Clinical Update in General Internal Medicine

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Osteoporosis Therapy

Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. (Horizon Trial).

Osteoporosis—major problem

- affects millions of women worldwide
- associated with significant morbidity and mortality
- existing treatments modestly effective, but up to half of patients are not compliant with therapy due to side effects/inconvenience
Osteoporosis

- Bisphosphonates are widely prescribed
  - Inhibit osteoclast bone reabsorption and improve bone density
  - Two have been shown to reduce hip fractures (risedronate and alendronate)
  - Both may cause gastroesophageal upset and have burdensome instructions
- IV zoledronic acid yearly shown to reduce bone turnover and improve bone density
Zoledronic Acid for Osteoporosis– **Methods**

- 7765 postmenopausal women with osteoporosis or osteopenia + vertebral fractures
  - randomized to once yearly (3 total) infusions of zoledronic acid or placebo
  - all had daily calcium and vitamin D usual doses
- multicenter, multinational study
- follow-up for 36 months
Zoledronic Acid for Osteoporosis - **Results** (% of subjects)

- **Vertebral fracture**
  - Zoledronic acid: 3%
  - Placebo: 1%

- **Hip fracture**
  - Zoledronic acid: 1%
  - Placebo: 0%

- **A fib**
  - Zoledronic acid: 0%
  - Placebo: 0%
Zoledronic Acid for Osteoporosis –

Results (con’t)

- increase in BMD (5-8%) vs. 1-2% reduction in placebo group
- Zoledronic acid effective at reducing vertebral and hip fractures after 3 years
- NNT = 67 for hip fractures
- NNT = 13 for vertebral fractures (x-ray)
- increased risk of atrial fibrillation (1.3% vs. 0.5%)
- well-tolerated in other ways except mild transient myalgias, headaches after infusions
Implications for Internal Medicine

- Zoledronic acid infusion (annually) is an acceptable alternative to oral bisphosphonates in the treatment of osteoporosis.
- Small risk (?) of atrial fibrillation in this one study (subsequent large study did not show this).
- Subsequent study showed reduction in fracture and mortality in patients after hip fracture.
- Direct comparison to oral bisphosphonates not done, cannot compare efficacy—more effective?
- At this point, probably second-line therapy for patients who cannot take oral bisphosphonates.
Obesity

Effects of bariatric surgery on mortality in Swedish obese subjects.

A heavy duty problem...

- 1/3 of adult Americans are obese (BMI >30)
  - most observational and epidemiological studies show that obesity increases mortality
  - BMI > 40 (severely obese) live 10 years less on average
- no studies have shown weight loss results in reduced mortality
  - largely due to poor success of most treatments???
Bariatric Surgery

- minimally invasive approaches have increased interest in these procedures
  - gastric banding procedures
  - gastrointestinal bypass procedures
- body weight reductions of 10-50% achieved
- significant improvements in many disease states
  - diabetes mellitus, hypertension, sleep apnea
  - musculoskeletal pain, quality of life
- mortality, cardiovascular outcomes???
Turning to this study...

Bariatric Surgery and Long-term Outcomes - Objectives

To determine:

- Does bariatric surgery reduce long-term mortality?

- What are the effects of bariatric surgery on weight loss and multiple morbidity measures?
Bariatric Surgery and Long-term Outcomes - Methods

- 4047 obese subjects enrolled at 25 different centers in Sweden
- Recruitment 1987-2001 of patients with BMI > 34 for men, BMI > 38 for women
  - These cutoffs corresponded to approximate BMI that results in doubling of mortality rate
  - Minimal exclusion criteria, centered around operative candidacy (diabetes, CAD, CVA included)
Bariatric Surgery and Long-term Outcomes

Methods

- prospective matched trial
  - patients who desired surgery matched with patients who declined surgery but agreed to participate in the study
- slight differences between the two groups
  - surgery group slightly heavier (BMI 42 vs. 41), more likely to smoke (27% vs. 20%) and slightly younger (46 vs. 47 years of age)
Bariatric Surgery and Long-term Outcomes - Methods (con’t)

- surgical Group (2010 patients)
  - most underwent banding gastroplasty (1745)
  - 265 had gastric bypass surgery
- conventional group (2037) received “usual care” from their primary care site
  - no attempt to standardize the care
  - ranged from no formal obesity treatment to behavioral techniques and lifestyle modification
Bariatric Surgery and Long-term Outcomes - Results

- status (alive or dead) known for 99.9% of patients
- range of follow-up 5-18 years (11 years mean)
- participation/follow-up rates of 94% at 2 years and 66% at 15 years
Mortality

Surgery Group
- Other: 29
- Cancer: 29
- Cardiovascular: 43

Conventional
- Other: 28
- Cancer: 48
- Cardiovascular: 53
Bariatric Surgery and Long-term Outcomes - Results

- Surgery group total mortality hazard ratio 0.76 (0.59-0.98, p=.04), adjusted ratio 0.71 (p=.01)
- 5% of surgery group died vs. 6.3% in control (p=.02)
- In the first 90 days postoperatively, 5 patients in surgery group died vs. 2 in the control group
  - None of the postoperative deaths occurred in patients with known coronary artery disease
Bariatric Surgery and Long-term Outcomes - Results

- other independent risk factors for death
  - tobacco use
  - age
  - diabetes
  - weight

- effects of underlying CAD
  - 25% mortality in controls vs. 19% in surgical group
  - compared to 6% and 5% in patients without CV
Bariatric Surgery and Long-term Outcomes - Conclusions

- Bariatric surgery reduces mortality
- First study to prospectively show that weight loss (from any intervention) results in reduction in mortality
- Weight loss with bariatric surgery is sustainable over 10+ years
- Results may be generalized (study done in multiple sites across Sweden)
MAJOR LIMITATION: is mortality benefit from increased exposure to health care system??

not a randomized trial

realistically could not do a randomized trial

most of the benefits found in patients with known CAD—does benefit extend to others?

most of these patients had banded gastroplasty, not bypass procedures
Implications for Internal Medicine

- bariatric surgery procedures may reduce long-term mortality
  - this is in addition to well-described benefits in other measures including quality of life
  - at the very least, does not INCREASE mortality
- as internists we should feel comfortable recommending these procedures to our obese patients who have failed other interventions
Hazards of Radiologic Testing

Estimating risk of cancer associated with radiation exposure from 64-slice computerized tomographic coronary angiography

Accuracy of CTCA vs. Cath for Lesions >75%

(88%, or 935/1065, of all segments could be evaluated)

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients (n=70)</td>
<td>38/40 (95%)</td>
<td>27/30 (90%)</td>
<td>38/41 (93%)</td>
<td>27/29 (93%)</td>
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<tr>
<td>arteries (n=279)</td>
<td>631/693 (91%)</td>
<td>194/210 (92%)</td>
<td>63/79 (80%)</td>
<td>194/200 (97%)</td>
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<tr>
<td>segments (n=935)</td>
<td>79/82 (86%)</td>
<td>802/843 (95%)</td>
<td>79/120 (66%)</td>
<td>802/815 (98%)</td>
</tr>
</tbody>
</table>

*JACC 2005; 552-7*
The Role of CT Coronary Angiography for Diagnosing CAD

- gold standard - catheterization
  - 1.7% rate of major complications
- non-invasive tests
  - difficult to obtain
  - problems of specificity
- CTCA emerging as diagnostic test of choice for chest pain patients with intermediate probability of CAD
  - takes 20 minutes
  - 6 million ED chest pain patients per year
  - 15% to 25% had ACS
However ...

- concern regarding overuse of CT
  - 62 million scans in U.S.
  - pediatric and young adults
  - screening studies
- mechanism for oncogenesis
  - creation of hydroxyl radicals
  - DNA strand breaks
  - point mutations, translocation and gene fusion
- estimates of impact
  - 1996 - .4% of all cancers attributable to CT
  - 2006 - as high as 1.5 to 2.0%

*Brenner DJ, Hall EJ. NEJM 2007; 357:2277-84*
Estimating Lifetime Attributable Risk of Cancer from 64-slice CTCA - Objectives

To determine:

- radiation exposure associated with CTCA
  - effect of scan protocol, including ECTCM, and cranial extension (the “triple rule-out”)
- LAR of cancer associated with this level of exposure
  - age
  - sex
  - organ-specific
Estimating Lifetime Attributable Risk of Cancer from 64–slice CTCA - **Methods**

- radiation exposures based on computerized simulation (phantoms)
- BEIR VII risk modeling
  - framework for estimating age-, sex-, and organ-specific cancer risks
  - expert panel review of world literature, including experience in Japan and other exposed populations
  - accepted by most important international expert panels
# Radiation Exposures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Radiation (millisieverts)</th>
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<tbody>
<tr>
<td>chest x-ray (PA &amp; lat)</td>
<td>0.1</td>
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<tr>
<td>screening mammogram</td>
<td>3</td>
</tr>
<tr>
<td>cardiac catheterization</td>
<td>5-8</td>
</tr>
<tr>
<td>Japanese atomic bomb survivors</td>
<td>40 (mean)</td>
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</table>
# Radiation Doses to Internal Organs from CTCA Protocols

<table>
<thead>
<tr>
<th>Sex</th>
<th>ECTCM</th>
<th>Aorta</th>
<th>Dose, mSv</th>
<th>Breast</th>
<th>Lung</th>
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<tbody>
<tr>
<td>F</td>
<td>No</td>
<td>No</td>
<td>21</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>M</td>
<td>No</td>
<td>No</td>
<td>15</td>
<td>65</td>
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<tr>
<td>F</td>
<td>Yes</td>
<td>No</td>
<td>14</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>M</td>
<td>Yes</td>
<td>No</td>
<td>9</td>
<td>42</td>
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</tr>
<tr>
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<td>29</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>M</td>
<td>No</td>
<td>Yes</td>
<td>23</td>
<td>90</td>
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</table>
LAR of Cancer from a Single CTCA Scan
By Age and Sex

## Estimated Relative Risks of Attributable Cancer Incidence Associated with a Single CTCA Scan

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Std</th>
<th>ECTCM</th>
<th>Std</th>
<th>ECTCM</th>
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<tr>
<td>80</td>
<td>M</td>
<td>1.0</td>
<td>.7</td>
<td>1.4</td>
<td>.9</td>
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<tr>
<td>40</td>
<td>M</td>
<td>3.2</td>
<td>2.1</td>
<td>4.7</td>
<td>3.0</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>4.8</td>
<td>3.1</td>
<td>6.9</td>
<td>4.5</td>
</tr>
<tr>
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<td>2.4</td>
<td>1.6</td>
<td>3.1</td>
<td>2.0</td>
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<tr>
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<td>F</td>
<td>11.5</td>
<td>7.5</td>
<td>14.2</td>
<td>9.3</td>
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<tr>
<td>20</td>
<td>F</td>
<td>22.9</td>
<td>14.9</td>
<td>28.6</td>
<td>18.6</td>
</tr>
<tr>
<td>Age, y</td>
<td>Sex</td>
<td>Std</td>
<td>ECTCM</td>
<td>Std</td>
<td>ECTCM</td>
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<td>F</td>
<td>22.9</td>
<td>14.9</td>
<td>28.6</td>
<td>18.6</td>
</tr>
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</table>
Implications for Internal Medicine

- CTCA helpful to rule out ACS
  - neg pred value > 95%
  - fast
  - avoids complications and burden of coronary angiography
- associated with substantial radiation exposure
  - protocol dependent
- LAR of cancer remains a concern
  - especially in younger women
Hazards of Radiologic Testing

Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents

*MMWR Weekly. 2007; 56:137-141*
Nephrogenic Systemic Fibrosis (aka nephrogenic fibrosing dermopathy)

- first identified in dialysis patients in 1997
- skin thickening with brawny hyperpigmentation and tethering
  - symmetric limb involvement
  - evolves over weeks
  - loss of motion and contractures
  - pain and severe disability
NSF and Exposure to MRI with Gadolinium Contrast Agents - Methods

- report to CDC
- case control study
  - cases - 19 biopsy confirmed cases from single dialysis unit over 6 years
  - controls - three per case from same unit, matched by date of treatment
### Characteristics of NFS Cases and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case pts. (n=19)</th>
<th>Controls (n=57)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>median age (yrs)</td>
<td>50</td>
<td>58</td>
<td>.04</td>
</tr>
<tr>
<td>sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>47</td>
<td>54</td>
<td>.60</td>
</tr>
<tr>
<td>male</td>
<td>53</td>
<td>46</td>
<td>---</td>
</tr>
<tr>
<td>months on dialysis</td>
<td>30</td>
<td>24</td>
<td>.20</td>
</tr>
<tr>
<td>type of dialysis</td>
<td></td>
<td></td>
<td>.64</td>
</tr>
<tr>
<td>hemo</td>
<td>58</td>
<td>60</td>
<td>---</td>
</tr>
<tr>
<td>peritoneal</td>
<td>32</td>
<td>23</td>
<td>---</td>
</tr>
<tr>
<td>none</td>
<td>11</td>
<td>18</td>
<td>---</td>
</tr>
<tr>
<td>comorbidities (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>diabetes</td>
<td>37</td>
<td>47</td>
<td>.42</td>
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<tr>
<td>DVT</td>
<td>37</td>
<td>12</td>
<td>.02</td>
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<tr>
<td>hypothyroid</td>
<td>32</td>
<td>9</td>
<td>.01</td>
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<tr>
<td>autoimmune</td>
<td>21</td>
<td>7</td>
<td>.08</td>
</tr>
<tr>
<td>dependent edema</td>
<td>78</td>
<td>31</td>
<td>.001</td>
</tr>
<tr>
<td>median days in hospital during preceding year</td>
<td>21</td>
<td>17</td>
<td>.40</td>
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</table>
## Odds ratios for selected characteristics among NSF patients and matched controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>history of DVT</td>
<td>5.05 (1.25 - 20.42)</td>
<td>3.37 (0.60 - 18.85)</td>
</tr>
<tr>
<td>dependent edema</td>
<td>7.11 (1.95 - 25.82)</td>
<td>3.15 (0.67 - 14.77)</td>
</tr>
<tr>
<td>history of hypothyroid</td>
<td>4.10 (1.14 - 14.70)</td>
<td>4.18 (0.66 - 26.57)</td>
</tr>
</tbody>
</table>

### Medications received

<table>
<thead>
<tr>
<th>Medication</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
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<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>EPO</td>
<td>2.95 (0.48 - 17.93)</td>
<td>----</td>
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<td></td>
</tr>
<tr>
<td>Iron</td>
<td>0.79 (0.15 - 4.32)</td>
<td>----</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>2.01 (0.60 - 6.66)</td>
<td>----</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>1.92 (0.50 - 7.33)</td>
<td>----</td>
<td>-------</td>
<td></td>
</tr>
</tbody>
</table>

### Exposure to gadolinium

<table>
<thead>
<tr>
<th>Time</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>in preceding 6 months</td>
<td>6.11 (1.92 - 19.52)</td>
<td>----</td>
</tr>
<tr>
<td>in preceding year</td>
<td>7.99 (2.22 - 28.77)</td>
<td>8.97 (1.28 - 63.01)</td>
</tr>
</tbody>
</table>
Odds ratios for selected characteristics among NSF patients and matched controls

<table>
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<tr>
<td>Exposure to gadolinium</td>
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</tbody>
</table>
Results (con’t)

- five cases had no gad exposures within 1 year
  - four of these exposed within 5 years
- cases more likely to have had multiple MRI with gad exposures
- attack rate: 4.6 per 100 peritoneal dialysis pts
  0.61 per 100 hemodialysis pts
Other recent observations re: NSF and gadolinium exposure in CKD

- Cross sectional cohort study of dialysis population
  - 13% had findings of NSF
  - Exposure to gadolinium associated with OR for NSF of 14.7 (95% CI 1.9 - 117.0)
- Gadolinium identified in skin biopsy specimens
- Time from exposure to NSF
  - 2 days to years
  - Median 76 days
- Dose dependent
- Attack rates reported in other studies 2% - 5% in patients with advanced CKD

Implications for Internal Medicine

- avoid gadolinium-containing contrast in patients with stage IV-V CKD (GFR less than 30 mL/min per 1.73 m²)
- if absolutely required, consider post-procedure hemodialysis to prevent NSF
Cardiovascular Risk

Independent impact of gout on mortality and risk for coronary heart disease

Choi HK, Curhan G. Circulation 2007;116:894-900
Hyperuricemia and Gout: on the rise

- rising incidence
  - doubled between 1970 and 1990
  - currently 46/100,000
- age and male sex are most important risk factors
- also:
  - obesity
  - alcohol intake
  - high purine diet
  - hypertension
  - cardiovascular disease
  - renal disease
  - metabolic syndrome
Hyperuricemia (SUA) and Cardiovascular Disease (CVD) 

(\textit{guilt by association})

- observational studies over past 60 years
- prospective cohort studies
  - NHANES Follow-up Study finds strong, independent association
  - Framingham Heart Study reaches negative conclusion
- most other epidemiologic studies suggest independent association between SUA and CVD, especially in populations with high CVD risk
Turning to this study...

Gout, Mortality and CHD - Methods

- Health Professionals Follow-up Study
  - prospective cohort study
  - 51,529 men (91% white)
- self assessment of gout and CHD
- tracked with biennial questionnaires x 12 years
- multivariate adjustment for other risk factors on outcomes:
  - incidence of CVD, CHD
  - total death
  - death from MI
Gout, Mortality and CHD - Results

- 6% prevalence of gout at baseline

- Increased relative risk for:
  - all cause mortality: $\text{RR} = 1.28$ (95% CI 1.15 to 1.41)
  - death from CVD: $\text{RR} = 1.38$ (95% CI 1.15 to 1.66)
  - fatal CHD: $\text{RR} = 1.55$ (95% CI 1.24 to 1.93)
  - non-fatal MI: $\text{RR} = 1.59$ (95% CI 1.04 to 2.41)
Results (con’t)

- for gout, adjusted RR of CVD and CHD mortality was 25%
- independent of age, BMI, smoking, family history, use of diuretics and aspirin, dietary factors, diabetes, hypercholesterolemia, hypertension
  - n.b. exercise capacity and kidney function not assessed
- in men without prior CHD, increased mortality associated with gout due to CVD death, particularly from CHD
SUA elevation can produce subtle glomerulo-tubular damage
- activation of renin-angiotensin system

SUA elevation affects endothelial function
- free radical generation
- increase in platelet adhesiveness

decreased SUA may account for some of the benefit of losartan vs. atenolol in LIFE trial

gout as an inflammatory condition
Implications for Internal Medicine

- gout patients are at increased risk of CVD, especially CHD
- still no evidence to treat elevated SUA as an independent risk factor
- but presence of gout may justify more aggressive approach to other CV risk factors, and perhaps to elevated SUA
Treatment of Coronary Artery Disease

Optimal medical therapy with or without PCI for stable coronary disease (COURAGE).

Percutaneous coronary intervention (PCI)

- increasingly used
  - over 1,000,000 procedures in the U.S. in 2005
  - implantation of bare metal stents and drug-coated stents make up the majority of procedures
Proven Success

- patency rates >80% at one year in studies
- reduce MI in unstable angina
- reduce mortality in acute coronary syndromes
- reduce angina scores compared to medication management alone
- improve exercise capacity (in the short-term) compared to medication management
Concerns raised...

- concerns over safety of drug-eluting stents
  - ? increased death, MI due to in-stent thrombosis?
- costs, risks of taking Clopidogrel (Plavix)
- patients undergoing major surgery did not benefit from preoperative stenting
- no data showing mortality or outcomes benefit in patients with stable angina
  - comprise the majority of stent procedures
Turning to this study...

PCI in Stable Coronary Disease - Objective

- to determine whether PCI in patients with stable coronary artery disease reduces future cardiovascular outcomes (MI, death) compared to medical therapy alone
PCI in Stable Coronary Disease - Methods

- 2287 patients with stable CAD 1999-2004
  - at least 70% stenosis plus positive stress test
  - or 80% stenosis and classic angina
- randomly assigned to have PCI plus optimal medical therapy or medical therapy alone
- involved 50 different centers in U.S. and Canada
- primary outcome measure: death+nonfatal MI
PCI in Stable Coronary Disease - Methods

- many exclusions:
  - severely + stress test (e.g. hypotension)
  - class IV angina
  - EF < 30% or clinical CHF
  - previous revascularization within 6 months
- patients were mostly white males (85%), average age 61, more than ½ from VA
  - most had more than one reversible defects on nuclear stress imaging
PCI in Stable Coronary Disease - Results

- mean LDL 71, mean bp 124/70
- 95% on asa, 93% on statin, 85% on beta blockers, 76% on ace-i/arb (no differences between the two groups)
- medical management group more likely to be on nitrates 57% vs. 40%
Results at 5 years
PCI in Stable Coronary Disease - Results

- at 5 years, no differences in angina scores between two groups (75% no angina)
- however, at 1 and 2 years PCI group had less angina than medication group (68% vs. 59%)
- no difference between groups in future need for CABG (about 7%)
- 40% of PCI group patients had > 2 stents placed at the original procedure
PCI in Stable Coronary Disease - **Limitations**

- mostly white, male patients
- subjects were a very select group of patients
  - about 10% of all of those screened for study
- medical therapy was superior to that typically achieved in the ‘real world’ setting
  - common problem in these types of studies
- mostly bare metal stents were used
- some concerns that the ‘success’ of PCI was lower than that achieved in other studies
Conclusions

- PCI for stable coronary artery disease is not superior to optimal medical management in preventing death, MI, CHF or other CVD events
  - makes sense—acute MI, sudden death usually involves coronary arteries with baseline ‘noncritical’ stenosis
- PCI is modestly more effective at reducing angina (short-term) than medications alone
- Would drug-eluting stents perform differently?
- How do these results apply to patients with LV dysfunction and other study exclusions?
Implications for Internal Medicine

- PCI has not been shown to reduce MI or death in patients with stable coronary disease in any situation.
- In many patients with stable CAD, PCI should be reserved for patients who fail proven medical therapies, with the goal of reducing angina and improving symptoms.
- Keeping in mind risks of PCI procedures and costs/risks of clopidogrel use post-procedure.
Type 2 Diabetes Mellitus

Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes.

Phillips & Associates
Avandia lawyer who can help you if you've been injured from taking Avandia. Free consultation.
(800) 706-3000
Rosiglitazone

- The most prescribed branded diabetes drug in 2006
  - comprised 1/7 of Rx for diabetes meds
- total sales 2006: $3 billion
Rosiglitazone—what is well known

- Thiazolidinedione (TZD) that works intracellularly to enhance insulin sensitivity
  - numerous other cellular (nuclear) effects
- reduces hemoglobin A1C 1-1.5%
  - similar to other oral agents
- doubles risk of CHF (as does pioglitazone)
- **NO** evidence of reduction in microvascular or macrovascular complications
  - cardiovascular diseases cause > 1/2 of deaths in DM
Turning to this study...

Rosiglitazone and Risk of Cardiovascular Events - Objectives

To determine:
- whether rosiglitazone alters the risk of cardiac events and/or cardiovascular death in patients using the drug for type 2 diabetes mellitus
Rosiglitazone and Risk of Cardiovascular Events - **Methods**

- meta-analysis of all 42 trials that had:
  - rosiglitazone vs. placebo
  - lasted > 24 weeks
  - reported CV outcomes (MI, cardiac death)

- involved data from published papers, pharmaceutical company records, FDA

- excluded papers that did not have any cardiac outcomes reported
Rosiglitazone and Risk of Cardiovascular Events - Results

- 27,000 subjects pooled from these studies
- Patients on rosiglitazone had 43% (RR 1.43 CI 1.03-1.98) greater risk of MI and 64% greater risk of CV death (RR 1.64 CI 1.01-2.74)
- Concluded that rosiglitazone is associated with increased risk of both MI and cardiovascular death
Rosiglitazone and Risk of Cardiovascular Events - **Results (problems)**

- Total event rates only about 0.5%
- No single study had more than 5 deaths
- Studies widely variable
- Different definitions of cardiac death, MI?
- Individual studies were not powered to detect differences in adverse cardiac events; cardiac events were not primary outcomes
- Is it acceptable to exclude the studies with zero events?
Rosiglitazone and Risk of Cardiovascular Events - other studies

- RECORD (July 2007, two months later)
  - 4000 patients in randomized placebo controlled study with rosiglitazone looking at cardiovascular outcomes
  - interim analysis done (halfway point) as a result of the previous study showed RR 1.1 (0.9-1.3) for CV events in rosiglitazone group
  - CHF RR = 2.25 (1.4-3.5)
- CONCLUSION: no evidence of risk
Rosiglitazone and Risk of Cardiovascular Events - other studies

- Singh et. al. JAMA 9/2007 (1 month later)
  - meta-analysis of 4 largest RCTs (4000 pts.)
  - MI RR 1.42 (1.06-1.9)
- GSK analysis—31% increase in CV risk
  - separate meta-analysis using different methods found NO statistically significant increase in cardiovascular risk
Rosiglitazone and Risk of Cardiovascular Events - Conclusions

- Rosiglitazone doubles the risk of clinical CHF
- Rosiglitazone MAY increase risk of MI and cardiovascular death
- There is no evidence that rosiglitazone reduces cardiovascular risk
- There is (still) no evidence that rosiglitazone reduces microvascular risks
- Rosiglitazone is equal to (not better than) other oral agents in improving glycemic control
Rosiglitazone and Risk of Cardiovascular Events - compared to pioglitazone?

- PROACTIVE study 2005 (Lancet) studied 5000 high risk patients
  - nonsignificant reduction in CAD/PVD events
  - significant reduction in composite of death, MI, stroke
  - increased CHF (2-fold) without increase in CHF mortality
  - favorable effects on all lipid parameters (unlike rosiglitazone)
Implications for Internal Medicine

- Rosiglitazone should be used with caution in diabetics given possible increase in cardiovascular risk.

- There is no obvious rationale for using rosiglitazone over other oral agents, including the similar drug pioglitazone which has not had similar cardiovascular risk concerns to date and has the advantage of having beneficial lipid effects.
Asthma

Randomized comparison of strategies for reducing treatment in mild persistent asthma: LOCCS Trial


Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma: BEST Trial

### Patients with Mild Persistent Asthma

<table>
<thead>
<tr>
<th>Severity</th>
<th>Frequency of general symptoms</th>
<th>Frequency of symptoms at night</th>
<th>Flare-ups (exacerbations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent</td>
<td>Two times a week or less</td>
<td>Two times a month or less</td>
<td>Brief (a few hours to a few days) with varying intensity</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>Two times a week or more - but less than one time each day</td>
<td>More than two times a month</td>
<td>May be severe enough to restrict physical activity</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Daily, often accompanied by daily use of rescue inhaler</td>
<td>More than one time a week</td>
<td>Twice a week or more, possibly severe enough to restrict physical activity</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Continual, with limited physical activity</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

*Adapted from NAEPP Guidelines, NHLBI, 1997*
## Why Step Down?

<table>
<thead>
<tr>
<th>Cost</th>
<th>Per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>inhaled beta agonists</td>
<td>$11</td>
</tr>
<tr>
<td>inhaled glucocorticoids</td>
<td>$50</td>
</tr>
<tr>
<td>combination inhaler</td>
<td>$100</td>
</tr>
<tr>
<td>(salmeterol and fluticasone)</td>
<td></td>
</tr>
<tr>
<td>leukotriene modifiers</td>
<td>$90</td>
</tr>
</tbody>
</table>

### Side Effects
- beta agonists - unusual with inhaled delivery
- inhaled glucocorticoids - skin atrophy, decrease bone density, cataracts, adrenal suppression
- leukotriene modifiers - liver dysfunction with zileuton

### Patient Preference
Turning to these studies...

LOCCS (Leukotriene or Corticosteroid or Corticosteroid-Salmeterol) Trial - Methods

- 500 stable patients with mild persistent asthma
- 6 week run-in with BID inhaled fluticasone
- randomly assigned for 16 weeks, double blind, double dummy, to one of three regimens
- outcomes
  - treat failure, defined as
    - hospitalization
    - urgent visits
    - need for open label steroids
    - deterioration in FEV$_1$ or PEFR
    - need for rescue beta-agonist for 2 consecutive days
    - patient dissatisfaction
    - symptom scores
LOCCS Trial Protocol

- **Run-in Period**
  - Randomization
  - Fluticasone (100 μg twice daily)

- **Double-Blind Treatment Period**
  - Montelukast (5 or 10 mg each night)
  - Fluticasone (100 μg twice daily)
  - Fluticasone (100 μg) + salmeterol (50 μg) each night

- **Timeline**:
  - Enrollment
  - Stable asthma
  - Weeks: -6, -4, -2, 0, 2, 4, 6, 8, 10, 12, 14, 16
LOCCS Trial - Results

- similar failure rates (20.2% and 26.4%) for BID inhaled corticosteroid and daily inhaled combination Rx
- higher failure rate (30.3%) for daily montelukast
- similar percent of days symptom free
- preference to continue current treatment regimen
  - one-daily combination inhaler (78.4%)
  - twice-daily inhaled corticosteroid (69.7%)
  - once-daily po montelukast (56.4%)
BEST (Beclomethasone plus Albuterol Treatment) Trial - Methods

- 455 stable patients with mild persistent asthma
- 4 week run in with 500 ug/day (250ug BID) beclomethasone
- randomly assigned to 6 months, double blind, double dummy, to one of four regimens
- outcome variables
  - peak expiratory flow rates
  - symptom scores (self report)
  - number and severity of exacerbations
BEST Trial - Results

- PEFR and frequency of exacerbations similar for twice daily inhaled corticosteroid, twice daily inhaled combination therapy, and as-needed combination therapy
- these three regimens were superior to as-needed albuterol
- as-needed inhaled combination regimen group had lowest cumulative dose of beclomethasone (equivalent to 100 mg daily)
Caveats and Concerns

- patient selection
  - mild persistent asthma, well controlled
- duration of trial
  - potential impact of untreated, subclinical airway inflammation upon disease progression
- combination corticosteroid/short acting, rapid onset beta agonist not currently available in US
Implications for Internal Medicine

For stable patients with mild, persistent asthma “stepping down” treatment may be an option for:

- decreasing cost
- decreasing side effects
- improving compliance
- meeting patient preference
Kidney Stones

A systematic review of medical therapy to facilitate passage of ureteral calculi

Kidney Stones: more than a passing problem

- lifetime prevalence in USA
  - 13% for men
  - 7% for women
- recurrence rate - 50% in 5 years
- 2 million office visits annually
- most stones < 5 mm in diameter
  - pass spontaneously within 4 weeks
- morbidity of persistent ureteral stones
  - strictures
  - renal damage
  - cost and complications of lithotripsy, ureteroscopy and percutaneous nephrolithotomy
Systematic Review of Medical Therapy – **Methods**

- meta-analysis of 211 studies
  - 22 selected - all randomized or controlled trials
    - $\alpha$-antagonist (n=13) 1,235 patients
    - calcium channel blocker (n=6) 686 patients
    - both drugs (n=3)
  - Jadad scores 0 to 3 (median score 2)
  - median stone diameter > 5 mm in almost all trials
α-antagonist (tamsulosin) - Results

- benefit in achieving stone expulsion
  - RR 1.59 (95% CI 1.44 to 1.75)
  - NNT 3.3 (95% CI 2.1 to 4.5)
- 2-6 day average improvement in time to expulsion
  - mean time to expulsion in treatment group < 14 days
- minimal adverse effects
calcium channel blocker (nifedipine) - Results

- benefit in achieving stone expulsion
  - RR 1.50 (95% CI 1.34 to 1.68)
  - NNT 3.9 (95% CI 3.2 to 4.6)
- improved time to expulsion found in 7 of 9 trials
- minimal adverse effects
Biologic Rationale

- Ureteral stones increase amplitude and decrease frequency of smooth muscle contraction.
- Ureteral relaxation may facilitate stone passage.
Implications for Internal Medicine

- a one-month trial of “medical expulsive therapy” should be considered to enhance passage (and avoid more costly and complicated approaches) for ureteral stones larger than 5 mm.
Cervical Cancer and HPV Vaccination

Quadrivalent Vaccine against human Papillomavirus to Prevent High-Grade Cervical Lesions

HPV and Cervical Cancer

- Cervical cancer is the leading cause of cancer death in women in developing nations.
- HPV is responsible for virtually all cervical cancer.
  - HPV-16 and HPV-18 involved in about 2/3 of these.
- Cervical cancer develops from pre-malignant pathologic changes (cervical intraepithelial neoplasia, CIN grade 2-3).
- Vaccine exists against HPV-6, 11, 16, 18.
Turning to this study...

Cervical Cancer and HPV Vaccination - Objectives

- to determine whether vaccination with quadrivalent HPV vaccine reduces incidence of cervical cancer precursors (CIN 2 and 3)
- to determine the effectiveness of this vaccine in preventing infections with covered strains of HPV
Cervical Cancer and HPV Vaccination

Methods

- multicenter, international randomized placebo-controlled double blind study
- over 12,000 women enrolled
  - no history of HPV infection or abnormal paps
  - given three vaccines (or placebo) over a 6 month period
- periodic follow-up pap smears, HPV tests
- primary endpoints: CIN 2, CIN 3, cancers
Cervical Cancer and HPV Vaccination - Results

- average age of subjects: 20 years old
- no differences in two groups at baseline
- most patients were European (7% North America)
- most were sexually active prior to the study
- average follow-up: 3 years
- HPV 16 or 18 identified in 10% of subjects at the baseline examination
### Results
(negative HPV and normal pap at baseline)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>New HPV 16 or 18</td>
<td>3 (&lt;0.1%)</td>
<td>67 (1.3%)</td>
<td>83</td>
</tr>
<tr>
<td>CIN 2 or 3 (HPV 16/18)</td>
<td>1 (&lt;0.1%)</td>
<td>57 (1.1%)</td>
<td>91</td>
</tr>
<tr>
<td>CIN 2 or 3 (any)</td>
<td>95 (2%)</td>
<td>130 (2.7%)</td>
<td>142</td>
</tr>
<tr>
<td>adenocarcinoma</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>
Cervical Cancer and HPV Vaccination - Results – intention to treat analysis

- Vaccine subtype related CIN 2 or 3
  - 1.6% in vaccine group, 3.2% in placebo
  - 50% effective

- All CIN 2 or 3
  - 4.6% in vaccine group, 5.7% in placebo
  - 17% effective

- In patients with baseline pap abnormalities or HPV infection – vaccine ineffective overall
HPV vaccination is nearly 100% effective at preventing infections in women who have not been previously infected.

HPV vaccination reduces incidence of cancer precursor lesions (CIN 2 or 3).

HPV vaccination is ineffective in women who are already infected with HPV subtypes included in the vaccine.
Cervical Cancer and HPV Vaccination - Limitations

- most women were sexually active
  - more effective in younger women prior to onset of sexual activity?
  - length of protection from vaccine?
- no reduction in adenocarcinoma
  - surrogate endpoints widely accepted in this field however, given length of time to cancer development and well-described biology
Implications for Internal Medicine

- Vaccination with quadrivalent HPV vaccine may be offered to females to reduce HPV infection and advanced cervical lesions.
- HPV vaccine appears to be safe.
- Pap smears will still be necessary.
Colorectal Cancer Screening

CT colonography versus colonoscopy for the detection of advanced neoplasia

Colorectal Cancer Screening Guidelines –
American Cancer Society

- beginning at age 50, both men and women at average risk for developing colorectal cancer should use one of the screening tests below.
  - flexible sigmoidoscopy every 5 years
  - colonoscopy every 10 years
  - double contrast barium enema every 5 years
  - CT colonography (virtual colonoscopy) every 5 years
CT colonography - how it works

- same cathartic preparation as traditional colonoscopy
- CO2 gas ‘enema’
- oral barium ‘tagging’
- CT scanning supine and erect
- less radiation than BE
- 3d computer analysis
- no sedation, no risks of perforation (0.2-1.0% for colonoscopy)
Turning to this study...

CT Colonography Compared to Colonoscopy - Methods

- 3000 consecutive patients undergoing CT colonography (CTC) compared to 3000 patients undergoing screening optical colonoscopy
- CTC patients had same day colonoscopy if:
  - any polyps 10mm or with villous components
  - polyps 6-9mm and patient preference for polypectomy (or could choose one year f/u)
## CT Colonography Compared to Colonoscopy - Results

<table>
<thead>
<tr>
<th></th>
<th>CTC</th>
<th>Optical Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced neoplasms</td>
<td>123 (3.4%)</td>
<td>121 (3.2%)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Perforations</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Any ‘positive’ finding</td>
<td>12.9%</td>
<td>13.4%</td>
</tr>
</tbody>
</table>
CT Colonography Compared to Colonoscopy - Results

- Overall 87% of each group had normal/negative studies.
- Patients with 6-9mm polyps on CTC had no advanced neoplasms found in two years of follow-up CTC/colonoscopy.
- CTC resulted in 90% fewer colonoscopies.
CT Colonography Compared to Colonoscopy- **Conclusions**

- CT colonography compares favorably to colonoscopy in identifying colorectal cancers and advanced neoplasms in average risk patients
  - no evident risk of the procedure
  - many fewer colonoscopies required with this screening approach
CT Colonography Compared to Colonoscopy—**Limitations**

- not a randomized trial - selection biases
- one center study---CTC highly user dependent, may not be reproducible
- CTC is time consuming and not necessarily money saving
- CTC rarely covered by third party payers
- same-day colonoscopy for ‘positive’ CTC results not viable in most cases
Implications for Internal Medicine

- CT colonography is an acceptable alternative to optical colonoscopy for colorectal cancer screening in average risk patients who prefer it for various reasons.
- CTC cannot be considered equal to colonoscopy until results are replicated.
- CTC cannot be recommended for screening in higher risk individuals.
Annual Check-Ups

Systematic review: the value of the periodic health evaluation

Should we still be recommending annual check-ups?

“From both medical and lay sources requests have come to the American Medical Association to prepare a description of the objects to be attained, the methods to be employed, and results which may be expected from inquiry into and observation of the tissues and physiologic functions of persons, young and old, who are not at the time aware of any disease or defect which is causing them to seek medical relief.”

Emerson H. JAMA 1923;80:1376-1381
Finding little value in periodic health evaluation (PHE)

- 1979 - Canadian Task Force on the Periodic Health Examination
- 1981 - American College of Physicians
- 1991 - U.S. Preventive Services Task Force
- 1994 - U.S. Department of Health, Office of Disease Prevention and Health Promotion
- yet multiple studies demonstrate physicians and patients still prefer PHE
A systematic review of the value of PHE - Methods

- defined PHE
- developed model for benefits (e.g. reassurance, improved outcomes) and harms (e.g. loss of time at work, inappropriate tests) of PHE
- systematic review of literature comparing PHE vs “usual care”
- outcomes categorized by:
  - direction: beneficial, mixed, harmful
  - magnitude: small, intermediate, large
A systematic review of the value of PHE - Results

- 7,000 articles screened
- 33 studies selected for inclusion
  - 10 RCTs
  - 23 observational studies
## Systematic Review of PHE - Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect (magnitude)</th>
</tr>
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<tbody>
<tr>
<td><strong>Delivery of preventive service</strong></td>
<td></td>
</tr>
<tr>
<td>Gyn/Pap</td>
<td>beneficial (small to large)</td>
</tr>
<tr>
<td>counseling</td>
<td>mixed</td>
</tr>
<tr>
<td>immunizations</td>
<td>mixed</td>
</tr>
<tr>
<td>cholesterol screening</td>
<td>beneficial (small to large)</td>
</tr>
<tr>
<td>colon ca screening</td>
<td>beneficial (large)</td>
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<td><strong>Proximal clinical outcomes</strong></td>
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<tr>
<td>disease detection</td>
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</tr>
<tr>
<td>patients’ attitudes</td>
<td>beneficial</td>
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<td>health status</td>
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<td>BP</td>
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<td>serum cholesterol</td>
<td>mixed</td>
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<td><strong>Distal econ &amp; clinical outcomes</strong></td>
<td></td>
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</table>
Implications for Internal Medicine

- PHE can be justified based on its beneficial effects on some preventive measures and as a means of allaying patients’ worries.