

# Diagnostic Tests

## What Physicians Need to Know

### PLAC Test for Lp-PLA<sub>2</sub> Activity to Predict Coronary Heart Disease

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The PLAC test is a blood test used to measure serum activity of lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>), an enzyme that breaks down oxidized low-density lipoprotein in the vascular wall. Higher levels of Lp-PLA<sub>2</sub> activity are thought to promote atherosclerotic plaque formation.<sup>1</sup> The PLAC test was approved by the U.S. Food and Drug Administration for this indication in 2014.<sup>2</sup>

Test	Indication	Population, age range, and frequency	Cost*
PLAC test for Lp-PLA <sub>2</sub> activity	Predicting coronary heart disease risk in conjunction with clinical and other risk assessments	Adults 45 years and older with no history of cardiovascular events Frequency uncertain	\$121

Lp-PLA<sub>2</sub> = lipoprotein-associated phospholipase A<sub>2</sub>.  
\*—Payment rate according to Healthcare Bluebook.<sup>14</sup>

#### Accuracy

In a prospective multiethnic cohort of 5,456 asymptomatic patients followed over a median of 10.2 years, Lp-PLA<sub>2</sub> activity was associated with an increased risk of incident cardiovascular disease. Patients included persons with baseline subclinical vascular disease (n = 3,228 [450 events]; hazard ratio [HR] = 1.17 [95% CI, 1.06 to 1.30]) and without subclinical disease (n = 2,228 [66 events]; HR = 1.30 [95% CI, 1.01 to 1.68]), as determined by coronary artery calcium score and carotid intima-medial thickness. These associations persisted after adjustment for age, sex, race, and ethnicity. However, when further adjusted for body mass index, diabetes mellitus, smoking status, education, systolic blood pressure, use of antihypertensive medications, total and high-density lipoprotein cholesterol, use of lipid-lowering medications, and C-reaction protein, the associations were no longer significant.<sup>3</sup> The analysis suggested that Lp-PLA<sub>2</sub> activity does not add significant information to the standard cardiovascular risk assessment.

Contrast this with a 2010 collaborative analysis of 18 prospective studies of Lp-PLA<sub>2</sub> activity. A subanalysis (12 studies), representing a

heterogeneous population of 41,121 patients with and without a history of vascular disease and a total of 3,963 fatal and nonfatal cardiovascular events, showed an increased risk of coronary heart disease (CHD) per one standard deviation higher Lp-PLA<sub>2</sub> activity (risk ratio [RR] = 1.10 [95% CI, 1.05 to 1.16]). This association persisted after adjusting for standard risk factors. Other subanalyses showed a similar risk-adjusted association between Lp-PLA<sub>2</sub> activity and vascular death (n = 38,105 [nine studies; 2,689 events]; RR = 1.16 [95% CI, 1.09 to 1.24]) and nonvascular death (n = 37,084 [eight studies; 2,795 events]; RR = 1.10 [95% CI, 1.04 to 1.17]).<sup>4</sup>

There is less evidence to support risk assessment using the manufacturer's suggested binary cut-off of 225 nmol per minute per mL or higher to define high Lp-PLA<sub>2</sub> activity.<sup>5,6</sup> The validation study referenced on the test website and package insert is a published abstract containing only a summary of data from a subanalysis case-cohort study (n = 5,025; including 771 participants with incident CHD and 4,254 without CHD) sampled from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) trial.<sup>7,8</sup> The abstract reports HRs for CHD using sex-specific cut-offs for elevated Lp-PLA<sub>2</sub> activity (defined as greater than 80th percentile): 250 nmol per minute per mL for men and 200 nmol per minute per mL for women. Given that statistically significant differences in Lp-PLA<sub>2</sub> activity between men and

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women have been demonstrated elsewhere, it is unclear why the PLAC test does not also have sex-specific cut-offs.<sup>9,10</sup>

A subanalysis of the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial suggested that the PLAC test binary cut-off is neither sensitive nor specific as a marker of CHD. Baseline Lp-PLA<sub>2</sub> activity levels were measured in 10,439 patients randomized to placebo or rosuvastatin (Crestor) for primary prevention. Lp-PLA<sub>2</sub> activity levels were categorized in quartiles, with the 4th quartile representing Lp-PLA<sub>2</sub> activity levels greater than 222 nmol per minute per mL, similar to the manufacturer's cut-off of 225 nmol per minute per mL. Among the patients randomized to placebo (n = 5,446; 149 primary events at one year of follow-up), the sensitivity and specificity of a baseline Lp-PLA<sub>2</sub> activity in the 4th (highest) quartile were 37% and 75%, respectively. This translates to a positive likelihood ratio (LR+) of 1.48 and a negative likelihood ratio (LR-) of 0.8. Among the patients randomized to rosuvastatin (n = 5,496; 80 events), the sensitivity and specificity were similar, at 31% and 75%; LR+ = 1.24; LR- = 0.92.<sup>11</sup>

### Benefit

There is no clear benefit to using the PLAC test as a binary indicator of high risk or low risk (less than 225 nmol per minute per mL) in addition to other standard cardiovascular risk markers. No studies have demonstrated improved outcomes from using the PLAC test to reclassify a patient from a lower to higher cardiovascular risk level.

Although there is some short-term (one year of follow-up) evidence that pravastatin (Pravachol)-mediated reduction of Lp-PLA<sub>2</sub> activity may have predictive value for future CHD events, the JUPITER trial did not show any predictive benefit of measuring Lp-PLA<sub>2</sub> activity after statin treatment.<sup>11,12</sup> Trials of the direct Lp-PLA<sub>2</sub> inhibitor (darapladib) have not shown improvements in patient-oriented cardiovascular outcomes.<sup>13</sup>

### Harms

Given the lack of consistent patient-oriented outcomes from use of PLAC in risk assessment, as well as the sex-specific differences in Lp-PLA<sub>2</sub> activity that are not accounted for in the test cut-off, there is potential for harm in using it to reclassify a patient's cardiovascular risk. A high PLAC score might lead to the unnecessary and

potentially harmful cardiac testing for further risk stratification, or to unnecessary use of statin medication. Conversely, a low PLAC score might falsely reassure a patient and clinician, thus resulting in underutilization of statins and other measures for primary prevention of cardiovascular events.

### Cost

The estimated cost of the PLAC test for Lp-PLA<sub>2</sub> activity is \$121 according to Healthcare Bluebook.<sup>14</sup> The 2019 Medicare reimbursement rate for the test is \$46.31.<sup>15</sup> In comparison, a standard lipid panel is estimated to cost \$39, with a Medicare reimbursement of \$14.88.<sup>14,15</sup>

### Bottom Line

The PLAC test for Lp-PLA<sub>2</sub> activity provides little additional value beyond standard cardiovascular risk assessment, and any potential benefits are likely outweighed by harms. Current guidelines do not include the PLAC test nor other tests for Lp-PLA<sub>2</sub> activity in risk assessment.<sup>16,17</sup> Other tests with greater utility that are supported by the American College of Cardiology/American Heart Association guidelines for primary prevention include high-sensitivity C-reactive protein, lipoprotein(a), apolipoprotein B, ankle-brachial index, and the coronary artery calcium score.<sup>16</sup>

**The opinions and assertions** expressed herein are those of the author and do not necessarily reflect the official policy or position of the Uniformed Services University of the Health Sciences or the Department of Defense.

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