

Inflammatory markers are useful risk assessment tools



Peter Libby, MD

Markers of systemic inflammation, such as C-reactive protein (CRP), have emerged as useful biomarkers for cardiovascular (CV) risk assessment and show potential for guiding risk-reducing therapy, said Peter Libby, MD.

Although lipid screening is a major element of CV risk assessment, CV events often occur in the absence of elevated lipid levels. The Framingham Heart Study demonstrates that even applying the best lipid criteria fails to identify many people with cholesterol levels below the median who subsequently have CV events, Dr. Libby noted.

Inflammation and markers

Understanding the usefulness of other potential risk markers requires appreciation of the biology of inflammation. Inflammation plays a central role in the development of coronary heart disease (CHD) and the clinical sequelae of atherosclerotic plaques.

During an inflammatory state, the liver decreases the synthesis of house-

keeping proteins, such as albumin, while increasing the synthesis of proteins involved in host defenses. Among the factors mobilized into serum during the inflammatory process are CRP, serum amyloid-A (SAA), and fibrinogen. Pro-inflammatory risk factors that raise levels of inflammatory mediators include constituents of modified low-density lipoprotein (LDL). These proinflamma-

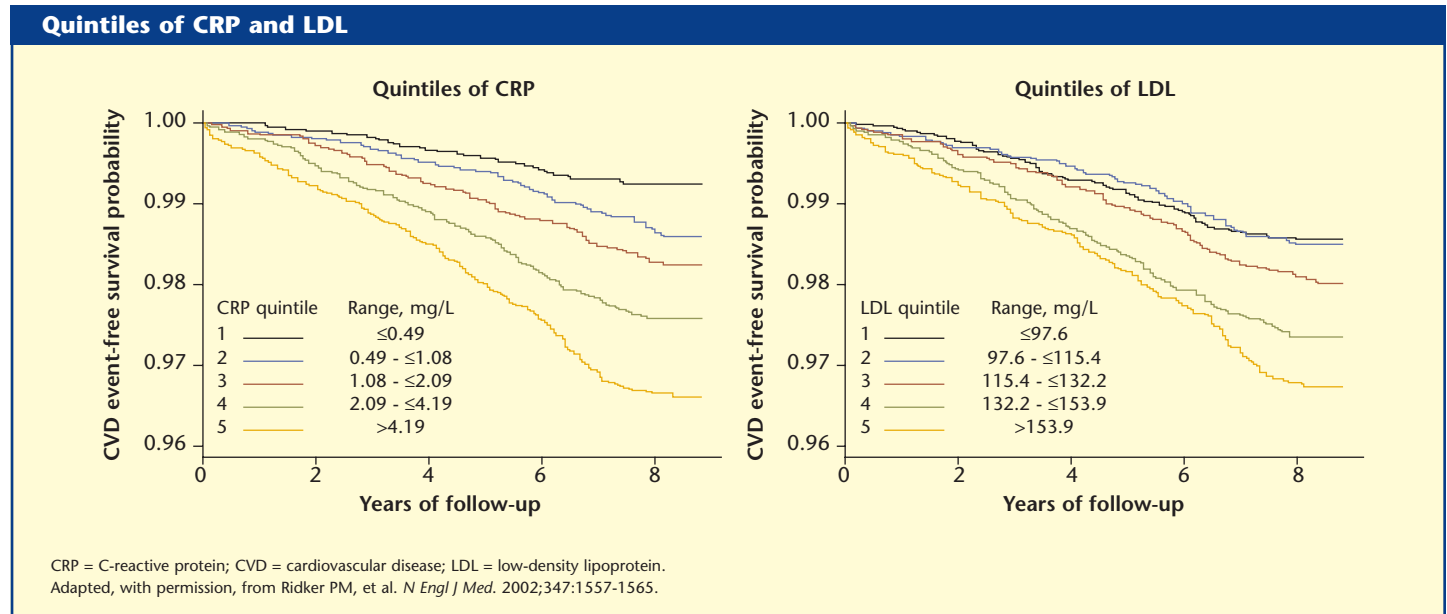
tory substances initiate production of primary proinflammatory cytokines and immunity mediators, such as interleukin-1 and tumor necrosis factor. These substances then signal a profound change in protein synthesis in the liver, and the resulting elevations of CRP, SAA, and fibrinogen are readily detectable in the peripheral blood.

The proinflammatory cytokines also

impinge on endothelial cells, where they express adhesion molecules, such as intercellular adhesion molecule-1, and other surface molecules. Adhesion molecules furnish a molecular “fly paper” that captures inflammatory leukocytes from the blood. The soluble forms of these adhesion molecules shed into the circulation and can be measured through simple

CONTINUED ON PAGE 7

Figure



A FORUM ON NEW TREATMENT ADVANCES

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CONTINUED FROM PAGE 6

venous blood sampling, Dr. Libby said.

A plethora of potential mediators and soluble adhesion molecules can be assessed in blood. Of these, CRP has emerged as the “champion” marker for a variety of reasons, he said. CRP is chemically stable with a long half-life (approximately 24 hours) and little diurnal variation. Also, in healthy individuals, CRP levels fluctuate little from day to day. In addition, the high-sensitivity CRP assay is reliable, standardized, convenient, and inexpensive, Dr. Libby explained.

CRP offers additional predictive value beyond the lipid profile. In both the Physicians Health Study and the Women’s Health Study, a gradient of risk was observed between CRP tertiles at each cholesterol tertile. More recent data from the Women’s Health Study showed that CRP outperformed the LDL cholesterol level in predicting all CV events and CHD events in every quintile (Figure) (*N Engl J Med.* 2002; 347:1557-1565). “These data show that we can obtain help from the inflammatory markers in addressing the quandary of what to do in people who do not meet lipid criteria, but who are at risk nonetheless,” Dr. Libby said. CRP should be viewed as an adjunct to, not a

replacement for, more traditional and well-established risk factors, including the lipid panel, he added.

CRP as a nonspecific marker

CRP has both vascular and nonvascular sources, but the very nonspecificity of CRP probably renders it a more potent risk marker, Dr. Libby continued. “The culprit lesion is just the tip of the iceberg and is a marker for tremendous [disease] burden,” he said. Elevated CRP reflects inflammation occurring outside the coronary tree as well as that occurring in coronary arteries.

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Further analysis of Women’s Health Study data demonstrated that CRP levels were incrementally higher with each metabolic syndrome risk factor identified in the patient. This finding indicates that CRP reflects inflammation caused by factors other than elevated LDL cholesterol. Metabolic syndrome risk factors include abdominal obesity, low high-density lipoprotein cholesterol, and

elevated levels of blood pressure, fasting glucose, and triglycerides. The CRP level integrates inflammatory burden from a variety of sources, hence “nonspecificity is not a disadvantage; it is actually the reason CRP works,” according to Dr. Libby.

CRP screening

The test for CRP is standardized, and consistent prospective study results show that CRP may add to the utility of screening with lipid profiles alone in selected populations, said Dr. Libby. Recent American Heart Association/Centers for Disease Control and Prevention guidelines suggest that CRP screening may have a role in patients deemed at intermediate risk from a global risk assessment, defined as a 10-year CHD risk in the 10% to 20% range (*Circulation.* 2003;107: 499-511). Screening of patients with stable coronary disease or acute coronary syndromes may also be useful as a tool for predicting the risk of recurrent events. “Screening of the entire adult population is not warranted at this time. We have no indication that this would lead to cost-effective intervention,” he said. Nor does Dr. Libby believe that CRP screening is warranted in individuals with established atherosclerosis. “These patients need

every arrow in our preventive quiver so that risk stratification by CRP is superfluous,” he commented.

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Most important, CRP screening can identify individuals without traditional risk factors who might benefit from therapy. An analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) population showed that lovastatin was beneficial in those with both above-median cholesterol and CRP, with elevated cholesterol alone, or with elevated CRP levels with below-average cholesterol (*N Engl J Med.* 2001;344:1959-1965).

The JUPITER trial (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) will enroll 15000 patients to evaluate the use of rosuvastatin in the primary prevention of CV events in those with low levels of LDL cholesterol and elevated CRP. “We hope that this clinical trial will provide a scientific answer to whether we can use CRP as a way to guide therapy in primary prevention,” Dr. Libby concluded. ■