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## ACAT inhibition and progression of carotid atherosclerosis. The CAPTIVATE trial

The single most effective, cost-effective, and safest method to reduce CVD risk and events is cholesterol-lowering therapy, especially by statins. Research efforts continue to be directed at additional targets for treatment.

One potential target is the inhibition of intracellular enzyme of the acyl coenzyme A: cholesterol acyltransferase (ACAT), which is key to controlling the accumulation of cholesterol within cells, including macrophages and the arterial wall. Pactimibe, an ACAT inhibitor, was developed to assist in the prevention of CV disease. The CAPTIVATE<sup>1</sup> (Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition Treatment Effects) was a prospective, randomized, stratified, double-blind, placebo-controlled study, which evaluated the effect of pactimibe 100 mg/d on the progression of carotid atherosclerosis evaluated by ultrasound intima-media thickness (CIMT). A total of 892 patients with heterozygous familial hypercholesterolemia participated in the study. Pactimibe was added to a standard treatment of familial hypercholesterolemia. LDL-C increased on pactimibe significantly by 7.3% compared with 1.4% in the placebo group.

The CAPTIVATE<sup>1</sup> study was terminated prematurely after a follow-up of 15 months. Pactimibe had no effect on annual progression of carotid atherosclerosis, as assessed by changes in maximum CIMT; however, the less variable mean CIMT measurement revealed an increase in patients treated by pactimibe vs placebo. Results are shown in the *Table*.

**Table. Baseline, 12-Months follow-up for maximum and mean CIMT in the CAPTIVATE<sup>1</sup> study.**

Variable	Placebo (mean, SD)	Pactimibe (mean, SD)	P value
Baseline			
Maximum CIMT	0.927 (0.185)	0.937 (0.224)	0.51
Mean CIMT	0.775 (0.141)	0.785 (0.167)	0.41
12 mo follow-up			
Maximum CIMT	0.940 (0.199)	0.955 (0.223)	0.36
Mean CIMT	0.781 (0.146)	0.804 (0.165)	0.05

The annual progression of maximum CIMT showed no difference between both groups (difference from baseline at 12 months being 0.004, 95% CI -0.023 to 0.015 mm,  $P=0.64$ ), however the annual progression of the mean CIMT showed a significant difference between groups as greater relative mean CIMT increase was observed in patients receiving pactimibe (difference -0.014, 95% CI -0.927 to 0.000 mm,  $P=0.04$ ).

Serious adverse events were reported more frequently in patients treated by pactimibe (10.0% vs 7.7%,  $P=0.24$ ). Nonfatal MI occurred also more frequently in patients receiving pactimibe 6/443, 1.4% vs 0% in the placebo group ( $P=0.03$ ) and also the composite of cardiovascular death, MI, and stroke has been observed significantly more frequently in the pactimibe group (10/443 – 2.3% vs 1/438 – 0.2%;  $P=0.01$ ).

In the parallel ACTIVATE<sup>2</sup> (ACAT Intravascular Atherosclerosis Treatment Evaluation) study published previously, the effects of pactimibe were studied in a group of patients with established coronary artery disease using intravascular coronary ultrasound. Although the primary efficacy variable defined as the change in percentage atheroma volume was neutral, both major secondary efficacy measures showed that less progression of atherosclerosis was present in the placebo group than in the pactimibe group.

The A-PLUS study<sup>3</sup> with a similar design to the ACTIVATE study investigated the effect of ACAT inhibitor avasimibe. Avasimibe tended to modestly increase the plaque burden and significantly increased LDL-C by 8% to 11%.

**These negative results of ACAT inhibitors are in contrast with the positive experimental results. The explanation is not clear. A plausible explanation is that inhibition of ACAT-1 leads to the accumulation of free cholesterol to toxic levels in the macrophages, leading to cell death.<sup>4</sup>**

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**References:** 1. The CAPTIVATE Randomized Trial. *JAMA*. 2009;301:1131-1139. 2. Nissen SE et al. *N Engl J Med*. 2006;354:1253-1263. 3. Tardif JC, et al. *Circulation*. 2004;110:3372-3377. 4. Warner GJ et al. *J Biol Chem*. 1995;270:5772-5778.

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