

**Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk
Patients with primary hypercholesterolemia:
A randomized, double-blind, active-controlled, multicenter study**

BACKGROUND:

- Despite lipid-lowering with the use of statins, many patients with high cardiovascular risk and/or severely elevated LDL-C do not achieve target LDL levels recommended by currently treatment guidelines.
- LDL reductions beyond what can be achieved with statins alone are recommended for many patients. Clinical trials have demonstrated that combining ezetimibe with a statin more effectively lowers LDL-C compared to a statin alone. Furthermore, combining ezetimibe with simvastatin has been shown to lower LDL-C more than doubling the statin dose in patients with hypercholesterolemia, patients who are at high risk for CHD, and patients with diabetes.

OBJECTIVE:

- The objective of this study was to assess the efficacy and tolerability profile of switching to ezetimibe/simvastatin combination compared to doubling the baseline atorvastatin dose to 40 mg in high cardiovascular risk subjects with primary hypercholesterolemia and not at LDL-C goal of <100 mg/dL with atorvastatin 20mg after 6 weeks of treatment.

METHODS:

- **Design:** Randomized, double-blind, active-controlled, 2-arm (parallel), multicenter study.
- **Duration:** 6 weeks
- **Inclusion Criteria:**
 - Adults 18-79 years of age at high risk for CHD with primary hypercholesterolemia.
 - Taking atorvastatin 20 mg or another less potent lipid-lowering therapy 6 weeks prior to the start of the study
 - Those not being treated with a statin and/or ezetimibe.
- **Exclusion Criteria:**
 - Taking simvastatin 80mg, atorvastatin 40 or 80 mg, or rosuvastatin 10, 20, or 40 mg
 - Taking other Rx or OTC drugs with the potential to produce significant changes in lipids
 - Taking drugs known to interact with statins.
 - Females who were pregnant or lactating
- **Primary endpoints:** Percent change from baseline LDL-C
- **Secondary endpoints:** Attainment of LDL-C targets, percent change from baseline in other lipids, lipid ratios, and high-sensitivity C-reactive protein after 6 weeks of treatment.
- **# enrolled per group:** 250 patients were randomized. 120 patients received ezetimibe/simvastatin 10/40mg and 130 patients received atorvastatin.
- **Drug Regimen:** During a 5 week run-in period, subjects received open label atorvastatin 20mg. At the end of the run-in period, subjects were randomized in a 1:1 ratio to atorvastatin 40mg or ezetimibe/simvastatin 10/40mg.
- **Power:** 95% power to detect a treatment difference of 10% change from baseline between ezetimibe/simvastatin 10/40 mg and atorvastatin 40 mg assuming a standard deviation of 20% at an $\alpha = 0.05$.
- **Data Handling:** Intent to treat analysis

RESULTS:

- **Number of patients completing study:** 116 in ezetimibe/simvastatin group; 125 in atorvastatin group.
- **Primary outcome measure:** ezetimibe/simvastatin 10/40 mg resulted in greater reductions in LDL-C levels compared with doubling the dose of atorvastatin to 40 mg (-26.8% vs -11.8%; $p < 0.001$)
- **Secondary outcome measures:** ezetimibe/simvastatin 10/40mg treatment resulted in significantly greater reductions in TC ($p < 0.001$), non-HDL-C ($p < 0.001$), Apo B ($p = 0.002$), Apo A-I ($p < 0.001$), and all lipid ratios (all

p<0.001. There were no significant differences between treatments in change from baseline in triglycerides (p=0.593), HDL-C (p=0.211), or CRP (p=0.785).

- **Authors Conclusions:** Switching to ezetimibe/simvastatin 10/40mg resulted in greater reductions in LDL-C, TC, non-HDL-C, Apo B, and Apo A1 than atorvastatin 20mg. No significant differences in triglycerides, HDL-C, or CRP were found.

STRENGTHS

- Gold standard study design
- Statistical tests used and power
- Data handling methods
- Minimal dropouts

LIMITATIONS

- Funding by Merck caused potential bias
- It is unknown where subjects were enrolled from or how many patients from each study site (country of origin) were included in randomization.
- Unequal assignment of subjects into groups based on baseline LDL-C values.
- Inclusion/exclusion criteria could be better explained
- Possible unblinding

CONCLUSIONS

- Overall, Vytorin may be an effective option for patients not currently achieving cholesterol goals. Health care providers should take into account patient specific cholesterol goals and what medications they are currently taking before switching to Vytorin.
 - Vytorin may only be useful for lowering LDL-C in patients between the ages of 18 and 79, with LDL-C levels greater than 100, who are currently being treated with atorvastatin 20mg.
 - Vytorin is not effective at lowering triglycerides or raising HDL-C. Other medications should be used in patients with high triglycerides or low HDL.
 - This study cannot be used to determine if switching to Vytorin is beneficial in patients taking simvastatin 80mg, atorvastatin 40 or 80mg, or rosuvastatin 10,20, or 40mg.
 - Based on this study alone, it is unknown whether patients taking other statins, such as lovastatin or pravastatin, may benefit from Vytorin.
 - Switching to Vytorin may not be theoretically beneficial in patients required to take itraconazole, erythromycin, and protease inhibitors, due to increased plasma levels of statins.
- Future studies need to be conducted that are not funded by the drug manufacturer to validate the full cholesterol lowering benefits of Vytorin. Since Vytorin not available as generic, further cost-benefit studies should be conducted as well.

Reference: Paul Kah Hing Ling, Fernando Civeira, Andrei Gheorghe Dan, et al. "Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study." *Lipids in Health and Disease*. 1/2012; 11(1):18

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