Torcetrapib’s failure: Find more stories in the ILLUMINATE trial. (Dr. Eriksson MD, PhD)
Atherosclerosis is a chronic inflammatory disease with LDL-C at the core.
Only 2 Surrogate Endpoints For Cardiovascular Disease Drugs

“The only surrogate endpoints currently used as a basis for approval of cardiovascular drugs are blood pressure and serum cholesterol level”

LDL-C (apo B) Lowering As a Surrogate Endpoint for Reduced CVD risk

- Epidemiology/pathology/clinical observation
- Experiment of nature: heFH, PCsk9
- The LRC-CPPT and NHLBI trials demonstrated that resins reduced CV events and slowed progression, associated with lowering LDL-C
  - Lovastatin was then approved on the basis of LDL-C reduction in 700 patients
  - Ezetimibe was also approved on the basis of LDL-C reduction
FRAMINGHAM: CHD RISK

CHD RISK

LDL-cholesterol (mg/dL)

HDL-C (mg/dL)

0 0.5 1 1.5 2 2.5 3

100 160 220 85 65 45 25

* Men aged 50-70
AMORIS, fatal myocardial infarction

Apolipoprotein B/Apolipoprotein A-I

Risk ratio

Men

Women

0.64 0.86 1.04 1.39

0.52 0.70 0.87 1.21

p<0.0001

p<0.05

Men

Women

p<0.001

p<0.05

p<0.0001

p<0.001

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Torcetrapib – Final Results of the ILLUMINATE Trial

Philip J Barter¹ for the ILLUMINATE Steering Committee and Investigators

¹Heart Research Institute, Sydney, Australia

Steering Committee: P. Barter, Chair (Australia), M. Caulfield (UK), M. Eriksson (Sweden), S. Grundy (US), J. Kastelein (The Netherlands), M. Komajda (France), J.-L. Lopez-Sendon (Spain), L. Mosca (US), J.-C. Tardif (Canada), D. Waters (US)

Statistical analysis: The Department of Biostatistics and Medical Informatics at the University of Wisconsin-Madison

Sponsor: Pfizer, Inc

Published online today in the New England Journal of Medicine
HDL protects against cardiovascular disease

A novel mechanism for raising HDL levels is to inhibit CETP. This protein transfers cholesterol from HDL to LDL fraction and thus retains cholesterol in the protective HDL.

Torcetrapib inhibits CETP and had been shown in humans to raise the level of HDL-C and lower that of LDL-C.

Inhibiting CETP with torcetrapib protects against atherosclerosis in rabbits.

The ILLUMINATE trial was designed to test the hypothesis that inhibiting CETP with torcetrapib would also protect against cardiovascular disease in humans.
**ILLUMINATE: Long-term Outcomes in Patients With CHD or CHD Risk Equivalence**

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events

### Patient Population
- Men or postmenopausal women
- Statin eligible
- Any HDL-C level
- CHD or risk equivalent (type 2 DM)

### Subjects
- 15,067
- 7 countries

### Primary End Point
- Major cardiovascular events
- Power=0.9 for 21% reduction

---

**Atorvastatin run-in to LDL <100 mg/dL (2.6 mmol/L) 4-10 weeks**

**Torcetrapib + titrated atorvastatin dose**

**Planned 4.5 years of treatment**

**Titrated atorvastatin dose**
On Dec 2, 2006, after a median follow-up on-treatment of 550 days, the sponsor was informed by the Steering Committee, acting on advice from the independent Data Safety Monitoring Board, to terminate the trial based on a statistically significant excess of deaths and cardiovascular events in the group treated with torcetrapib. The sponsor immediately terminated the trial. All data were censored for the primary analyses on December 2, 2006.
Primary Endpoint:
Time to First MCVE*: Kaplan-Meier Plot

Major cardiovascular event: CHD death, non-fatal MI, stroke or hospitalization for unstable angina

Event Free (%)

Days from Randomization

Atorvastatin (A) events = 373
Torcetrapib/Atorvastatin (T/A) events = 464

Hazard Ratio 1.25
P=0.001

*Major cardiovascular event: CHD death, non-fatal MI, stroke or hospitalization for unstable angina
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=7,534)</th>
<th>Torcetrapib/Atorvastatin (n=7,533)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>77.8</td>
<td>77.7</td>
<td>0.90</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>93.3</td>
<td>93.2</td>
<td>0.82</td>
</tr>
<tr>
<td>Age, yrs, mean</td>
<td>61.3</td>
<td>61.3</td>
<td>0.82</td>
</tr>
<tr>
<td>BMI, kg/m², mean</td>
<td>30.2</td>
<td>30.1</td>
<td>0.14</td>
</tr>
</tbody>
</table>
On Trial Lipid Levels By Study Month

Atorvastatin Group (Post Run-In)

Lipids (mg/dL)

<table>
<thead>
<tr>
<th>Study Month</th>
<th>HDL-C</th>
<th>LDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>128</td>
<td>79.9</td>
<td>48.5</td>
</tr>
<tr>
<td>1</td>
<td>127</td>
<td>79.3</td>
<td>48.2</td>
</tr>
<tr>
<td>3</td>
<td>128</td>
<td>80.5</td>
<td>48.9</td>
</tr>
<tr>
<td>6</td>
<td>130</td>
<td>80.5</td>
<td>49.2</td>
</tr>
<tr>
<td>12</td>
<td>129</td>
<td>80.7</td>
<td>48.9</td>
</tr>
</tbody>
</table>

Legend:
- ▲ HDL-C
- ▼ LDL-C
- ■ TG
On Trial Lipid Levels By Study Month

Torcetrapib/ Atorvastatin Group (Post Run-In)

Lipids (mg/dL)

<table>
<thead>
<tr>
<th>Study Month</th>
<th>TG</th>
<th>HDL-C</th>
<th>LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>127</td>
<td>79.7</td>
<td>48.6</td>
</tr>
<tr>
<td>1</td>
<td>115</td>
<td>71.8</td>
<td>59.7</td>
</tr>
<tr>
<td>3</td>
<td>112</td>
<td>77.5</td>
<td>59.3</td>
</tr>
<tr>
<td>6</td>
<td>112</td>
<td>80.9</td>
<td>58.2</td>
</tr>
<tr>
<td>12</td>
<td>112</td>
<td>82.9</td>
<td>58.3</td>
</tr>
</tbody>
</table>

* median % change (IQR) for TG at month 12; p<0.001 vs atorvastatin
† mean % change (SD) for LDL-C, HDL-C at month 12; p<0.001 vs atorvastatin
# Estimated hazard ratio for pre-specified cardiovascular outcomes

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin n (%)</th>
<th>Torcetrapib/Atorvastatin n (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHD death</strong></td>
<td>33 (0.4)</td>
<td>40 (0.5)</td>
<td>1.21 (0.77, 1.92)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Non-fatal MI</strong></td>
<td>118 (1.6)</td>
<td>142 (1.9)</td>
<td>1.21 (0.95, 1.54)</td>
<td>0.13</td>
</tr>
<tr>
<td>(excluding procedure related)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>40 (0.5)</td>
<td>43 (0.6)</td>
<td>1.08 (0.70, 1.66)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Hospitalization for unstable angina</strong></td>
<td>201 (2.7)</td>
<td>270 (3.6)</td>
<td>1.35 (1.13, 1.62)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>59 (0.8)</td>
<td>93 (1.2)</td>
<td>1.58 (1.14, 2.19)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
## Causes Of Death

<table>
<thead>
<tr>
<th>Cause</th>
<th>Atorvastatin (n=59)</th>
<th>Torcetrapib/Atorvastatin (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiovascular death</td>
<td>35</td>
<td>49</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Fatal MI - not procedure related</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Other cardiac death</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Fatal heart failure</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other vascular death/procedure related MI</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Any non-cardiovascular</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Cancer</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Other non-cardiovascular</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Trauma/suicide/homicide</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Reason unknown</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
Investigator-reported SAEs of neoplasms

Atorvastatin Group 136
Torcetrapib/atorvastatin Group 128

Investigator-reported SAEs of infections/infestations

Atorvastatin Group 177
Torcetrapib/atorvastatin Group 182
On-Trial Blood Pressure By Study Month

Atorvastatin Group

Blood Pressure (mmHg)

Study Month

Torcetrapib Atorvastatin Group

Blood Pressure (mmHg)

Study Month

* p<0.001 vs atorvastatin at month 12
Patients receiving torcetrapib/atorvastatin had changes in serum electrolytes that differed significantly from those in patients taking atorvastatin alone.

- Serum potassium was reduced (p<0.001)
- Serum bicarbonate was increased (p<0.001)
- Serum sodium was increased (p<0.001)
Serum Aldosterone

Performed after study termination on the 87% of patients with stored baseline and month 3 samples
55% of the analyzed samples had aldosterone levels below the lower limit of quantification by the technique
It was, however, possible to determine unambiguously whether or not an analyzed sample had an aldosterone level of 8 ng/dL or more.

<table>
<thead>
<tr>
<th>Percentage of patients with aldosterone &gt; 8 ng/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>A Group</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Month 3</td>
</tr>
</tbody>
</table>

* Wilcoxon comparisons after truncating the data below 8 ng/dl
Reported events occurring after Dec 2, 2006

The following events were reported up to July 15th 2007:

Deaths

Atorvastatin: 20 \( (n=7,475) \)
Torcetrapib/atorvastatin: 14 \( (n=7,440) \)

MCVEs

Torcetrapib/atorvastatin: 38 \( (n=7,475) \)
Atorvastatin: 38 \( (n=7,440) \)
Cox proportional hazard model adjusted for age, gender and baseline HDL-C. Excludes 265 patients with missing month 3 HDL-C. Preliminary analysis initiated and authorised by P Barter and conducted by Pfizer.
Figure 2. Fecal excretion of bile acids and neutral steroids 9 days before (left bars) and 9 days after (right bars) infusion of proapoA-I liposomes. Individual mean levels are shown for 2 periods; individual changes in total steroid excretion (mg/d) are indicated above each pair of bars. Increase in response to treatment was significant for bile acids ($P<0.03$), neutral sterols ($P<0.03$), and total steroid excretion ($P<0.02$).
### Effect of nicotinic acid, cholestyramine, clofibrate and combination on biliary lipids and lithogenic index

<table>
<thead>
<tr>
<th></th>
<th>Bile cholesterol (molar %)</th>
<th>Lithogenic index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nicotinic acid n=13</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before</td>
<td>8.5 +/- 0.7</td>
<td>0.85 +/- 0.07</td>
</tr>
<tr>
<td>during</td>
<td>10.0 +/- 0.9 p&lt;0.01</td>
<td>1.00 +/- 0.09 p&lt;0.01</td>
</tr>
<tr>
<td><strong>Cholestyramine n=19</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before</td>
<td>8.7 +/- 0.5</td>
<td>0.87 +/- 0.05</td>
</tr>
<tr>
<td>during</td>
<td>7.0 +/- 0.4</td>
<td>0.71 +/- 0.05 p&lt;0.001</td>
</tr>
<tr>
<td><strong>Clofibrate n=11</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before</td>
<td>8.5 +/- 0.3</td>
<td>0.85 +/- 0.3</td>
</tr>
<tr>
<td>during</td>
<td>12.1 +/- 0.9 p&lt;0.001</td>
<td>1.30 +/- 0.13 p&lt;0.01</td>
</tr>
<tr>
<td><strong>Combination with cholestyramine</strong></td>
<td>9.0 +/- 1.0 p&lt;0.01</td>
<td>0.92 +/- 0.10 p&lt;0.05</td>
</tr>
</tbody>
</table>

*Angelin et al. 1979*
HDL and atherosclerosis

Does the way HDL is increased influence clinical outcome?
ApoA-I infusion

HDL

Fecal BA

Fecal NS

Regression of atherosclerosis!
CETP inhibition

Torcetrapib

Brousseau et al. NEJM 2004

HDL 106%
Torcetrapib

HDL
C4
Latho
Fecal BA
Fecal NS

2X
Torcetrapib

Negative outcome in illuminate-patient end-point study
LDL-cholesterol cardiovascular disease (CVD) – secondary preventive studies

Patients with CVD events (%)

LDL-cholesterol

Summary and Conclusions

Use of the CETP inhibitor, torcetrapib, in the ILLUMINATE trial was associated with:

♦ a predicted substantial increase in HDL-C and decrease in LDL-C
♦ an off-target pharmacology consistent with activation of the renin-angiotensin-aldosterone system
♦ an increased risk of all-cause mortality and CVD morbidity that triggered a premature termination of the trial

The adverse clinical outcome associated with use of torcetrapib may have been the consequence of an off-target pharmacology but the possibility of an adverse effect of CETP inhibition cannot be excluded by the results of this randomized trial.

Possibilities: 1. Blood pressure
   2. No effect on the excretion of sterols from the human body
   3. Enrichment of cholesterol in HDL
   4. 40 % of the population had diabetes-is increasing HDL among a good thing per se.