Update in General Medicine
Fall 2015

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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 10/1/14 through 10/1/2015 in
  • Annals of Internal Medicine
  • JAMA
  • JAMA Internal Medicine
  • New England Journal of Medicine
  • BMJ
  • The Lancet

• Surveyed articles reviewed in ACP Journal Club, various updates, and other sources

• Selected ~50 for review of abstracts

• Chose ~30 abstracts, ranked according to potential for practice change

• Reviewed the most interesting few for this presentation
Notes and Cautions

• **Highly** idiosyncratic selection process
• Limited subset of huge research database
• Risk of publication bias
• A single study needs to understood in context
  • I may lack depth of contextual knowledge for understanding a study properly
  • Particularly with regard to inpatient – especially ICU – medicine
• Where you land depends on where you start
Special Concern for 2015

• Remarkably small number of candidate articles:
  • Based on:
    • Strength of the Science
    • Relevance to General Internists (in- or out-patient)
    • Potential to affect practice
  • It might just be me
    • Or the journals I survey?
  • Has been a growing issue

• Is the medical research system serving our needs?
  • Who sets the agenda?
  • Should something change?
Audience Response

• For patients who need major surgery and take warfarin, I:
  A. Usually hold the warfarin and bridge with heparin or a LMWH
  B. Usually hold the warfarin but do not bridge
  C. Usually continue the warfarin unless the bleeding risk is very high
  D. Do something else
  E. Punt to the surgeon
Warfarin and Surgery – Two Studies

• Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation
  • James Douketis et al
  • NEJM
  • August 2015
  • Funded by the US government

• Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures
  • Nathan Clark et al
  • JAMA Intern Med
  • July 2015
  • Funding by a health plan in Colorado
Warfarin and Surgery

• Study Questions
  • Does perioperative bridging offer advantages in patients with atrial fibrillation, on warfarin undergoing surgery?
  • In patients with VTE?

• Background
  • The balance of hemorrhagic risks and thromboembolic risks is difficult
  • Guidelines are rather weakly stated
  • Practice varies widely
A Fib Study Design – Blinded RCT

• 1900 subjects in US and Canada
  • Age 18+
  • A Fib or Flutter on warfarin (valve disease included)
  • CHADS 1+
  • Elective surgery felt to require interruption of warfarin
  • Excluded mechanical valve, recent stroke, intracranial or intraspinal surgery

• Randomized to
  • Dalteparin pre- and post-op OR
  • Placebo

• Followed 30 days for clotting and bleeding
  • Sought non-inferiority for clots (1% each group), reduction from 3% to 1% for bleeds
# Results – Baseline

<table>
<thead>
<tr>
<th></th>
<th>Bridge</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Female</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>CHADS2</td>
<td>2.4</td>
<td>2.3</td>
</tr>
<tr>
<td>ASA</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>Low bleeding risk surgery</td>
<td>89%</td>
<td>89%</td>
</tr>
</tbody>
</table>
Cautions

• Lower than expected thromboembolic events, unclear why
• Lower bleeding risk surgeries in general
• Unclear how this relates to NOA’s
• Only about 15% with CHADS score over 3
Conclusions

• Bridging is probably not helpful, clearly harmful, in many A Fib patients having surgery
  • Does not apply in setting of
    • Mechanical Valves
    • Perhaps very high thromboembolic risk settings
VTE Study Design

• Historical Cohort/Database study in Kaiser Permanente Colorado
  • 1800 procedures in 1200 patients
  • Age 18+ on Warfarin for VTE
  • INR < 1.5 1 day pre-procedure
• Classified according to whether they were bridged or not
• Followed 30 days for bleeding, VTE, and death
## Results – Baseline

<table>
<thead>
<tr>
<th></th>
<th>Bridged (555)</th>
<th>Not Bridged (1257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>Female</td>
<td>53%</td>
<td>55%</td>
</tr>
<tr>
<td>VTE &lt; 12 months prior</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>GI Scope procedure</td>
<td>34%</td>
<td>39%</td>
</tr>
<tr>
<td>Orthopedic Procedure</td>
<td>21%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Results – Outcomes

- Overt Bleed
- Major Bleed
- VTE
- Death

Legend:
- Blue: Bridge
- Orange: Not Bridged
Cautions

• Cohort studies always troubling
  • How did providers decide who got bridged?
  • How good are the measurements in the historical administrative dataset?
Conclusions

• This is a limited study
  • By itself would not affect practice
  • Supports, indirectly, the A Fib RCT
Overall Warfarin Bridging Conclusions:

• In many patients with either A Fib or VTE on coumadin, bridging anticoagulation is likely to be more harmful than helpful

• I will restrict bridging to highest clot risk patients
  • Balance will remain difficult when bleeding risk is also high
  • This is not really a change, more a confirmation
Audience Response

For my diabetic patients, my best chance to reduce early mortality is to use:

A. Insulin
B. Metformin
C. SGLT2 inhibitors
D. Anything that lowers A1C below 7
E. Something else
SweetWater

• Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
  • B Zinman et al
  • NEJM
  • Not yet in print (e-published 9/17/015)
  • Designed, executed, analyzed, written and funded by makers of empagliflozin
    • Most authors are employees of the company
SweetWater

• Study Question
  • Is empagliflozin non-inferior to placebo for major cardiovascular events in DM-2?
  • !!

• Background
  • Empagliflozin causes the kidneys to leak glucose, thereby reducing A1C
  • To date, no strategy for blood sugar management has compelling evidence for CV risk or mortality reduction in DM-2
    • Best case is for metformin
Design – Blinded RCT

- 7000 patients worldwide with DM type 2
  - Age 18+, BMI < 45 GFR > 30, A1C 7-10
  - Established CAD

- Received
  - Empagliflozin 10mg OR 25 mg daily OR
  - Placebo
  - Also usual care

- Followed 4 years for CV death, MI, stroke
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>North America/Europe</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Metformin</td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>ACEI</td>
<td>81</td>
<td>80</td>
</tr>
</tbody>
</table>
Cautions

• The only disease outcome with an effect was CHF
  • No effect on MI, CVA, Angina
  • Were the deaths due to CHF?
  • Was something else causing this?
    • Pursuit of low A1C?
    • Addition of glitazones in placebo group?

• Unexpected effect
  • Not previously noted with other SGLT2 drugs
  • Not previously noted with anything for DM-2
Conclusions

• I don’t really believe it
  • No evident reason for it
  • No prior evidence to support it
  • Pervasive role of financially interested party
  • Implausibly large effect
  • Unclear role of pursuing lower A1C

• I will wait
  • Similar study of Canagliflozin due to finish in 2017
  • (Where you end depends on where you start)
Audience Response

• When dealing with various sorts of back problems
  A. I’ve been surprised how well steroids work
  B. I look to my surgical colleagues for help
  C. I find imaging helpful
  D. I focus on mind-body techniques like yoga
  E. I have no good answers
A Triptych: 3 things that may not help the bad back

• Oral Steroids for Acute Radiculopathy Due to a Herniated Lumbar Disk
  • Harley Goldberg et al
  • JAMA, May 2015
• Surgery Versus Nonsurgical Treatment of Lumbar Spinal Stenosis
  • Anthony Delitto et al
  • Ann Int Med, April 2015
• Association of Early Imaging for Back Pain With Clinical Outcomes in Older Adults
  • Jeffrey Jarvik, et al
  • JAMA, March 2015
• All funded by US Government
Steroids for Herniated Disk

• RCT, Blinded
• Almost 300 adults with recent symptoms and MRI-proven disk
• Prednisone taper (60-40-20) over 2 weeks, OR Placebo
• Followed for Oswestry disability score at 3 weeks
• Steroids achieved statistically significant, but clinically trivial relative improvement in reported function
  • No effect on pain
Surgery for Lumbar Stenosis

• RCT, Unblinded
• Almost 200 adults with LSS by symptoms and MRI, judged to need, and consented to have, surgical decompression
• Randomized to surgery or moderate PT program
• Followed for Pain and Disability
• Surgery was not superior at any time over 2 years
  • But 57% of PT patients eventually got surgery
  • (So 43% did not)
Early Imaging in Older Adults

• Retrospective Cohort
• Over 5000 patients over age 65 with acute low back pain
• Evaluated according to whether they got imaged within 6 weeks
• Followed for disability, resource use, and finding of serious problem
• Imaged patients used more resources (mostly the imaging costs)
  • No difference in disability at 1 year
  • Several spinal fractures found
  • No other serious diagnoses causing pain
Summary of the Spine Studies

• Steroids don’t help much (for disks)
• Even when lumbar stenosis looks surgical, it might be sensible to wait
• Imaging the older adult with back pain may not be useful
  • Unless other clinical cues are present?
Audience Response

• When faced with severe alcoholic hepatitis, I:
  A. Begin glucocorticoids
  B. Avoid glucocorticoids
  C. Have another medication in mind
  D. Wonder if we should try Prohibition again
Alcoholic Hepatitis

• Prednisone or Pentoxyphylline for Alcoholic Hepatitis
  • Mark Thursz et al.
  • NEJM
  • April 2015

• Funded by British government
Alcoholic Hepatitis

• Study Question
  • Do steroids or pentoxyphylline improve outcomes in alcoholic hepatitis?

• Background
  • Severe alcoholic hepatitis has remarkable mortality – 20-40%
  • Trials of steroids and pentoxyphylline have been conflicting so far
Design – Blinded RCT

• 1100 patients in 65 UK hospitals
  • Clinical diagnosis of alcoholic hepatitis
  • Bili 4.7+, Discriminant score 32+
  • Excluded Cr>5.7
• Received (for 28 days)
  • Prednisolone 40 mg daily OR
  • Pentoxyphylline 400 mg tid OR
  • Both OR
  • Neither

• Followed 1 year for mortality
• Sought decrease from 30% to 21% at 28 days
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49</td>
</tr>
<tr>
<td>Female</td>
<td>37%</td>
</tr>
<tr>
<td>Pro Time</td>
<td>21</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>18</td>
</tr>
<tr>
<td>Discriminant Score</td>
<td>63</td>
</tr>
</tbody>
</table>
Results – Outcomes

![Bar chart showing 28 DayDeath outcomes for different treatments.](chart.png)

- **Prednisolone**: 14
- **Pentoxyphylline**: 18
- **Both**: 13
- **Neither**: 15

* indicates a statistically significant difference.
Cautions

• 28 Day mortality was considerably better than expected
• The prednisolone benefit disappeared at 90 days and 1 year
Conclusions

• Not strong enough to draw much conclusion about usefulness of prednisolone
  • I lean away, mildly
  • Others prefer a trial, continuing if apparently responsive

• No evident value to pentoxyphylline
  • But if you are unconvinced, at least it is not very risky
Audience Response

• If steroids aren’t too great for hepatitis, maybe they work for pneumonia?
  A. I use them
  B. I don’t use them
A Two-Fer: Steroids in Pneumonia

• Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients with Severe Community-Acquired Pneumonia and High Inflammatory Response
  • Antoni Torres, et al
  • JAMA, Feb 2015
  • Funded by Spanish government

• Adjunct Prednisone Therapy for Patients with Community-Acquired Pneumonia
  • Claudine Blum et al
  • Lancet, April 2015
  • Funded by the Swiss government
Steroids in Pneumonia

• Study Question
  • Does the addition of steroids improve outcomes in community acquired pneumonia?

• Background
  • Some of the morbidity of infection is due to excessive host response
  • Steroids might usefully suppress some of that response
  • Lots of smaller studies have hinted at benefits
Design – the Spanish study

• Blinded RCT
• 120 adults with severe pneumonia (by ATS or PSI) and a CRP over 150
  • Excluded immunosuppression, uncontrolled diabetes
• Received
  • 0.5 mg/kg methylprednisolone q 12 hours x 5 days OR
  • Placebo
• Followed 3-5 days for treatment failure (shock, intubation, death, worse CXR)
  • Sought reduction from 35% to 15%
Design – the Swiss study

• Blinded RCT
• 800 adults admitted with CAP (infiltrate plus a symptom, sign, or lab finding)
• Received
  • Prednisone 50 mg daily x 7 days OR
  • Placebo
• Followed for time to clinical stability
  • Amount of benefit sought is unclear
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Spanish</th>
<th>Swiss</th>
</tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>PSI Score 5</strong></td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>
Results – Spain

- 3 Day Fail
- 5 Day Fail
- Mortality

Steroids vs Placebo
Cautions

• In Spain, many of the treatment failures were simply CXR progression
  • But CXR progression is one predictor of poor outcomes

• In Switzerland, mortality was considerably lower than expected
Conclusions

• Clearly some effect of steroids for pneumonia
  • Effect may be modest
  • But a possible mortality benefit?
  • Consider how freely we use them for COPD

• I will start giving steroids for pneumonia
  • At least the more severe, PSI class 4-5
Audience Response

• Regarding High-Flow Oxygen
  A. I like it because it’s more pleasant than BiPAP
  B. I’m using it for acute respiratory failure
  C. I haven’t run into it – is it different from face mask oxygen?
Another Two-Fer: High Flow Oxygen

- High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure
  - Jean-Pierre Frat et al
  - NEJM, June 2015
  - Funded by the French government

- High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients after Cardiothoracic Surgery
  - Francois Stephan et al
  - JAMA, June 2015
  - Funding not stated – possible internal
High-Flow Oxygen

• Study Question
  • Does high-flow oxygen improve outcomes in acute, non-hypercapnic respiratory failure

• Background
  • Non-invasive positive pressure ventilation (BiPAP) has been useful in some respiratory failure settings for reducing intubation
  • High-flow oxygen is more comfortable and more easily managed
Design – The Medical Study

• Unblinded RCT
• 300 French/Belgian adults in ICU’s with
  • RR>25
  • PaO2/FIO2 < 300 on 10 lpm
  • PCO2 < 45
  • No chronic respiratory failure
  • Not from asthma or CHF, and hemodynamically stable

• Received
  • 50 lpm warmed/humidified 50% O2 by nc OR
  • Standard O2 by mask OR
  • BiPAP at least 8 hours/day, with standard O2 when off

• Followed 28 days for intubation and death
• Sought improvement from 60% to 40% requiring intubation
Design – The Surgical Study

• Unblinded RCT (Consent not obtained!!)
• 830 French patients after cardio-thoracic surgery
  • Failed initial post-op breathing trail or failed extubation attempt
• Received
  • High-Flow O2 OR
  • BiPAP at least 4 hours per day
• Followed 72 hours for intubation
• Sought non-inferiority of High-Flow O2
  • Expected 20% BiPAP failure
## Results – Baseline Characteristics – Medical

<table>
<thead>
<tr>
<th></th>
<th>High Flow</th>
<th>Mask O2</th>
<th>NIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61</td>
<td>59</td>
<td>61</td>
</tr>
<tr>
<td>Female</td>
<td>29%</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>CAP</td>
<td>67</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>HCAP</td>
<td>11</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>157</td>
<td>161</td>
<td>149</td>
</tr>
</tbody>
</table>
Results – Baseline Characteristics – Surgical

<table>
<thead>
<tr>
<th></th>
<th>High-Flow</th>
<th>BiPAP</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>CABG</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Valve</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>CABG+Valve</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
Results – Outcomes – Surgical

Chart Title

Failed

Died in ICU

High Flow

NIPPV
Cautions

• Fail rate in the medical study fell short of expected 60%
• Mortality benefit in the medical study was not replicated in the surgical study
• Does NOT apply to hypercapnic patients
Conclusions

• High flow oxygen offers a relatively simple (compared to BiPAP) respiratory support
• May have a substantial mortality advantage in non-hypercapnic acute respiratory failure
• Should be available, probably should be first choice for medical patients like these
• Is a reasonable option for cardiothoracic surgery patients as well
Transfusion Threshold in Cardiac Surgery

• Liberal or Restrictive Transfusion after Cardiac Surgery
  • Gavin Murphy, et al
  • NEJM
  • March 2015

• Funded by British government
Transfusion Threshold

• Study Question
  • Does a restrictive transfusion threshold perform as well as a liberal one following cardiac surgery?

• Background
  • In medical patients, a restrictive threshold of 7.0 is preferable to a liberal one of 9.
  • Some surgical settings show rough equivalence of liberal and restrictive thresholds
  • Cardiovascular surgery is in question
Design – RCT

• 2000 patients in UK cardiac surgery centers
  • Age 16+, non-emergent

• Received blood 1 unit at a time for
  • Hgb < 7.5 OR
  • Hgb < 9

• Followed 3 months for composite of serious infection, CVA, MI, bowel infarction, acute kidney injury

• Sought a reduction from 17% to 11%
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Restrictive</th>
<th>Liberal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>Female</td>
<td>31%</td>
<td>32%</td>
</tr>
<tr>
<td>CAD</td>
<td>69%</td>
<td>69%</td>
</tr>
<tr>
<td>CABG</td>
<td>41%</td>
<td>41%</td>
</tr>
<tr>
<td>Valve</td>
<td>31%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Cautions

• 90 Day mortality was not expected to differ and was not a primary outcome
• Many violations of transfusion protocol
• Incomplete blinding
Conclusions

- Restrictive transfusion was not better than liberal transfusion in these cardiac surgery patients
  - May have been worse

- This was not strong enough to conclude that liberal transfusion is clearly better

- I will use other criteria to inform the transfusion decision in cardiac surgery patients with Hgb between 7 and 9.
Summary

- This was not a great year for practice-changing research in General Internal Medicine
  - Confirmed that bridging is not needed for many anticoagulated patients having surgery
  - Learned that a new diabetic medication might have unanticipated mortality benefits (but might not)
  - Found that the low transfusion threshold that works in many circumstances might be too low after cardiac surgery
  - Saw that prednisolone offers little, and pentoxyphylline might offer nothing, for alcoholic hepatitis
  - Learned that steroids my be useful in pneumonia – especially more severe pneumonia
  - Identified a potentially important role for high-flow oxygen in selected respiratory failure patients
  - Found that a lot of what we do for people with troubled backs may not be helping them much

- Not useless, but seems to be thin soup
My Questions for You

• Is the medical research establishment serving your needs?
  • Are you getting the research results you need to improve your care of patients?
  • Is this persistent problem? A transient irritation?

• Can you do anything about it?
  • Is there something we can do together?