Aggressive Lipid-Lowering Therapy for Hypercholesterolemia

Smilde TJ, van Wissen S, Wollershim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP): a prospective randomised, double-blind trial. Lancet 2001:357;577–81.

Study Overview

Objective. To determine whether aggressive lipid lowering has greater effects than conventional lipid lowering on intermediate outcomes of atherosclerotic vascular disease.

Design. Double-blind, randomized, clinical trial. Analysis was by intention to treat.

Setting and participants. Between 1997 and 1998, patients aged 30 to 70 years with familial hypercholesterolemia were recruited for this multicenter European study. Eligible patients were previously untreated or treated with serum low-density lipoprotein (LDL) cholesterol levels remaining higher than 4.5 mmol/L. Of the 325 subjects included in the analysis, 61% were women. Participants had a mean age of 48 years, mean body mass index of 26 kg/m^2, and mean blood pressure of 131/79 mm Hg. 31% of patients had known cardiovascular disease, 32% smoked, and 52% used concomitant medications. These characteristics were equally distributed between treatment groups.

Intervention. After an 8-week placebo run-in period, during which all lipid-lowering drugs were discontinued, patients received either atorvastatin 40 mg or simvastatin 20 mg once daily, with matching placebo (ie, 2 tablets per day). After 4 weeks, doses of each agent and matching placebo were doubled (4 tablets per day). Patients remained on this dosage for 2 years. In both groups, a cholesterol-binding resin was added to treatment if a patient's serum cholesterol level remained higher than 8.0 mmol/L on 2 consecutive visits after a maximal dose of study medication was reached.

Main outcome measures. The primary endpoint was change in carotid intima media thickness (IMT) over 2 years. Changes in lipid indices (total, LDL and HDL cholesterol levels; triglycerides; apolipoprotein B-100; and lipoprotein [a]) were secondary outcomes.

Main results. 86% of patients completed the study. Noncompleters dropped out for a wide variety of reasons, including increased transaminases (1 patient in each study group), muscle ache (2 in each group), insufficient response to treatment (7 in the simvastatin group and 1 in the atorvastatin group), death (3 patients total; 2 died from cardiovascular disease), transient ischemic attack (1 in the atorvastatin group), and unstable angina pectoris (2 in the simvastatin group and 1 in the atorvastatin group). The remaining reasons likely did not result from adverse effects of medication or hypercholesterolemia.

After 2 years, patients taking atorvastatin showed an IMT regression (mean, –0.031 mm [95% confidence interval {CI}, –0.007 to –0.055]), while IMT increased in patients taking simvastatin (mean, 0.036 mm [95% CI, 0.014 to 0.058]). These changes differed significantly between groups (P = 0.0001). IMT regression was observed among 66% of atorvastatin patients and 42% of simvastatin patients. In addition, atorvastatin had a greater effect on LDL cholesterol (changes from baseline, –4.32 mmol/L [–50.5%] in the atorvastatin group versus –3.51 mmol/L [–41.2%] in the simvastatin group; P = 0.0001) and triglyceride levels (–0.64 mmol/L [–29.2%] versus –0.44 mmol/L [–17.7%], respectively; P = 0.0023). LDL cholesterol was reduced below 3.0 mmol/L in 27% of atorvastatin-group members compared with 7% of simvastatin-group members. 25 simvastatin and 4 atorvastatin patients also received resin therapy.

Conclusion. Aggressive lipid lowering in patients with familial hyperlipidemia may increase the likelihood of carotid IMT regression.

Commentary

This study was generally well designed; however, as with all studies using intermediate endpoints that have no intrinsic value for patients, results must be considered as preliminary. Smilde and colleagues note that published data support a strong correlation between carotid IMT and cardiovascular outcomes [1–3]. Yet the influence of statins extends well be-

yond their effects on IMT. Thus, Smilde et al may either over- or underestimate benefits associated with aggressive lipid lowering.

Applications for Clinical Practice

This study extends results from the Post Coronary Artery Bypass Graft (PCABG) trial [4], which found that aggressive lipid-lowering therapy decreased progression of atherosclerotic disease in saphenous vein grafts and reduced need for revascularization compared with moderate lipid lowering. Of note in the PCABG study, mean serum LDL cholesterol was just under 100 mg/dL in the aggressive-therapy group, while the moderate therapy group had a mean LDL level of around 130 mg/dL. These studies highlight National Cholesterol Education Program guidelines. Ultimately, clinicians should strive to reach guideline goals and treat patients as aggressively as necessary without causing harm.

References

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