Bringing Best Hypertension Evidence To Front Line Clinicians

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Declaration

• None of the faculty have any conflicts of interest to declare
Special Thanks!!!

“...We need a Hero...”

fraserhealth
The Faculty
Is there an (unbiased) doctor in the house?

Journalists often forget that conflicts of interest might bias the opinions of their expert sources. Jeanne Lenzer and Shannon Brownlee explain how, in a bid to disentangle commercial messages from science, they have compiled a list of around 100 independent medical experts that reporters can turn to.

Beyond the list’s usefulness to journalists, we hope that it will also be used by government agencies, medical journal editors, and professional societies as they seek out experts to serve as editorialists and members of clinical guideline and advisory panels. The FDA, for example, has a copy of the list. We would
Is there an (unbiased) doctor in the house?

Journalists often forget that conflicts of interest might bias the opinions of their expert sources. Jeanne Lenzer and Shannon Brownlee explain how, in a bid to disentangle commercial messages from science, they have compiled a list of around 100 independent medical experts that reporters can turn to.

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Making the Numbers Less Confusing
What is a Randomized Controlled Trial?

• Benefits of randomization
  – Assures everyone has an equal chance of receiving treatment or control
  – Attempts to balance known and unknown characteristics between treatment groups
    • Assures that differences in outcomes at the end of the trial can ONLY be attributed to differences in allocated treatment

• Allocation concealment (critical!)
  – Limits selection bias
  – Maintains benefits of random allocation
  – What is it?
Not Random, No Allocation Concealment…So What?

• “On average, non-randomized trials and randomized trials with inadequate concealment of allocation tend to result in larger estimates of effect than randomized trials with adequately concealed allocation. However, it is not generally possible to predict the magnitude, or even the direction, of possible selection biases and consequent distortions of treatment effects.”

Relevant Critical Appraisal Concepts

• The number of patients that experienced a first serious adverse event (SAE)
  – Death, life threatening, hospitalization (or prolonged), permanent/significant disability, need for emergent medical treatment

• *Comparing SAE rates allows for an assessment of net effect (or “net worth” of therapy)*
Serious adverse events (SAE)

• All “really bad things”
• Definition:
  – results in death,
  – is life-threatening
  – requires inpatient hospitalization or prolongation of existing hospitalization
  – results in persistent or significant disability/incapacity, or
  – is a congenital anomaly/birth defect.
Why is an SAE analysis so critical?

- The net worth of the drugs cannot be assessed by comparing events and anticipated adverse events alone.
- You need to consider assets and debts.
- Expected and unexpected adverse events are primary outcome measures as well.

Net worth of drugs = comparison of SAE rates

The only outcome measure that determines the benefit/harm ratio.

- What is my net worth now?
  - $120,000 in the red
ASA vs Placebo

Myocardial Infarction
ASA reduces risk by 3%

SAE Result if net benefit?
What are SRs?
Systematic Reviews

- “Systematic” search for all articles to answer a focused clinical question
- Systematic method of data extraction and analysis
- Methods are transparent and reproducible
- Limits probability of missing important trials by searching for all possible trials – i.e. you get to see the whole picture
What is a MA?
When is it appropriate to do a MA?

• Taking data from several trials and pooling it together (using specific statistical methodology)
• To pool data trials must have similar clinical questions (PICOS)

• Increased statistical power
  – E.g. 1 trial of 100 people may miss a difference in an outcome, but 10 trials of 100 people each may have enough statistical power

• TIP: only meaningful if PICOS are the same
**Figure 2.** Effect of long-acting β-agonists compared with placebo on odds ratio of hospitalizations for asthma exacerbation.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Patients Receiving β-Agonist, n/n</th>
<th>Patients Receiving Placebo, n/n</th>
<th>Peto Odds Ratio (95% CI)</th>
<th>Weight, %</th>
<th>Peto Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensch et al., 2002 (33)</td>
<td>18/342</td>
<td>0/176</td>
<td></td>
<td>26.3</td>
<td>4.8 (1.8–12.9)</td>
</tr>
<tr>
<td>Busse et al., 2004 (34)</td>
<td>1/80</td>
<td>0/80</td>
<td></td>
<td>1.7</td>
<td>7.4 (0.2–372.4)</td>
</tr>
<tr>
<td>Foradil 040 trial, 2001 (43)</td>
<td>5/269</td>
<td>0/135</td>
<td></td>
<td>7.4</td>
<td>4.6 (0.7–29.5)</td>
</tr>
<tr>
<td>Foradil 041 trial, 2001 (44)</td>
<td>6/275</td>
<td>2/141</td>
<td></td>
<td>11.9</td>
<td>1.5 (0.3–6.6)</td>
</tr>
<tr>
<td>Foradil 2307 trial, 2005 (45)</td>
<td>7/1054</td>
<td>1/527</td>
<td></td>
<td>12.0</td>
<td>2.6 (0.5–11.2)</td>
</tr>
<tr>
<td>Levy et al., 2005 (37)</td>
<td>1/127</td>
<td>0/122</td>
<td></td>
<td>1.7</td>
<td>7.1 (0.1–358.3)</td>
</tr>
<tr>
<td>Lockey et al., 1999 (38)</td>
<td>2/240</td>
<td>2/240</td>
<td></td>
<td>6.7</td>
<td>1.0 (0.1–7.1)</td>
</tr>
<tr>
<td>Rosenthal et al., 1999 (40)</td>
<td>2/202</td>
<td>1/206</td>
<td></td>
<td>5.0</td>
<td>2.0 (0.2–19.3)</td>
</tr>
<tr>
<td>Serenvent 3014 trial, 2001 (46)</td>
<td>1/229</td>
<td>0/110</td>
<td></td>
<td>1.5</td>
<td>4.4 (0.1–289.1)</td>
</tr>
<tr>
<td>Steffensen et al., 1995 (41)</td>
<td>0/103</td>
<td>1/101</td>
<td></td>
<td>1.7</td>
<td>0.1 (0.0–6.7)</td>
</tr>
<tr>
<td>Taylor et al., 1998 (42)</td>
<td>6/60</td>
<td>3/65</td>
<td></td>
<td>14.2</td>
<td>2.2 (0.6–8.6)</td>
</tr>
<tr>
<td>Weinstein et al., 1998 (49)</td>
<td>4/102</td>
<td>2/105</td>
<td></td>
<td>9.9</td>
<td>2.0 (0.4–10.3)</td>
</tr>
</tbody>
</table>

Total 53/3083 12/2008

Test for heterogeneity: chi-square = 6.24 (P = 0.86); I² = 0%
Test for overall effect: Z = 3.69 (P < 0.001)
Forest Plots

- **Weight**
  - Based on inverse variance
  - The narrower the confidence interval of a trial
    - The more precise the finding
    - The higher the weight
    - i.e., trials with large sample sizes and more precise findings get more weight

- **Horizontal line**
  - Width of confidence interval

- **Box (the effect size for a trial)**
  - Effect size: bigger the box the more precise the result is

- **Diamond (overall effect size)**
  - Width of diamond = confidence interval of overall result
Heterogeneity

• Heterogeneity = when different studies report different results for the same outcome
  – You need to know if the differences across trials are:
    • Real differences (i.e. heterogenous)
    • Due to chance (i.e. trials are really estimating the similar effect size; homogenous)

• Heterogeneity is present if…
  – Chi square test p<0.1
  – I² >30%
Surrogate (vs Clinical Outcomes)

MOST IMPORTANT QUESTION:
Does the relationship hold in reverse when a drug reduces the surrogate marker?

Drug

Surrogate marker goes down

Risk of “Bad Things” isn’t reduced to the “same extent”

Adding drugs to reduce the surrogate doesn’t reduce the risk of “Bad Things”

Surrogate e.g. A1c
Surrogate Markers
(vs Clinical Outcomes)

The “Bad Clinical Outcome” Train has left the station

“But the surrogate improved…I don’t understand???”

Big Bag of Drugs
Confidence Intervals

• The more precise the Narrower they are.
• The less precise the Wider they are.
• What makes them wide or narrow?
  – i.e what determines “how precise” an effect estimate is?
    a) Source of study funding
    b) The outcome being measured (dichotomous or continuous)
    c) The statistic used (i.e OR, HR, ARR)
    d) The number of people and events
Confidence Intervals

- Important points
  - Confidence intervals for RATIOS (OR, HR, RR)
    - The risk of an event in treatment group/the risk in placebo
    - If they include “1.0” there is no statistically significant difference i.e. risk is the same in both groups
      - E.g. hypotensive episode with new treatment
        » **RR 0.89 (95%CI 0.70 to 1.20)**
        » RR>1.0 more hypotensive episodes
        » RR<1.0 less hypotensive episodes
Confidence Intervals

• Important points
  – Confidence intervals for ABSOLUTE numbers
    • If they include “0” there is no statistically significant difference
  – E.g

<table>
<thead>
<tr>
<th>Length of stay in ICU — days</th>
<th>6.5±6.6</th>
<th>6.2±6.2</th>
<th>0.24 (−0.06 to 0.54)</th>
<th>0.44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay in hospital — days†</td>
<td>15.3±9.6</td>
<td>15.6±9.6</td>
<td>−0.24 (−0.70 to 0.21)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

– ARR>0, more days in hospital
– ARR<0, less days in hospital
Thoughts on Interpretation of CIs

• Would you recommend a therapy based on the worst/best case scenario of the confidence interval?

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Clopidogrel (nys=17636)</th>
<th>Aspirin (nys=17519)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient years at risk, MI-myocardial infarction; PAD-peripheral arterial disease.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table 7: Treatment effect by subgroup—ischaemic stroke, MI, or vascular death</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ARR</th>
<th>95% CI</th>
<th>NNT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst case:</td>
<td>0.02%</td>
<td>0.02% to 0.98%</td>
<td>5000</td>
<td>102 to 5000</td>
</tr>
<tr>
<td>Best case:</td>
<td>0.98%</td>
<td>0.98% to 0.98%</td>
<td>102</td>
<td>102</td>
</tr>
</tbody>
</table>

ARR in favour of clopidogrel: 0.50% (95% CI 0.02% to 0.98%)
NNT: 199 (95% CI 102 TO 5000)

CAPRIE Trial: Clopidogrel vs ASA in patients at Risk of Ischemic Events
P-Values

• The probability that the results observed in a study (or results more extreme) could have occurred by chance.
  – P value of 0.05 means that there is a 5% probability that the results are due to chance
• p-value needs to be adjusted for multiple comparisons
Adjusting P-values for Multiple Comparisons

Basic principle:

– Each research question has an associated probability of error
– You need to account for all the error when asking more than one question
– P-value of <0.5 is only applicable to the primary research question
  • It doesn’t account for error for anything other then the primary outcome
– Unadjusted “p<0.05” for other outcomes could lead to seeing false-positives (differences that only occurred due to chance)
Have I got a deal for you!

- Special offer: 50% off
- Any takers?
Absolute vs Relative Risk

• E.g. MI were reduced by 50% with ASA versus placebo
  – Data table says ASA MI rate= 1%, placebo MI Rate=2%
• Absolute difference= Placebo rate- ASA rate=2-1=1%
  – The ARR=1%
• Relative difference=
  – Placebo-ASA / placebo rate= 1% / 2% = 0.50 or 50%
  – The RRR= 50%
• Compare the two numbers 50% vs 1%...which looks better?
# Real Clinical Scenarios

## Table 2: Examples of Evidence of Benefit of Common Drug Therapies

<table>
<thead>
<tr>
<th>Clinical trial (measured outcome events)</th>
<th>Event incidence %</th>
<th>RR</th>
<th>RRR %</th>
<th>ARR %</th>
<th>NNT</th>
<th>Trial duration years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors for congestive heart failure <em>(total mortality or hospitalisation for CHF)</em></td>
<td>32.6</td>
<td>22.4</td>
<td>0.69</td>
<td>31</td>
<td>10.2</td>
<td>10</td>
</tr>
<tr>
<td>Diuretics and beta blockers in old patients with hypertension <em>(total mortality or cardiovascular event)</em></td>
<td>22.5</td>
<td>13.7</td>
<td>0.61</td>
<td>39</td>
<td>8.8</td>
<td>11</td>
</tr>
<tr>
<td>Simvastatin for elevated cholesterol in patients with coronary heart disease <em>(total mortality or coronary event)</em></td>
<td>31</td>
<td>22.6</td>
<td>0.73</td>
<td>27</td>
<td>8.4</td>
<td>12</td>
</tr>
<tr>
<td>Long-term beta blockers after myocardial infarction <em>(total mortality or non-fatal reinfarction)</em></td>
<td>17.6</td>
<td>13.7</td>
<td>0.78</td>
<td>22</td>
<td>3.9</td>
<td>26</td>
</tr>
<tr>
<td>Gemfibrozil in male patients with high cholesterol <em>(total coronary events)</em></td>
<td>4.1</td>
<td>2.7</td>
<td>0.66</td>
<td>34</td>
<td>1.4</td>
<td>71</td>
</tr>
<tr>
<td>Aspirin in healthy male physicians <em>(total myocardial infarctions)</em></td>
<td>2.2</td>
<td>1.3</td>
<td>0.56</td>
<td>44</td>
<td>0.9</td>
<td>111</td>
</tr>
<tr>
<td>Misoprostol in rheumatoid arthritis patients taking NSAIDs <em>(serious gastrointestinal complications)</em></td>
<td>0.95</td>
<td>0.57</td>
<td>0.60</td>
<td>40</td>
<td>0.38</td>
<td>263</td>
</tr>
</tbody>
</table>

RR = Relative Risk  
RRR = Relative Risk Reduction  
ARR = Absolute Risk Reduction  
NNT = Number Needed to Treat  
* Inclusion in the table does not necessarily imply endorsement by the Therapeutics Initiative.  
* Total mortality not included because not statistically different; if total mortality were added NNT is even greater.
Number Needed to Treat (NNT)

- Tool to place results into “humanistic” terms
- Number needed to treat (NNT)
  - Benefit of therapy
- Number needed to harm (NNH)
  - Harm of therapy
- NOTE: conflicting evidence for the usefulness of these numbers when making treatment decisions
Number Needed to Treat

• Calculation of Number Needed to Treat (NNT)
  \[ NNT = \frac{100}{ARR(\%)} \]
  Previous example
  \[ ARR = 1\%, \quad NNT = \frac{100}{1} = 100 \]
  Treat 100 people to prevent 1 MI

• Calculation of Number Needed To Harm (NNH)
  \[ NNH = \frac{100}{ARI(\%)} \]
• Example
  – Treatment GI bleed rate = 10%
  – Control GI bleed rate = 5%
  – ARI = 10 - 5 = 5% increased risk with treatment for a GI bleed
  – NNH = 100 / 5 = 20
  – 1 GI bleed will occur for every 20 people treated
When to Calculate ARR/ARI

- Do not calculate ARR/ARI when there is no statistically significant difference
- Cannot be calculated for continuous outcomes
Much More Comfortable with Numbers?

“The average human has one testicle.”