Ezetimibe and SimvastatiN in Hypercholesterolemia EnhANces AtherosClerosis REgression (ENHANCE)

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- A double-blind, randomized, 24-month trial comparing the effects of daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe in 720 patients with familial hypercholesterolemia.
- Patients underwent B-mode ultrasonography to assess the intima–media thickness of the walls of the carotid and femoral arteries.
- The primary outcome measure was the change in the mean carotid-artery intima–media thickness, which was defined as the average of the means of the far-wall intima–media thickness of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries.

Kastelein JJP, et al. N Engl J Med 2008;358:1431-43.

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- Primary outcome, the mean (± SE) change in CIMT was 0.0058 (± 0.0037) mm in the simvastatin-only group and 0.0111 ± 0.0030 mm in the simvastatin/ezetimibe group (p = 0.29)
- Secondary outcomes (consisting of other variables regarding the intima–media thickness of the carotid and femoral arteries) did not differ significantly between the two groups.
- At the end of the study, the mean (± SD) LDL-C level was 192.7 ± 60.3 mg/dL in the simvastatin group and 141.3 in the combination group, a between group difference of 16.5%
- The reductions in TG and hs-CRP was 6.6 and 25% respectively with greater reductions in the combination group
- Both therapies were safe

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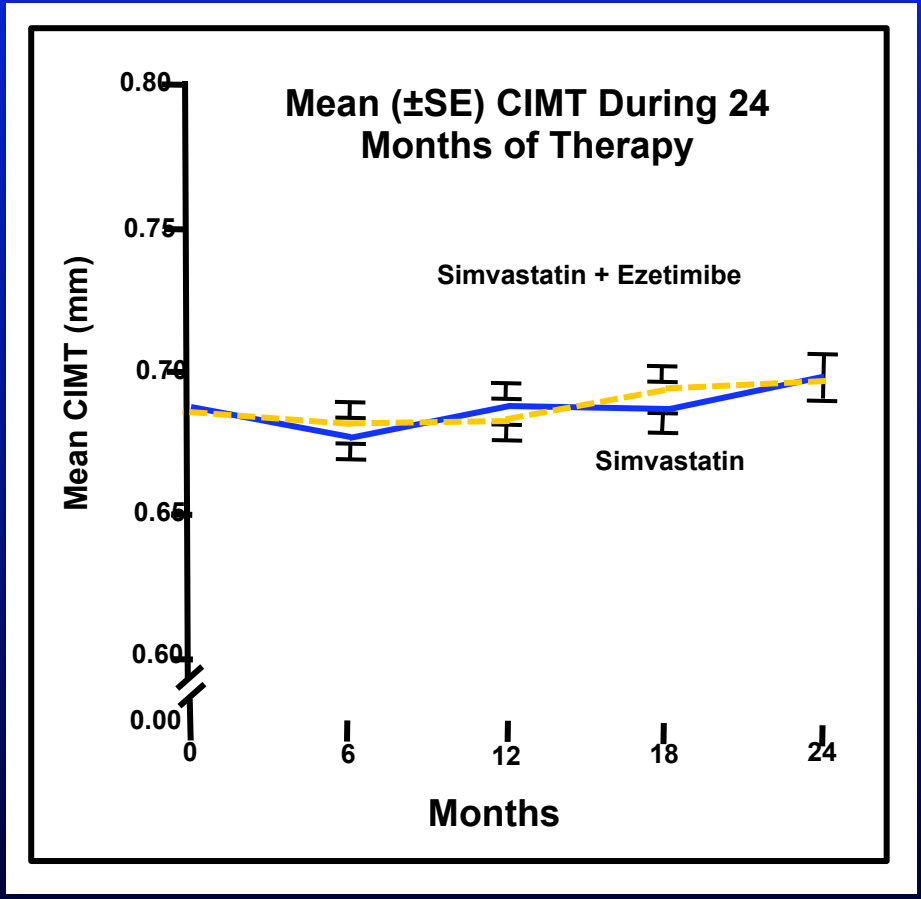

Patients with familial hypercholesterolemia are known to be at greatly increased risk for premature coronary artery disease, accompanied by accelerated progression of intima–media thickness starting in childhood. However, the treatment of patients with familial hypercholesterolemia has witnessed profound changes.

Currently, the majority of patients with familial hypercholesterolemia are treated with high-dose statins starting at an early age. Such therapy can be expected to attenuate the progression of intima–media thickness, as was shown in the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study.

Thus, it is not unexpected that the baseline carotid intima–media thickness in our study was lower than that observed in earlier trials involving patients with familial hypercholesterolemia and in most other previous lipid-modifying trials

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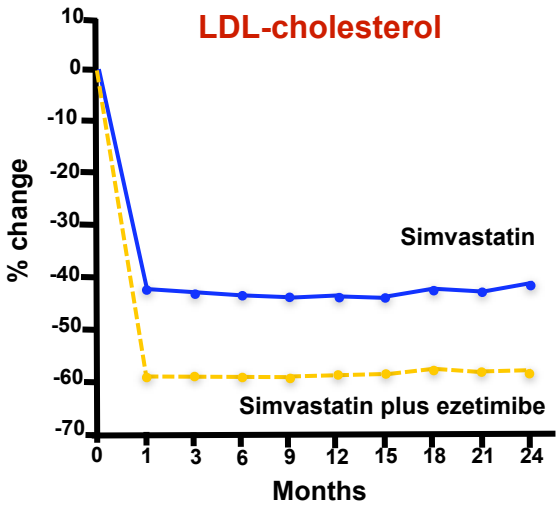

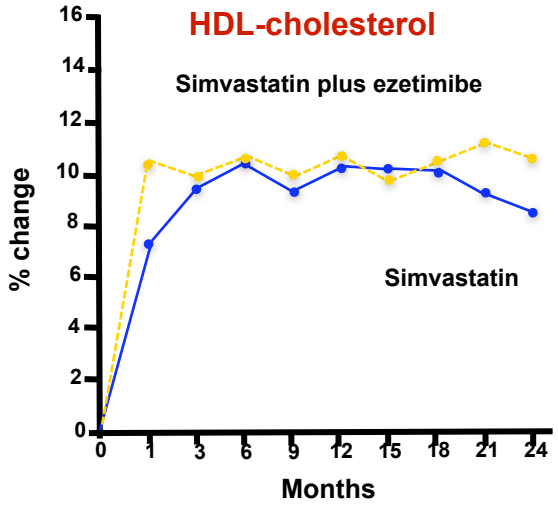

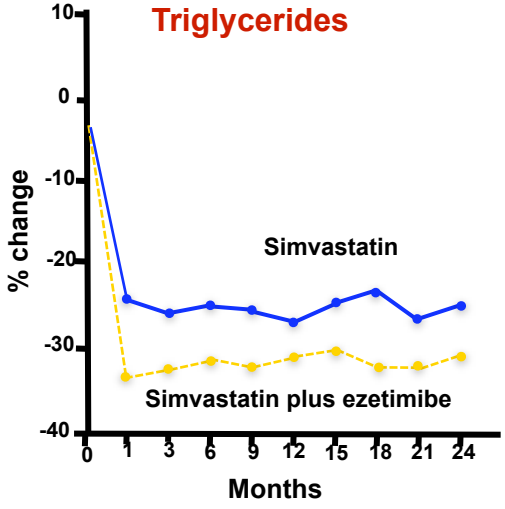

Variable	Simvastatin n=363	Simvastatin plus ezetimibe (n=357)	
C-reactive protein			
Median	-23.5	-49.2	<0.01
Interquartile range	-55.9 to 18.2	-66.7 to -7.4	
Apolipoproteins			
B	-33.1 ± 0.9	-46.7 ± 0.9	<0.01
A-I	6.9 ± 0.8	6.3 ± 0.8	0.56

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Conclusions

In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not result in a significant difference in changes in intima–media thickness, as compared with simvastatin alone, despite decreases in levels of LDL cholesterol and C-reactive protein.

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Understanding Ezetimibe and SimvastatiN in Hypercholesterolemia EnhANces AtherosClerosis REgression (ENHANCE)

- In the ENHANCE trial,4 720 patients with heterozygous familial hypercholesterolemia were randomly assigned to receive 80 mg/day of simvastatin plus either ezetimibe 10 mg/day or a placebo for two years.
- The primary outcome variable was the change from baseline in a composite measure of the CIMT, a surrogate marker for progression of atherosclerosis.
- Despite significantly lower levels of low-density lipoprotein cholesterol (LDL-C; 141 vs. 193 mg/dL), apolipoprotein B (ApoB; 135 vs. 169 mg/ dL), triglycerides (108 vs. 120 mg/dL), and C-reactive protein (CRP; 0.9 vs. 1.2 mg/L) during treatment (*P 0.01 for* all), the group receiving ezetimibe showed a mean change in CIMT (0.011 mm) that was no different (*P 0.29) from* that in the group receiving placebo (0.0058 mm)

Toth P & Maki K. Journal of Clinical Lipidology (2008) 2, 313–317

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- The participants in the ENHANCE trial may have had a lower than expected risk of progression, limiting the ability of the study to demonstrate a benefit.
- Results from a meta-regression conducted by Robinson et al showed that the relationship between LDL-C lowering and the reduction in risk of coronary heart disease and stroke over 5 years of treatment was not dependent on the type of treatment that induced the LDL-C reduction.
- Thus, lowering LDL-C with dietary intervention (five studies), bile acid sequestrants (three studies), ileal bypass (one study) and statin therapy (10 studies) produced similar reductions in risk for a given reduction in LDL-C, arguing against a large influence of “pleiotropic” benefits beyond those of the reduction in LDL-C.

Robinson et al. J Am Coll Cardiol. 2005;46:1855–1862.
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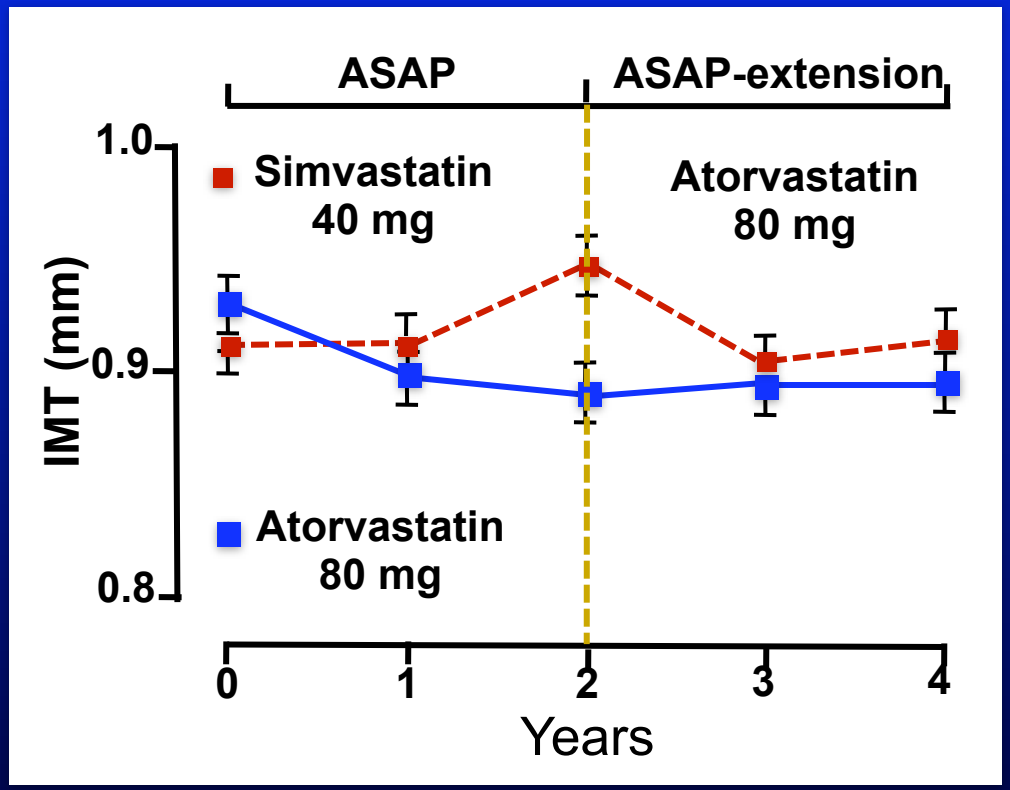
Atorvastatin vs Simvastatin on Atherosclerosis Progression (ASAP) & ASAP-Extension



Mean (SEM) values for carotid intima-media thickness in the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) and ASAP-extension studies.

Blue Squares represent values for subjects who received 80 mg atorvastatin throughout and *red squares* represent values for subjects who received simvastatin 40 mg for the first two years and switched to atorvastatin 80 mg for the second two years.

Van Wissen S et al. Am J Cardiol. 2005;95: 264–266.
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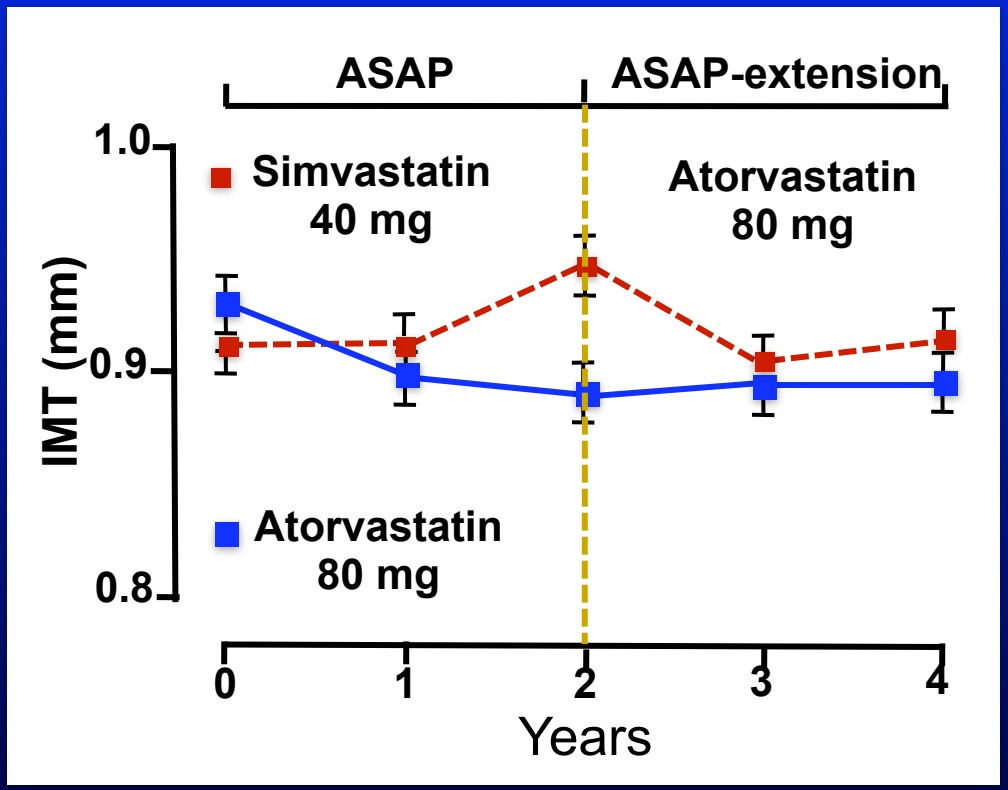
Atorvastatin vs Simvastatin on Atherosclerosis Progression (ASAP) & ASAP-Extension



ASAP-EXTENSION

Subjects who continued on 80 mg/day of atorvastatin had little additional change in CIMT (0.005 mm/year or 0.010 mm over 2 years).

This is nearly identical to the degree of progression observed over 2 years in the simvastatin plus ezetimibe group in the ENHANCE trial (0.011 mm).

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Stop Atherosclerosis in Native Diabetics Study (SANDS)

Stop Atherosclerosis in Native Diabetics Study (SANDS), which investigated the effects of aggressive management of lipids and blood pressure in Native Americans with diabetes, but who were free of coronary heart disease.

In this trial, subjects were assigned to receive standard care for lipids and blood pressure (LDL-C goal 100 mg/dL and systolic blood pressure goal 130 mm Hg) or aggressive treatment (LDL-C goal 70 mg/dL and systolic blood pressure goal 115 mm Hg) for three years. Changes in CIMT and left ventricular mass were the main outcome variables.

Among subjects unable to reach their LDL-C target with statin therapy, ezetimibe was added. The average number of lipid medications used per subject was 1.5, in the aggressive treatment group. Approximately one-third (31%) took ezetimibe, although some did receive other therapies, such as niacin, fibrates, or fish oil.

Mean on-treatment levels of LDL-C (72 mg/dL) and systolic blood pressure (117 mm Hg) in the aggressive treatment arm show that approximately half of subjects were able to achieve and maintain the treatment goals, even in the setting of a clinical trial (68% of subjects had LDL-C at goal for 50% of the visits and 46% had LDL-C at goal for 75% of the visits).

Howard BV et al JAMA. 2008;299:1678 –1689.
Toth P & Maki K. Journal of Clinical Lipidology (2008) 2, 313–317

Stop Atherosclerosis in Native Diabetics Study (SANDS)

►The baseline CIMT value was greater than was the case in ENHANCE (0.808 and 0.797 mm in the aggressive and standard groups, respectively) and CIMT progressed significantly less in the aggressive treatment arm (0.012 vs. 0.038 mm, respectively; P < 0.001) over 36 months. The aggressive treatment group also showed a greater decline in left ventricular mass index (P = 0.03). No significant difference between treatment groups was observed with regard to adverse events related to lipid drug therapy (P = 0.22).

►Subjects in the aggressive treatment group who maintained an LDL-C 73 mg/dL consistently during the last 12 months of treatment showed a greater decline in CIMT cross-sectional area than those who had higher LDL-C levels (0.300 and 0.022 mm^2, respectively).

►When entered into the same model, the probability of a decline in CIMT was significantly related to the decrease in LDL-C (P <0.005), but not to the decline in systolic blood pressure (the opposite was true for left ventricular mass index, where systolic blood pressure change, but not LDL-C change, predicted a reduction).

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- The fact that the comparator arm in the ENHANCE trial showed very little CIMT progression suggests that the ability of an additional therapy to provide incremental benefit may have been limited.
- The situation may therefore have been analogous to the conduct of a cardiovascular event trial in children. No matter how effective the lipid alteration, one would not expect to find a difference between treatments in event rates, because events would be too infrequent in both groups to demonstrate a benefit.
- In the ENHANCE trial, based on the baseline CIMT of 0.070 mm, it is likely that there was very little lipid in the carotid artery wall to mobilize and remove.

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- The authors believe that the net impact of a recommendation to move ezetimibe to the back of the line as a lipid treatment will likely be fewer patients reaching their treatment targets.
- In our view, the lack of additional benefit associated with ezetimibe therapy in the ENHANCE trial is not sufficient evidence to move this agent to a tertiary position in lipid management.

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- For those individuals who do not achieve and maintain their treatment goals on a statin, combination therapy should be considered. All of the drugs available for use in combination with a statin have limitations and no large-scale outcome trials are available to guide use of combination therapy.
- Accordingly, our view is that until such data are available, effects on the lipid profile and tolerability should drive the decision regarding which agent to employ.
- Finally, given the various issues discussed herein, does ENHANCE represent a failed approach to lipid lowering or a failed trial? In the context of hindsight being 20/20, we believe it is the latter.

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►The ENHANCE trial, unlike the METEOR trial, did not require a minimum CIMT or exclude prior statin use (80% of patients in ENHANCE were on statins before the trial). Therefore, a relatively low risk population with higher LDL-C levels may not have CIMT progression.

►In the ENHANCE trial, the CIMT progression was minimal in the two groups for the common carotid artery (0.0012 mm/y for the treatment group and 0.0010 mm/y for the placebo group, compared with 0.0004 mm/y for the treatment group and 0.0088 mm/y for the placebo group in the METEOR trial).

►The CASHMERE trial, which enrolled a low-risk patient population with higher LDL-C levels, also failed to demonstrate a difference between atorvastatin, 80 mg, and placebo, even though atorvastatin has proven hard outcome benefits.

Davidson M , Dembowski E. Current Cardiology Reports 2008, 10: 521 – 525

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- The failure of the ENHANCE and CASHMERE trials to demonstrate a difference on CIMT progression for ezetimibe and atorvastatin, respectively, has called into question CIMT's validity as a surrogate end point.
- An important lesson learned in these trials is the proper selection of higher-risk patients who have significant progression in the control group.
- This same issue is true for hard end-point trials. In a subgroup analysis of relatively low-risk patients in the TNT trial, no difference was noted in events between atorvastatin, 80 mg, and atorvastatin, 10 mg (7% vs 5%)

Davidson M , Dembowski E. Current Cardiology Reports 2008, 10: 521 – 525

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- ASAP: showed there was significant progression (0.03 mm) of atherosclerosis with moderate dose of simvastatin (far more than seen in either arm of ENHANCE
  - Of course moderate dose simvastatin is associated with event reduction: i.e. plaque stabilization (more difficult to assess)
- METEOR: rosuvastatin 40 mg vs placebo on CIMT over 2 years
  - No change in CIMT despite 49% LDL-C reduction
- ORION: plaque assessed by MRI in pts on 40-80 mg rosuvastatin
  - No change in plaque volume, but 41% of lipid-rich necrotic core: i.e. stabilization of plaque
- CIMT cannot assess plaque composition: thus is it the best imaging technique as a proxy endpoint for clinical outcomes

Musunuro K, Blumenthal RS Clin Card 2008;31:288-290

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- Approximately 17% of the internal CIMT images obtained from the study participants were discarded for the final analysis, suggesting some of the retained images were of borderline quality
- Baseline CIMT in ENHANCE was 0.70 mm, significantly less than the baseline mean CIMT in ASAP, which was 0.92 mm.
  - Best explanation is that 80% of ENHANCE participants had been on lipid-lowering therapy which likely altered the natural history of carotid disease and affected how CIMT responded to further therapy

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- There is a large body of literature now showing a correlation between extent of reduction of LDL-C levels and improvement with clinical outcomes in both primary and secondary prevention patients with the caveat that virtually all those trials used statins
- The event-reduction successful JUPITER trial using 20 mg of rosuvastatin, a dose not associated with CIMT regression underscores the notion that changes in LDL-C are a more faithful proxy for clinical outcomes than CIMT
  - Note: Ezetimibe conferred an incremental 26% reduction in mean CRP level

Musunuro K, Blumenthal RS Clin Card 2008;31:288-290