2006 (and early 2007) Medicine Year in Review
Jeffrey Kohlwes, MD, MPH
No conflict of interest

How to make this talk….
- Areas Searched
- Medline
- ACP Journal Club
- Residency Journal Clubs
- Faculty Suggestion
- Practical, Applicable, Fun
- Whatever is not being covered elsewhere....

Topics!
1- NSAIDS and CV Risk
2- Its an acquired taste for health
3- Influenza update
4- Carotid Stents
5- LAB2A and Asthma
6- A study I wish I had done....

NSAIDS and Cardiovascular Risk
74 year old woman s/p small MI and subsequent 3V CABG 6 months ago arrives in your office doing well on cardiac meds. She states her biggest problem is her chronic knee DJD pain. She saw Celecoxib advertised on TV and asks about using it. She has a distant history of PUD and a previous GI bleed that was positive for H. Pylori infection- (since treated). How do you advise her?

NSAIDS are 16th leading cause of death in US

VIOXX (Refocoxib)
- 1999- VIGOR (Vioxx GI Outcomes Trial)
  - Refocoxib roughly 2/3 less GIB than Naprosyn
  - 5X increase in CV events...
  - Due to cardio-protective naprosyn?
- 2004- APPROVE Trial (adenoma prevention)
  - Increase CV events 2 fold
  - APC Trial- similar risk for Celecoxib
    » APPROVE- NEJM 2005:352:1092-1102
    » APC- NEJM 2005: 352:1071-80
Refocoxib-magnitude of risk

APPROVE Trial
MI/CVA rate
3.5% rofecoxib
1.9% placebo (P<0.001)
ARR=1.6
NNH=62.5

Tens of millions of patients using this medication......

Vioxx withdrawn Oct. 04

Biologic Plausibility??

Endothelial effects:
- Inhibits prostacyclin
- Vasoconstriction
- Decreased Plt inhibition

Unopposed COX-1
Platelet aggregation

Thrombotic Badness

Magnitude of CV Risk of NSAIDS

- Meta-analysis in Primary Prevention Patients
  - 138 RCTs, >145K patients
- COX-2 vs. Placebo (121 trials)
  - 86% RRI Myocardial Infarction (0.6% vs. 0.3%)
  - NNH=333
  - 3 MI/1,000 pts treated/over a year of treatment
- Placebo vs. other NSAIDS (17 trials; Sig. heterogeneity!)
  - Rate Ratio's:
  - Naproxen=0.92, ibuprofen=1.51, diclofenac=1.63

Kearney et al. BMJ. 2006;332:1302-1308
Implication of the relative degrees of selectivity

Step-Care Approach-DJD
- Step 1 (RCT data to support these Tx’s)
  - Regular Exercise
  - Glucosamine (1500mg daily)
  - Acetaminophen or ASA
  - Opioids- for short term relief
- Step 2 (with ASA and PPI/misoprostel)
  - NSAIDS (naproxen>ibuprofen>diclofenac)
  - Care for ASA/NSAID interaction for plt effect
- Step 3 (informed risk discussion**)
  - COX-2 inhibitors
  **For at risk patients for CV dz - NNH=14-333/MI over 1 year**

Bottom Line NSAIDS
- NSAID risk is a spectrum- GI vs. CV
- Pro-thrombotic risk is dose/time related
  - Use lowest effective dose for shortest possible time!
- More risk with atherosclerotic patients (CABG, CAD)
  - Estimates up to 6 deaths/100 patient years
- Avoid COX-2 unless REALLY pushed

Case Resolution: 74 yo woman carefully started on monitored exercise program, tylenol and glucosamine.

Case #2- Delicious Brew of Health- update in “naturopathy”
65 year old woman who takes no medicines presents to your clinic for her routine exam. She is curious what “natural” products she can use to improve her health? She eats well but is slightly overweight and has a FH of CAD and DM.
Saw Palmetto (doesn’t work-especially for the case patient)


Green Tea

2nd most consumed beverage in world (behind water)

80% of Japanese drink daily, average 2 cups!

Polyphenols inhibit CVDz and carcinogenesis in vitro

Green Tea

Biologic Plausibility

• Polyphenols are present in fruits, vegetables and bee pollen which cause enzymatic browning- bad for fruit.. Good for tea.

• Powerful free radical scavengers!

Green Tea and CVDz Prevention

• 40,543 Japanese Adults from Ohsaki NHI Cohort
• Green Tea Consumption (*Multivariate HR’s)

<table>
<thead>
<tr>
<th>Consumption</th>
<th>Overall Mortality</th>
<th>CV Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 cup/day</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1-2/day</td>
<td>0.95</td>
<td>0.87</td>
</tr>
<tr>
<td>3-4/day</td>
<td>0.92</td>
<td>0.77</td>
</tr>
<tr>
<td>&gt;5/day</td>
<td>0.85</td>
<td>0.74</td>
</tr>
</tbody>
</table>

(P for trend <.001)

- Threshold effect evident
- Effect strongest for women, ischemic stroke
  - Controlled for age, sex, BMI, DM, smoking, exercise
  - JAMA, Sept 13, 2006-Vol. 296, No. 10:1255-1265

Green Tea and Diabetes

• 17,413 Japanese Adults – 5 year survey
• Green Tea Coffee (age/BMI adj)

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<tr>
<td>&lt;1 cup/wk</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1-6 /week</td>
<td>0.66</td>
<td>0.82</td>
</tr>
<tr>
<td>1-2 /day</td>
<td>0.72</td>
<td>0.93</td>
</tr>
<tr>
<td>3-5 /day</td>
<td>0.81</td>
<td>0.58</td>
</tr>
</tbody>
</table>

- Likely caffeine effect
- OR=0.49 for women. P=0.0005 (fewer smokers!)

Green Tea

• Green Tea data encouraging for CV Dz
  - Not for cancer prevention (gastric, colon, lung)
• Antioxidants good prevention
  - More proof for diet/exercise/healthy lifestyle

Case Resolution: Advised patient to continue healthy habits, exercise, consider green tea as there seems to be no side effects to its use although more studies needed!
Case #3 - Influenza Update

- 74 year old woman who did not get a flu shot developed fevers, body aches and sweats for 7 days during a visit to see her grandchildren in Ankara, Turkey. She is better now but is very worried she had avian influenza.
- How should she be evaluated and treated?

Impact of Influenza (non-pandemic year)

- Annual infection rate of 10-15%
  - Worldwide!
- 30-35K deaths in U.S. (5th leading cause)
  - 90% deaths >65
- Total annual costs >$15 billion in the US annually
  - 90% indirect costs (lost productivity, employee absenteeism)

Influenza A Surface Proteins - Unstable

Subtypes infecting humans are: H1N1, H1N2, H3N2

How does influenza

Antiviral Drugs for the Prevention of Treatment of Influenza

<table>
<thead>
<tr>
<th>Antiviral Drug</th>
<th>Flu Type</th>
<th>Approved for Prophylaxis</th>
<th>Daily Dose (Adults)</th>
<th>Daily Dose (Adults)</th>
<th>Most Common Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>A</td>
<td>YES</td>
<td>9.38 200mg</td>
<td>100mg</td>
<td>GI and CNS symptoms</td>
</tr>
<tr>
<td>Rimantadine</td>
<td>A</td>
<td>YES</td>
<td>18.87 200mg</td>
<td>100mg</td>
<td>GI symptoms</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>A &amp; B</td>
<td>YES</td>
<td>44.40 20mg</td>
<td>20mg</td>
<td>None</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>A &amp; B</td>
<td>YES</td>
<td>53.00 150mg</td>
<td>150mg</td>
<td>GI symptoms</td>
</tr>
</tbody>
</table>

Adamantine Resistance!

- 2 Studies demonstrated this!
  - 209 isolates from 29 states (10/04-3-05)
    - H3N2 92% resistance (H1N1 2/8 resistant)
    - A.A. 31, ser → asparagine in M2 protein
  - 415 isolates in Japan
    - 65% resistance 11/05-4/06
- Fallout from SARS?
  - Resistance <2% 2000, 12.3% in 2004...
    - JAMA Feb 22, 2006-Vol:265:8
    - NEJM JAN 18, 2007-Vol:356:3
Effectiveness of Influenza Vaccination

<table>
<thead>
<tr>
<th>Group and Variable</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>People &gt; 65 Years old</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for acute and chronic respiratory illness</td>
<td>32%</td>
</tr>
<tr>
<td>Hospitalization for pneumonia and influenza</td>
<td>39%</td>
</tr>
<tr>
<td>Hospitalization for congestive heart failure</td>
<td>27%</td>
</tr>
<tr>
<td>Deaths from all causes</td>
<td>50%</td>
</tr>
</tbody>
</table>

Flu Vaccine Cross-Protection

- RCT of 1247 (18-46 years) vaccinated in ‘04
  - Poor antigenic match (antigenic drift H3N2 and 2 type-B strains)
  - Intramuscular or intranasal or placebo
  - Diagnosis by viral culture:
    - 77% for inactivated i.m. vaccine
    - 57% for live attenuated nasal (40% type B)
  - Both have similar efficacy for Type A=74%
  - Would this provide some protection for H5N1?

1918 – 1919 Influenza Pandemic

“Killed more humans than any other disease in a period of similar duration in the history of the world”

Gina Kolata Flu

75% of US population infected, 550,000 dead
Life expectancy reduced 13 years!
30-90 million dead worldwide (2% world’s pop)
Combat dead WWI + WWII (25 million)

2006: H5N1 in Bird Populations

Avian Influenza-H5N1

- Eastern Turkey reports 1st deaths in Europe
- 8 patients infected (ages 5-15)
  - 50% Mortality rate
  - ALL had contact with sick or dead chickens
- Dx made by PCR
  - Diagnosis, treatment and isolation based on Hx!
  - Rapid Influenza tests ineffective
Case Resolution

- 65 year old woman SHOULD have been vaccinated. Likely had circulating (H3N2 or H1N1) influenza but due to lack of contact with dead birds/hospitals/rural areas avian influenza is VERY unlikely (even in Turkey).
- Cleared infection impossible to diagnose by PCR, convalescent titers not specific!
- Reassurance only needed intervention (and future flu shots!)

Case #3- Carotid Stents

65 year old woman with unstable angina is found to have triple vessel disease. On CT surgery pre-op she is found to have a 90% distal LICA stenosis. The CT surgeon calls you for advice on how to proceed. On ROS she has a h/o transient monocular blindness.

NASCET- (North American Symptomatic Carotid Endarterectomy Trialists)

-70-99% stenosis; major ipsilateral stroke or death at 2 years
-2.5% surgical vs. 13.1% medical (P<0.001)  NNT=8/2 years
-Remained constant over 7 years of follow-up
-Requires <6-10% surgical side effects

NASCET Subgroup Analysis

- Elderly > 75 years had increased benefit
- Early surgery (< 30 days) no difference in outcomes
- 6 baseline characteristics predicted surgical risk
  1) Hemispheric TIA
  2) Left sided procedure
  3) Contralateral carotid occlusion
  4) Ipsilateral ischemic lesion on CT
  5) Irregular or ulcerated plaque
  6) High Carotid Lesion

CEA vs. Protected Stenting (in high risk patients)

334 High Risk patients
- >80% stenosis asymptomatic
- >50% stenosis symptomatic
- death, ipsilateral stroke at 1yr
20/167 - 12.2% stent
32/167 - 20.1% CEA
NNT=11

Sapphire investigators. NEJM 2004;351

SPACE (not The Final Frontier)

Stent-supported percutaneous angioplasty of the carotid vs. endarterectomy trial

European Trialists

1183 symptomatic, >70% stenosis
- CEA
  1183
  6.34%
- Stent
  1183
  6.84%
RR=1.09

30-day CVA or death
P=0.09 (no difference)

Did not prove non-inferiority
High surgical complications (>6%)
Encouraging results...

EVA-3S Trial (Endarterectomy vs. Angioplasty in patients with symptomatic severe carotid stenosis)

French Trial
- 527 symptomatic, >70% stenosis
- 3.9% CEA Stent
- 9.6% Stent
- (30-day CVA or death P<0.05)

6 month data- 6.1% vs. 11.7%
RR (6 mos.) = 1.9
NNH=18 over 6 mos.
Trial stopped due to harm

Problems:
- 27% used embolic protection devices
- Surgeons> angiographers in experience

Current Indications for Carotid Stents
1. Lesions not suitable for surgery
   - High cervical lesions
   - Post XRT stenosis
   - Unacceptable surgical risk
2. Center of Excellence! (and in a trial, await CREST)
   Current Opinion in Neurology 2004, 17:481-87

Resolution of case: 65 yo pre-3V CABG with 90% high LICA stenosis\(\rightarrow\)IR for stent placement referred to local University for trial. Stent placed safely.

Case #5- LAB2A and Asthma?
45 yo man with long h/o moderate asthma on inhaled corticosteroids is well controlled during the day but still has nocturnal awakenings. You read about problems with adding LAB2A but want to accelerate his therapy so he can sleep.

Asthma
- 5% of population (M=F)
  - Minorities (AA) and children
- 500K hospitalizations
- Pathogenesis
  - Inflammation/airway edema
  - Smooth muscle hypertrophy
  - Mucous gland hypertrophy
  =airway hyper-reactivity

NHLBI Guidelines
Chronic disease model: Suppress symptoms
- Long-term-control and Quick-Relief
- Increased mortality with SAB2A alone
- Anti-inflammatory medications (ICS)
  - Initiate at higher doses then "step down"
  - Prevent flairs and exposures
  - Protects airways from irreversible damage
- Step-up adding more long-term medications for breakthrough symptoms
  - http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Long Term Medications
- ICS- reduces symptoms and mortality!
  - 21%RRR/ICS canister prescribed
  - No difference from SAB2A alone
  - Arg-Arg mutation B2 receptor\(\rightarrow\)COPD like
- Antileukotrienes (Cochrane Database 2006: CD003137)
  - RRI 1.17 favoring LAB2 as add on (NNH=38/hosp)
- Mast Cell Stabilizers (Cromolyn or nedocromil)
  - Exercise/Cold induced asthma
- LAB2A (Salmeterol, formoterol)
**Long Acting Beta-2 Agonists**

- 12 hour bronchodilation, second add-on med

**RCT:** salmeterol vs. triamcinolone

- Exacerbations: 13/54 (24%) vs. 3/54 (6%) \(P=0.004\)
- Large increase in Eos, inflammation on BAL
- ICS reductions of 50%, further \(\rightarrow\) increased exacerbations
  - Adding minimizes ACS SE’s (cataracts, osteo)
  - (JAMA, May 23/30, 2001-Vol285:No.20 2583-2603)

**Asthma Bottom Line**

- It’s all about the inflammation!
  - MUST coach patients to stay on ICS with LABA!!
  - Monitor for worsening/breakthrough
  - AA patients with Arg-Arg
    • Consider anticholinergics
  - Canadian Guidelines Unchanged!

45 year old asthmatic with nocturnal symptoms add salmeterol and monitor carefully.

**Studies I wish I had done…**

Ski Helmet safety in 8 Norwegian ski resorts...

Case #6. Any patient who is active comes in for a routine visit.

**8 Norwegian Ski Resorts**

- Case-Control study
  - 3277 injured skiers and 2992 controls
  - 578 head injuries (17.6% of injuries)
  - Helmets \(\rightarrow\) 60% RRR for head injuries
    - 57% RRR severe \(p<0.05\)
  - Trend towards fewer neck injuries
    - OR=0.68 (CI 0.34-1.35)
  - Helmets are effective and should be counseled for all patients who are active!
    - JAMA, Feb 22, 2006-Vol 295, No. 8
Thanks for your attention!!