Clinical trials that may change your practice®:
Primary Care Edition

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Outline

- Late-breakers from the world of osteoporosis:
  - Calcium and risk of vascular events (Jan 2008)
  - Bisphosphonates and osteonecrosis (Jan 2008)

- Combination therapy with ASA and warfarin:
  - Good for patients with atrial fibrillation?
  - Good for patients with peripheral artery disease?
  - (Good for anyone?)

Mrs. Maple

- 84 year-old woman with history of fragility fracture in 1967, currently taking:
  - Elemental calcium 1000 mg (carbonate form) x 4 years
  - Vitamin D 800 IU x 4 years
  - Risedronate 5 mg od x 3 years

- Asks about some recent stories:
  - “Calcium supplements raise heart-attack risk: study” (CTV news January 9, 2008)
  - “Osteoporosis drugs may cause destructive bone disease: study” (CBC news, January 18, 2008)

Mrs. Maple’s concern:

- Wants to be sure that she is protected from broken bones when she jumps up and down celebrating Toronto Maple Leafs victories

Handouts…

- Not available in CD

- Email: jnagge@uwaterloo.ca for a copy of presentation

Disclosure

Me (age 6)
Disclosure

- No conflicts to disclose

Osteoporosis medications in the news

- Calcium and the risk of vascular events
- Oral bisphosphonates and the risk of osteonecrosis

Evaluating studies

- Identify the study design
- Understand how subjects are selected
- Understand how exposure and outcomes are defined and measured
- Evaluate potential bias and confounding
- Determine if the statistical evaluation is appropriate
- Make decisions about whether the outcome measures are statistically significant and/or clinically important
- Use good judgment

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Vascular events in healthy older women receiving calcium supplements

**ABSTRACT**

**Objective:** To determine the effect of calcium supplementation on myocardial infarction, stroke, and sudden death in healthy postmenopausal women.

**Design:** Randomized, placebo-controlled trial.

**Setting:** Academic medical center in an urban setting in New Zealand.

**Participants:** 1,617 postmenopausal women (mean age 74.0 ± 7.3 years) randomized to calcium supplementation and 1,794 placebo.

**Main outcome measures:** Adverse cardiovascular events (myocardial infarction, stroke, and sudden death).

**Results:** The calcium group had a lower risk of myocardial infarction and stroke compared to the placebo group. The risk of sudden death was not significantly different between groups.

**Conclusion:** Calcium supplementation may reduce the risk of adverse cardiovascular events in healthy older women.

Bolland MJ et al. BMJ 2008: Online first. bmj.com

Or by just reading the abstract!
Randomized trial of calcium in healthy older women

1471 post-menopausal women
Mean age = 74 (SD = 4)
Excluded if receiving treatments for osteoporosis or taking calcium, or if serum 25-hydroxyvitamin D < 25

1 g elemental calcium (citrate form) (n=732)
Placebo (n=739)
Mean follow-up 4.5 years

Primary Endpoint:
• Time to first fracture

Results: Primary outcome

Outcome: Time to fracture
Calcium (n=732) Placebo (n=739) Hazards Ratio (95% CI) p value
Number of fractures (length of U/a) 119 (4.4 years) 132 (4.5 years) 0.91 (0.71 to 1.16) 0.46

Safety results

Outcome Calcium (n=732) Placebo (n=739) p value
Constipation 132 (18%) 82 (11%) 0.0002
Discontinuation of calcium due to health reasons 133 105 0.04

Vascular events in healthy older women receiving calcium supplements
BMJ 2008: Online first bmj.com

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Primary Endpoint:
• Time to first fracture
Secondary endpoints:
BMD, fracture incidence at various sites

Internal validity problem 1: What is the primary outcome?
Main outcome measures:
■ Death, sudden death, myocardial infarction, angina, other chest pain, stroke, TIA or sudden death and a composite endpoint of myocardial infarction, stroke or sudden death

Internal validity problem 2: How was the outcome ascertained?
■ Self-report
■ Adjudicated by blinded experts
■ Verified by hospital admissions and adjudicated by blinded experts
### Self-reported outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Calcium (n=732)</th>
<th>Placebo (n=739)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>31</td>
<td>14</td>
<td>2.24 (1.20 to 4.17)</td>
<td>0.0099</td>
</tr>
<tr>
<td>Stroke</td>
<td>40</td>
<td>28</td>
<td>1.37 (0.99 to 2.31)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sudden death</td>
<td>4</td>
<td>1</td>
<td>4.04 (0.45 to 36)</td>
<td>0.22</td>
</tr>
<tr>
<td>MI, stroke, or sudden death</td>
<td>69</td>
<td>42</td>
<td>1.66 (1.13 to 2.40)</td>
<td>0.0075</td>
</tr>
</tbody>
</table>

### Verified outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Calcium (n=732)</th>
<th>Placebo (n=739)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>31</td>
<td>22</td>
<td>1.49 (0.86 to 2.57)</td>
<td>0.16</td>
</tr>
<tr>
<td>Stroke</td>
<td>34</td>
<td>25</td>
<td>1.37 (0.83 to 2.28)</td>
<td>0.23</td>
</tr>
<tr>
<td>Sudden death</td>
<td>3</td>
<td>6</td>
<td>0.51 (0.13 to 2.01)</td>
<td>0.51</td>
</tr>
<tr>
<td>MI, stroke, or sudden death</td>
<td>60</td>
<td>50</td>
<td>1.21 (0.64 to 2.31)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

### Internal validity issue problem 3: Potential confounding

- **Demographics:**
  - Information not provided about other medications (e.g. ASA, ACE-I, statins)
  - Calcium group tended to have more current and former smokers, more folks with previous hypertension, Ischemic Heart Disease, dyslipidemia, and stroke/TIA, and they had marginally higher baseline LDL-c concentrations

### Calcium supplements and the risk of vascular events: Summary

- **Strengths of the trial:**
  - No pre-defined primary outcome
  - Multiple outcome ascertainment methods
  - Important demographic information missing
- **Weaknesses:**
  - Retrospective, exploratory analysis
  - No pre-defined primary outcome
  - Multiple outcome ascertainment methods
  - Important demographic information missing
- **Bottom-line:** Not practice-changing

### Tip: Exercise caution when reading headlines and abstracts

**Headline:**

*Australia warns travelers of Canada's perils: terrorists, tornadoes*

_Linda Nguyen and Bal Brach, Canwest News Service_

Published: Saturday, January 26, 2008

### Osteoporosis medications in the news

- **Calcium and the risk of vascular events**
- **Oral bisphosphonates and the risk of osteonecrosis**
Evaluating studies

- Identify the study design
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Bisphosphonates and the risk of Osteonecrosis of the Jaws (ONJ)

- Case reports and case-series linking bisphosphonates to ONJ
- Mechanism – ↓ bone turnover?
- Consequences – pain, dysfunction
- Over 90% of cases appear to be in patients with CA receiving IV bisphosphonates
- Estimated incidence between 1/10,000 to 1/100,000 person-years

Bisphosphonates and risk of Aseptic Osteonecrosis: A nested Case-control Study

Study population
n= 87,837
Aged 65+ in Quebec
April 1995 to December 2002

Cases:
Hospitalization secondary to aseptic osteonecrosis
n=196

Exposed to bisphosphonate
Not exposed to bisphosphonate

Controls:
10 controls/case (matched for age, calendar time, length of follow-up)
n=1,960

Exposed to bisphosphonate
Not exposed to bisphosphonate

Results

Incidence of aseptic osteonecrosis
267 per million person-years

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Cases</th>
<th>Controls</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bisphosphonates (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever used</td>
<td>14.8</td>
<td>3.8</td>
<td>2.87 (1.71 to 5.05)</td>
</tr>
<tr>
<td>Current use</td>
<td>11.2</td>
<td>2.3</td>
<td>3.14 (1.68 to 5.88)</td>
</tr>
<tr>
<td>Past use</td>
<td>3.5</td>
<td>1.2</td>
<td>2.52 (1.01 to 6.26)</td>
</tr>
</tbody>
</table>

Bisphosphonate use

- Oral agents only (IV use not identified by this database)
  - Alendronate
  - Etidronate
  - Risedronate
- Current users: Rx within 90 days of admission
- Past users: Rx earlier than 90 days
- Ever users: Rx within the last year (current plus past users)

Internal validity problem #1: How was the outcome defined and measured?

- ICD-9 code 733.4 “osteonecrosis at any non-specified site”
  - What does it measure? Likely represented diagnosis of osteonecrosis of hip (versus jaw) – but not sure
  - How well does it perform? Diagnostic utility of this code has not been validated
Internal validity problem # 2: Confounding

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=196)</th>
<th>Controls (n=1960)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>55.6%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Use of oral corticosteroids %</td>
<td>18.4%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Cancer %</td>
<td>3.1%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Mrs. Maple: Plan

- Reassurance (about her osteoporosis medications, not her choice of hockey teams)
  - Risedronate reduces her risk of an osteoporosis fracture from about 25% in 10-years to around 12%.
  - Calcium and vitamin D may also contribute to a reduction in fractures.

Oral bisphosphonates and the risk of osteonecrosis: Summary

- Strengths:
  - Provides hypothesis
- Weaknesses:
  - What was being measured?
  - How well was it being measured?
  - Important confounding present
- Bottom-line: hypothesis generating (versus practice changing)

Mrs. Maple: Plan

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  - Risedronate reduces her risk of an osteoporosis fracture from about 25% in 10-years to around 12%.
  - Calcium and vitamin D may also contribute to a reduction in fractures.

Mr. Leaf – part 1

- 82 year-old male with non-valvular atrial fibrillation
- New patient to your anticoagulation clinic
- Warfarin 4mg od
- EC ASA 81 mg
- “To keep the heart ticking while watching the Maple Leafs”

Combined ASA-Oral Anticoagulant Therapy (OAT) compared with OAT alone among Patients at Risk for Cardiovascular Disease

- Meta-analysis of Randomized Trials
- Study selection
  - Medline/EMBASE/Cochrane (1966 to 2005)
- Criteria
  1. RCT in adult patients requiring OAT
  2. Compared ASA plus OAT with OAT alone in which OAT was adjusted to the same INR in both arms
  3. Patients followed-up for at least 3 months
  4. At least 1 pre-specified outcome (TE, mortality or bleeding) was objectively documented

Study characteristics

- 10 studies selected (n=4180)
- Populations:
  - Mechanical heart valves = 5
  - Atrial fibrillation = 2
  - Coronary artery disease = 2
  - Primary prevention for cardiovascular disease = 1
- Interventions:
  - ASA < 100 mg per day in 6 trials
  - ASA 200 to 1000 mg per day in 4 trials
  - INR ≥ 1.8 in 8 studies; INR ≥ 2.0 in 2 studies
- Quality:
  - 4 studies were high quality
  - 6 studies were low quality

Results - Overall

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OAT</th>
<th>OAT plus ASA</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Arterial thromboembolism</em></td>
<td>179</td>
<td>128</td>
<td>0.66 (0.52 to 0.84)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>141</td>
<td>139</td>
<td>0.98 (0.77 to 1.25)</td>
<td>0.88</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>60</td>
<td>80</td>
<td>1.43 (1.00 to 2.02)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Test for heterogeneity p = 0.02

Results - Subgroups

Risk of arterial thromboembolism:

- Mechanical heart valves:
  - ASA plus OAT versus OAT alone:
    - OR = 0.27, 95% CI, 0.15 to 0.49
- Atrial fibrillation:
  - ASA plus OAT versus OAT alone:
    - OR = 0.99, 95% CI, 0.47 to 2.07
- Coronary Artery Disease:
  - ASA plus OAT versus OAT alone:
    - OR = 0.69, 95% CI, 0.35 to 1.36

Summary of meta-analysis

- Strengths:
  - Technically sound meta-analysis
  - Designed to answer clinically relevant question
- Weakness:
  - Not much data to meta-analyze
- Bottom line:
  - Combination therapy increases risk of bleeding
  - Combination therapy may be beneficial in patients with mechanical heart valves; current evidence does not support use in other populations
  - Coronary Stents

Mr. Maple - part 2

- Mr. Maple and his MD are grateful for your recommendation to discontinue his ASA in light of the increased bleeding risk without any documented evidence of benefit for combination therapy
- Mr. Maple’s MD asks:
  - What about my patients with peripheral artery disease? Is combination therapy more effective than ASA alone?

Oral Anticoagulant and Antiplatelet therapy and Peripheral Arterial Disease – The WAVE trial

- Peripheral arterial disease
  - Most commonly caused by atherosclerosis
  - Sign that widespread atherosclerosis present (e.g. coronary and carotid arteries)
- Standard therapy:
  - Antiplatelet therapy (AP)
- Hypothesis:
  - Will adding warfarin to APs further reduce major cardiovascular events?

**Antiplatelet therapy (AP)**
ASA 81mg to 325mg, ticlopidine or clopidogrel
n=1081

**Primary Endpoints:**
1. MI, CVA, Death from CV causes
2. Above plus severe ischemia leading to urgent intervention

**Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AP plus OAT</th>
<th>AP</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, CVA, Death from CV causes</td>
<td>132 (12.2%)</td>
<td>144 (13.3%)</td>
<td>0.92 (0.73 to 1.16)</td>
<td>0.48</td>
</tr>
<tr>
<td>Above plus severe ischemia</td>
<td>172 (15.9%)</td>
<td>188 (17.4%)</td>
<td>0.91 (0.74 to 1.12)</td>
<td>0.37</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>43 (4.0%)</td>
<td>13 (1.2%)</td>
<td>3.41 (1.84 to 6.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Mean follow-up 35 months**

**Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OAT plus AP (n=1080)</th>
<th>AP alone (n=1081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>63.9 (SD = 9.4)</td>
<td>63.8 (SD =9.5)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>73.7</td>
<td>73.5</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>44.7</td>
<td>49.9</td>
</tr>
<tr>
<td>ASA (%)</td>
<td>92.5</td>
<td>91.2</td>
</tr>
<tr>
<td>Ticlopidine (%)</td>
<td>2.8</td>
<td>4.1</td>
</tr>
<tr>
<td>Clopidogrel (%)</td>
<td>3.2</td>
<td>3.7</td>
</tr>
</tbody>
</table>

**WAVE Summary**

**Strengths:**
- Well-designed and executed - randomized, placebo controlled trial, blinded adjudication of outcomes
- Compared gold standard treatment (antiplatelet) versus most common intensity OAT therapy (INR range 2 to 3)

**Weakness:**
- Run-in phase increases apparent safety

**Bottom-line:**
- Adding OAT therapy to antiplatelet therapy in Peripheral Artery Disease does not affect mortality or cardiovascular adverse effects, but increases the risk of life-threatening bleeding

**Summary**

- Late-breakers from the world of osteoporosis:
  - Calcium and risk of vascular events (Jan 2008)
  - Bisphosphonates and osteonecrosis (Jan 2008)

- Combination therapy with ASA and warfarin:
  - Good for patients with atrial fibrillation?
  - Good for patients with peripheral artery disease?
  - (Good for anyone?)

- **WAVE trial**

2417 patients with Peripheral Artery Disease

2-4 week run-in phase
Warfarin given to everyone

Mean follow-up 35 months

- Primary Endpoints:
  1. MI, CVA, Death from CV causes
  2. Above plus severe ischemia leading to urgent intervention