ENHANCE[1]: 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** VYTORIN (n=357)
  - NOTE: n = 720 for initial and safety analysis; N = 642 for ITT efficacy analysis (Monotherapy: n = 320, Combo: n = 322)
- **720 patients**: ~46yr, ♂ 51%, avg BMI 27↑ in combo arm, diabetes 2%, HTN 51%, ~ BP 125/78, smoking 29%, previous MI 6%, Framingham 10yr risk: ♂=13%, ♀=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 III 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 8.2**mmol/L, C-reactive protein 1.7mg/L

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

Endpoints (Reductions in size or concentration, not event rates)	**Simvastatin** (n = 320) Change from baseline (%)	**Simvastatin + Ezetimibe** (n = 322) Change from baseline (%)	p value
1° Mean change in carotid artery intima-media thickness (mm±SE) (Both groups ↑ thickness, but **combination** trended to **more of an increase**)	**0.0058±0.0037**	**0.0111±0.0038** Differences not statistically significant	**0.29**
2° Mean change in femoral artery intima-media thickness (mm±SE)	-0.0067±0.0132	0.0182±0.0135 Differences not statistically significant	0.16
2° Total Cholesterol change (mmol/L)	-3.3 (-32)	-4.7 **(-45)**	<0.01
2° LDL (mmol/L)	-3.2 (-39)	-4.6 **(-56)**	**<0.01**
2° C-reactive protein (mg/L)	1.2 (-24)	0.9 **(-49)**	**<0.01**

Other surrogate results: ↑HDL 8 vs 10%, ↓Triglycerides 23 vs 30%, ↓ Apolipoprotein B 33 vs 47%, ↔ Apolipoprotein A1 7 vs 6%

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

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

* Cardiovascular events: Non-fatal MI 2 vs 3 events, non-fatal stroke 1 vs 1 event, coronary revascularization 5 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 IMT (relative to other studies)[2].
- Despite significant reduction in LDL & CRP in the combination group no primary benefit on atherosclerosis over statin monotherapy.
  (**Caution with surrogate markers:** ie. **α -blockers** vs thiazides in ALLHAT trial: both ↓BP, but ↑HF&stroke with doxazosin; **HRT**: ↓LDL, but ↑ MI, stroke, clots & breast cancer; in **ACCORD**: ↓A1C, 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 1 in 500 people: most 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 treatment[2]. Conversely, studies have shown that statins alone slow or even ↓ IMT[2].
- 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 Simv 40mg+Ezetimibe10mg in 18000 pts with recent ACS), almost a decade later.
  - -↑ Ezetimibe prescriptions: especially in the USA (From 2003→2006: U.S. 0.1→15.2%, Canada 0.2→3.4%, of all lipid-lowering medications).[3]
  - USA direct advertising $200 million/yr; 1 in 6 of all lipid↓ prescriptions & had **$5 billion sales** in 2007 → "Marketing beyond science" –Dr.S.Nissen.
- Statins not only lower LDL but have proven benefit in ↓ morbidity & mortality, however relative statin use has declined in the U.S. since 2002.
  - **2° prevention trials**: 4S↓total mortality, LIPID↓ cardiac death, CARE↓MI/cardiac death, HPS↓fatal/non-fatal vascular event, TNT high dose in stable coronary pts, Ideal high dose after MI
  - **1° prevention trials**: CARDS↓1st CHD event in diabetics, ASCOT↓MI/cardiac death in high risk hypertensives, WOSCOPS↓MI/cardiac death in higher risk Scottish males, & AFCAPS↓1st CV event
- ↓ LDL with statins is beneficial, but benefit/risk of LDL reduction with ezetimibe is unknown. Note: Torcetrapib did ↓ LDL & ↑HDL 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 have been 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.

AE=adverse event **BP**=blood pressure **dx**=diagnosis **FH**=familial hypercholesterolemia **fx**=function **HDL**=high density lipoprotein **HF**=heart failure **HTN**=hypertension **hx**=history **IMT**=intra-media thickness **LDL**=low density lipoprotein **MI**=myocardial infarction **Pt**=patient **SE**=side effect **sx**=symptoms **tx**=treatment **ULN**=upper limit of normal www.RxFiles.ca **Prepared by**: Z. Dumont, B. Jensen, L. Regier

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