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Scientific Update™

The ENHANCE Study: What Do We Know Now?

Originally presented by: John Kastelein, MD

A review of a presentation at the ACC.08 Scientific Showcase during the 57th Annual Scientific Session of the American College of Cardiology

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Reported by: GORDON MOE, MD

Results from recent clinical trials, comparing various statins or the same statin at various doses, demonstrated that treatment regimens markedly lowering the levels of low-density lipoprotein cholesterol (LDL-C) were associated with a reduction in rates of cardiovascular (CV) events. This has led to recommendations of aggressive LDL-C lowering as standard therapy in multiple groups of patients at risk for CV events. Significant numbers of patients, however, are either unable to reach treatment goals despite statin therapy or they are intolerant to statins. Ezetimibe is a specific cholesterol-uptake inhibitor that produces additional lowering of LDL-C levels beyond those achieved with a statin. The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial addressed the question of whether additional lowering of LDL-C with ezetimibe, beyond the levels achieved with simvastatin, beneficially affects the progression of atherosclerosis. The primary results of ENHANCE were recently presented and published; the clinical implications of these results are reviewed in this issue of *Cardiology Scientific Update*.

Overwhelming evidence has accumulated supporting the use of statins as first-line therapy for patients with hypercholesterolemia and those deemed at high-risk for vascular events.[1-9] Results from recent clinical trials have demonstrated that CV event rates can be further lowered by reducing LDL-C to even lower levels.[10,11] Yet, despite treatment with higher doses of powerful statins that achieve lower goals of LDL-C, a high residual risk remains and an estimated 65%-70% of events are not prevented. Further, many patients are either unable to reach their treatment goals despite statin therapy or they are intolerant to the statins, particularly at higher doses.[12] Ezetimibe is a specific cholesterol-uptake inhibitor that acts by binding to the Niemann-Pick C1-like protein-1 transporter complex.[13] In monotherapy, ezetimibe lowers LDL-C levels by about 18% and, in combination with statins, ezetimibe produces an additional 23% reduction in LDL-C above that achieved with a statin.[14]

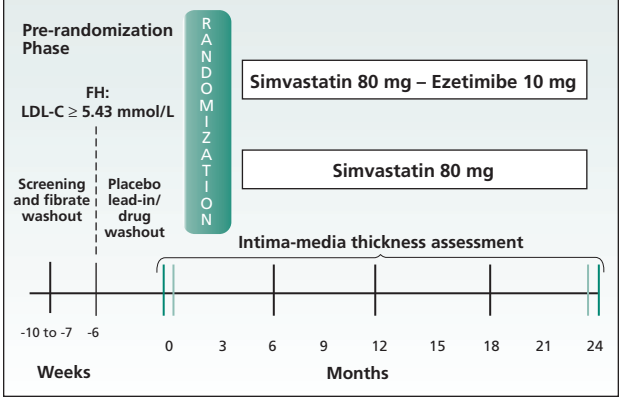
The ENHANCE trial was specifically designed to determine whether the daily administration of ezetimibe (10 mg) in combination with simvastatin (80 mg) could reduce the progression of atherosclerosis in patients with familial hypercholesterolemia, as assessed by sonographic measurements of arterial intima-media thickness. Patients with familial hypercholesterolemia were chosen because these patients are known to have greatly increased risks of premature coronary artery disease (CAD) and a high rate of intima-media thickness progression beginning in childhood.[15,16]

Methods

The rationale and design of the study have been reported in detail previously.[17] Briefly, the trial was conducted at 18 centres in the United States, Canada, South Africa, Spain, Denmark, Norway, Sweden, and the Netherlands between 2002 and 2006. Men and women aged 30 to 75 years were eligible to participate in the study if familial hypercholesterolemia was diagnosed either by genotyping or by their having met the diagnostic criteria outlined by the World

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Figure 1: Study design of the ENHANCE trial[17]



FH = familial hypercholesterolemia

Health Organization. Patients were enrolled regardless of their prior treatment with lipid-lowering drugs; LDL-C levels in untreated patients were ≥5.43 mmol/L. The study design is summarized in Figure 1. Major exclusion criteria included high-grade stenosis or occlusion of the carotid artery, a history of carotid endarterectomy or stenting, homozygous familial hypercholesterolemia, New York Heart Association class III or IV heart failure, arrhythmia, angina pectoris, or recent CV events.

The predefined primary outcome was the change from baseline in sonographic measurements of the mean carotid artery intima-media thickness, defined as the average of the means from the far-wall intima-media thickness of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries. Key secondary outcomes included the proportion of patients with regression in mean carotid artery intima–media thickness from baseline, the proportion of patients with new carotid-artery plaques >1.3 mm, and the change from baseline in the mean, maximal, carotid artery intima–media thickness.

Table 1: Baseline clinical characteristics and lipid values[18]

	Simvastatin n=363	Simvastatin + Ezetimibe n=357	*P*
Age (yr)	45.7±10.0	46.1±9.0	0.69
Male sex no. (%)	179 (49%)	191 (54%)	0.26
Body-mass index (kg/m^2)	26.7±4.4	27.4±4.6	0.047
History of diabetes	5 (1%)	8 (2%)	0.38
Hypertension	51 (14%)	67 (19%)	0.09
Current smoking	104 (29%)	102 (29%)	0.98
History of MI	26 (7%)	14 (4%)	0.06
Prior use of statins	297 (82%)	286 (80%)	0.56
Systolic pressure BP (mm Hg)	124±15	125±15	0.31
Diastolic pressure BP (mm Hg)	78±10	78±9	0.41
Total cholesterol (mmol/L)	10.4±1.8	10.4±1.7	0.96
LDL cholesterol (mmol/L)	8.2±1.7	8.3±1.7	0.85

MI = myocardial infarction; BP = blood pressure

Results

The primary results of the ENHANCE study were reported at the ACC.08 and the results have also been published.[18] From August 2002 to April 2004, a total of 1180 patients with familial hypercholesterolemia underwent screening. Of these patients, 720 were randomized; 363 were assigned to the simvastatin-monotherapy group, while 357 were assigned to the simvastatin + ezetimibe combined-therapy group. The intention-to-treat population consisted of 642 patients (320 in the simvastatin-only group and 322 in the combined-therapy group). Among these subjects, 64 in the simvastatin-only group and 41 in the combined-therapy group did not complete the trial. Baseline characteristics of the randomized subjects are shown in Table 1. With the

Figure 2: Effects of simvastatin and combined therapy with simvastatin plus ezetimibe on lipid values[18]

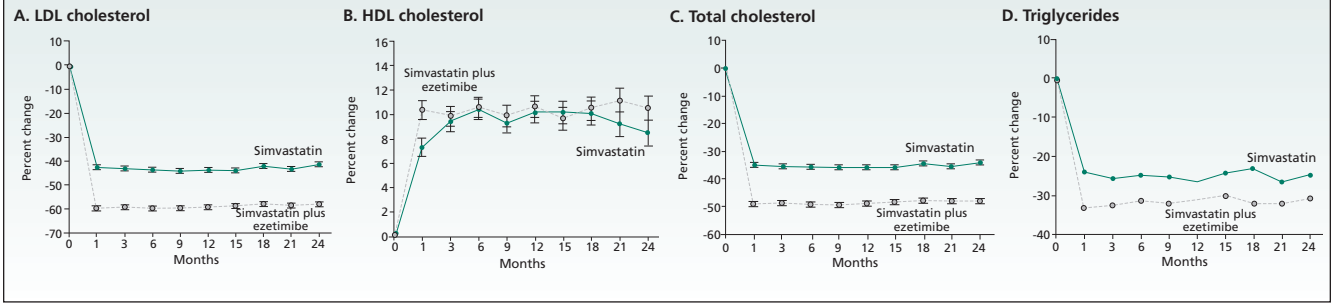


Figure 3: Effects of simvastatin and combined therapy with simvastatin plus ezetimibe on C-reactive protein

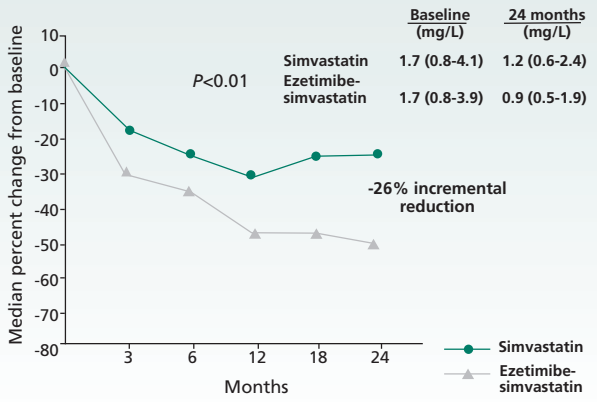
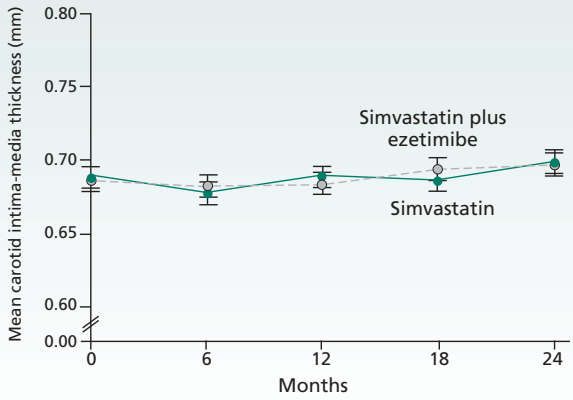


Figure 4: Effects of simvastatin and combined therapy with simvastatin plus ezetimibe on carotid artery intima-media thickness over 24 months[18]



exception of body-mass index (BMI), which was significantly greater in the combined-therapy group, the two treatment groups were comparable in baseline clinical characteristics and lipid values. Approximately 80% of patients in each group had previously received statins. Figure 2 illustrates the effects of randomized treatment on the lipid values. After 24 months, mean levels of LDL-C decreased from 8.2±1.7 to 5.0±1.7 mmol/L in the simvastatin-only group and from 8.3±1.7 to 3.7±1.4 mmol/L in the combined-therapy group, a between-group difference of 16.5% ($P<0.01$). Reductions in levels of total cholesterol and triglycerides, as well as apolipoprotein B (–46.7±0.9 versus –33.1±0.9 mg/dL, $P<0.01$), were significantly greater in the combined-treatment compared to the simvastatin-only treatment group. Reductions in C-reactive protein (CRP) were also significantly greater in the combined-treatment group (Figure 3).

Results of the primary efficacy endpoint are shown in Table 2. The primary outcome measure, the change from baseline in the mean intima-media thickness of the carotid artery, was 0.0058±0.0037 mm in the simvastatin-only group and 0.0111±0.0038 mm in the combined group. This small difference of 0.0053 mm was not statistically significant ($P=0.29$). No significant change was observed in the mean maximum carotid artery intima-media thickness, an increase of 0.0103±0.0049 mm in the simvastatin-only group and 0.0175±0.0049 mm in the combined group ($P=0.27$). The results of the longitudinal, repeat-measures analysis are shown in Figure 4. The change in the average intima-media thickness over time did not differ between the two study groups ($P=0.17$), for the interaction between treatment and time. Indeed, there was a slight increase in the mean intima-media thickness for both groups over time.

Results of the secondary endpoints are shown in Table 3. No significant changes were observed between groups in the mean measures of the intima-media thickness of the common carotid artery, carotid bulb, internal carotid artery, and the femoral artery, or in the average mean values for intima-media thickness in the carotid and femoral arteries. In addition, regression in the mean carotid artery intima-media thickness was seen in 44% of the subjects in the simvastatin-only group and in 45% of the combined-therapy group ($P=0.92$).

Both regimens were well tolerated, with overall safety profiles generally similar and consistent with those listed in the product labels. Adverse events, considered related to treatment, occurred in 107 of 363 patients (29.5%) in the simvastatin-only group and in 122 of 357 patients (34.2%) in the combined-therapy group ($P=0.18$). The rates

Table 2: Measures of carotid intima-media thickness, primary outcome[18]

Variable	Simvastatin		Simvastatin + Ezetimibe		*P*
	Mean	Median	Mean	Median	
Baseline	n=342		n=338		
Mean IMT	0.70±0.13	0.69	0.69±0.13	0.68	0.64
Mean max. IMT	0.80±0.16	0.78	0.80±0.17	0.76	0.94
24 months	n=320		n=322		
Mean IMT	0.70±0.14	0.69	0.71±0.15	0.68	0.29
Mean max. IMT	0.81±0.17	0.79	0.82±0.18	0.78	0.27
Difference					
Mean IMT	0.0058±0.0037	0.0095	0.0111±0.0038	0.0058	0.29
Mean max. IMT	0.0103±0.0049	0.0103	0.0175±0.0049	0.0160	0.27

IMT, intima-media thickness (mean ± standard error [SE] and median, mm)

Table 3: Measures of carotid intima-media thickness, secondary outcomes

Variable	Simvastatin		Simvastatin + Ezetimibe		*P*
	Mean	Median	Mean	Median	
Baseline	n=342		n=338		
CCA	0.68±0.16	0.66	0.67±0.16	0.64	0.45
CB	0.80±0.20	0.78	0.79±0.22	0.76	0.51
ICA	0.61±0.17	0.58	0.62±0.17	0.60	0.42
24 months	n=320		n=322		
CCA	0.68±0.15	0.66	0.68±0.16	0.64	0.93
CB	0.81±0.22	0.79	0.81±0.22	0.77	0.37
ICA	0.62±0.17	0.59	0.64±0.17	0.60	0.21
Difference	n=320		n=322		
CCA	0.0024±0.0043	0.0043	0.0019±0.0044	0.0010	0.93
CB	0.0062±0.0069	0.0099	0.0144±0.0070	0.0107	0.37
ICA	-0.0007±0.0064	0.0057	0.0099±0.0065	0.0066	0.21

CCA = common carotid artery; CB = carotid bulb; ICA = internal carotid artery

of discontinuation owing to adverse events were similar as well: 34 of 363 patients (9.4%) in the simvastatin-only group and 29 of 357 patients (8.1%) in the combined-therapy group (*P*=0.56). The numbers of subjects with consecutive increases in liver and muscle enzymes are shown in Table 4. There was one case of viral hepatitis A in the simvastatin-only group. One case of myopathy (defined as creatine kinase [CPK] >10 times the upper limit of normal [ULN] and with associated muscle symptoms) was observed in the simvastatin-only group arm and 2 cases in the combined-therapy group.

Discussion and clinical implications

The primary results of the ENHANCE study demonstrated that the addition of ezetimibe to an optimal recommended dose of simvastatin did not reduce the intima-media thickness of the carotid artery. This commonly used risk surrogate for vascular disease revealed no reduction in this cohort of patients with familial hypercholesterolemia, despite significant incremental reductions in levels of both LDL-C and CRP. The primary outcome, the change in the mean intima-media thickness, did not differ significantly between the two study groups nor did the secondary outcome measures. There are three possible explanations for these neutral results that may be related to:

- inabilities for the imaging modality employed in the study to accurately detect changes in atherosclerotic burden
- differential mechanisms of action with ezetimibe and statins in terms of vascular protection

Table 4: Safety observations

	Simvastatin	Simvastatin + Ezetimibe	*P*
	n=360	n=356	
ALT and/or AST ≥ 3 × ULN	8	10	0.62
CPK ≥10 × ULN	8	4	0.25

ALT = alanine aminotransferase; AST= aspartate aminotransferase; ULN = upper limit of normal; CPK= creatine phosphokinase

Subjects with 2 consecutive measurements for ALT and/or AST; a single last measurement ≥3 × ULN; a measurement ≥3 × ULN followed by <2 × ULN that was taken more than 2 days after the last dose of study medication

- low risks in the patient cohort compared with previous studies.

It seems unlikely that the measurement technique would be unable to detect meaningful changes in arterial-wall measures, given the high precision of the measurements as evidenced by the high intraclass coefficients (>0.93) and low standard deviations between paired measurements (<0.053 mm), as well as the completeness of follow-up (>83%). A linear relationship is known to exist between the level of LDL-C and intima-media thickness,[19] and the progression in intima-media thickness is attenuated consistently in statin intervention studies,[20,21] suggesting that intima-media thickness is a reasonable marker for atherosclerosis.

A second potential explanation is that ezetimibe reduces LDL-C, but exerts no effect on the progression of atherosclerosis unlike the statins. An analogous argument was used to explain the effects of torcetrapib that increased high-density lipoprotein cholesterol (HDL-C) by 50%, reduced LDL-C by 20%, but had no effect on carotid intima-media thickness[22] or atheroma volume.[23] In addition to the capacity of statins to lower LDL-C levels, the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase may also result in lipid-independent effects possibly involving anti-inflammatory action and improvements in endothelial function.[24] These effects may not necessarily be shared by ezetimibe. Yet, CRP was reduced 26% by the addition of ezetimibe.

Comparison between ezetimibe and statins revealed differential effects on endothelial function that marginally favoured statin therapy, despite similar reductions in LDL-C;[25] however, these findings are not consistent across studies. For example, in patients with metabolic syndrome, a combination of ezetimibe and atorvastatin was superior to atorvastatin alone in restoring endothelial function.[26] On the other hand, to date, almost every mode of reducing LDL-C has been beneficial on slowing the progression of atherosclerosis, even including apheresis, diet, or bile acid sequestrants.[27] Furthermore, a recent

Table 5: Ongoing clinical outcome trials with ezetimibe/statin therapy

Trial	Patient Population	Treatment	Endpoint
SEAS[30]	Aortic stenosis (n=1,400)	Ezetimibe 10 mg/Simvastatin 40 mg vs placebo	Progression of aortic stenosis: major CV events
SHARP[31]	Chronic kidney disease (n=9,000)	Ezetimibe 10 mg/Simvastatin 20 mg vs placebo	Major vascular events (MI, cardiac death, stroke, or revascularization)
IMPROVE-IT[32]	Acute coronary syndrome (n=18,000)	Ezetimibe 10 mg/Simvastatin 40 mg vs Simvastatin 40 mg	Death, major coronary events

SEAS: Simvastatin + Ezetimibe in Aortic Stenosis[30]
SHARP: Study of Heart and Renal Protection[31]
IMPROVE IT: IMProved Reduction of Outcomes: Vytorin® Efficacy International Trial[32]

metaregression analysis of 5 diet, 3 bile acid sequestrant, 1 surgery, and 10 statin trials, (n = 81,859) suggests that the reduction of CV events relates directly to the reduction of LDL-C. Consequently, statins may not confer any additional risk reduction beyond that expected from the degree of LDL-C lowering, notwithstanding their well-documented pleiotropic effects.[6]

A third and plausible explanation for the failure of further LDL-C reduction to decrease intima-media thickness progression may relate to the population of patients in the ENHANCE study. Although patients with familial hypercholesterolemia represent a group at very high risk for premature CAD,[15] the treatment of patients with familial hypercholesterolemia has undergone profound changes in the past two decades. The use of high-dose statins starting at an early age might have attenuated the progression of intima-media thickness in these patients, as was shown in the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study.[20] Thus, it is not surprising to find that baseline mean carotid intima-media thickness in the ENHANCE study (0.70±0.13 mm) was far smaller than that in the ASAP study (0.92±0.20 mm), the results of which were published in 2001.[20] Furthermore, patients in the ENHANCE study had longer and more intensive statin therapy than those subjects who entered the ASAP study 6 years earlier. If long-term therapy before entering a trial favourably alters the plaque, the potential for demonstrating a treatment benefit could be greatly diminished in these patients.

The ASAP extension study[28] revealed that treatment with atorvastatin 80 mg daily for an additional 2-year period beyond the initial 2 years of the original study did not further reduce intima-media thickness, but was associated with a complete arrest of the progression in mean carotid intima-media thickness (0.89 mm at the start vs 0.90 mm at the end of the extension study; *P*=0.58). In contrast, patients previously taking simvastatin (40 mg) had a significant regression of intima-media thickness (0.95 mm at the start of the extension study vs 0.92 mm at the end of the study, *P*=0.01). At 4 years, there was no longer any difference in the mean carotid intima-media thickness between the 2 groups (0.90 vs 0.92 mm; *P*=0.06). This suggests that once arteries have the majority of the mobile lipid removed by aggressive lipid-lowering, further reductions in intima-media thickness may not be possible. Most patients in the ENHANCE study had received vigorous lipid reduction for many years prior to the study and, consequently, their carotid arteries may have not been as modifiable as those of patients enrolled in earlier studies.

Data from ENHANCE, based on measurements of carotid intima-media thickness instead of hard clinical endpoints, do not address the question of whether the lowering of LDL-C with ezetimibe is useful in improving hard clinical outcomes. Considering whether the rate of change in carotid intima-media thickness serves as an effective marker for cardiovascular events, it is useful to note that intima-media thickness has been measured in many lipid-therapy trials. In studies comparing various statins with placebo or with lower-dose statins and demonstrating improved clinical outcomes, the progression of intima-media thickness has consistently been attenuated with higher doses of statins.[29] However, all of the studies demonstrating a reduction in clinical outcomes followed patients for longer than 2 years and, to date, there have been no studies with ≤2 years of follow-up indicating a significant reduction in such events. Therefore, whether ezetimibe in combination with statins would improve clinical outcomes remain an open question. A list of ongoing trials with ezetimibe, examining hard clinical outcomes is shown in Table 5. In particular, the results of the Improved Reduction of Outcomes: Vytorin® Efficacy International Trial (IMPROVE-IT)[32] are expected, not only to help define the role of ezetimibe in the treatment of hypercholesterolemia, but also to provide insight into the biology of LDL-C-lowering and the use of carotid intima-media thickness as a surrogate marker of coronary events.

What are the clinical implications of the primary results from the ENHANCE study? Until further outcome data are available, definitive conclusions cannot be drawn from the ENHANCE results as they relate to the clinical use of ezetimibe. At this stage, physicians should continue to use a statin as first-line therapy. In patients whose LDL-C levels remain high despite treatment with an optimal dose of a statin, or if patients do not tolerate the statin, efforts on diet and exercise should be maximized and considerations should be given to using alternative cholesterol-lowering agents, which can include the fibrates, resins, niacin, and ezetimibe.

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