Update in New Drugs 2010
SGIM Annual Session
Minneapolis

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Agenda

- Introduction
- Novel Drugs for Primary Care
  - Jerry Smetana
  - 35 minutes + 10 minutes Q&A
- New Applications and Guidelines for Existing Drugs
  - Jane Sillman
  - 35 minutes + 10 minutes Q&A

Important New Drugs for 2010: What We Need to Know

Novel Drugs
- Relevant for PCP
- No “Me Too” Drugs

Few Drugs Approved by the FDA Meet These Criteria!

Why?

FDA Approved Drugs 2009: Only Two Approved Novel Drugs for Primary Care

- Tolvaptan for treatment of SIADH
- Dronedarone for maintenance of NSR in atrial fibrillation
- Roflumilast as a controller medication for COPD (in the pipeline)
Tolvaptan for the Treatment of SIADH

<table>
<thead>
<tr>
<th>124</th>
<th>96</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>24</td>
<td>1.2</td>
</tr>
</tbody>
</table>

FDA Approved May 2009

Ms. Salinas

- Several months of Na 120-125 range
- Idiopathic SIADH with no reversible etiology
- Unsteadiness and cognitive impairment as potential consequences
- Will this new med increase my Na and improve my wellbeing?

Treatment of SIADH: Existing Therapies Limited

- Water restriction
  - Challenging for patients to maintain on long term basis
- Urea administration
  - Not widely available or used in U.S.
- Demeclocycline
  - Until now the primary drug Rx of chronic SIADH
  - Causes nephrogenic DI

Tolvaptan: A Novel Selective V2 Antagonist

- Vasopressin (ADH) receptors
  - V1a, V1b – vasoconstriction and ACTH release
  - V2 – antidiuresis
- Conivaptan
  - Approved in 2006 for Rx SIADH
  - IV formulation only
  - Nonselective
- Tolvaptan
  - Selective V2 antagonist
  - PO
  - Nonpeptide

Pharmacology of Tolvaptan

- PO formulation
- Half life 7 hours
- Dose range 15 - 60 mg daily
- Single daily dose

Is Tolvaptan Effective in SIADH? The SALT-1 and SALT-2 Trials

- Two identical RCT’s
  - N=448
- Eligible patients
  - > 18 y.o.
  - Euvolemic or hypervolemic
  - Serum Na < 135 mmol/l
  - CHF, cirrhosis, or SIADH
- Excluded:
  - Psychogenic polydipsia
  - Head trauma
  - Hypothyroidism
  - Adrenal insufficiency
  - Medication induced hyponatremia
  - Hypovolemia

NEJM 2006;355:2099
**SALT-1 and SALT-2: Intervention**

- Randomly assigned to tolvaptan 15 mg daily or placebo for 30 days
- Allowed dose increase up to 60 mg daily to achieve Na ≥ 136
- Hospitalized to initiate Rx
- Most discharged by day #4

**Mean Serum Sodium Results at Day 4 and Day 30**

**Increase in Serum Sodium: 4-8 Mmol/L Among Tolvaptan Users**

**Adverse Events are Mostly Minor**

**Important Considerations**

- FDA approval only for Na < 125 or symptoms
- Drug interactions with macrolides, fluconazole, itraconazole
- FDA/PDR insert recommend starting as inpatient black box warning
- Don’t use for hypovolemic hyponatremia
- Improved physical and mental wellbeing
- Has not been shown to ↓ mortality
- Effect disappears within 1 week of drug d/c
- AWP for 10 tablets (either 15 mg or 30 tabs) $3000!
Implications for Practice

- Requirement for inpatient initiation will limit its applicability
- Well tolerated with only minor side effects in both short and long term use
- More effective than existing Rx
- Very expensive even in short term use
- Cost may be prohibitive in longer term use

Advice for Ms. Salinas?

- Strict water restriction to no more than 1 liter / day
- If you can maintain Na > 130, leave well enough alone
- For persistent Na < 130 and symptoms, consider tolvaptan if you have good insurance...

Dronedarone for Atrial Fibrillation

Mr. D. Fibrillate

- 67 year old man with a h/o CABG
- Under stress due to recent loss of job
- Notes palpitations when angry and comes to see you with recurrent AF
- What about this new drug dronedarone?
- Will this keep my heart rhythm and life regular?

Indications to Restore and Maintain Sinus Rhythm

- AFFIRM: No mortality benefit
- Alleviation of symptoms
- Prevention of tachycardia induced cardiomyopathy
- Prevention of hemodynamic compromise
- Improvement in exercise capacity

Does Maintaining NSR Improve Outcomes in Patients with AF?

Is There a Role for Antiarrhythmic Drugs in AF?
Drug Classes to Maintain Sinus Rhythm

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na+ channel blockers</td>
</tr>
<tr>
<td>A</td>
<td>Quinidine, procainamide, disopyramide</td>
</tr>
<tr>
<td>B</td>
<td>Lidocaine, mexiletine</td>
</tr>
<tr>
<td>C</td>
<td>Flecainide, propafenone</td>
</tr>
<tr>
<td>2</td>
<td>Beta blockers</td>
</tr>
<tr>
<td>3</td>
<td>K+ channel blockers</td>
</tr>
<tr>
<td></td>
<td>Sotalol, Amiodarone, dofetilide, dronedarone</td>
</tr>
<tr>
<td>4</td>
<td>Calcium channel blockers</td>
</tr>
</tbody>
</table>

Pharmacology

- Analogue of amiodarone
  - Iodine moieties removed
  - Methyl sulfonamide added
- α and β antagonist
- Inhibits slow and rapid K+ channels
- Na+ channel inhibition
- Potential benefits
  - Reduced half life
  - Decrease tissue accumulation
  - Avoid iodine related side effects
  - Half life 13-19 hours

EURIDIS and ADONIS: Dronedarone vs. Placebo to Maintain NSR in AF or Atrial Flutter

- 1411 adult patients
- ≥ 1 episode AF in past 3 months
- In NSR at time of randomization
- Dronedarone 400 mg bid vs. placebo

Excluded
- Permanent AF (>12 months)
- Reproductive age women not using birth control
- Persistent HR < 40
- Heart block
- Class III or IV CHF
- Creatinine < 1.7

NEJM 2007;357:987

Modest Reduction in Rates of Recurrent AF with Dronedarone

Hazard ratio, 0.75 (95% CI, 0.65 to 0.87)

Secondary Results

- No difference in mortality
- No difference in hospitalization rates
- Slower mean heart rate (103 vs. 117)
- No increase in pulmonary, thyroid, or neurologic side effects
- Nonsignificant increase in GI side effects
- Higher rates of creatinine elevation (0 vs. 2%)
ANDROMEDA: Does Dronedarone Improve Outcome in Patients with Severe CHF?
- 627 patients
- Hospitalized for new or worsened CHF
- NYHA Class III or IV
- EF ≤ 35%
- Excluded:
  - Recent MI
  - HR < 50
  - Heart Block

Increased Deaths Due Primarily to CHF

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Dronedarone (n=310)</th>
<th>Placebo (n=317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Progressive CHF</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmia or SCD</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Non CV</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total deaths</td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>

All Cause Mortality and Hospitalization ↑ with Dronedarone: Study Stopped at 7 Months by Safety Board

Mortality 8.1% vs. 3.8%

Increased Deaths Due Primarily to CHF

ATHENA
Does Dronedarone Reduce CV Hospitalizations or Death?
- N= 4628 (largest trial to date)
- More varied patient population than earlier trials
- PAF or persistent AF
- NSR at some time in past 6 months
- At least one of:
  - Age ≥ 70
  - DM
  - h/o stroke
  - ↑ LA size

Dronedarone Reduces 1st Hospitalization and Death

DIONYSOS: Dronedarone is Less Effective than Amiodarone in Maintaining NSR

Primary Endpoint:
Recurrent AF or drug w/d due to Intolerance or Lack of Effect

Recurrent AF: 37% vs 24%
### Pooled Safety Data: Dronedarone
Well Tolerated and without Principal Amiodarone Toxicities

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Placebo</th>
<th>Dronedarone 400 mg bid</th>
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</thead>
<tbody>
<tr>
<td>Any</td>
<td>67.5</td>
<td>70.4</td>
</tr>
<tr>
<td>GI</td>
<td>20.8</td>
<td>24.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Rash</td>
<td>3.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Creatinine elevation</td>
<td>1.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5.9</td>
<td>5.2</td>
</tr>
<tr>
<td>LFT abnormalities</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Thyroid abnormalities</td>
<td>1.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

### Many Drug Interactions
- Digoxin
- Calcium channel blockers
- Beta blockers
- CYP 3A inhibitors
  - Ketoconazole
  - Macrolide antibiotics
- Grapefruit juice
- Statins

### Contraindications
- Class IV CHF
- Class II-III CHF with recent decompensation
- 2nd or 3rd degree heart block
- Sick sinus syndrome
- HR < 50
- QTc > 500 ms
- Severe liver disease
- Pregnancy

### Cost of Antiarrhythmics:
30 Days Rx at Lowest Daily Dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td></td>
</tr>
<tr>
<td>IA. Quinidine</td>
<td>$83</td>
</tr>
<tr>
<td>IC. Propafenone</td>
<td>$151</td>
</tr>
<tr>
<td>IC. Flecainide</td>
<td>$167</td>
</tr>
<tr>
<td>Type 3</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>$145</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>$103</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>$260</td>
</tr>
</tbody>
</table>

### Key Points: Dronedarone
- Well tolerated without the liver, thyroid, and pulmonary side effects of amiodarone
- Less effective at maintaining NSR than amiodarone
- Increases mortality in patients with class III to IV CHF: Black box FDA warning
- Consider primarily for patients with indication for amiodarone who have contraindication or side effects

### What to Advise Mr. Fibrillate?
Advice for Mr. D. Fibrillate

- Use meds to maintain NSR if symptomatic AF
- Amiodarone is 1st choice
- Use dronedarone in its place if toxicities limit use of amiodarone
- Don’t use if recent admit to Walter Reed for CHF

Roflumilast for Maintenance Treatment of COPD

Mr. Salem

- 74 yo man with chronic bronchitis, CAD, HTN
- Cigarettes 2 ppd x 30 years
- Dyspneic at 3 blocks level ground despite tiotropium and albuterol MDI
- Chronic daily productive cough
- Will roflumilast improve my breathing?

Stratify Rx Based on Severity

<table>
<thead>
<tr>
<th>GOLD Stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting bronchodilator</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Long acting bronchodilator (β agonist +/- anticholinergic)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inhaled glucocorticoids</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider O2 Rx</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Problem: Many Patients with Stage 3 or 4 COPD Remain Impaired Despite Current Rx

<table>
<thead>
<tr>
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<th>I</th>
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<th>III</th>
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<td></td>
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<table>
<thead>
<tr>
<th>PDE Family</th>
<th>Related disease area</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE1</td>
<td>Fertility, Inflammation, Olfaction</td>
</tr>
<tr>
<td>PDE2</td>
<td>Heart disease, Anti-angiogenic</td>
</tr>
<tr>
<td>PDE3</td>
<td>Obesity, restinosis, diabetes</td>
</tr>
<tr>
<td>PDE4</td>
<td>COPD, arthritis, learning, stroke, PD, leukemia</td>
</tr>
<tr>
<td>PDE5</td>
<td>ED, pulmonary hypertension, migraine</td>
</tr>
<tr>
<td>PDE6</td>
<td>Retinopathies</td>
</tr>
<tr>
<td>PDE7</td>
<td>Unknown</td>
</tr>
<tr>
<td>PDE8</td>
<td>Hyperthyroidism, metabolic bone disease</td>
</tr>
<tr>
<td>PDE9</td>
<td>Fertility</td>
</tr>
<tr>
<td>PDE10</td>
<td>PD, OCD, addictions</td>
</tr>
<tr>
<td>PDE11</td>
<td>Fertility</td>
</tr>
</tbody>
</table>
Pharmacology of Roflumilast: A Selective PDE 4 Inhibitor

- Once daily PO administration
- No apparent drug interactions
- Suppresses recruitment and activation of inflammatory cells
- Decreases sputum production
- Reduces number of neutrophils and eosinophils in sputum

1st Clinical Study: Roflumilast vs. Placebo for 6 Months

- 1413 patients
- Dx by GOLD criteria
- ≥ 40 years old
- Current smoker or ex-smoker of at least 10 pack yrs
- FEV1 30-80% pred
- FEV1/FVC < 70%
- Randomly assigned to placebo or 2 doses of roflumilast
- Primary outcome post bronchodilatory FEV1
- Secondary outcome # exacerbations

Modest Improvement in FEV1 with Roflumilast

- FEV1 74 ml c/w placebo

Secondary Findings

- Greater improvement in FEV1 among patients with moderate to severe COPD (post hoc)
- Nonsignificant improvement in COPD symptoms scores
- Significant reduction in exacerbations

Questions for Further Research

- Which subsets of patient benefit most?
- Is benefit maintained over longer courses of Rx?
- What is incremental value above long acting beta agonists or anticholinergics?
- What is side effect profile?

Similar Benefit for Prolonged Rx Among Patients with Severe COPD

- 3093 Patients
- FEV1 < 50% Predicted
- Roflumilast 500 mcg

Lancet 2005;366:563

Lancet 2009;374:685
Prolonged Treatment of Severe COPD: Secondary Findings

- No difference in mortality rates
- Small difference in study d/c due to adverse events (14% vs. 11%)
- 17% reduction in exacerbations

Does Roflumilast Add Benefit to Salmeterol or Tiotropium?

1676 Patients with Mod to Severe COPD
FEV1 40-70% Predicted

17% reduction in exacerbations

Symptoms Improve When Added to Tiotropium but Not to Salmeterol

Roflumilast % | Placebo %
--- | ---
Diarrhea | 8 | 3
Weight loss | 10 | 3
URI symptoms | 3 | 4
Headache | 3 | 2
Nausea | 4 | 2
Insomnia | 2 | 2
Treatment d/c due to adverse effect | 33 | 31

Adverse Effects: GI Symptoms Most Common

Implications for Practice

- Roflumilast improves lung function over time
- The first medication to do so
- Modest reduction in symptom scores and exacerbation rates
- Additive benefit to tiotropium
- GI side effects but rarely lead to Rx discontinuation
- Benefit unknown for mild COPD
- Has also shown benefit in asthma

What to Advise Mr. Salem?

- Stop smoking
- Continue tiotropium
- Pulmonary rehab program
- Add roflumilast to tiotropium
- This may stop the progression of your COPD
- You can expect improved symptoms
Summary

- Tolvaptan improves serum Na+ in SIADH but is expensive and requires hospital admission
- Dronedarone does not have the side effects of amiodarone but is less effective and also harmful if class III or IV CHF
- Roflumilast may halt the progression of COPD and modestly improves symptoms

Treatment Updates for the PCP
Jane S. Sillman, MD
SGIM 2010

We’ll look at...

- Osteoporosis
- Vitamin D
- Aspirin

Updates on osteoporosis treatment

- Role of BMDs in monitoring treatment
- Bisphosphonates and risk of atypical femur fractures

Mrs. Fragila

- 70 year old woman with osteoporosis, on alendronate x 5 years. BMD: T of – 3, improved from - 4
- Asks if she should continue rx.

Monitoring treatment with BMD: National Osteoporosis Foundation

- BMD every 2 years

www.nof.org
Follow-up BMD: NAMS 2010 guideline

- ONCE, after 2 years of rx
- If BMD stable or improved, no value in repeating it
  - limited use in predicting effectiveness of treatment
  - changes in BMD lag behind therapeutic benefits

Bisphosphonates and femur fractures

- Recent case reports: small numbers of patients on bisphosphonates with atypical femur fractures:
  - subtrochanteric
  - diaphyseal

Menopause 2010;17:25

Common hip fractures

- Subcapital neck fracture
- Transcervical neck fracture
- Intertrochanteric fracture

Atypical hip fractures

Subtrochanteric Diaphyseal

Case reports: atypical femur fractures and bisphosphonates

- Associated with bisphosphonate use for five or more years

Danish cohort study: doesn’t support this association

- Cohort study in patients with baseline fractures:
  - 5,187 patients on alendronate
  - 10,374 patients matched by sex, age, location of baseline fracture


J Bone Miner Res 2009;24:1095
Danish cohort study

• Endpoint: Hip fractures
• Results: No increase in atypical femur fractures with alendronate

J Bone Miner Res 2009;24:1095

Danish cohort study: conclusions

• Subtrochanteric and diaphyseal fractures: same epidemiology as typical hip fractures
• Alendronate users: at risk for atypical and typical hip fracture due to their underlying risks for fracture

J Bone Miner Res 2009;24:1095

NEW review of bisphosphonates and fractures of subtrochanteric or diaphyseal femur

• Reviewed fractures from 3 large randomized bisphosphonate trials:
  FIT: alendronate up to 4.5 yrs
  FLEX: alendronate up to 10 yrs
  HORIZON-PFT: zoledronic acid up to 3 yrs

Published 3/24/2010 at NEJM.org

Results

• 283 fractures among 14,195 women
• Total of 12 fractures in 10 patients occurred in subtrochanteric or diaphyseal femur: combined rate of 2.3 per 10,000 patient-years

Relative hazard of treatment compared with placebo

<table>
<thead>
<tr>
<th></th>
<th>Relative hazard (CI)</th>
</tr>
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<tbody>
<tr>
<td>FIT</td>
<td>1.03 (0.06-16.46)</td>
</tr>
<tr>
<td>FLEX</td>
<td>1.33 (0.12-14.67)</td>
</tr>
<tr>
<td>HORIZON-PFT</td>
<td>1.50 (0.25-9.00)</td>
</tr>
</tbody>
</table>

Increases in risk not significant
Confidence intervals wide

Conclusions

• Subtrochanteric or diaphyseal fracture rare even in women treated with bisphosphonates for up to 10 years
• No significant increase in risk but study underpowered for definitive conclusions

Published 3/24/2010 at NEJM.org
NEJM editorial

- Subtrochanteric and diaphyseal fractures are very rare
- Many more hip fractures are PREVENTED by bisphosphonates than are potentially caused by them

Published 3/24/2010 at NEJM.org

Use of alendronate for 10 years vs. 5 years

- Associated with significantly fewer new non-vertebral fractures in women with BMD T scores of ≤ -2.5 after 5 years of alendronate

J Bone Miner Res 2010 Jan. 8 (Epub)

Implications for practice

- Subtrochanteric and diaphyseal fractures seem to be due to osteoporosis, not due to bisphosphonates
- Beneficial to continue bisphosphonates for at least 10 years in high risk patients

Vitamin D deficiency

- Scope of problem
- Benefits of treatment
  - fractures
  - falls
  - everything else

Mrs. Rickety

- 75 yo woman with vitamin D level of 10.
- What are the benefits of treating her vitamin D deficiency?

Epidemiology

- 1 billion people worldwide with vitamin D insufficiency or deficiency
- In U.S.: 36% of healthy young adults and 57% of general medicine inpatients have vitamin D deficiency

N Engl J Med 2007;357:266
**Definitions of vitamin D levels**

- Sufficient: 25(OH)D greater than 30 ng/ml
- Insufficient: 20-30 ng/ml
- Deficient: less than 20 ng/ml

**Causes**

- Inadequate sun exposure
- Inadequate food sources
- ? Obesity epidemic

**Risk factors**

- Dark skin
- Poor nutrition
- Chronic renal or liver disease
- Drugs: anticonvulsants, steroids
- Elderly, housebound, nursing home

**Vitamin D deficiency is increasing**

- Comparison of 25(OH)D levels from NHANES 1988-1994 and NHANES 2001-2004
- Marked decrease in vitamin D levels in 2001-2004 cohort

**Vitamin D in NHANES 1988-1994 and 2001-2004**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Mean 25(OH)D</td>
<td>30 ng/ml</td>
<td>24 ng/ml</td>
</tr>
<tr>
<td>D &lt; 10 ng/ml</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>D &gt; 30 ng/dl</td>
<td>45%</td>
<td>23%</td>
</tr>
<tr>
<td>D &lt; 10 ng/ml in blacks</td>
<td>9%</td>
<td>29%</td>
</tr>
<tr>
<td>D &gt; 30 ng/ml in blacks</td>
<td>12%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Vitamin D deficiency and obesity**

- Fat soluble vitamin
- Readily taken up by fat cells
- Obesity leads to sequestration of vitamin D in large fat pool
- Worsening of vitamin D deficiency may be related to increasing obesity in the population
**Vitamin D: two main forms**

- **Cholecalciferol (D3)**
  - formed in skin after exposure to UVB radiation
  - found in animal sources (cod liver oil, salmon)
- **Ergocalciferol (D2)**
  - formed in plants

**Vitamin D and bones**

Low vitamin D ->
- Decreased intestinal absorption of calcium ->
- Negative calcium balance ->
- Rise in PTH ->
- Bone resorption

**Vitamin D and osteoporosis**

- Patients with a Z score < -2.0 (secondary osteoporosis):
  - commonest reason is vitamin D deficiency

**Vitamin D and fractures**

**Women’s Health Initiative**

- RCT of 36,282 women ages 50-69 assigned to calcium 1000 mg/day plus vitamin D 400 IU/day or placebo
- Average f/u: 7 years
WHI: results

• Hip BMD was 1.06% higher in calcium-vitamin D group
• Compliant patients (those who took more than 80% of medicine): significant decrease in hip fracture (HR 0.71, 95% CI 0.52-0.97)

Meta-analysis: decreased fractures

• Meta-analysis of 7 RCTs in 9820 elderly subjects (mean age 79)
• Results: higher dose vitamin D (700-800 IU) reduced RR of hip and vertebral fracture
  RR 0.74, 95% CI 0.61-0.88 and
  RR 0.77, 95% CI 0.68-0.87

Vitamin D and fall prevention

Meta-analysis: falls

• Meta-analysis of 5 RCTs of vitamin D involving 1237 older subjects (mean age 60)

Results

• Vitamin D use reduced risk of falls by 22% compared with patients receiving calcium or placebo
  (OR 0.78, 95% CI 0.64-0.92)
• NNT to prevent 1 fall: 15 patients

Elderly women with poststroke hemiplegia

• RCT: 96 elderly women rx'd with 1000 IU vitamin D or placebo
• Results of vitamin D rx:
  – improved muscle strength
  – 59% decrease in falls
**Elderly women in Australia**

- 1 yr RCT of 302 women aged 70-90, 25(OH)D less than 24, h/o falling
- Randomized to vitamin D2 1000 IU or placebo.
- Vitamin D2 significantly decreased risk of fall:
  \[ \text{OR} \ 0.61, \ 95\% \ \text{CI} \ 0.37-0.99 \]

  Arch Intern Med 2008;168:103

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**Vitamin D and cancer: conflicting evidence**

- Observational studies: high vitamin D levels associated with decreased cancer risk
- RCTs: no decreased risk of cancer

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**WHI: vitamin D and colorectal cancer**

- RCT of 36,282 postmenopausal women rx’d with 1000 mg calcium and 400 IU vitamin D3 or placebo for average of 7 years
- Result: no difference in incidence of colorectal cancer


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**WHI: vitamin D and breast cancer**

- RCT of 36,282 postmenopausal women rx’d with 1000 mg calcium and 400 IU vitamin D3 or placebo for average of 7 years
- Serial breast exams, mammograms
- Result: no difference in incidence of invasive breast cancer

  J Natl Cancer Inst 2008;100:1581

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**All-cause mortality**

- Observational studies: associations between low vitamin D levels and increased all-cause and cardiovascular mortality


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**All-cause mortality**

- Meta-analysis of RCTs of vitamin D supplementation: decreased risk of all-cause mortality
  \[ \text{RR} \ 0.93, \ 95\% \ \text{CI} \ 0.87-0.99 \]

  Arch Intern Med 2007;167:1730
Needed

- Population-based RCT with mortality as the main end point

Testing for vitamin D deficiency

- Not necessary to test all adults
- Recommend 800-1000 IU vitamin D daily for average risk adults: to maintain level of > 30 ng/ml
- Test adults with risk factors for vitamin D deficiency

Implications for practice

- Aim for 25(OH)D level > 30 ng/ml
- Good data that this will lessen risk of osteoporosis, fractures, falls
- Not clear if this will decrease risk for cancer or mortality

Aspirin for primary prevention of CV disease

Mr. and Mrs. Hart

Mr. and Mrs. Hart are 55 yo patients who ask if they should take aspirin to decrease their risk of cardiovascular disease. Neither has a history of ulcer disease and neither takes NSAIDs.

American Heart Association 2008 recommendations

- Men: aspirin for men with 10 year risk of CHD > 10% for primary prevention of MI
- Women: aspirin if benefit of ischemic stroke prevention outweighs risks

Circulation 2008;117:2844
**USPSTF 2009 guideline**

- Based on review of literature since 2002
- Assesses benefits vs. harms of aspirin

*Ann Intern Med* 2009;150;396

**Men should take aspirin to decrease risk of MI**

- Men age 45-79
- When the benefit outweighs potential harm of increase in GI hemorrhage
- “A” recommendation

**Men: Risk level at which CV benefit exceeds GI harms**

<table>
<thead>
<tr>
<th>Age</th>
<th>10 year MI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-59 years</td>
<td>≥ 4%</td>
</tr>
<tr>
<td>60-69 years</td>
<td>≥ 9%</td>
</tr>
<tr>
<td>70-79 years</td>
<td>≥ 12%</td>
</tr>
</tbody>
</table>

**Men: Use Framingham Risk Score to calculate 10 year risk**

- Google: “Framingham risk score”

**Women should take aspirin to reduce risk of stroke**

- Women age 55-79
- When benefit of reduction in ischemic stroke outweighs potential harm of increase in GI hemorrhage
- “A” recommendation

**Women: Risk level at which stroke benefit exceeds GI harm**

<table>
<thead>
<tr>
<th>Age</th>
<th>10-Year Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-59 years</td>
<td>≥ 3%</td>
</tr>
<tr>
<td>60-69 years</td>
<td>≥ 8%</td>
</tr>
<tr>
<td>70-79 years</td>
<td>≥ 11%</td>
</tr>
</tbody>
</table>
Women: use stroke risk estimation tool

- Google: “stroke risk calculator”

Risks for GI bleeding

- Increasing age
- Men: 2x the risk of women
- NSAIDs plus asa: 4x
- History of GI ulcer: 2-3x
- Enteric coated or buffered asa: doesn’t decrease risk

Aspirin dose

- Optimum dose unknown
- Primary prevention trials:
  - 75 and 100 mg daily
  - 100 and 325 mg every other day
- 81 mg/d as effective as higher doses
- GI bleed risk may increase with dose

Insufficient evidence to recommend aspirin in people > 80 years old

- An “I” statement
- Consider aspirin when other risk factors for bleeding are absent

Don’t recommend aspirin for men younger than 45 and women younger than 55

- A “D” recommendation
- Little evidence of benefit

The Framingham Risk Calculator

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Untreated Systolic Blood Pressure</th>
<th>Treated Systolic Blood Pressure</th>
<th>History of Diabetes Mellitus</th>
<th>Smoke Cigarettes</th>
<th>Cardiovascular Disease</th>
<th>History of Atrial Fibrillation</th>
<th>Left Ventricular Hypertrophy</th>
</tr>
</thead>
</table>

Ann Intern Med 2009;150:396

Ann Intern Med 2009;150:396
Antithrombotic Trialists’ Collaboration meta-analysis 2009

- Method: Meta-analyses of serious vascular events and major bleeds in 6 primary prevention trials and 16 secondary prevention trials of aspirin vs. control

ATT Collaboration: primary prevention trials’ results

- Aspirin
  - 12% reduction in serious vascular events due to reduction in MI
  - No effect on stroke
  - No effect on vascular mortality
  - Increase in bleeds: 0.1% vs. 0.07% per year, RR 1.54

ATT Collaboration conclusion

- Aspirin of uncertain net value for primary prevention
- Need to weigh reduction in occlusive events against increase in major bleeds

Meta-analysis results: aspirin compared to placebo

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV events</td>
<td>0.90</td>
<td>0.81-1.00</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.94</td>
<td>0.72-1.23</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.93</td>
<td>0.82-1.05</td>
</tr>
</tbody>
</table>

Aspirin and risk of MI in diabetics: gender differences

<table>
<thead>
<tr>
<th>Gender</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.57</td>
<td>0.34-0.94</td>
</tr>
<tr>
<td>Women</td>
<td>1.08</td>
<td>0.71-1.65</td>
</tr>
</tbody>
</table>
ADA 2010 recommendations

• Consider aspirin for primary prevention in DM patients at increased CV risk (10 yr risk > 10%):
  – Men > 50 years old
  – Women > 60 years old
  – With at least 1 additional risk factor (FH, HTN, smoking, elev chol, albuminuria)

ADA 2010 recommendations

• Not enough evidence to recommend aspirin in lower risk diabetics:
  – Men < 50 years
  – Women < 60 years
  – Without other major CV risk factors

Implications for practice

• Individualize decisions about starting aspirin
• Assess benefits vs. potential harms

Summary

• Continue bisphosphonates for 10 years in high risk patients.
• Vitamin D helps skeletal health and prevents falls. We need RCTs to support other possible benefits.
• Individualize decisions about aspirin for primary prevention: assess risks vs. benefits