



56th Annual Scientific Session of the American College of Cardiology (ACC)

New Orleans, LA, USA  
24 - 27 March 2007

**Sunday 25 March 2007**

ACC.07 late breaker: Further challenges for PPAR- $\alpha$  agonist therapy, but statin pre-treatment before percutaneous coronary intervention shows benefit

MedWire – ACC.07 (New Orleans, LA, USA) – March 25, 2007: Any remaining optimism regarding the use of potent, selective, peroxisome proliferator-activated receptor alpha (PPAR- $\alpha$ ) agonists to stabilize atherogenic dyslipidemia or hypercholesterolemia with elevated low-density lipoprotein cholesterol (LDL-C) was dashed today as disappointing results were announced. However, the results of the Atorvastatin for Reduction of Myocardial Damage During Angioplasty (ARMYDA-ACS) study show that statin pre-treatment is of benefit in early percutaneous coronary intervention (PCI).

**Safety and efficacy of LY5: Results from two trials**

*Dr. Steven Nissen, Cleveland Clinic Lerner School of Medicine, Cleveland, OH, USA*

Reporting the results of two randomized controlled trials evaluating the use of the PPAR- $\alpha$  agonist LY5 18674 (LY5), Dr. Nissen noted that LY5 is approximately 1000 times more potent than fenofibrate, which has been shown to markedly reduce levels of serum triglycerides and to modestly increase levels of high-density lipoprotein cholesterol (HDL-C).

In the first trial, Dr. Nissen and colleagues studied 309 patients with atherogenic dyslipidemia. This was defined as having HDL-C levels of <45 mg/dL in men and <50 mg/dL in women; triglyceride levels of between 150 mg/dL and 600 mg/dL, and low density lipoprotein cholesterol (LDL-C) levels of >160 mg/dL. Patients were randomized to screening for up to 8 weeks followed by 4 weeks placebo plus therapeutic lifestyle intervention. This was followed by treatment with LY5 (10  $\mu$ g, 25  $\mu$ g, 50  $\mu$ g, or 100  $\mu$ g), fenofibrate (200 mg), or placebo for 12 weeks in those that did not respond to lifestyle interventions.

In the second trial, 304 patients with hypercholesterolemia were screened for up to 6 weeks and then randomized to treatment with atorvastatin 10 mg or 40 mg or placebo for 4 weeks. This was

followed by treatment with LY5, 10 µg or 50 µg, for 12 weeks. Follow-up was conducted in both trials for roughly 2–4 weeks. Hypercholesterolemia was defined as LDL-C levels of 100–160 mg/dL if concomitant statin therapy was being taken, or as LDL-C levels of 130–190 mg/dL in statin-naïve patients.

Dr. Nissen reported that in atherogenic dyslipidemic patients, both fenofibrate and LY5 treatment led to marked reductions in triglycerides and modest improvements in HDL-C. However, LY5 treatment did not yield a statistically significant advantage compared to fenofibrate, although a trend toward greater reduction was seen at the 50 mg dose of the PPAR- $\alpha$  agonist.

Dr. Nissen added that an unusual u-shaped dose-response pattern was observed in patients receiving LY5, with the 25 µg dose producing the best improvement, and higher doses, in particular the 100 µg dose, producing almost no improvement.

He said that both LY5 and fenofibrate treatment was well-tolerated, although LY5 had a noticeable additional 'safety signal'; increases in serum creatinine exceeding the upper limits of normal (ULN) were noted in 35% to 38% of patients on LY5.

Dr. Nissen commented that among hypercholesterolemic patients, the 10 µg and 50 µg doses of LY5 monotherapy significantly:

- reduced triglyceride levels by 36.9% and 37.5%, respectively;
- raised HDL-C by 15.0% and 12.5%, respectively, and;
- reduced LDL-C by 13.2% and 15.8%.

However, "the combined effects of atorvastatin and LY5 yielded statistically significant large reductions of triglycerides that exceeded 40% for the 10 µg dose and 50% for the 50 µg dose."

When given with atorvastatin or placebo, LY5 also resulted in an incremental 6% to 18% increase in HDL-C. Dr. Nissen emphasized that while combination therapy also raised HDL-C by 0.6% to 11.9%, it importantly had no additional effects on LDL-C. Up to 22% patients in this trial similarly experienced increases serum creatinine exceeding ULN.

Noting the disappointing results in both trials, Dr. Nissen said that "these data demonstrate the enormous challenges in developing new PPAR [agonist] agents."

He added that over the past decade, nearly all PPAR agonists had been discontinued for investigation due to various toxicities, but that there have been few if any publications and further, none had detailed the reasons for discontinuation of development."

In the panel discussion that followed, Dr. Nissen said virtually every PPAR agonist that he is aware of has had some mixture of a fairly prominent toxicity with beneficial effects. He suggested that in moving forward, caution should be taken when conducting dose ranging trials before major outcomes research is undertaken.

## **Time to reconsider statin use just prior to elective PCI?**

*Dr. Germano Di Sciasio, Campus Bio-Medico University, Rome, Italy*

It appears that administration of high-dose atorvastatin just prior to early elective PCI improves clinical outcomes in patients with acute coronary syndromes (ACS), according to the latest results of the ARMYDA-ACS study. These data support the findings of an earlier ARMYDA trial, which demonstrated an 81% risk reduction in periprocedural myocardial infarction (MI) in patients with stable angina who received 40 mg atorvastatin during PCI.

Presenter and senior investigator Dr. Germano Di Sciasio emphasized that despite observational data suggesting a lower incidence of periprocedural events such as myonecrosis, and improved survival, statins are rarely used by interventional cardiologists.

Consequently, he and his colleagues randomized 171 patients to 80 mg atorvastatin loading dose administered 12 hours before coronary angiography followed by a further 40 mg dose approximately 2 hours before the procedure or placebo. Thereafter, all patients received long-term atorvastatin (40 mg/daily) treatment.

Dr. Di Sciasio said that by the study's 30 day endpoint, only 5% of patients in the atorvastatin arm compared with 17% of patients in the placebo arm experienced a major adverse cardiac event (MACE) in the form of heart attack, death or target vessel revascularization ( $p=0.01$ ).

"The reduced incidence of MACE was largely driven by post-procedural MI among the study patients," he said (5% for atorvastatin versus 15% for placebo), adding that the data, which clearly demonstrated significantly better event-free survival at 30 days among patients receiving active treatment, were confirmed by Kaplan-Meier analysis.

Multivariable analysis also indicated an 88% risk reduction of MACE at 1 month in treated patients.

"While the possible mechanisms underlying early protection remain unclear, observed benefits are likely due to atorvastatin's cholesterol-lowering effects as well as its ability to reduce arterial inflammation and improve blood vessel functioning" commented Dr. Di Sciasio.

He concluded by emphasizing that the study's most important finding was that short-term atorvastatin load just prior to coronary intervention in patients with ACS appears to improve clinical outcomes.