ILLUMINATE. Effects of torcetrapib in patients at high risk for coronary events
ILLUMINATE
The most important trial since 2000?
Inhibition of cholesteryl ester transfer protein (CETP) has been shown to have a substantial effect on plasma lipoprotein levels. We investigated whether torcetrapib, a potent CETP inhibitor, might reduce major cardiovascular events.
Methods

- Randomized, double-blind study involving 15,067 patients at high cardiovascular risk.
- Patients received either torcetrapib plus atorvastatin or atorvastatin alone.
- The primary outcome was the time to the first major cardiovascular event, which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina.
Results

- At 12 months in patients who received torcetrapib, there was an increase of 72.1% in high-density lipoprotein cholesterol and a decrease of 24.9% in low-density lipoprotein cholesterol, as compared with baseline (P<0.001 for both comparisons).
- Cardiovascular events were significantly increased (hazard ratio, 1.25; 95% CI, 1.09 to 1.44; P=0.001)
- Death from any cause was increased (hazard ratio, 1.58; 95% CI, 1.14 to 2.19; P=0.006).
Total serious adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>torcetrapib Events</th>
<th>torcetrapib Total</th>
<th>placebo Events</th>
<th>placebo Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILLUMINATE</td>
<td>1699</td>
<td>7533</td>
<td>1503</td>
<td>7534</td>
<td>100.0%</td>
<td>1.13 [1.06, 1.20]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>7533</td>
<td>7534</td>
<td>100.0%</td>
<td></td>
<td></td>
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</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 3.90 (P < 0.0001)
ILLUMINATE
The most important trial since 2000?

- SAEs, ARI = 2.6% (p <0.0001).
- Total mortality, torcetrapib 82 (1.1%), placebo 51 (0.7%) RR 1.61 [1.14, 2.28] (p <0.01). ARI = 0.4%.
- Torcetrapib has a net health harm.
Why is ILLUMINATE the most important trial since 2000?

- This class of drugs were being touted as the next blockbusters based on the effects on HDL and LDL (surrogate markers).
- Prior to 2004 this drug probably would have been approved by the FDA based on surrogate markers.
- It caused the death of 31 people but saved tens of thousands of lives.
Anacetrapib vs placebo: DEFINE trial

- 1623 patients with CHD or high risk for CHD randomised to anacetrapib or placebo and followed for 1.5 years (NEJM Nov 2010).
- **100 mg of Anacetrapib:**
  - Decreased LDL by 40%, increased HDL by 138%
  - Had acceptable side effect profile.
  - Did not increase cardiovascular SAEs as seen with torcetrapib.
Total serious adverse events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Anacetrapib Events</th>
<th>Placebo Events</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFINE 2010</td>
<td>123</td>
<td>119</td>
<td>1.03 [0.82, 1.30]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>808</td>
<td>804</td>
<td>1.03 [0.82, 1.30]</td>
</tr>
</tbody>
</table>

Total events: 123 vs 119

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
Case Scenario

- Your son was born on November 30, 2005 and has just started school in Grade one.
- Your son has always been very bright and active.
- He has been difficult for you and your spouse to keep up with.
- Your son’s teacher arranges to meet you and your spouse.
Case Scenario (cont)

- The teacher says your son won’t stay in his seat and is disruptive to others in the class.
- She thinks he may have Attention Deficit Hyperactivity Disorder (ADHD) and need drug therapy.
- She suggests you have him seen by a Pediatrician.
Case Scenario (cont)

- The Pediatrician confirms the diagnosis and prescribes methylphenidate.
- What would your concerns be?
- How would you approach this problem?
- What would you do?
Minimum amount of information needed before prescribing or taking a drug?

- Patient problem and goal of therapy.
- Therapeutic options.
- Choice of therapy and evidence to justify choice.
- Prescription (dose and regimen).
- Method of assessing drug effect.
- Mechanism of action.
- Major route of inactivation.
- Important contraindications and adverse effects.
What is required before prescribing or taking a drug?

- Patient problem or diagnosis:
- ADHD:
- How is it diagnosed?
- What does diagnosis mean?
- Do subjective behavioral criteria represent a diagnosis?
What is required before prescribing or taking a drug?

- **Goal of therapy**
- To achieve full potential in terms of growth, development, academic achievement, employment, health and survival.
- “To make him behave so he can remain in Grade One”
What is required before prescribing or taking a drug?

- **Therapeutic Options**
- CNS stimulants
- Methylphenidate, dextroamphetamine, mixed amphetamine salts.
What is required before prescribing or taking a drug?

- Choice of therapy and evidence to justify choice.
- Methylphenidate?
- Short-term benefit (4 - 6 points out of 31) in terms of teacher and parent ratings of behavior?
What is required before prescribing or taking a drug?

- Prescription dose and regimen.
- Methylphenidate 5 mg twice daily at 8 AM and 12 Noon.
- Dispense 30 day supply.
What is required before prescribing or taking a drug?

- Method of assessing drug effect.
- Behavior in school is improved.
- Staying in seat.
- Appears to be more attentive.

Getting better marks in school.
What is required before prescribing or taking a drug?

- **Mechanism of action.**
- Release of dopamine and noradrenaline from nerve endings in the central nervous system.
- Associated with tolerance, dependence and addiction.
What is required before prescribing or taking a drug?

- **Major route of inactivation and half-life.**
- Liver metabolism, CYP450.
- Half-life, 4 hours.
What is required before prescribing or taking a drug?

- Important contraindications and adverse effects.
- Contraindications: emotionally unstable patients.
- Adverse effects.
- Decreased appetite.
- Insomnia.
- Headache.
- Stomach ache.
- Dizziness.
Would you agree to have your son take this medication?
Are doctors, teachers and parents treating children with CNS stimulants in BC?

YES

3.5% of boys and 1% of girls (6 to 12 years of age) are treated with these drugs.
Influence of relative age on diagnosis and treatment of attention-deficit/hyperactivity disorder in children

Richard L. Morrow MA, E. Jane Garland MD, James M. Wright MD PhD, Malcolm Maclure ScD, Suzanne Taylor PharmD, Colin R. Dormuth ScD
Treatment of ADHD in BC

- Cohort study involving 937,943 children in BC.
- 6-12 years of age between 1997 and 2008.
- Drugs: methylphenidate, dextroamphetamine, mixed amphetamine salts or atomoxetine.
% of boys and girls diagnosed or treated for ADHD by birth month

<table>
<thead>
<tr>
<th>Month of birth</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children, no.</td>
<td>Received diagnosis, %</td>
</tr>
<tr>
<td>January</td>
<td>39 136</td>
<td>5.7</td>
</tr>
<tr>
<td>February</td>
<td>36 586</td>
<td>5.9</td>
</tr>
<tr>
<td>March</td>
<td>41 512</td>
<td>6.0</td>
</tr>
<tr>
<td>April</td>
<td>40 605</td>
<td>6.1</td>
</tr>
<tr>
<td>May</td>
<td>42 724</td>
<td>6.5</td>
</tr>
<tr>
<td>June</td>
<td>40 720</td>
<td>6.7</td>
</tr>
<tr>
<td>July</td>
<td>41 829</td>
<td>7.3</td>
</tr>
<tr>
<td>August</td>
<td>40 859</td>
<td>7.3</td>
</tr>
<tr>
<td>September</td>
<td>41 111</td>
<td>7.6</td>
</tr>
<tr>
<td>October</td>
<td>39 773</td>
<td>7.9</td>
</tr>
<tr>
<td>November</td>
<td>37 409</td>
<td>7.8</td>
</tr>
<tr>
<td>December</td>
<td>38 977</td>
<td>7.4</td>
</tr>
<tr>
<td>Overall</td>
<td>481 241</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Trend test (p value)*

-19.7 (< 0.0001) -19.3 (< 0.0001) -16.5 (< 0.0001) -14.1 (< 0.0001)

RD (95% CI)

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<thead>
<tr>
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<th>Boys</th>
<th>Girls</th>
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<tbody>
<tr>
<td>Dec. v. Jan.†</td>
<td>(1.36 to 2.05)</td>
<td>(1.48 to 2.11)</td>
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RR (95% CI)

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<td>Dec. v. Jan.†</td>
<td>(1.23 to 1.37)</td>
<td>(1.33 to 1.50)</td>
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Figure 1: Percentage of children aged 6 to 12 years receiving pharmacologic treatment for ADHD, by month of birth. ADHD = attention-deficit/hyperactivity disorder.
Conclusions

- The potential harms of overdiagnosis overprescribing and the lack of an objective test for ADHD strongly suggest caution be taken in assessing children for this disorder and providing treatment.
- Further research into the determinants of ADHD and approaches to its assessment and treatment should consider a child’s age within a grade.
Questions??

- What would you do if confronted with this case scenario?
- What options besides drugs are available?
- Is using CNS stimulants to treat ADHD in children “snake oil”.
- What should doctors do?
- What should pharmacologists do?
- Should ADHD drugs be included in pharmacology textbooks and courses?
Questions??

WHAT SHOULD THE GOAL OF THERAPY BE FOR TREATING BEHAVIORAL SYMPTOMS IN SCHOOL CHILDREN?
Assignment

READ THERAPEUTICS
LETTER #69
“Is there a pill I can take to feel better about all the pills I take?”
Critically appraising a clinical trial report

- Are the conclusions of the authors true?
- What outcomes would matter most to patients?
- What is wrong with composite outcomes?
- How does one assess the risk of bias of a trial?
Hierarchy of outcomes

- All cause mortality.
- All cause mortality and morbidity (total people with at least one serious adverse event).
- Disease specific serious adverse event.
- Quality of life measures.
- Withdrawals due to adverse effects.
- Surrogate outcomes.
Serious adverse events

ANY DEATH, HOSPITALIZATION, LIFE THREATENING EVENT, EVENT LEADING TO PROLONGATION OF HOSPITALIZATION, EVENT LEADING TO DISABILITY, NEW CANCER.
<table>
<thead>
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<th>Risk of bias tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Random sequence generation (selection bias).</td>
</tr>
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<td>• Allocation concealment (selection bias).</td>
</tr>
<tr>
<td>• Blinding (performance bias and detection bias).</td>
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<tr>
<td>• Incomplete outcome data (attrition bias).</td>
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<td>• Selective reporting (reporting bias).</td>
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<td>• Publication bias (reporting bias).</td>
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<tr>
<td>• Patient selection bias (selection bias).</td>
</tr>
<tr>
<td>• Sponsorship (undetectable bias).</td>
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Decide for each category

- High risk of bias.
- Unclear risk of bias. (method of preventing bias not reported).
- Low risk of bias. (methods well reported and no evidence of bias).
GISSI-HF

- Random sequence generation (selection bias).
- Baseline characteristics (eg blood pressure) equal in both groups.
- Low risk of bias.
• Allocation concealment (selection bias).
• Baseline characteristics (e.g., blood pressure) equal in both groups.
• Low risk of bias.
Blinding (performance bias and detection bias).

Patients and doctors were aware of lipid levels?

High risk of bias in favor of drug.
GISSI-HF

- Incomplete outcome data (attrition bias).
- Losses to follow up were similar in both groups.
- Low risk of bias.
Selective reporting (reporting bias).
All important outcomes were reported.
Low risk of bias.
GISSI-HF

- Publication bias (reporting bias) – Not applicable.
- Patient selection bias (selection bias) – Not applicable.
- Sponsorship (undetectable bias) – Not applicable.
- Low risk of bias.