10. Zhao XQ, Morse JS, Dowdy AA, et al. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). *Am J Cardiol* 2004; 93:307–312.
11. Davignon J, Roederer G, Montigny M, et al. Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia. *Am J Cardiol* 1994; 73:339–345.

How useful is high-sensitivity CRP as a risk factor for coronary artery disease?

EVIDENCE-BASED ANSWER

Little evidence supports the use of the high-sensitivity C-reactive protein assay (hs-CRP) as a screening test for cardiovascular disease (CVD) in the healthy adult population. There is significant debate about its use in populations at moderate risk for cardiovascular disease, with some evidence suggesting its use if the results of the test will alter treatment recommendations[1] (strength of recommendation [SOR]: **C**, based on extrapolation of consistent level 2 studies). Research to date is inadequate to determine the role of hs-CRP in risk-stratification of patients when considered in light of other standard risk factors (**Table**).

EVIDENCE SUMMARY

C-reactive protein is a nonspecific serum marker of inflammatory response. While it is elevated in a variety of conditions, a link has been suggested between CRP and pathogenesis of clinical cardiovascular disease.[1]

Several retrospective studies have reported risk ratios for developing cardiovascular disease, ranging from 2.3 to 4.4 when comparing subjects with the highest levels of hs-CRP with those who have the lowest levels.[2–9] Though systematic bias in retrospective study design limits the interpretation of these findings, the findings are of some benefit to answering this question when large, prospective, randomized studies are not available.

One of the largest and most recent of these studies reports adjusted odds for development of coronary artery disease of 1.45 (95% confidence interval [CI], 1.25–1.68) for subjects in the top third of hs-CRP levels compared with those in the bottom third.[9] Odds ratios (OR) for other predictors of coronary artery disease are higher than this, in particular total cholesterol (OR=2.35; 95% CI, 2.03–2.74), cigarette smoking (OR=1.87; 95% CI, 1.62–2.22), and elevated systolic blood pressure (OR=1.50; 95% CI, 1.30–1.73). This shows that hs-CRP does not contribute as much as these factors to the established risk profile for coronary heart disease.

These same authors go on to provide a systematic review of 22 prospective studies of hs-CRP involving 7068 patients, which showed that an elevated hs-CRP was associated with higher odds of developing coronary artery disease (OR=1.58; 95% CI, 1.48–1.68). They also examined the largest 4 studies in their review (which included 4107 cases) and found a slightly lower OR of 1.49 (95% CI, 1.37–1.62). This meta-analysis included only studies published since 2000 because earlier studies, which had yielded higher odds for hs-CRP, suggested a pattern consistent with publication bias.

Two very recent studies evaluating statin therapy for CVD suggest that CRP may be monitored as an independent factor for predicting CVD outcomes for patients undergoing aggressive lipid therapy.[10,11] These randomized, masked trials suggest that CRP is directly predictive of recurrent events among patients with known CVD. Its usefulness may be greatest when trying to decide whether to pursue aggressive (high-dose) statin therapy for these patients.

It is not clear whether hs-CRP is a direct, causative marker for atherosclerosis or whether it is simply a proxy marker elevated in conjunction with other known risk factors. This issue, combined with the fact that its elevation does not contribute as significantly as other risk factors, makes hs-CRP an inappropriate screening test for cardiovascular disease in the healthy adult

CONTINUED

TABLE

Evidence-based use of C-reactive protein in cardiovascular disease

Known CV disease	Framingham risk score	Screen with CRP for risk assessment?	Follow CRP along with lipids if treated with statins?
No	Low risk (1%–5%)	No	No
No	Moderate or high risk (6% or higher)	Little evidence to support screening	Only if trying to decide whether to use aggressive (high-dose) statin therapy. In this situation, if moderate-dose therapy does not lower CRP, consider this as a possible reason to move to higher doses.[10,11] (strength of recommendation: **B**, based on 2 very recent level 2 studies)
Yes	Any score	No—disease is established, screening is not appropriate	

population. If results continue to accrue supporting the relationship between statin therapy and reduction of CVD outcomes attributable to CRP, we may find that monitoring CRP levels becomes appropriate in the management of patients with known moderate or severe risk or known disease.

RECOMMENDATIONS FROM OTHERS

A consensus statement from the American Heart Association and the Centers for Disease Control and Prevention discourages use of hs-CRP for screening in the healthy adult population. It offers support for using hs-CRP for assessment of patients at medium risk levels for whom the test will alter treatment decisions.[1] Guidelines from the Institute for Clinical Systems Improvement for lipid management in adults state that, "nontraditional risk factors (C-reactive protein [CRP] and total homocysteine) have been shown to have some predictive values in screening vascular disease. The value of screening for these risk factors is not yet known."[12]

Sharon K. Hull, MD, *Department of Family Medicine, Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill,*
Linda J. Collins, MSLS, *Health Sciences Library, University of North Carolina at Chapel Hill*

REFERENCES

1. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; 107:499–511.
2. Tracy RP, Lemaitre RN, Psaty BM, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* 1997; 17:1121–1127.
3. Speidl WS, Graf S, Hornykewycz S, et al. High-sensitivity C-reactive protein in the prediction of coronary events in patients with premature coronary artery disease. *Am Heart J* 2002; 144:449–455.
4. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347:1557–1565.
5. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336:973–979.
6. Koenig W, Sund M, Frohlich M, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999; 99:237–242.
7. Folsom AR, Aleksic N, Catellier D, Juneja HS, Wu KK. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J* 2002; 144:233–238.
8. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000; 321:199–204.
9. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004; 350:1387–1397.

CONTINUED

It is not clear whether hs-CRP is a causative marker for atherosclerosis or simply a proxy marker

10. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005;352:29–38.
11. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005; 352:20–28.
12. Institute for Clinical Systems Improvement. Lipid Management in Adults. Available at: www.guideline.gov. Accessed on February 7, 2005.
13. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110:227–239.
14. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation* 2003; 108:2292–2297.

CLINICAL COMMENTARY

hs-CRP may be useful as a risk marker in some moderately high-risk patients

Elevated hs-CRP is not a standard cardiovascular risk factor, but may be useful for patients with Framingham Risk scores of 10% to 20%. The updated National Cholesterol Education Panel Adult Treatment Panel III guidelines list elevated hs-CRP (>3 mg/L) as an influencing factor in deciding whether to use an LDL-lowering drug for moderately high-risk patients with LDL-cholesterol values <130 mg/dL.[13] However, no prospective studies prove that elevated hs-CRP should guide therapy. The JUPITER trial is a prospective, placebo-controlled trial evaluating cardiovascular events with statin therapy in primary prevention patients with LDL values <130 mg/dL and hs-CRP values >2 mg/L.[14] When this study is completed, the definitive clinical utility of hs-CRP will be known. Until then, hs-CRP is a risk marker that may be useful for some moderately high-risk patients.

***Joseph Saseen, PharmD, FCCP, BCPS**, University of Colorado Health Sciences Center, Denver*

This study was supported by a grant from the Health Resources and Services Administration (#T32-HP14001).

How should we follow up a positive screen for anemia in a 1-year old?

EVIDENCE-BASED ANSWER

Healthy infants who test positive for anemia on routine screening at 1 year of age are most likely iron-deficient and may be treated empirically with a trial of iron therapy (3–6 mg of elemental iron/kg/d). Documentation of response to iron confirms the diagnosis of iron-deficiency (strength of recommendation [SOR]: **B**; evidence from randomized controlled trials with some conflicting results; lack of evidence for long-term benefits/harms of screening strategies).

In these cases, further testing with a complete blood count, mean corpuscular volume, red cell distribution width (RDW), serum ferritin concentration, as well as hemoglobinopathy screening when appropriate, may be effective in determining the cause of anemia (SOR: **C**, expert opinion).

EVIDENCE SUMMARY

A prospective study of 1128 children identified as anemic with a screening hemoglobin level showed that subsequent testing—which included mean corpuscular volume, protoporphyrin, transferrin, and ferritin measurements—did not reliably distinguish potential responders from nonresponders to a 3-month trial of empiric iron therapy.[1] In fact, more than half of the responders would have been missed if treatment had been restricted to infants with abnormal mean corpuscular volume or iron studies.

Because of the simplicity, low cost, and relative safety of iron therapy for infants, this trial suggests that a therapeutic trial of iron be given first, reserving further work-up for the small number of infants that still have unexplained hemoglobin concentrations of <11.0 g/dL after a therapeutic trial. Similar results were found in a prospective controlled treatment trial among Alaskan Native children[2] as well as a trial of empiric iron therapy among infants with anemia.[3]

CONTINUED