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PLAC® Lp-PLA$_2$

Medical Affairs Bulletin

Reduction in Lp-PLA$_2$ activity may account for over half of the benefits of pravastatin and can reduce coronary heart disease (CHD) risk.

This bulletin summarizes the results of a sub-study from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study as published by White HD et. al in the Journal of the American Heart Association[1].

Study Design

The LIPID study enrolled 9014 patients with stable coronary disease with initial cholesterol levels between 155 and 271 mg/dl. (4 to 7 mmol/L). Patients were randomized to either 40 mg of pravastatin or placebo and were followed for secondary coronary heart disease events for over six years. Pravastatin treatment resulted in a 25% reduction in LDL-cholesterol (LDL-C) vs. placebo and a 29% reduction in all cardiovascular events.[2]

A sub-study from the LIPID Study (n=6657) was designed to address the following questions:

- What is the effect of pravastatin treatment on Lp-PLA$_2$ levels?
- Does baseline Lp-PLA$_2$ activity predict coronary events (CHD death or nonfatal MI)?
- Is the pravastatin effect on Lp-PLA$_2$ associated with disease outcomes?

For this analysis, baseline and on-treatment Lp-PLA$_2$ levels were divided into quartiles.

Lp-PLA$_2$ levels were measured on all baseline and 1-year samples using the diaDexus clinical trial activity assay, which is now a CE marked test.

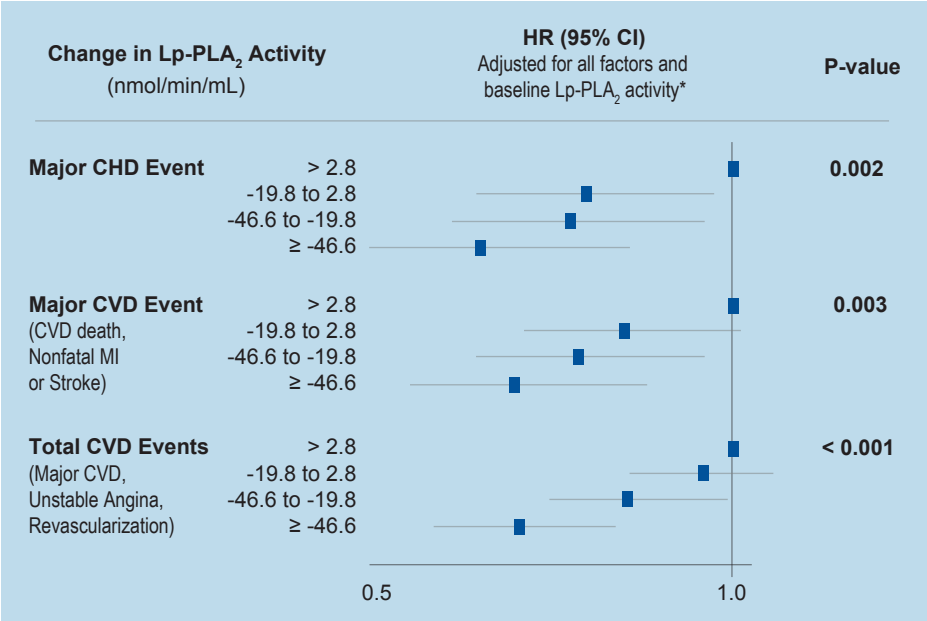
Reduction in Lp-PLA$_2$ activity during the first year was a highly significant predictor of CHD events, independent of change in LDL cholesterol, and may account for over half of the benefits of pravastatin in the LIPID study.

Study Results

- Pravastatin 40 mg/day reduced Lp-PLA$_2$ activity 16% on average, from 262 to 218 nmol/min/ml. There was a greater absolute benefit with pravastatin among those with higher baseline levels of Lp-PLA$_2$.
- The median baseline Lp-PLA$_2$ value was 262 nmol/min/ml in patients who had experienced a myocardial infarction 3 to 36 months prior to enrollment in the study. The median LDL-C level at enrollment was 152 mg/dL (3.9 mmol/L).
- Lp-PLA$_2$ reduction with pravastatin accounted for 59% of the treatment effect, while LDL-C reduction accounted for 44% of the treatment effect.

Clinical Conclusions

- The extent of reduction of Lp-PLA$_2$ with pravastatin treatment predicted CHD death and MI and total CVD events, even after adjustment for all baseline factors. The reduction of Lp-PLA$_2$ with statin therapy, independent of baseline Lp-PLA$_2$ levels, can help determine the effectiveness of statin therapy and predict the reduction in CVD events.
- Baseline Lp-PLA$_2$ levels predicted CHD death after full adjustment for all baseline risk factors.
- Tracking the reduction in Lp-PLA$_2$ and LDL-C in response to therapy, is a better indicator of future CVD events than the reduction of LDL-C levels alone.



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Clinical Implications

It is well understood that reduction in LDL cholesterol (LDL-C) is a key mechanism by which statins reduce risk. This study proves that other mechanisms are also important—reduction in Lp-PLA$_2$ activity during the first year may account for over half of the benefits of pravastatin in the LIPID Study. There was a 24% (P<0.001) reduction in death from CHD and a 22% (P<0.001) reduction in overall mortality.

The patients who had the biggest drop in Lp-PLA$_2$ activity levels (by quartile analysis) on statin therapy were most likely to have the greatest benefit, with fewer CHD deaths and heart attacks, as well as significantly fewer total cardiovascular disease events (p<0.001).

This study suggests that, in addition to measuring and treating LDL-C, Lp-PLA$_2$ should also be monitored, prior to and during treatment, to assess the potential efficacy of statin therapy and to help direct cardiovascular disease (CVD) risk management.

"...reduction in Lp-PLA$_2$ activity during the first year may account for over half of the benefits of pravastatin in the LIPID Study...these results elevate Lp-PLA$_2$ to that of a risk factor for CHD."

Harvey White
Lead Investigator, LIPID Study

A biomarker will become a risk factor when it plays a causal role in the disease pathway and can be modified by lifestyle changes and drug treatment

Adjusted Factors

HR and 95% CI are adjusted for baseline variables: treatment, sex, stroke, diabetes, smoking, hypertension, total cholesterol, apolipoprotein B and A1, HDL-C, age, nature of prior ACS, timing of coronary revascularization, SBP, atrial fibrillation, eGFR, BMI, dyspnea class, angina grade, WBC, peripheral vascular disease, triglycerides, fasting glucose, aspirin at baseline and change in LDL. ACS indicates acute coronary syndromes; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, HDL cholesterol; HR, hazard ratio; Lp-PLA$_2$, lipoproteinassociated phospholipase A$_2$; MI, myocardial infarction; SBP, systolic blood pressure; WBC, white blood cell count.

References

1. White, HD, et al. "Changes in Lipoprotein-Associated Phospholipase A$_2$ Activity Predict Coronary Events and Partly Account for the Treatment Effect of Pravastatin: Results From the Long-term Intervention with Pravastatin in Ischemic Disease Study". J Am Heart Assoc. 2013;2:e000360 doi: 10.1161/JAHA.113.000360)
2. "Prevention of Cardiovascular Events and Death with Pravastatin in patients with coronary heart disease and with a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin and Ischaemic Disease (LIPID) Study Group." NEJM 339:19,1349-1357

Ask your Diazyme Representative for information on the PLAC® Test for Lp-PLA$_2$ Activity for your practice.

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