

COMMENTS AND RESPONSES

The USPSTF Recommendation Statement on Coronary Heart Disease Risk Assessment

TO THE EDITOR: The statement from the U.S. Preventive Services Task Force (USPSTF) (1) that “persons with low (<10%) Framingham risk scores do not benefit from aggressive risk factor modification” and the conclusion that high-sensitivity C-reactive protein (CRP) does not improve a physician’s ability to guide treatment do not reflect current randomized trial data. The USPSTF conclusions should be of particular concern for women, almost all of whom have Framingham risk scores less than 10%.

JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) (2) studied apparently healthy men and women with high-sensitivity CRP levels of 19 nmol/L or greater. The study group almost exclusively comprised persons with Framingham risk scores in the “intermediate” and “low” range who, under current guidelines, would not qualify for statin therapy because they also had low-density lipoprotein cholesterol levels less than 3.37 mmol/L (<130 mg/dL). Nonetheless, compared with placebo, allocation to rosuvastatin, 20 mg/d, resulted in a 44% reduction in the primary trial end point of major vascular events ($P < 0.001$), 54% reduction in myocardial infarction ($P < 0.001$), 48% reduction in stroke ($P = 0.002$), 46% reduction in the need for angioplasty or bypass surgery ($P < 0.001$), and 20% reduction in all-cause mortality ($P = 0.021$) (2). As reported in 2008 (2), these risk reductions were observed at all levels of Framingham risk.

To provide more detail, in 6091 JUPITER participants with elevated high-sensitivity CRP levels but Framingham risk scores of 5% to 10%, a 45% reduction in major vascular events was observed (hazard ratio, 0.55 [95% CI, 0.36 to 0.84]; $P = 0.005$), whereas in 7340 persons with elevated high-sensitivity CRP levels but Framingham risk scores of 11% to 20%, a 49% reduction in major vascular events was observed (hazard ratio, 0.51 [CI, 0.39 to 0.68]; $P < 0.001$). Absolute risk reductions were large in JUPITER, so estimated numbers needed to treat were smaller than those estimated from primary prevention trials of antihypertensive agents, aspirin, and statin regimens directed by other indications (3).

Clinicians interested in alternate evidence-based recommendations for the use of novel biomarkers in cardiovascular disease (CVD) are referred to the 2009 Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult (4) and the 2009 National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines (5).

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Potential Conflicts of Interest: Dr. Glynn has received research support from AstraZeneca. The Brigham & Women’s Hospital holds patents that relate to the use of inflammatory biomarkers in cardiovascular disease.

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TO THE EDITOR: The USPSTF (1) updated its statement on non-traditional risk factors and cardiovascular risk assessment. It is not surprising that their opinion of the clinical utility of coronary artery calcium (CAC) scanning is the same as in 2004, because they did not consider any of the new and available evidence on the topic. Their “comprehensive review of the literature” failed to uncover 19 published reports on CAC outcomes, contributing 103 124 additional patients and 2883 events. It is disturbing that the USPSTF makes recommendations on the utility of CAC testing for risk stratification but only identified 8 studies. Most worrisome is the glaring omission of MESA (Multi-Ethnic Study of Atherosclerosis) (2), which has been described as one of the best epidemiologic studies ever done.

This prospective, population-based study, which included 6814 asymptomatic persons, showed that patients with high CAC scores were 10 times more likely to have cardiac events and reclassified most intermediate-risk patients. The primary outcome article (3) was published in *New England Journal of Medicine* in March 2008. To date, more than 200 published articles (dating back to 2002) report the design and results of MESA, including CAC reclassification of risk; independent and incremental ability of CAC to predict events in intermediate-risk cohorts; and the ability of this measure to outperform both traditional risk factors and other subclinical markers, such as carotid intima-media thickness.

This study, funded by the National Heart, Lung, and Blood Institute, is clearly an exceptional epidemiologic study that meets all the USPSTF criteria of good quality and proved that CAC scanning provides both robust incremental and independent prediction of future coronary events, reclassifies many intermediate-risk patients, and raises the area under the receiver-operating characteristic curve (AUC) for prediction of events (2).

Had the USPSTF neglected to include only 1 major CAC study, even of the magnitude of MESA, one could argue that mistakes of omission occur. However, the authors included only 8 outcome studies in their systemic review. To date, at least 20 such prospective outcome studies are available, including many large prospective, population-based studies. The St. Francis Heart Study (4), a prospective, population-based study of 4903 asymptomatic persons aged 50 to 70 years who underwent CAC scanning and were followed for 4.3 years, showed robust prediction of events by using

CAC over Framingham models. Most of the patients were intermediate risk, and more than 70% were reclassified to either high or low risk with use of CAC scanning. The USPSTF also did not include the recently completed Heinz Nixdorf Recall Study (5), a prospective, population-based trial of 5000 persons with 5.0 years of follow-up, showing that 77% of intermediate-risk patients were reclassified on the basis of CAC testing (14% were classified to higher risk and 63% to lower risk). This robust reclassification is much greater than that reported for either ankle-brachial index or CRP.

Even the Rotterdam Study (6), which was cited by the USPSTF, described the reclassification of their cohort, yet the USPSTF did not acknowledge this. In the Rotterdam Study, 64% of intermediate-risk men were reclassified, 38% moved to the low-risk category (<10% risk) and 26% to the high-risk category (>20% risk). In women at intermediate risk, 58% were reclassified (38% moved downward and 20% upward). All participants were reclassified into more accurate risk categories, and this was much more robust than CRP reclassification in that particular study.

Each of the 20 studies on CAC outcome has similar results, with an approximate 10-fold increase in risk in asymptomatic persons with high CAC score, and each provides evidence of incremental risk prediction and ability to reclassify significant portions of the population. The USPSTF conclusion that not enough data exist for the validation of CAC testing is not due to lack of existing published data but to the failure of the Task Force to evaluate available studies. The disparity between its recommendations and those of other organizations, such as the National Cholesterol Education Panel, the American Heart Association (AHA), and the American College of Cardiology (ACC), is attributable to this.

The USPSTF must immediately revisit this topic and analyze all available literature to make more cogent and complete recommendations.

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TO THE EDITOR: We read with interest the USPSTF statement (1) on emerging risk factors for coronary heart disease (CHD). Specifically, the authors suggest that the current evidence does not support the use of CAC scoring “for further risk stratification of intermediate-risk persons.” The authors identify a 2004 study by Greenland and colleagues (2) as the “best-quality” study and suggest “flaws in the other studies.” This overall conclusion from the USPSTF is at odds with current recommendations from the AHA and ACC (2).

Why was MESA not considered a high-quality study? The primary objective of MESA was “to determine characteristics related to progression of subclinical to clinical cardiovascular disease” (3). MESA enrolled an ethnically diverse, population-based sample of 6814 asymptomatic men and women aged 45 to 84 years from 6 field centers across the United States. All patients received a common scanning protocol. During the 3.8-year follow-up, doubling of CAC score increased the risk for any coronary event by 18% to 39%, and CAC score increased the AUCs for the prediction of coronary events when added to standard risk factors (4).

Increasing the AUC is the elusive “holy grail” of all new risk markers, and the USPSTF correctly points out how difficult it is for a risk factor to increase the AUC. While we await publication of the MESA reclassification analysis in 2010, existing publications suggest a reclassification benefit with CAC. For example, women in MESA characterized as low risk by Framingham risk score but with CAC score greater than 300 had a 6.7% and 8.6% risk for CHD and CVD events, respectively, during the 3.75-year follow-up (5). These women with higher CAC scores were indeed at increased risk, despite low calculated risk by the Framingham risk score.

The MESA study is 1 of 10 population-based studies of CVD risk funded by the National Heart, Lung, and Blood Institute, and its goal was to assess the same thing as the USPSTF authors: the value of subclinical atherosclerosis in predicting coronary events. If MESA is not considered high-quality, what type of study will be sufficient to show the importance of selective CAC testing in persons with risk factors who do not yet qualify for treatment with statin and aspirin therapy?

In the future, the USPSTF should include an experienced preventive cardiologist to avoid these major oversights.

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TO THE EDITOR: The recently published USPSTF (1) statement and systematic review summary of emerging risk factors for CHD (2) highlight important recognized risk factors but neglect an important and emerging aspect of CHD.

In the past decade, it has become increasingly clear that accelerated atherosclerosis and CHD are more common in patients with systemic inflammatory diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Women with SLE have a more than 2-fold increased risk for CVD, including myocardial infarction (MI), compared with women without SLE, and the incidence of CHD in women aged 35 to 44 years with SLE is estimated to be 50-fold greater than that in control populations (3). Patients with RA have a more than 2-fold increased risk for CHD, including heart failure, compared with patients without RA (4). This increased risk is not fully explained by traditional risk factors or by treatment with corticosteroids, although it may be related to the cumulative burden of inflammatory disease (3, 4).

The population burden of these and related inflammatory diseases is significant. Systemic lupus erythematosus affects 161 000 to 322 000 adults, and RA affects 1.3 million adults in the United States (5). Patients with SLE and RA have a range of detectable coronary risk factors that are not fully reflected in the Framingham risk model or in the nontraditional risk factors summarized by the USPSTF (1) and by Helfand and colleagues (2). The nontraditional risk factors assessed by the Task Force did include CRP, a marker of inflammation. However, the inclusion of CRP as a risk factor for CHD does not adequately address this issue, because a single CRP measurement cannot fully explain the increased risk for CHD in persons with systemic inflammatory diseases.

We suggest that systemic inflammatory diseases should be identified as risk factors for CHD to better and fully reflect their effect on CHD-related morbidity and mortality and to increase awareness of the need for screening of these patients, who often have premature CVD unexplained by traditional risk factors or by treatment of the underlying inflammatory disease with corticosteroids or other anti-inflammatory drugs.

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Potential Conflicts of Interest: None disclosed.

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IN RESPONSE: We appreciate the thoughtful letters in response to our recommendation statement. Dr. Glynn asserts that JUPITER is convincing with regard to the use of CRP to identify patients who are at low or intermediate risk for CHD on the basis of traditional Framingham risk scores and who would benefit from statin therapy. The implications of JUPITER are still being considered. It has been noted, however, that 41% of patients in JUPITER met criteria for the metabolic syndrome and as many as 25% might have had undiagnosed diabetes (1). In addition, 11% of patients had a family history of premature coronary disease. Whether the JUPITER results are truly generalizable to patients who are eligible for risk stratification by using "traditional" risk factors (that is, patients without diabetes) remains a matter of debate. An efficient and inexpensive approach to prediction of absolute risk for CHD that has proven discriminatory ability should guide interventions to prevent CHD. The CRP level may well emerge as a component of such an approach.

Dr. Budoff and Dr. Blaha and colleagues express concern that CAC scoring by means of electron-beam computed tomography was insufficiently evaluated as a risk factor for CHD. In fact, MESA was carefully reviewed and assessed by the evidence-based practice center that performed the systematic evidence reviews for this USPSTF recommendation (2). Some of the studies mentioned by Dr. Budoff and Dr. Blaha and colleagues were released after the end of the search period (September 2008). However, the USPSTF recommendation statement clearly says that the critical gap in the evidence for screening with nontraditional risk factors is the lack of information on subsequent reductions in risk for CHD events in persons identified by the new risk factors. We therefore conclude that the USPSTF need not revisit the topic "immediately" as suggested, but rather when sufficient evidence examining this specific gap has been published.

Dr. Matteson and colleagues' concern about the effect of systemic inflammatory conditions is noted, but their suggestion that the USPSTF consider inflammatory disease as a risk factor itself for CHD exceeds the scope of the USPSTF, which is tasked with examining the evidence relevant to the otherwise well, asymptomatic population.

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Potential Conflicts of Interest: None disclosed.

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The Case for C-Reactive Protein as a Risk Marker for Coronary Heart Disease

TO THE EDITOR: Buckley and colleagues (1) state that the utility of measuring C-reactive protein (CRP) is uncertain and conclude that routine screening by CRP levels cannot be recommended. The reasoning behind this conclusion, however, seems flawed. First, since the literature review in 2007, additional articles have been published, particularly ones featuring risk reclassification (including the Reynolds Risk Score for men [2] and the analysis of high-sensitivity CRP in the Framingham cohort [3]). The latter work should replace the cited negative study from Framingham, which did not use the high-sensitivity assay.

Second, the authors cite a lack of evidence that change in CRP level directly links to prevention. Whether CRP level is causal does not limit its use as a predictive marker. The same criterion has not been applied to other risk factors, such as high-density lipoprotein cholesterol, which has been a well-accepted risk marker for decades. There is a notable lack of randomized trial data showing that increasing high-density lipoprotein cholesterol directly leads to prevention of cardiovascular events (4).

Third, although the focus on risk reclassification is appreciated, it is not the most meaningful measure of a marker's value as stated by Buckley and colleagues (1). JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) presents stronger evidence, showing that persons with high CRP levels who had Framingham risk scores both above and below 10% had the same sizable reduction in risk. Given these results, whether these persons would be reclassified into a higher-risk group seems moot for clinical utility and relevant only for cost-effectiveness analyses.

The authors should note the recent statement from the American Heart Association (AHA) (5) regarding evaluation of novel markers. The AHA proposes that markers be evaluated in phases, including case-control studies, prospective evaluation, and incremental value, all of which the U.S. Preventive Services Task Force

(USPSTF) agrees are fulfilled by CRP. An additional phase assesses clinical utility and evaluates whether a novel marker changes the predicted risk enough to change therapy. Risk reclassification suggests that this is true for CRP, similar to well-accepted markers. A stronger criterion is whether use of the marker improves clinical outcomes, especially in randomized trials. JUPITER used CRP levels to identify persons who would not otherwise be treated and found a substantial reduction in cardiovascular events. A final question is whether the additional costs of testing and treatment are justified. The low cost of the test and the dramatic results of treatment should make this simple test worthwhile in avoiding cardiovascular events and perhaps saving lives.

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Potential Conflicts of Interest: None disclosed.

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IN RESPONSE: Dr. Cook asserts that, in our systematic review and assessment of the body of evidence, we conclude that "routine screening of CRP cannot be recommended." This is incorrect. We made no recommendations about routine screening. Rather, we presented our findings to the USPSTF, which is solely responsible for USPSTF recommendations.

We found that CRP level is associated with coronary heart disease events and that adding CRP level to a global risk score in initially intermediate-risk persons reclassifies some patients. However, we also found that the benefit of reclassifying patients in this manner is uncertain.

We agree that direct causality is not an essential criterion. We also agree that a marker's ability to improve clinical outcomes is better evidence of usefulness than its ability to improve risk classification, but we disagree about whether CRP meets this criterion. Reclassification means that CRP identifies some patients for more intensive treatment and not others. Is CRP really better than the alternatives for selecting patients for more intensive treatment? For example, would randomly selected intermediate-risk patients benefit as much from intensive statin therapy? A trial that compares CRP testing with no CRP testing, or one that compares treatment in

patients with high CRP levels with treatment in patients with intermediate or low CRP levels, could answer this question.

JUPITER, a trial of high-dose statin treatment, did neither (1). It found that high-dose statin treatment improved cardiovascular disease outcomes in participants with an elevated CRP level, but did not test the hypothesis that use of CRP level improves outcomes compared with the alternative of intensifying therapy without a CRP test. The study did not determine whether reclassification based on CRP might identify intermediate-risk patients who are most likely to benefit from high-dose statin therapy in addition to therapeutic lifestyle changes. For example, JUPITER excluded intermediate-risk patients with low-density lipoprotein cholesterol levels greater than 3.37 mmol/L (>130 mg/dL), a group that might also be considered for intensifying therapy.

Dr. Cook suggests that we take note of the AHA statement (2) regarding the evaluation of novel markers. Although it uses different terminology, the AHA statement is consistent with the criteria we proposed (3) to the USPSTF in 2005 to assess CRP level and other markers. In AHA terms, our review found that CRP meets the criteria at several evaluation phases, including “proof of concept,” “prospective validation,” and “incremental value.” We also found that CRP probably meets the next criterion, “clinical utility,” corresponding to reclassification in our system. The AHA then calls for randomized trials of whether use of the marker improves clinical outcomes. As we discussed, CRP has not met this criterion. Finally, the AHA considers cost-effectiveness, which we did not evaluate in our review.

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Potential Conflicts of Interest: None disclosed.

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CLINICAL OBSERVATION

Pseudohypoglycemia in a Patient With the Eisenmenger Syndrome

Background: Pseudohypoglycemia is an artifactually low glucose concentration due to either in vitro glycolysis (venous blood pseudohypoglycemia) or impaired digital microcirculation (finger-

stick blood pseudohypoglycemia). These 2 conditions rarely occur together, so when pseudohypoglycemia is suspected in one type of blood sample, measuring glucose concentration in the other type of blood sample usually makes the diagnosis.

Objective: To describe a case of pseudohypoglycemia in both venous and finger-stick blood in a patient with the Eisenmenger syndrome.

Case Report: A 44-year-old white woman with known Eisenmenger syndrome due to a large ventricular septal defect was hospitalized for an exacerbation of exertional dyspnea. Her venous serum glucose level was reported to be very low (2.05 mmol/L [37 mg/dL]). Two consecutive finger-stick values of 1.4 mmol/L (25 mg/dL) and 1.55 mmol/L (28 mg/dL) confirmed severe hypoglycemia. Laboratory tests revealed secondary erythrocytosis with microcytosis and hypochromia (erythrocyte count, 10.45×10^9 cells/L; hemoglobin level, 179 g/L; hematocrit, 62.5; mean corpuscular volume, 58.2 fL; mean corpuscular hemoglobin, 16.2 pg/cell), severe iron deficiency (ferritin level, 12.6 pmol/L; iron level, 3.8 μ mol/L [21 μ g/dL]), and hyperuricemia (uric acid level, 731.7 μ mol/L). Leukocyte and platelet counts were in normal range. Liver and kidney function test results were normal. Insulin, adrenocorticotropic hormone, thyroid hormones, cortisol, prolactin, and gonadotrophins serum levels were all within normal ranges. On physical examination, we found cyanosis (resting SaO₂, 75%) and clubbing, blood pressure of 110/70 mm Hg, heart rate of 75 beats/min, and temperature of 36.5 °C. Her medications included clopidogrel, aspirin, and furosemide. Her medical history did not include diabetes mellitus, and she did not report taking insulin; oral antidiabetic agents; or drugs, such as β -blockers, that may cause hypoglycemic unawareness. Because she did not report symptoms of hypoglycemia despite having low glucose values, we suspected pseudohypoglycemia and measured a glucose level immediately after taking another venous sample. It was normal, with a value of 4.9 mmol/L (88 mg/dL).

Discussion: Pseudohypoglycemia in venous and finger-stick blood are caused by different mechanisms. In venous blood, it is caused by in vitro consumption of glucose by high levels of cells in the blood after the sample is drawn and before it is processed (1). In this case, the Eisenmenger syndrome led to secondary erythrocytosis, which provided the high levels of erythrocytes that we believe caused the pseudohypoglycemia in combination with delayed processing of the sample. However, pseudohypoglycemia also has been reported (2) in patients with high levels of other types of cells, including leukocytes due to leukemia or a leukemoid reaction. This process can be minimized by cooling samples promptly or by using inhibitors of anaerobic glycolysis (2). In finger-stick blood, pseudohypoglycemia is caused by impaired blood flow in the digital microcirculation, which leads to a local increase in glucose consumption (3, 4). Because the Eisenmenger syndrome has been connected with vascular and intravascular disorders of the microcirculation (5), we believe that this process explains why our patient had low glucose values in finger-stick blood. This process also has been described in patients with the Raynaud phenomenon, peripheral vascular disease, and shock.

Conclusion: To our knowledge, this is the first report of pseudohypoglycemia in both venous and finger-stick blood in the same patient.

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CORRECTION

Correction: Chronic Noncancer Pain Management and Opioid Overdose

The editorial by McLellan and Turner (1) states that "Opioid overdose is among the most common causes of death nationwide." Reference 3 gave a total of 9798 deaths from opioids plus cocaine in 2004. Because some deaths were due to cocaine use, the number of opioid deaths was fewer than 9798.

Reference

1. McLellan AT, Turner BJ. Chronic noncancer pain management and opioid overdose: time to change prescribing practices [Editorial]. *Ann Intern Med*. 2010;152:123-4. [PMID: 20083830]

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