Update in General and Hospital Medicine
Fall 2014

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Objectives

• At the end of this session you should be able to:
  • Describe the main results of several important reports from the past year
  • Decide how you want to change your practice in the context of these findings
Disclosure

• I have no direct financial relationships with any commercial firm having any interest in any of the reports or topics I am about to discuss.

• There is some discussion of non-FDA approved medications or indications.
Method

- Examined the title of every original research article published from 10/1/13 through 10/1/2014 in
  - Annals of Internal Medicine
  - JAMA
  - New England Journal of Medicine
  - BMJ
  - The Lancet
- Surveyed articles reviewed in ACP Journal Club, various updates, and other sources
- Selected ~150 for review of abstracts
- Chose ~80 abstracts, ranked according to potential for practice change
  - Valuable assistance from colleagues in my department
- Reviewed the most interesting few for this presentation
Notes and Cautions

• Highly idiosyncratic selection process
  • Substantial risk of “confirmation bias” or splash factor
• Limited subset of huge research database
• Risk of publication bias
• A single study should be handled carefully – it may bite
• I may lack depth of contextual knowledge for understanding a study properly
  • Particularly with regard to inpatient medicine
• My interpretation is not handed to me by angels
Audience Response

• For patients who need major surgery and take aspirin, I:
  A. Hold the aspirin regardless of indication
  B. Continue the aspirin regardless of indication
  C. Continue the aspirin for those with coronary disease, otherwise hold it
  D. Punt to the surgeon
Aspirin and Surgery

- Aspirin in Patients Undergoing Noncardiac Surgery
  - PJ Devereaux et al.
  - NEJM
  - April 17, 2014

- Funding - mostly Canadian government
Aspirin in Surgery

• Study Question
  • Does perioperative aspirin improve surgical outcomes?

• Background
  • Aspirin reduces MI and death in some non-surgical applications
  • MI is a major postoperative concern, and preventive strategies are few
  • Any benefit in surgery could be offset by bleeding risks
Design – Blinded RCT

• 10,000 subjects in many nations
  • Age 45+
  • One or more major indicators of CAD risk
  • Having inpatient non-cardiac surgery

• Randomized to
  • ASA 200 load then 100 daily OR
  • Placebo
    • Continued 7d (Prior ASA use) or 30d (no Prior ASA)

• Had to be ASA free at least 3 d pre-op (!)

• Followed 30 days for Death + MI
  • Sought reduction from 6.1% to 4.6%
## Results – Baseline

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69</td>
</tr>
<tr>
<td>Female</td>
<td>47%</td>
</tr>
<tr>
<td>Prior CAD</td>
<td>23%</td>
</tr>
<tr>
<td>Major Surgery</td>
<td>78%</td>
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</table>
Results – Outcomes

- MI+Death
- Bleed

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI+Death</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
| Bleed     |         |         | *
Cautions

• Few patients with RCRI > 2
  • Non-significant but larger benefit in the few with high risk
• Hard to understand the 3+ day aspirin interruption
• Aspirin was started immediately pre-op
Conclusions

• Aspirin is, at best, not very helpful in this context
• Unsurprisingly, it increases bleeds
• I am stopping it in most settings
  • But may continue it in particularly high risk settings, such as RCRI 3+
Audience Response

For patients who have had a stroke, I avoid surgery:

A. At least 6 weeks
B. At least 9 months
C. Determined by degree of stroke recovery
D. Something else
Surgical Outcomes After Stroke

• Time Elapsed after Ischemic Stroke and Risk of Adverse Cardiovascular Events and Mortality Following Elective Noncardiac Surgery
  • ME Jorgensen et al.
  • JAMA
  • July 16, 2014

• Funded by Danish government, mostly
Surgical outcomes after stroke

• Study Question
  • How does the time interval between ischemic stroke and subsequent non-cardiac surgery relate to outcome?

• Background
  • Surgery after MI is high risk
  • Risk reduced by waiting 3-12 months
  • Little information after stroke
Design – Registry-based Historical Cohort

• 451,000 surgeries in Denmark from 2005-2011
  • Age 20+, non-cardiac surgery
  • Excluded surgeries thought plausibly due to stroke

• Classified as
  • No prior stroke
  • Stroke <3, 3-6, 6-12, or >12 months prior

• Followed 30 d after procedure for death, cardiac event, stroke
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No Stroke</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54</td>
<td>69</td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td>44</td>
</tr>
<tr>
<td>CAD</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Antiplatelet Med</td>
<td>11</td>
<td>65</td>
</tr>
</tbody>
</table>
Results – Outcomes (Odds Ratios)

Death Cardiac Stroke

No CVA <3 3 to 6 6 to 12 >12

*
Cautions

• Despite strong statistical methods, confounding MUST exist
  • Why does anyone do major surgery within 3 months of a stroke?
  • Is the urgency of surgery a risk for bad outcomes?
• Are these actually risks of surgery-related outcomes? Or just things that happen after a stroke?
  • Risks were similar regardless whether surgery would be considered high or low risk
Conclusions

• Bad surgical outcomes are common after recent stroke
• I will postpone surgery to the extent possible for at least 6 months post stroke
  • Authors feel their data support 9 months
Injecting Spinal Stenosis

• A Randomized Trial of Epidural Glucocorticoid Injections for Spinal Stenosis
  • JL Friedly et al.
  • NEJM
  • July 3, 2014

• Funded by US government - AHRQ
Injecting Spinal Stenosis

• Study Question
  • Are glucocorticoid injections effective in symptomatic spinal stenosis?

• Background
  • Spinal stenosis is common
  • Epidural steroid injections for spinal stenosis are increasing
  • Injections may not be entirely benign
Design – Blinded RCT

• 400 US Adults
  • Age 50+, referred for injection, pain > 4/10
  • Lumbar Stenosis by advanced imaging

• Received Lidocaine epidural injection followed by
  • Glucocorticoid OR
  • Placebo
  • Repeated at 3 weeks if wanted

• Followed 6 weeks for pain and disability
  • Sought 30% reduction in pain and Roland Score
    • Roland: 24 points, such as “I have difficulty sleeping because of the pain”
## Results – Baseline Characteristics

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</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68</td>
</tr>
<tr>
<td>Female</td>
<td>56</td>
</tr>
<tr>
<td>Pain Score (of 10)</td>
<td>7.2</td>
</tr>
<tr>
<td>Roland Score (of 24)</td>
<td>16</td>
</tr>
</tbody>
</table>
Results – 30% Improvement at 6 Weeks
Cautions

• Variety of steroids and injection approaches
• Steroid patients reported higher satisfaction (67% vs 54%)
• 6 weeks of pain control is not the goal
• No sham injection
  • Did the lidocaine do something that lasted 6 weeks?
Conclusions

• Little apparent benefit from steroid injection in a reasonable time frame
• I am counselling my patients with symptomatic lumbar stenosis not to seek this
• If I could use just one dose of an antibiotic to treat a severe skin infection I’d:
   A. Run with it and not look back
   B. Worry – It’s too good to be true
   C. Reserve it for special circumstances
Long-Acting Antibiotics – Two Articles

• Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection
  • HW Boucher
  • NEJM, June 5 2014

• Single Dose of Oritavancin in the Treatment of Acute Bacterial Skin Infections
  • GR Corey
  • NEJM, June 5, 2013

• Both studies funded, designed, conducted, written by the drug makers
Long Acting Antibiotics

• Study Question
  • Do these once or once-weekly antibiotics give satisfactory results in skin infections?

• Background
  • Skin infection is a common cause of hospitalization
  • Frequent IV dosing may prolong hospitalization
  • Frequent oral dosing may strain adherence
Design – Dalbavancin – Blinded RCT

• Two identical studies combined
• 1300 patients worldwide
  • Adults, with cellulitis, major abscess, or wound infection
  • Systemic signs
  • Expected to require at least 3 days of IV antibiotics
• Received
  • IV Dalbavancin on Days 1 and 8 OR
  • Vancomycin/linezolid for 10-14 days
• Followed for objective response at 3 days
  • Non-inferiority – No worse than 10% worse than Vanco
Design – Oritavancin – RCT

- 950 patients worldwide
  - Adults with cellulitis, major abscess, or wound infection
  - Systemic signs
  - Thought to need at least 7 days IV antibiotics

- Received
  - IV Oritavancin, single dose OR
  - Vancomycin for 7-10 days

- Followed for objective response at 3 days
  - Non-inferiority, same 10% margin
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dalbavancin</th>
<th>Oritavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>41%</td>
<td>56%</td>
</tr>
<tr>
<td>Abscess</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>Fever</td>
<td>85%</td>
<td>15% (!)</td>
</tr>
</tbody>
</table>
Results – Outcomes - Dalbavancin

- 3 Day Cure
- Dalbavancin
- Vancomycin
Results – Outcomes - Oritavancin

Low cure rate reflects patients lost to follow-up
Cautions

• Role of I&D for abscess not described
• Just 15% fever in Oritavancin study
  • But expected to require 7 days of IV antibiotics
  • These infections are a little unclear
• Dalbavancin report reveals a strategy of industry research
  • Multiple identical studies
  • Only publish the good ones?
• Troubling comparison
  • Vanco/Linezolid not the only option
• What if there is a drug reaction?
• Can’t “step down” to another drug
Conclusions

• New single-dose antibiotics may be very effective for major skin infections
• They are VERY pricey ($500 - $1000 per dose)
  • But reduced administration costs and hospital days could compensate
• Unclear how long they will be useful
  • But shorter if we start using them a lot
• Good to have them
  • For now, I’ll reserve them for extra-special occasions
Audience Response

• If my patient has an unexplained ischemic stroke I:
  A. Treat with an antiplatelet medication
  B. Treat with an anticoagulant
  C. Try harder to explain it
Atrial Fibrillation and Stroke – Two Articles

• Cryptogenic Stroke and Underlying Atrial Fibrillation
  • Sanna et al
  • NEJM
  • June 26, 2014
  • Funded by Medtronic

• Atrial Fibrillation in Patients with Cryptogenic Stroke
  • DJ Gladstone et al
  • NEJM
  • June 26 2014
  • Funded by Canada Stroke Network
A Fib and Stroke

• Study Question
  • Does prolonged invasive or non-invasive monitoring detect more A Fib after unexplained stroke, compared to usual care?

• Background
  • Around a third of strokes are unexplained
  • Some are surely due to paroxysmal A Fib
  • Anticoagulation is more effective than aspirin for stroke prevention in A Fib
  • Increased detection of A Fib could change therapy and outcomes
Design – Sanna - Non-binded RCT

- 441 adults US/Canada/Europe
  - Age 40+, stroke or TIA in prior 90 days
    - Negative evaluation including EKG, 24 hour holter, TEE, cerebral vessel studies
- Received
  - Insertable Cardiac Monitor (ICM) for at least 6 months OR
  - Ordinary follow-up with testing determined by treating physician
- Followed 6 months for diagnosis of Atrial Fibrillation
  - Anticipated 15% vs 5%
Design – Gladstone – Non-blinded RCT

- 572 Canadian patients
  - Age 55+, stroke or TIA within 6 months
  - Negative evaluation including at least 24 hour holter

- Received
  - 30 day event recorder OR
  - One additional 24 holter monitor

- Followed 90 days for diagnosis of Atrial Fibrillation
  - No stated expectations
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sanna – ICM</th>
<th>Gladstone – Event Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>61</td>
<td>72</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>36%</td>
<td>45%</td>
</tr>
<tr>
<td><strong>CHADS &gt; 2</strong></td>
<td>66%</td>
<td>--</td>
</tr>
</tbody>
</table>
Results – Outcomes

- Sanna - ICM: * (Extended)
- Gladstone - Event Monitor: * (Extended)

Legend:
- Blue: Extended
- Orange: Usual or 1 Day
Cautions

• Five of 200 ICM’s were removed for infection or erosion
• Uncertain paroxysmal A fib rate in similar adults without stroke
• Uncertain benefit of anticoagulation in these hard-to-find A fib patients
Conclusions

• Unsurprisingly, if you look hard for A fib you will find it
  • A lot of it, NNT between 8 and 13
• An external event monitor finds a lot in 30 days
• Whether an ICM is a worthwhile addition is unclear
  • Expensive, risky, perhaps limited additional findings
• I will use a 30 day event monitor in my cryptogenic stroke patients
  • Will probably not use an ICM
Audience Response

• Vitamin E helps with:
  A. Coronary Disease
  B. Dementia
  C. Libido
  D. Prostate Cancer
  E. Everything
Vitamin E in Alzheimer Disease

• Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease
  • W Dysken et al
  • JAMA
  • January 1, 2014
  • Funded by the VA (mostly)
Vitamin E in Alzheimer Disease

• Question
  • Do Vitamin E and/or Memantine improve functional decline in mild-moderate Alzheimer Disease?

• Background
  • Very common problem
  • Vitamin E and Memantine have some value in moderately severe A.D.
Design – Blinded RCT

• 613 US Veterans with Mild-Moderate AD
  • MMSE score 12-26
  • Already on acetylcholinesterase inhibitor

• Received
  • Vitamin E 2000 u/d OR
  • Memantine 20 mg/d OR
  • Both OR
  • Neither

• Followed several years for an ADL inventory score
Results – Baseline Characteristics

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>79</td>
</tr>
<tr>
<td>Female</td>
<td>3%</td>
</tr>
<tr>
<td>MMSE</td>
<td>21</td>
</tr>
<tr>
<td>ADL Score (0-78)</td>
<td>57</td>
</tr>
</tbody>
</table>

Note: 2 point change on ADL score considered significant
Results – Outcomes (ADL Score)

Baseline vs Follow-up:
- Vit E
- Mem
- Both
- Neither

* Indicates significant difference
Cautions

• High withdrawal rate (42%) mostly from death
• Additional medications are a burden
Conclusions

• Vitamin E probably helps mild-moderate dementia ADL decline
  • A little
    • But 3 points could be loss of independence in 1 ADL
  • Takes several years

• Fairly inexpensive, low risk

• I suspect most patients and families would want it

• I will offer it

• (Memantine doesn’t look like it adds anything)
Also Noted

• For intermediate risk PE (NOT high risk), fibrinolysis with tenecteplase caused more harm than benefit
  • NEJM April 10, 2013
• After cardiac arrest, “chilling” to 33 degrees offered no advantage over 36 degrees
  • NEJM December 5, 2013
• For unruptured brain AVM’s, preventive eradication (with surgery, embolization, radiation) provided worse outcomes than leaving them alone
  • JAMA April 23, 2014
  • Lancet February 15 2014
• Urine culture in young healthy women with UTI symptoms was often misleading. Treat for GNR’s.
  • NEJM November 14, 2013
And a Few More

- Renal denervation did not improve BP control over a sham procedure in resistant hypertension
  - NEJM April 10 2014
- Surgical repair of a degenerative tear of the medical meniscus was not better than a sham surgery
  - NEJM December 26, 2013
- Pregabalin joins the list of things that help symptoms in restless legs
  - NEJM February 13, 2014
- Colloids, and specifically albumin, offer little if any help in septic ICU patients
  - NEJM April 10, 2014
  - JAMA November 6, 2013
Summary

• It’s okay to hold aspirin in most pre-op situations
• Postpone surgery as long as you can after a stroke
• Vitamin E can help mild-moderate Alzheimer Disease
• A harder look will find more atrial fibrillation after stroke
• Some new long-acting antibiotics provide an option for severe skin infections
• Steroid injection doesn’t help lumbar stenosis symptoms
I am committing to...
Remember:

• Before acting on anything you heard here, you may wish to study the original research, and discuss with colleagues or domain experts