Clinical Update in General Internal Medicine

CS01:
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Anticoagulation Therapy

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Atrial Fibrillation

- Associated with a high rate of thromboembolic events
- Warfarin (Coumadin) reduces risk by >50% but...
  - Burdensome monitoring
  - Many drug-drug and food interactions
  - Narrow therapeutic window
  - Risk of serious bleeding
- Search for alternatives unsuccessful
  - Ximelagatran (direct thrombin inhibitor)—hepatotoxic
  - Aspirin, clopidogrel: much less effective than warfarin
CHADS2 Stroke Risk Score

- Congestive heart failure
- Hypertension
- Age > 75
- Diabetes mellitus
- Stroke history (2 points)

***based on Medicare data so unclear utility in younger patients
# CHADS2 Stroke Risk Score

<table>
<thead>
<tr>
<th>CHADS2 SCORE</th>
<th>Annual Stroke Risk</th>
<th>Usual Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1-2 %</td>
<td>Aspirin 81-325 mg</td>
</tr>
<tr>
<td>1</td>
<td>3 %</td>
<td>Aspirin 325 mg or Warfarin</td>
</tr>
<tr>
<td>2</td>
<td>4 %</td>
<td>Warfarin</td>
</tr>
<tr>
<td>3</td>
<td>6 %</td>
<td>Warfarin</td>
</tr>
<tr>
<td>4</td>
<td>8 %</td>
<td>Warfarin</td>
</tr>
<tr>
<td>5</td>
<td>12 %</td>
<td>Warfarin</td>
</tr>
<tr>
<td>6</td>
<td>16 %</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>
Dabigatran

- Potent oral direct thrombin inhibitor
- Serum half-life > 12 hours
- Causes predictable degree of competitive thrombin inhibition
- Does NOT require any monitoring
- Shown to be equal to warfarin in safety and efficacy in the prevention of venous thromboembolic disease in hip and knee arthroplasty patients
Patients with atrial fibrillation PLUS 1 or more:
- Previous stroke/TIA
- LV function < 40%
- CHF symptoms in past six months (Class II-IV)
- 75 years of age or older
- 65-74 years of age PLUS DM, hypertension, coronary artery disease

Excluded: recent MI, recent stroke, CKD > 3, significant valvular heart disease
Methods (Con’t)

- 951 clinical centers in 44 countries
- Patients randomized to one of three groups
  - Coumadin INR adjusted 2-3 at central facility
  - Dabigatran 110mg orally twice daily
  - Dabigatran 150mg orally twice daily
- Follow-up every 3-4 months for entire study
- Liver-associated enzymes monitored monthly for six months, then intermittently
Outcomes

- **Primary outcomes:**
  - Stroke or systemic embolism
  - Major hemorrhage (2+ g/dl hemoglobin drop, CNS bleeding, transfusion-requiring)

- **Secondary outcomes:**
  - MI
  - Pulmonary embolism
  - Hospitalization
  - Death
Results - Patient Characteristics

- 18,000 patients 2005-2007
- Mean age 71, 63% men
- Mean CHADS2 score 2.1
- Half had long-term warfarin use prior to study
- Median follow-up 2 years, 99.9% complete
### Results: Outcomes

<table>
<thead>
<tr>
<th></th>
<th>STROKE/EMBOLISM annual rate</th>
<th>HEMORRHAGIC STROKE annual rate</th>
<th>MORTALITY annual rate</th>
<th>MAJOR BLEEDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>1.69 %</td>
<td>0.38%</td>
<td>4.13%</td>
<td>3.36%</td>
</tr>
<tr>
<td>Dabigatran 110mg BID</td>
<td>1.53%</td>
<td>0.12% (*RR = 0.31 CI 0.17-0.56)</td>
<td>3.75% *</td>
<td>2.71% *</td>
</tr>
<tr>
<td>Dabigatran 150mg BID</td>
<td>1.11 % (*RR = 0.66 CI 0.53-0.82)</td>
<td>0.10% (*RR = 0.26 CI 0.14-0.49)</td>
<td>3.64% *</td>
<td>3.11%</td>
</tr>
</tbody>
</table>
More Results

- Dyspepsia more common with Dabigatran (11% vs. 6%)
- Slightly higher risk (trend) for MI with Dabigatran
- ALT+AST elevations > 3 times normal: 2% all groups
- No difference in patients previously on warfarin
- Discontinuation rates similar: 21% Dabigatran vs. 17% warfarin
- Warfarin group: INR in target range 64% of the time
Conclusions

- Dabigatran is non-inferior to warfarin in patients with atrial fibrillation with respect to prevention of systemic emboli, stroke, death, major hemorrhage.

- Dabigatran performs superiorly in some ways, though with slightly higher side effects (dyspepsia) and possibly more MI.
Comments

- Real world scenario: less compliance with dabigatran twice daily?
- Real world scenario: 64% of the time target INR range is not realistic, usually 30-50%
- No data on patients with valvular disease, prosthetic valves
Treatment of Venous Thromboembolism

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Background

- Venous thromboembolism (VTE) is common, and the third most common cause of vascular death (MI, CVA)
- Dabigatran has been shown to have similar efficacy and safety to enoxaparin (Lovenox LMWH) in the prevention of VTE in patients undergoing elective hip or knee arthroplasty
- Standard of care is to use warfarin (Coumadin), which is cumbersome to use safely
turning to this study...
Dabigatran Use in the Treatment of Venous Thromboembolism - Objectives

To determine whether dabigatran has equal safety and efficacy compared to warfarin when used to treat patients with venous thromboembolic disease
Dabigatran Use in the Treatment of Venous Thromboembolism - Methods

- Patients with acute symptomatic proximal DVT or pulmonary embolism
  - 18 years of age or older
  - Verified by VQ scan, spiral CT, angiography, doppler, venography
  - Six months of anticoagulant felt to be appropriate

- Exclusions:
  - Hemodynamic instability
  - Life expectancy < 6 months
  - Pregnancy, CKD 3-5, liver disease with ALT > 2x normal
Methods (Con’t)

- 228 clinical centers in 29 countries
- Treated with >5 days heparin or LMWH first then:
  - Randomized double blind double dummy trial:
    - Fixed dose dabigatran 150mg twice daily or
    - Warfarin adjusted to INR = 2-3 goal
    - Patients on dabigatran had ‘sham’ INR/adjustments
- Assessed monthly for a total of six months of treatment, plus an additional month after stopping treatment, for clinical recurrence of VTE or bleeding
- Primary efficacy outcome: death or symptomatic VTE
RE-COVER Results

- Nearly 2,500 patients (80% North America or Europe)
- Parental anticoagulation given for a mean of 10 days
- Mean age 55, 40% female, 95% white
- 69% had only DVT, 21% had only PE, 5% malignancy
- INR at target 60% of the time, 20% high and 20% low
## More RE-COVER Results

<table>
<thead>
<tr>
<th></th>
<th>Primary End-point: VTE or VTE-death</th>
<th>Major Bleeding</th>
<th>Any Bleeding Event</th>
<th>All-cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
<td>2.4%</td>
<td>1.9%</td>
<td>21.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>2.7%</td>
<td>1.6%</td>
<td>16.1% *</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
More Results

- Dabigatran group more likely to stop drug due to adverse event (9% vs. 6.8% hazard ratio 1.33 (1.01-1.76))
- Dabigatran group had higher rates of dyspepsia 2.9% vs. 0.6% in warfarin (p<.001)
- NO difference in elevation of liver associated enzymes
- NO difference in MI incidence (0.2% in both)
Implications for Internal Medicine

- Dabigatran is equal to warfarin in the prevention of stroke in patients with atrial fibrillation
- Dabigatran is equal to warfarin in the treatment of venous thromboembolism

Uncertainties
- Use of dabigatran in patients with prosthetic heart valves?
- Long-term risk of dabigatran?
- Use of dabigatran as initial therapy in VTE (without heparin/LMWH)?
Management of Hyperlipidemia

Extended-Release Niacin or Ezetimibe and Carotid Intima-Media Thickness

Background

- Therapy with statin drugs have been definitively shown to reduce cardiovascular events and death.
- Increased risk reduction with increasing magnitude of LDL reduction, down to at least 50 mg/dl.
- This reduction in risk is generally correlated with a reduction/delay in progression of carotid intima-media thickness (as a marker of atherosclerosis).
- Unclear what is the best approach to further reduce the residual risk (after statin use is maximized) in patients with residual lipid values that are not at goal.
Background: Ezetimibe and Niacin

- **Niacin:**
  - Raises HDL, lowers triglycerides, lowers LDL cholesterol
  - Reduces cardiovascular events (secondary prevention)

- **Ezetimibe (Zetia):**
  - Reduces LDL cholesterol
  - Has NOT been shown to reduce cardiovascular events or improve outcomes (when added to statins)
  - Has been shown in one study to increase cancer risk
  - Has had > $10 billion in sales
turning to this study...
Effects of Niacin vs. Ezetimibe on Carotid Intima-Media Thickness

Objectives:

To compare the effects on carotid intima-media thickness of Ezetimibe compared to extended-release niacin, in patients already on statin therapy.
Effects of Niacin vs. Ezetimibe on Carotid Intima-Media Thickness: Methods

- The patients:
  - Men and women > 30 years of age
  - Framingham risk score 10-year risk of >20%
    or
  - Known cardiovascular disease or
  - Diabetes mellitus (or other ‘cad equivalent’)
  - All were on statin therapy chronically
  - All had LDL < 100 mg/dl and HDL < 50 mg/dl
    (< 55 mg/dl in women)

- The setting: two centers, Walter Reed Army Medical Center and a private tertiary care hospital (Washington Adventist Hospital)
Effects of Niacin vs. Ezetimibe on Carotid Intima-Media Thickness: Methods

- Randomized open-label study:
  - Extended release niacin starting at 500 mg with a target dose of 2000 mg daily if tolerated or
  - Ezetimibe 10 mg daily

- Primary end point: between-group difference in the change in mean carotid intima-media thickness after 14 months (Reader blinded to treatment group)

- Secondary end points: lipid values, composite major adverse cardiovascular events
Effects of Niacin vs. Ezetimibe on Carotid Intima-Media Thickness: Results

- Baseline patient characteristics
  - Average age 65, 80% male
  - 65% had angiographic CAD
  - LDL 80 mg/dl; HDL 43 mg/dl
  - 95% on aspirin, 30% clopidogrel, 75% beta blocker

- Study was stopped prematurely due to mid-point analysis showing higher rates of cardiovascular events in the ezetimibe group compared to the niacin group
## Effects of Niacin vs. Ezetimibe on Carotid Intima-Media Thickness: Results

<table>
<thead>
<tr>
<th></th>
<th>Extended-release niacin</th>
<th>Ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL change</strong></td>
<td>- 10 mg/dl</td>
<td>-18 mg/dl ***</td>
</tr>
<tr>
<td><strong>HDL change</strong></td>
<td>+ 7 mg/dl ***</td>
<td>- 3 mg/dl</td>
</tr>
<tr>
<td><strong>Carotid thickness</strong></td>
<td>-.014 mm ***</td>
<td>-.001 mm</td>
</tr>
<tr>
<td>(14mo)</td>
<td>(significant change vs. baseline)</td>
<td>(no significant change vs. baseline)</td>
</tr>
<tr>
<td><strong>Major cardiovascular outcomes</strong></td>
<td>2/160 patients (1%)</td>
<td>9/165 patients (5%) ***</td>
</tr>
</tbody>
</table>
Limitations

- Study stopped prematurely, limiting its power
- What is the usefulness of carotid intima-media thickness as a surrogate marker for cv events?
  - Data are mixed, but generally positive
- These results, even if taken at face value, do not address patients with LDL that is NOT at goal
  - These patients had LDL < 100 and HDL < 50
  - What about statin intolerant patients?
  - What if LDL > 100 despite statin dose?
  - What if HDL > 50?
Implications for Internal Medicine

- For primary and secondary prevention of cardiovascular disease, maximize statin dose to achieve target LDL goal per published guidelines
- In patients in whom LDL goals are not met with statin therapy, extended-release niacin is a good second choice (shown to reduce cardiovascular outcomes)
- Ezetimibe has not been shown to reduce cardiovascular outcomes, unlike statins and niacin, and therefore should be used only as a third line agent
  - *Preliminary* evidence that ezetimibe is inferior
Concern About Use of Clopidogrel with Proton Pump Inhibitors

Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome

*JAMA, 2009;301:937-944*

A population-based study of the drug interaction between proton pump inhibitors and clopidogrel

*CMAJ, 2009;180:713-718*

Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with and without a proton pump inhibitor: an analysis of two randomized trials

*Lancet, 2009;374:989-997*
Is There a Reason for Concern?

- clopidogrel plus ASA standard for ACS and post-stent
- PPI often prescribed preventively
- however, PPI’s may reduce effect of clopidogrel on platelet aggregation
- variations in platelet reactivity associated with adverse outcomes after stents
turning to these studies...

- VA Study
  - retrospective cohort study of 8,205 post-discharge ACS patients
  - outcome measures:
    - all-cause mortality
    - rehospitalization for ACS

- Canadian study
  - case-control study of 13,636 post discharge MI patients
  - cases (on PPI’s)
    - readmission for MI within 90 days

- Lancet study
  - post-hoc analysis of PRINCIPAL-TIMI 44 and TRITON-TIMI 38 trials
Results – VA Study

- 64% of ACS-clopidogrel pts also received PPIs
- combination associated with death or rehospitalization for ACS 29.8% vs. 20.8% OR 1.25 (95% CI 1.11-1.41)
- revascularization more frequent with combination 14.6% vs. 6.9% OR 1.86 (95% CI 1.57-2.20)
Results

Canadian Case – Control Study

- Concurrent use of clopidogrel and all PPI’s post-MI associated with recurrent infarction OR 1.27 (95% CI 1.03-1.57)
- Association not seen with H2 antagonists and pantoprazole
- Other PPI’s associated with 40% increased risk of recurrent MI 95% CI 1.10-1.77
Results – Lancet Post-hoc Analysis of PRINCIPLE and TRITON Trials

- **PRINCIPLE** – inhibition of platelet aggregation attenuated with PPI

- **TRITON** – no association between PPI and risk of CV death, MI or stroke
Conclusions

- PPI’s do inhibit the active form of clopidogrel
  - pantoprazole least
  - omeprazole and esomeprazole most

- case-control and cohort studies suggest clinical significance

- post-hoc analysis of two thienopyridines trials do not support this concern
Implications for Internal Medicine

- PPI’s should be prescribed selectively, not routinely, in patients on clopidogrel and aspirin for ACS or post-stent

- pantoprazole may be PPI of choice in this situation
PPIs for Poorly Controlled Asthma

Efficacy of esomeprazole for treatment of poorly controlled asthma.

## Poorly Controlled Asthma

<table>
<thead>
<tr>
<th></th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sx</strong></td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td><strong>Nighttime awakenings</strong></td>
<td>&gt; 1x/wk</td>
<td>Often 7x/wk</td>
</tr>
<tr>
<td><strong>SABA for Sx control</strong></td>
<td>Daily</td>
<td>Several x’s/day</td>
</tr>
<tr>
<td><strong>Lung Function</strong></td>
<td>FEV. &gt;60% but &lt;80%</td>
<td>FEV. &lt;60%</td>
</tr>
</tbody>
</table>
NAEPP-III Guidelines for Diagnosis and Management of Asthma – Initial Assessment

- classify severity
- identify precipitating factors
- assess patient’s knowledge and skills
- identify comorbid conditions
  - OSA
  - obesity
  - stress and depression
  - sinusitis, rhinitis, ABPA
  - GERD
Gastroesophageal Reflux (GERD) and Asthma

- overlapping prevalence, both common
- possible mechanisms of interaction
- clinical observations and studies
  - early studies
  - RCTs
  - Cochrane review
turning to this study...
Study of Acid Reflux in Asthma (SARA)

- 412 participants (age ≥ 18) at 19 centers
- all “inadequately controlled but no sx of GERD”
- initial evaluation included ambulatory esophageal pH monitoring (blinded)
- randomized to Rx with 40mg BID esomeprazole vs. placebo
- outcomes (24 week study)
  - PEFR
  - asthma symptoms
  - beta agonist use
  - diary and spirometry every 4 weeks
### Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=193)</th>
<th>Esomeprazole (n=200)</th>
<th>RX vs. placebo (all subjects)</th>
<th>Subjects with GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>asthma flares</td>
<td>2.3</td>
<td>2.5</td>
<td>0.66</td>
<td>0.93</td>
</tr>
<tr>
<td>urgent care visits</td>
<td>0.6</td>
<td>0.6</td>
<td>0.79</td>
<td>0.44</td>
</tr>
<tr>
<td>new use of oral steroids</td>
<td>0.6</td>
<td>0.5</td>
<td>0.62</td>
<td>0.85</td>
</tr>
<tr>
<td>exacerbations</td>
<td>4.4</td>
<td>4.3</td>
<td>0.87</td>
<td>0.19</td>
</tr>
<tr>
<td>night awakenings</td>
<td>30</td>
<td>28</td>
<td>0.70</td>
<td>0.31</td>
</tr>
<tr>
<td>asthma scores</td>
<td>0.3</td>
<td>0.3</td>
<td>0.33</td>
<td>0.81</td>
</tr>
<tr>
<td>gastric scores</td>
<td>-0.17</td>
<td>-0.16</td>
<td>0.76</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Overview of Results

- no treatment effect for asthma measures or symptom scores
Subgroup Analysis of Patients with Silent GERD – 40% of population

- no interaction between abnl pH monitoring and effect of PPI on asthma
- BMI and night awakenings did not predict response to PPI
- nor did asthma severity, self-reported reflux or asthma severity scores
Additional Points

- excluded patients with symptoms of GERD
- no benefit of PPI’s on primary or secondary asthma outcomes
- PPI’s may benefit GERD symptoms in asthmatics, but have little effect on the asthma
- asymptomatic GERD may not be a frequent cause of poor asthma control
Implications for Practice

- little or no role for PPI’s in asthmatics unless warranted by GERD symptoms or findings
- these patients can be spared the cost and inconvenience of GERD evaluation and treatment
Breast Cancer Screening

Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement

Ann Intern Med. 2009;151(10):716-726
Breast Cancer

- The most frequently diagnosed non-cutaneous cancer in women
- Second leading cause of cancer death among women in the United States
- 40,480 women died of breast cancer in the United States in 2008
Mammography

- Screening is sensitive (77%-95%), specific (94%-97%)
- Identifies disease in a preclinical stage, resulting in a reduction in mortality and an increase in life-years
- Potential harms:
  - Radiation exposure
  - Pain during procedure
  - Patient anxiety
  - False positive mammograms
  - Unnecessary biopsies
  - Over diagnosis (women diagnosed with breast cancer that would not have clinically progressed or affected mortality)
Guidelines for Screening Mammogram

- An update from the 2002 guidelines

- Previous recommendations
  - Screen all women every 1 to 2 years after age 40 with mammography with or without clinical breast exam (CBE)
  - In 2002, the USPSTF stated insufficient evidence to recommend for or against teaching or performing CBE
turning to this article...
Guidelines for Screening Mammogram

- 2009 Guidelines:
  - “The USPSTF recommends against routine screening mammography in women aged 40 to 49 years.” [C]
  - “The USPSTF recommends biennial screening mammography for women aged 50 to 74 years.” [B]
  - “The USPSTF recommends against teaching BSE.” [D]
Why the change in guidelines?


Nelson HD et al. Screening for Breast Cancer: An Update for the US Preventive Services Task Force (USPSTF)

- A meta-analysis of randomized controlled trials from 2001-2008
- Funded by the Agency for Health Care Quality (AHRQ) and Research and commissioned by the USPSTF and the AHRQ
Nelson HD et al. Screening for Breast Cancer: An Update for the US Preventive Services Task Force (USPSTF)

- Key Questions:
  - Does screening with mammography or MRI decrease breast cancer mortality among women aged 40-49 y and >/ 70 y?
  - Does CBE dec breast ca mortality?
  - Does BSE dec breast ca mortality?
  - What are the harms assoc with screening with mammography and MRI?
  - What are the harms assoc wth CBE?
  - What are the harms assoc with BSE?
Nelson HD et al. Screening for Breast Cancer: Results

<table>
<thead>
<tr>
<th></th>
<th># Needed to Invite</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality reduction with mammography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age 40-49y</td>
<td>1904</td>
<td>RR=0.85 (The Age trial)</td>
</tr>
<tr>
<td>- Age 50-59</td>
<td>1339</td>
<td>RR=0.86</td>
</tr>
<tr>
<td>- Age 60-69</td>
<td>377</td>
<td>RR=0.68</td>
</tr>
<tr>
<td>- Age 70-74 y</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
<tr>
<td><strong>Harms with mammography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain from study is brief and not a deterrent to future screening. Radiation exposure relatively low.</td>
</tr>
<tr>
<td><strong>CBE benefits and harms</strong></td>
<td></td>
<td>Inconclusive</td>
</tr>
<tr>
<td><strong>BSE benefits and harms</strong></td>
<td></td>
<td>No reduction in mortality Increase in biopsies</td>
</tr>
</tbody>
</table>
Mandelblatt et al

- Used 6 established models to estimate the outcomes of 20 different breast cancer screening scenarios - e.g., screening from age 40 to 69 annually, screening from age 45 to 69 biennially, etc.
- Recommend biennial screening interval.
- If the goal is to reduce mortality then screening should start at age 50.
- If the goal is to maximize the number of life-years gained, start screening at age 40.
“The USPSTF reasoned that the additional benefit gained by starting screening at age 40 years rather than at age 50 years is small, and that moderate harms from screening remain at any age.”
### Another Way of Looking At It

S Woloshin et al. JAMA 2010;303(2):164

<table>
<thead>
<tr>
<th></th>
<th>Risks by Age, y</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>40-49</td>
</tr>
<tr>
<td><strong>Benefit of screening</strong></td>
<td></td>
</tr>
<tr>
<td>10y chance of dying from breast cancer</td>
<td></td>
</tr>
<tr>
<td>No screening</td>
<td>3.5/1000</td>
</tr>
<tr>
<td>Screening</td>
<td>3.0/1000</td>
</tr>
<tr>
<td><strong>Harms of screening</strong></td>
<td></td>
</tr>
<tr>
<td>False + req’ing bx</td>
<td>60-200/1000</td>
</tr>
<tr>
<td>Over diagnosis</td>
<td>1-5/1000</td>
</tr>
</tbody>
</table>
Implications for Internal Medicine

“The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient’s values regarding specific benefits and harms.”

The senate has passed an amendment to the health care reform bill requiring insurance companies to pay for mammograms starting at age 40.
Vitamin D for Fall and Fracture Reduction

Vitamin D and Vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis (Review)

Prevention of Nonvertebral Fractures with Oral Vitamin D and Dose Dependency

Fall Prevention with supplemental and active forms of vitamin D: a meta-analysis of randomized controlled trials
Bischoff-Ferrari HA et al. BMJ 2009;339:b3692
Vitamin D Overview

- Acts at the intestine to increase calcium and phosphate absorption
- Primary source is ultraviolet light, less so food such as fatty fish
- Vit D receptors are present in intestine, kidney, skeletal muscle, brain, breast and prostrate tissue
Osteoporosis Overview

- Loss of bone mass with aging, affects women > men
- US lifetime risk of hip fracture among white women is 17.5%
- Lifetime risk of vertebral fractures in white women is 15.6%
- Estimated nine million osteoporotic fractures worldwide in 2000
Unanswered Questions Regarding Vitamin D

- Despite numerous studies on Vit D and calcium on fracture and fall prevention, controversy remains regarding:
  - When to check blood levels for Vit D?
  - What is the target blood level of 25 (OH) Vit D?
  - When to treat, and with how much Vitamin D?
Vitamin D and Vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis (Review)

turning to these studies...

Vitamin D and Fracture Prevention

The Cochrane Library

- Inclusion criteria:
  - Any randomized trial or quasi-randomized trial
  - Men over age 65 and postmenopausal women
  - Included trials whose participants had neurological disease impairing mobility, but excluded those receiving steroids
  - Primary outcome was hip fracture, secondary outcome was any nonvertebral fracture, vertebral fracture, any new fracture
Vitamin D and Fracture Prevention
Gillespie et al. *The Cochrane Library*

- 45 trials were included, 84,585 participants
- Results
  - Vitamin D alone- 9 trials, n=24,749
    RR=1.15 vertebral fx, RR=0.90 new fracture
  - Vitamin D with calcium- 8 trials, n=45,658
    reduces hip fractures RR 0.84- subgroup analysis- institutionalized individuals RR 0.75 and community dwelling 0.91
Prevention of Nonvertebral Fractures with Oral Vitamin D and Dose Dependency

Vitamin D and Fracture Prevention
Bischoff-Ferrari *Archives of Internal Medicine*

- Previous meta analyses showed insignificant impact of Vit D on fracture prevention
- Inclusion criteria:
  - RCT
  - Minimum follow-up of 1 year
  - Required more than a total of 1 fracture in each trial
  - Mean age of 65 years or greater
- Exclusion criteria:
  - Patients at risk for falls (hx of stroke, Parkinson’s, steroids, organ transplant)
Vitamin D and Fracture Prevention
Bischoff-Ferrari Arch Intern Med

- 12 studies were included (n=42,279)
- Mean age 78
- 89% women
- Measured “received dose of vit D” (dose x adherence)
Hip fracture prevention by received dose and achieved 25-hydroxyvitamin D levels in the treatment groups

Vitamin D and Fracture Prevention - Results
Bischoff-Ferrari Arch Intern Med

- Nonvertebral fracture: with a received dose of > 400 IU/d RR was 0.8
- Hip fractures: with a received dose of >400 IU/day RR was 0.82
- Effect is independent of calcium supplements
- Fracture reduction seen in both community dwelling and institutionalized patients
- Subgrp analysis suggested better results with cholecalciferol compared to ergocalciferol
Fall Prevention with supplemental and active forms of vitamin D: a meta-analysis of randomized controlled trials

Bischof-Ferrari HA et al. BMJ 2009;339:b3692
Vitamin D and Fall Prevention (BMJ)

- Inclusion criteria:
  - Double blind randomized controlled trials
  - Mean age 65 or older
  - Defined oral doses of vit d
  - Specified fall assessment
  - Minimum 3 month follow-up

- Excluded
  - Studies that focused on patients at high risk for falls (Parkinson’s, stroke and organ transplant)
  - IM vit D
Vitamin D and Fall Prevention - Results

- 8 studies of supplemental vit d were included n=2426
- 2 studies of active forms of vitamin d
- Patients lived in the community or NH
- 81% women
- Average age 80 yo
- Vit D3 or Vit D2 given in daily doses ranging from 200 IU to 1000 IU
- Treatment duration ranged from 2 months to 36 months
Vitamin D and Fall Prevention - Results

Vitamin D and Fall Prevention - Results

- Pooled relative risk for studies with 700-1000 IU vitamin D was 0.81 NNT 11, treatment duration of 2-36 months
- No fall reduction was seen with serum Vit D below 60 nmol/l
- Results seen in studies as short as 2 months
- Results independent of calcium supplementation (supporting theory of action on skeletal muscle)
Implications for Internal Medicine

- Vit D with Calcium likely reduces hip fractures and falls, especially in institutionalized patients
- A reasonable dose Vit D should be at least 800 IU/day
- A reasonable target serum 25 (OH) vit D level is 74 nmol/L (30 ng/ml)
- A new report by the Institute of Medicine (IOM) on Vitamin D is expected to be released in May 2010
Prostate Cancer Screening

Mortality results from a randomized prostate-cancer screening trial (PLCO)


Screening and prostate cancer mortality in a randomized European study (ERSPC)

Prostate Cancer Screening

- PSA and DRE widely used
  - greatly increases cancers found
  - earlier stage at discovery
- no data conclusively shows benefit
  - no mortality data
  - morbidity data vary
  - benefits not seen for 10-15 years
  - downside morbidity is immediate
turning to these studies...

Objective

To determine if widespread prostate cancer screening programs reduce mortality
Methods

- Two large randomized *intention to screen* studies
- PLCO study
  - 10 centers across the United States
  - randomized to screening or no screening
  - rates of screening outside trial assessed by surveys
- ERSPC trial
  - seven European countries, slightly different protocols
  - randomized to screening vs. no screening
## Study Design

<table>
<thead>
<tr>
<th>Screening intervention</th>
<th>US Study (PLCO)</th>
<th>European Study (ERSPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA yearly for 6 years</td>
<td>PSA yearly for 6 years</td>
<td>PSA every 2-4 years</td>
</tr>
<tr>
<td>DRE yearly for 4 years</td>
<td>DRE yearly for 4 years</td>
<td>DRE yearly for 4 years</td>
</tr>
<tr>
<td>PSA cut off for biopsy</td>
<td>&gt; 4.0 mg/dl</td>
<td>&gt; 3.0 mg/dl</td>
</tr>
<tr>
<td>Age</td>
<td>55-74</td>
<td>55-69</td>
</tr>
<tr>
<td>Intervention for abnl PSA or DRE</td>
<td>Advised biopsy, local guidelines</td>
<td>Advised biopsy, local guidelines</td>
</tr>
<tr>
<td>Study Duration</td>
<td>Halted at 10 years</td>
<td>Median follow up – 9 years</td>
</tr>
</tbody>
</table>
# Results

<table>
<thead>
<tr>
<th></th>
<th>U.S. study (PLCO)</th>
<th>European (ERSPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of men in study</strong></td>
<td>76,000 (ten years)</td>
<td>162,000 (9 years)</td>
</tr>
<tr>
<td><strong>Screening rates</strong></td>
<td>85% study</td>
<td>45% control</td>
</tr>
<tr>
<td></td>
<td>&gt;80% study</td>
<td>(control zero?)</td>
</tr>
<tr>
<td><strong>Prostate cancers diagnosed</strong></td>
<td>3452 (9%)</td>
<td>2974 (7.5%)</td>
</tr>
<tr>
<td></td>
<td>(NS)</td>
<td>5990 (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4307 (5%)</td>
</tr>
<tr>
<td><strong>Stage 2 cancer</strong></td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Prostate cancer deaths</strong></td>
<td>92 (0.24%) NS</td>
<td>82 (0.22%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>214 (0.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR: 0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[0.65-0.98]</td>
</tr>
<tr>
<td><strong>Deaths (all cases)</strong></td>
<td>3953</td>
<td>4058</td>
</tr>
<tr>
<td></td>
<td>261</td>
<td>361</td>
</tr>
<tr>
<td></td>
<td>OR: 85</td>
<td>OR: 85</td>
</tr>
<tr>
<td></td>
<td>[.73-1.00]</td>
<td>[0.73-1.00]</td>
</tr>
</tbody>
</table>
Summary of Results

- PLCO Study
  - increase in prostate cancer detection
  - no reduction in mortality associated with screening at 7 years

- European Study
  - increase in prostate cancer detection
  - 20% reduction in mortality associated with screening (CI 0.65-0.98  p=0.04)
Additional Points

- In the PLCO study 40% of control group had PSA ‘off study’

- In the ERSPC the lower cutoff PSA = 3 led to large numbers of ‘false positives’ and needless biopsies
  - 1410 men screened → about 200 biopsy
    → 48 treated → 1 death prevented

- In both studies, the 9-10 years of follow-up was not enough to show large differences

- Quality of life comparison still pending
Implications for Internal Medicine

- we still are uncertain how to proceed and it is not likely that we will get clearer information any time soon

- unclear risk/benefit ratio in screening

- discussions with patients are essential, though not easily done
Effects of Glycemic Control on Vascular Complications

Glucose Control and vascular Complications in Veterans with Type 2 Diabetes

Background

- Cardiovascular disease is the leading cause of death in type 2 diabetes
  - 3-5 times higher in this population
  - Increased risk with worsening glycemic control patterns
  - Even impaired fasting glucose (110-125) elevates risk of cardiovascular events
Numerous studies have shown that intensive glycemic control in type 2 diabetics reduces ‘microvascular’ complications (retinal, renal, neuropathy)

No such data exist for ‘macrovascular’ complications such as stroke, MI, vascular death

ACCORD and ADVANCE trials 2008

- NO reduction in cardiovascular events or death
- ACCORD stopped at preliminary analysis due to excess deaths in the intensive treatment group (A1C average 6.4%)
Turning to this study...
Effects of Glycemic Control on Vascular Complications: Objectives

To determine whether intensive glycemic control in type 2 diabetics reduces macrovascular complications including death
Effects of Glycemic Control on Vascular Complications: Methods

- VA patients with poorly controlled type 2 diabetes
  - A1C > 7.5% on maximal oral agents +/- insulin therapy
- Exclusions
  - Recent MI
  - CKD stage 3-5
  - BMI > 40
  - Life expectancy < 7 years
Effects of Glycemic Control on Vascular Complications: Methods

- Randomly assigned (open label), followed 5-8 years
- Treatments
  - Metformin/rosiglitazone (BMI > 27)
  - Glimeperide/rosiglitazone (BMI < 27)
  - Insulin added if A1C > 6% (intensive) or > 9% (standard)
  - Other agents could be added at discretion of physicians
  - All patients started on aspirin and statin if possible
- Other treatments identical including nutrition counseling, hypertension control etc based on ADA
- Primary outcome: composite of cardiovascular outcomes
Effects of Glycemic Control on Vascular Complications: Results

- 1791 patients enrolled and randomized
  - Randomization stratified previous cad vs. none
- Mean age 60, >95% male
- Mean time since diabetes diagnosis: 11 years
- Baseline A1C 9.4%
- 75% had hypertension, 40% previous CV disease
# Effects of Glycemic Control on Vascular Complications: Results

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intensive Therapy</th>
<th>Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin A1C</strong></td>
<td>6.9% ***</td>
<td>8.4%</td>
</tr>
<tr>
<td><strong>Weight/BMI</strong></td>
<td>232 lbs/ 34 ***</td>
<td>223 lbs/ 32</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>127/68</td>
<td>125/69</td>
</tr>
<tr>
<td><strong>Cardiovascular events</strong></td>
<td>29.9%</td>
<td>33.5%</td>
</tr>
<tr>
<td><strong>Deaths (CV death)</strong></td>
<td>102 (40)</td>
<td>95 (33)</td>
</tr>
<tr>
<td><strong>Symptomatic hypoglycemic episodes</strong></td>
<td>1333</td>
<td>383</td>
</tr>
</tbody>
</table>
No difference in time to first CV event

No significant differences in microvascular complications overall

Overall mortality similar 11-12%

Adverse events 3 times more common in intensive therapy group, including hypoglycemia, dyspnea
Limitations

- These are all patients on multiple oral medications who were previously uncontrolled
  - Therefore this does NOT necessarily apply to patients who are slightly uncontrolled on one medication and a second medication is being considered
  - Also does not necessarily apply to younger patients who are starting out on therapy
Implications for Internal Medicine

- This is the third major study showing that cardiovascular outcomes/mortality are not reduced by tight diabetes control
- Control of comorbid conditions are proven to reduce cardiovascular events
  - Hypertension
  - Hyperlipidemia
- The guidelines for A1C targets for type 2 diabetics may be too stringent for some patients
  - Microvascular complications do seem to be reduced however with tighter glycemic control