

■ THE IMPORTANT ROLE OF INFLAMMATION IN ATHEROSCLEROSIS

Overview. Recent developments in basic and experimental sciences have forced the evolution of the definition of atherosclerosis. Once regarded as a bland lipid storage disease, atherosclerosis is now appreciated as being a dynamic disease involving an ongoing inflammatory response. It is now understood that inflammation plays a fundamental role in mediating all stages of atherosclerosis, from initiation to progression and the associated thrombotic complications.

It is becoming clear that an understanding of the important link between inflammation and atherosclerosis can yield clinically useful predictive and prognostic information. This information may include knowledge about the role of inflammation in atherosclerosis, about the markers indicative of inflammatory processes, and about the known trig-

gers for inflammation. Furthermore, insights into atherosclerosis-associated inflammation may help identify novel therapeutic strategies targeting better outcomes in patients with—or at risk for—this important disease.

Following an overview of inflammation in atherogenesis, this review goes on to identify triggers of inflammation including dyslipidemia, hypertension, diabetes, obesity and infection. A detailed look at inflammation in acute coronary syndromes is then presented, followed by discussions of the correlation between markers for inflammation and adverse prognoses, the prevalence of inflammation, and the implications of these data for preventive strategies.

Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; 105:1135-43.

■ EFFECT OF HIGH-DOSE ATORVASTATIN ON HS-CRP IN THE DALI STUDY

Results. High-dose (80 mg/day) atorvastatin was associated with significant reductions in high-sensitivity C-reactive protein (hs-CRP), a nonspecific marker of inflammation and a strong predictor of cardiovascular risk, compared to low-dose (10 mg/day) atorvastatin and to placebo. Median CRP increased by 6.6% in the placebo group and decreased by 15% and 47% with atorvastatin 10 mg and 80 mg, respectively. The differences between atorvastatin 80 mg and placebo, and between atorvastatin 80 mg and 10 mg, were statistically significant ($p < 0.001$). Furthermore, of subjects with baseline CRP levels > 3.0 mg/L, 56% treated with atorvastatin 80 mg reached a level < 3.0 mg/L compared to 23% of atorvastatin 10 mg subjects ($p < 0.01$) and 17% of placebo subjects ($p < 0.005$).

The overall effect of atorvastatin on CRP was observed to be independent of gender, body mass

index (BMI), leukocytes, fasting glucose levels and interleukin-6 levels, and only 8% of the overall change in CRP was associated with changes in plasma lipids.

Methods. The prospective, double-blind Diabetes Atorvastatin Lipid Intervention (DALI) study randomized 197 subjects with type 2 diabetes mellitus, plasma triglycerides between 1.5 mmol/L and 6.0 mmol/L and total cholesterol between 4.0 mmol/L and 8.0 mmol/L to receive either placebo, atorvastatin 10 mg or atorvastatin 80 mg. Of these subjects, 186 were eligible for this analysis of the effect of treatment on CRP.

Patients did not have manifest coronary artery disease nor history of MI or angina, and were followed for 30 weeks of treatment. Fasting blood samples were collected for analysis at the end of the study period.

van de Ree MA, Huisman MV, Princen HMG, et al, for the DALI Study Group. Strong decrease of high sensitivity C-reactive protein with high-dose atorvastatin in patients with type 2 diabetes mellitus. *Atherosclerosis* 2003; 166:129-35.

■ THE ATHEROGENE STUDY: IMPACT OF INFLAMMATION MARKERS AND STATIN THERAPY ON MORTALITY

Results. Among patients with angiographically diagnosed coronary artery disease (CAD), four determined inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], fibrinogen, von

Willebrand factor [vWF] and leukocyte count) were significantly higher among patients who died during follow-up than among survivors. Of these markers, only hs-CRP was assessed to be a significant predictor of CAD death in a multivariate, backward stepwise Cox regression model. Even among patients not treated with a statin

whose hs-CRP levels were not elevated, cardiac death was not increased compared to statin-treated patients (illustrating the strength of this inflammation marker as a prognostic indicator).

The predictive value of hs-CRP (and of the other three markers) was lost in statin-treated patients, in whom the levels of all four inflammatory markers were lower. Among subjects in the top quartile of hs-CRP, those not treated with a statin were at 2.3 times greater risk for fatal coronary events. Overall, compared to the absence of statin therapy, statin treatment was associated with a 51% reduction in relative risk of fatal coronary events ($p = 0.004$).

Methods. A total of 1,246 subjects who had undergone coronary angiography and been

■ CARDIOVASCULAR RISK IN PATIENTS WITH CHD: THE ROLE OF HS-CRP

Overview. High levels of high-sensitivity C-reactive protein (hs-CRP) have been correlated in many prospective studies with increased cardiovascular risk. Compared to other known markers of inflammation, hs-CRP yields results from standardized measurement methods that are reproducible and reliable. In clinical practice, these characteristics make hs-CRP valuable in identifying high-risk patients and monitoring the activity of inflammatory disease, and as a possible therapeutic target in altering the component of the disease process pertaining to inflammation.

This review briefly discusses atherosclerosis as a chronic inflammatory disorder and hs-CRP as an inflammatory marker before outlining the impor-

■ CRP AND LDL-C AS PREDICTORS OF CARDIOVASCULAR EVENTS

Results. C-reactive protein (CRP) level was a stronger predictor of cardiovascular events than low-density lipoprotein cholesterol (LDL-C) level. The adjusted relative risks of first cardiovascular events (myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes) among subjects, by increasing CRP quintile compared with the lowest quintile, were 1.4, 1.6, 2.0 and 2.3 ($p < 0.001$). For LDL-C, the adjusted relative risks (also by increasing quintile compared to lowest quintile) were 0.9, 1.1, 1.3 and 1.5 ($p < 0.001$). Similar results were seen for each component of this composite endpoint.

The two inflammatory markers were minimally

enrolled in the AtheroGene Study's cardiovascular registry were eligible for this analysis. Of these, 1,240 were followed for a median of 2.9 years; information about causes of death or cardiac events was obtained from hospital or general-practitioner charts. Blood samples were collected before coronary angiography was performed; 417 subjects had been treated with a statin for a minimum of four weeks at the time of sample collection.

Bickel C, Rupprecht HJ, Blankenberg S, et al, for the AtheroGene Investigators. Relation of markers of inflammation (C-reactive protein, fibrinogen, von Willebrand Factor, and leukocyte count) and statin therapy to long-term mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 2002; 89:901-908.

tant role of hs-CRP in stratifying the risk of patients with coronary heart disease and examining some preventive measures that may attenuate cardiovascular risk in these patients by reducing hs-CRP. A review of evidence in stable and unstable angina, acute myocardial infarction, coronary revascularization is provided. Furthermore, the association between other cardiovascular risk factors (such as smoking, hyperlipidemia, diabetes and obesity) and hs-CRP is discussed. Finally, measures aimed at modulating inflammatory response, including antiplatelet therapies and lipid-altering therapies, are reviewed in terms of their ability to reduce cardiovascular risk and, specifically, affect hs-CRP levels.

Rosenson RS, Koenig W. High-sensitivity C-reactive protein and cardiovascular risk in patients with coronary heart disease. *Curr Opin Cardiol* 2002; 17:325-31.

correlated ($r = 0.08$), leading to the conclusion that each identifies a separate high-risk group and the finding that screening for both provided better prognostic information than screening for either marker alone.

Methods. CRP and LDL-C measurements were made at baseline in 27,939 apparently healthy women aged 45 years or older, who were subsequently followed for a mean of eight years for the occurrence of any of the components of the composite endpoint. The value of CRP and LDL-C measurements in predicting the risk of these cardiovascular events was assessed.

Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347(20):1557-65.