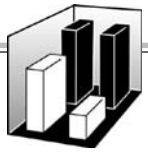
CLINICAL TRIALS REPORT



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High-Sensitivity C-reactive Protein, Lipoprotein-associated Phospholipase A_2, and Outcome After Ischemic Stroke

Elkind MS, Tai W, Coates K, et al.: **High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke.** *Arch Intern Med* 2006, **166:**2073–2080.

Rating: •Of importance.

Introduction: Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) has been associated with risk for first ischemic stroke in prospective case–cohort analyses from the population-based Atherosclerosis Risk in Communities (ARIC) [1] and Rotterdam [2] studies. The relation between inflammatory markers and outcomes after stroke has not been established.

Aims: A population-based incident ischemic stroke follow-up study from the Northern Manhattan Stroke Study was conducted to determine whether Lp-PLA_2 and high-sensitivity C-reactive protein (CRP) were predictive of recurrent stroke, other cardiovascular events, and death in individuals with previous ischemic stroke.

Methods: Lp-PLA_2 and CRP levels were measured in 467 participants with ischemic stroke. These participants were followed-up for a median of 4 years for recurrent stroke, myocardial infarction, vascular death, and death.

Results: Risk for recurrent stroke was increased in individuals in the highest quartile, compared with the lowest quartile, for Lp-PLA_2 (age-, sex-, and race-adjusted hazard ratio [HR], 2.23; 95% CI, 1.14 to 4.39) but not for CRP (HR, 0.74; 95% CI, 0.39 to 1.43). After additional adjustment for traditional risk factors and CRP, risk was attenuated but remained increased for the highest quartile, compared with the lowest quartile, for Lp-PLA_2 (HR, 2.08; 95% CI, 1.04 to 4.18). Risk was not increased for the highest quartile, compared with the lowest quartile, of CRP (HR, 0.67; 95% CI, 0.34 to 1.32). Risk for the composite outcome of recurrent stroke, myocardial infarction, or vascular death was increased in individuals in the highest quartile, compared with the lowest quartile, for Lp-PLA_2 (HR, 1.86; 95% CI, 1.01 to 3.42 in the fully adjusted model) but not for CRP (HR, 0.98; 95% CI, 0.54 to 1.78). However, risk of death was increased in the highest quartile compared with the lowest quartile for CRP (HR, 2.11; 95% CI, 1.18 to 3.75 in the fully adjusted model), but not for Lp-PLA_2 (HR, 1.36; 95% CI, 0.81 to 2.30). Also, CRP, but not Lp-PLA_2, was associated with stroke severity.

Discussion: The investigators concluded that Lp-PLA_2 and CRP may provide complementary information for prognosis after ischemic stroke, with Lp-PLA_2 being a better predictor for recurrent stroke risk and CRP a better predictor for mortality.

Editor's comments

Novel and emerging risk factors for cardiovascular disease (CVD) have been the subject of increasing clinical research, in an effort to improve risk assessment and potentially risk factor reduction for preventing CVD events. Two novel risk factors that have been the focus of research are CRP and Lp-PLA_2. Both risk factors are markers related to inflammation; CRP is an acute phase reactant primarily produced by the liver, whereas Lp-PLA_2 is a macrophage secretory product that may be a link between lipoproteins and vascular inflammation. Observational studies and interventional trials have reported that both CRP and Lp-PLA_2 are associated with CVD events, but existing data are still not conclusive as to how one could use measurement of either CRP or Lp-PLA_2 to improve patient care, and no published clinical trials have examined the effect of reducing CRP or Lp-PLA_2 on clinical events. However, accumulating clinical trial data suggest that inflammatory markers may play a role in identifying patients with increased risk for either initial or recurrent stroke.

An Assessment of Incremental Coronary Risk Prediction Using C-reactive Protein and Other Novel Risk Markers: the Atherosclerosis Risk in Communities Study

Folsom AR, Chambless LE, Ballantyne CM, et al.: **An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the Atherosclerosis Risk in Communities Study.** *Arch Intern Med* 2006, **166:**1368–1373.

Rating: •Of importance.

Introduction: In recent years, interest has increased in the possibility that the addition of novel biomarkers, such as CRP, to existing models, based on traditional risk factors, might improve the prediction of coronary heart disease (CHD) events.

Aims: In an analysis from the ARIC study, CRP and Lp-PLA_2 were among a number of novel biomarkers that were evaluated to determine their potential contribution to CHD prediction, beyond that provided by traditional risk factors.

Methods: Novel markers that included measures of inflammation, endothelial function, fibrin formation, and fibrinolysis were evaluated for potential associations with incident CHD (myocardial infarction, fatal CHD, or coronary revascularization) in a series of case-cohort analyses. The additional contribution of novel biomarkers to traditional risk factors was assessed by the change in the area under the receiver operating characteristic (ROC) curve.

Results: Age-adjusted hazard rate ratio for incident CHD was 1.20 for each 1–standard deviation (SD) increase in CRP and 1.49 for each 1-SD increase in Lp-PLA_2. After adjustment for traditional risk factors, hazard rate ratio for incident CHD was 1.17 for each 1-SD increase in either CRP or Lp-PLA_2. In a model with traditional risk factors, CRP did not increase the area under the ROC curve, whereas Lp-PLA_2 significantly but modestly increased the area under the ROC curve by 0.006.

Discussion: The investigators concluded that routine measurement of the novel risk markers examined in this study was not warranted in all middle-aged US adults to assess risk for CHD.

Editor's comments

In part because of the proven benefit observed in treating patients who are at increased risk for CVD with drugs, such as statins, efforts have been growing to improve CHD risk assessment through the identification of novel risk factors. In this analysis from the ARIC study, both CRP and Lp-PLA_2 were associated with risk for incident CHD, but their value beyond that of traditional risk factors for predicting cardiovascular events in a population of middle-aged Americans was very small. Of the 19 biomarkers studied, only Lp-PLA_2 significantly increased the area under the ROC curve, compared with major risk factors alone, but the increase was modest. Despite the recognition that atherothrombosis is an inflammatory process, measurement of plasma levels of inflammatory markers did not substantially improve population prediction of incident CHD.

The Effect of Including C-reactive Protein in Cardiovascular Risk Prediction Models for Women

Cook NR, Buring JE, Ridker PM: **The effect of including C-reactive protein in cardiovascular risk prediction models for women.** *Ann Intern Med* 2006, **145:**21–29.

Rating: •Of importance.

Introduction: The potential role of the addition of CRP in improving global cardiovascular risk prediction beyond models based on traditional risk factors was assessed in the Women's Health Study.

Aims: Global cardiovascular risk prediction models were developed and compared to determine whether models with CRP improved cardiovascular risk assessment, compared with models without CRP.

Methods: Initially healthy women without diabetes who had baseline measurements of CRP were followed-up for an average of 10 years for incidence of CVD events (myocardial infarction, ischemic stroke, coronary revascularization, and death from cardiovascular causes).

Results: In this analysis, the addition of CRP measurement was reported to improve prediction of CVD events, compared with models using only traditional risk factors, and CRP was found to contribute as much to global risk assessment as the separate contributions of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol but less than the contributions of age, smoking, and blood pressure. The area under the ROC curve was only minimally increased with the addition of CRP to global risk prediction models; the c-index was 0.814 with-

out CRP and 0.812 with CRP in the Adult Treatment Panel III model, and respective c-index values in the Women's Health Study model were 0.815 and 0.813. However, inclusion of CRP in models did improve risk prediction across categorical 10-year risk estimates of less than 5%, 5% to less than 10%, 10% to less than 20%, and greater than or equal to 20% (Framingham risk score as defined by the Adult Treatment Panel III guidelines [3]), particularly among women at intermediate risk; 21% of women categorized as having 10-year risk of 5% to less than 10% and 19% of women categorized as having 10-year risk of 10% to less than 20% were reclassified more accurately when CRP was included in the model.

Discussion: The authors concluded that including CRP in global cardiovascular risk prediction models improved risk classification in women, particularly in those with an estimated 10-year risk of 5% to 20%.

Editor's comments

Similar to the ARIC analysis [4], the area under the ROC curve was only modestly increased with the addition of CRP to global risk prediction models. In the accompanying editorial that compared similar analyses in published population-based studies, CRP was consistently found to add little predictive value to traditional CVD risk factors. The authors estimated that a moderate improvement in the c-statistic would require a multivariable-adjusted odds ratio of 3.4 for the highest quartile, compared with the lowest quartile, of CRP, whereas a marked improvement would require a multivariable-adjusted odds ratio of 6.9 [5]. In the Women's Health Study, inclusion of CRP in models did improve classification of women by 10-year Framingham risk estimates.

This analysis from the Women's Health Study supports the recommendations of a joint statement issued by the Centers for Disease Control and Prevention and the American Heart Association to consider the measurement of CRP for risk stratification of patients at intermediate risk [6]. Unlike low-risk and high-risk patients, for whom treatment strategies are more straightforward, additional information may be helpful to determine the appropriate intensity of preventive treatment in intermediate-risk patients, and novel biomarkers may prove useful in better classifying risk for CHD and stroke in these individuals. In light of the proven effectiveness of some preventive therapies and the reduction in price of statins, which are now generic, the definition of "moderate" risk might be reasonably expanded from 10% to 20%, as defined in the Adult Treatment Panel III guidelines, to 5% to 20%, as in this study.

References

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