ENHANCE: Simvastatin with or without Ezetimibe in Heterozygous Familial Hypercholesterolemia (FH) | June/08

ENHANCE Trial Overview:
- A 24 month, prospective, randomized, double-blind, active comparator multi-center study completed in 2006
- 2 treatment arms (both with 6 week placebo run-in): Simvastatin 80mg (n=363) vs Simvastatin 80mg + Ezetimibe 10mg (n=357)
- NOTE: n = 720 for initial and safety analysis; N = 642 for ITT efficacy analysis (Monotherapy: n = 320, Combo: n = 322)
- 720 patients: ~64yr, 31% men, avg BMI 27 kg/m² in combo arm, 31% diabetes, 25% HTN, 12.5% smoking, previous MI in 10%, Framingham 10yr risk = 13%, Q=9%
- Previous statin use: 82% in Simvastatin group, 80% in Combination group
- Pts included if LDL > 5.4mmol/L (after the 6 week) run-in and heterozygous FH; Pts excluded if: 
  - ↑ stenosis or occlusion of carotid artery, homozygous FH, history of carotid artery stenting or carotid endarterectomy, NYHA class II or IV heart failure, arrhythmias, angina, or recent CV events
- Baseline data: mean intima-media thickness (IMT) of carotid artery avg of 6 segments 0.7 vs 0.69mm, ~ LDL 8.2mmol/L, C-reactive protein 1.7mg/L

Table 1: ENHANCE Results (Simvastatin 80mg daily vs Combination of Simvastatin 80mg + Ezetimibe 10mg daily)

<table>
<thead>
<tr>
<th>Endpoints (Reductions in size or concentration, not event rates)</th>
<th>Simvastatin (n=320)</th>
<th>Simvastatin + Ezetimibe (n=322)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Mean change in carotid artery intima-media thickness (mm±SE) (Both groups)</td>
<td>0.0050±0.0037</td>
<td>0.0111±0.0038</td>
<td>0.29</td>
</tr>
<tr>
<td>2° Mean change in femoral artery intima-media thickness (mm±SE)</td>
<td>-0.0067±0.0132</td>
<td>0.0182±0.0135</td>
<td>0.16</td>
</tr>
<tr>
<td>2° Total Cholesterol change (mmol/L)</td>
<td>-3.3 (-32)</td>
<td>-4.7 (-45)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2° LDL (mmol/L)</td>
<td>-3.2 (-39)</td>
<td>-4.6 (-56)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2° C-reactive protein (mg/L)</td>
<td>1.2 (-24)</td>
<td>0.9 (-49)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Other surrogate results: ↑HDL (N=357), ↓Triglycerides (N=363), ↓Apolipoprotein B (N=363), →Apolipoprotein A1 (N=363)

Table 2: ENHANCE Adverse Events Results (Simvastatin 80mg daily vs Combination of Simvastatin 80mg + Ezetimibe 10mg daily)

<table>
<thead>
<tr>
<th>Adverse Events (% of events)</th>
<th>Simvastatin (n=363)</th>
<th>Simvastatin + Ezetimibe (n=357)</th>
<th>Absolute risk increase %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of discontinuation due to AE</td>
<td>9.4% (34)</td>
<td>8.1% (29)</td>
<td>-1.3% NS</td>
<td>0.56</td>
</tr>
<tr>
<td>Adverse events</td>
<td>29.5% (107)</td>
<td>34.2% (122)</td>
<td>4.7% NS</td>
<td>0.18</td>
</tr>
<tr>
<td>↑ in ALT or AST or both &gt;3 ULN</td>
<td>2.2% (8/360)</td>
<td>2.8% (10/356)</td>
<td>0.6% NS</td>
<td>0.62</td>
</tr>
<tr>
<td>↑ in CK &gt;10 x ULN</td>
<td>2.2% (8/360)</td>
<td>1.1% (4/356)</td>
<td>-1.1% NS</td>
<td>0.25</td>
</tr>
<tr>
<td>Myopathy: ↑ in CK &gt;10 x ULN assoc'd muscle symptoms</td>
<td>0.27% (1)</td>
<td>0.56% (2)</td>
<td>0.29% NS</td>
<td>0.99</td>
</tr>
<tr>
<td>Cardiovascular events *</td>
<td>1.9% (7)</td>
<td>2.8% (10)</td>
<td>0.9% NS</td>
<td>0.39</td>
</tr>
<tr>
<td>Deaths from Cardiovascular cause</td>
<td>2.7% (1)</td>
<td>0.56% (2)</td>
<td>0.29% NS</td>
<td>0.99</td>
</tr>
</tbody>
</table>

* Cardiovascular events: Non-fatal MI 2 vs 3 events, non-fatal stroke 1 vs 1 event, coronary revascularization 1 vs 6 events NS= not statistically significant

Of Note:
- **Efficacy**: No clinical outcomes data – short 2yr study, underpowered to show clinical outcomes; however, a modest positive correlation between IMT (a validated surrogate marker) and coronary atherosclerosis has been shown in 30 of 34 studies reviewed by Brown, et al.²
- **Safety**: No significant difference in efficacy or adverse effects seen, however being a short trial, it lacks long-term effects data.
- Results took quite a while to be published; congressional hearings expressed concern that they may have been delayed to protect Ezetrol sales?
- These patients have “low” baseline (relative to other studies)².
- Despite significant reduction in LDL & CRP in the combination group no primary benefit on atherosclerosis over statin monotherapy.

(Warning on surrogate markers: see α blockers vs diuretics in ALLHAT trial: both BP, but if HTN & stroke with diuretics; HRT; LDL, but MI, stroke, deaths & breast cancer; in ACCORD: ATC, but ↑ mortality).

Some concern regarding the trend to worsen IMT when hypothesis hoped for a benefit.

What we knew and what these results add to our knowledge:
- FH in 500 people: ~45yo patients have been on lipid meds for 1 or 2 decades – recent theory suggests that plaques stabilize with continued lipid-lowering therapy, thus are not easily reduced with progressive treatment². Conversely, studies have shown that statins alone slow or even ↓ IMT².
- Ezetimibe approved in the USA in 2002 Canada in 2003; concerns have been raised regarding extent of use & promotion despite lack of evidence: - No clinical outcomes data – not likely until 2012 (IMPROVE-IT trial: Simvastatin 40mg vs Simvastatin 40mg+Ezetimibe 10mg in 18000 pts with recent ACS), almost a decade later. ↑ Ezetimibe prescriptions: especially in the USA (From 2003→2006: U.S. 1.1→2.2%, Canada 0.2→3.4%, of all lipid-lowering medications).¹ - USA direct advertising $200 million/yr; 1 in 6 of all lipid-lowering medications). ¹ - USA direct advertising $200 million/yr; 1 in 6 of all lipid-lowering medications). ¹ - USA direct advertising $200 million/yr; 1 in 6 of all lipid-lowering medications). ¹ - USA direct advertising $200 million/yr; 1 in 6 of all lipid-lowering medications). ¹ - USA direct advertising $200 million/yr; 1 in 6 of all lipid-lowering medications). ¹ - USA direct advertising $200 million/yr; 1 in 6 of all lipid-lowering medications). ¹

- Statins not only lower LDL but have proven benefit in ↓ morbidity & mortality, however relative statin use has declined in the U.S. since 2002.

- **2nd prevention trials**↓49% total mortality, ↓LIPID heart failure, ↓CARE cardiac death, ↓HPS↓CHD non-fatal cardiac event, ↓ TNT high dose stable coronary, ↓ Ideal high dose after MI, ↓LIPSOCAPS prostate cancer, ↓SPARCL high risk hypertension, ↓ASCOT cardiac death in high risk hypertensives, ↓WOSCOPS cardiac death in higher risk Scottish males, ↓, & AFCAPS²

- ↓ LDL with statins is beneficial, but benefit/risk of LDL reduction with ezetimibe is unknown. Note: Torcetrapib did ↓ LDL & Fx but ↑ mortality in phase III trials.

- Combinations further lower LDL, but cardiovascular outcome benefit cannot be assumed (eg. statins with either fibrates or ezetimibe)

Questions remaining:
- Would clinical outcomes be better or worse with ezetimibe? →Awaiting IMPROVE-IT trial (results likely 2012 or 2013).
- Would different results be expected in patients with more advanced IMT, if statin naïve, or in other subtypes of hypercholesterolemia?
- Is the benefit from statins beyond an LDL reduction? Is the correct amount of importance placed on this one surrogate?
- Would results be different if a low/moderate dose statin + ezetimibe was compared to high-dose statin monotherapy?

**Take Home**: Ezetimibe still lacks evidence for reducing CV events. Lack of benefit on atherosclerosis in ENHANCE calls into question whether it offers any clinical benefit. Statins have the cornerstone of evidence for lipid therapy.

References:
¹Kastelein JP, Akdim F et al. Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia. NEJM 2008;358:14-1431-1443
²Brown BG, Taylor AJ. Does ENHANCE Diminish Confidence in Lowering LDL or in Ezetimibe? NEJM 2008;358:14-1504-1507
³Jackevicius CA, Tu JV et al. Use of Ezetimibe in the United States and Canada. NEJM 2008;10.1506-1-10