric fracture makes up 2-4% of all hip fractures
  – No estimate of population prevalence
• In population based registries, fracture rates higher in alendronate users
  – Increased alendronate use in high risk individuals
RESULTS

- 284 hip or femur fractures in 14,195 women in 3 randomized trials
  - 12 were subtrochanteric or diaphyseal
- Relative hazards
  - RH 1.03 (95% C.I. 0.06, 16.46) for alendronate use in FIT
  - RH 1.50 (95% C.I. 0.25, 9.00) for zoledronic acid use in HORIZON-PFT
  - RH 1.33 (95% C.I. 0.12, 14.67) for continued alendronate use in FLEX

CONCLUSIONS

- Fracture of subtrochanteric or diaphyseal femur was very rare even in women on bisphosphonates for up to 10 years
- There was no significant increase in risk but confidence intervals were wide
  - Small number of events

Impact for Practice

- Even if there is a small risk of atypical fracture associated with bisphosphonate use, this must be weighed against the population benefits associated with an overall reduction in hip fractures with bisphosphonates in women with osteoporosis

Key Article

- USPSTF Recommendations on Screening for Osteoporosis
- Screen women aged 65 and older
- Screen younger women whose fracture risk is equal to or greater than a 65 year old white woman who has no additional risk factors
  - FRAX tool (http://www.sheffield.ac.uk/FRAX)

Key Article

- Lasofoxifene (0.5 mg per day) reduced risk of vertebral and nonvertebral fractures, ER-positive breast cancer, CHD and stroke but increased DVT

Key Articles

- Bisphosphonates were associated with a lower risk of breast cancer in two observational studies
- Proton pump inhibitors were not associated with hip fractures but were associated with clinical spine, forearm and wrist fractures
Key Article

- Management of osteoporosis in postmenopausal women: 2010 position statement of the North American Menopause Society
  - Menopause 2010: 17:25-54

- Highlights
  - Periodic review of calcium, Vitamin D and lifestyle
  - Assess fall risk annually and when physical/mental status changes

NOF Highlights

- Pharmacologic treatment:
  - women with fractures or osteoporosis
  - osteopenia who have a 10 year fracture risk of at least 20% and a 10 year hip fracture risk of at least 3%

- Drug choices
  - Bisphosphonates are first line
  - Consider PTH for women with osteoporosis at high risk

- Fracture risk after discontinuing therapy has not been adequately evaluated

Summary

- Issues for Reproductive Aged Women
- Diseases of Early Adulthood into Mid-Life
- Management of the Menopausal Woman
- Osteoporosis and Bone Health

Questions?