Perspective

Is hsCRP Back on Board?
Implications from the JUPITER Trial

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Identifying Individuals at Risk for Cardiovascular Diseases: The Traditional Approach

In primary prevention, measurement of traditional risk factors is considered a useful first step in determining those at risk for cardiovascular disease (CVD).[2] In the era of "global risk assessment," the use of scores such as the Framingham Risk Score or the European Society of Cardiology SCORE (Systematic Coronary Risk Evaluation), derived from multivariable statistical models, is recommended (1). However, it has been noted that a considerable number of those at risk cannot be identified on the basis of traditional risk factors alone (2), and it has also been shown that these scores are not generally applicable because they lead to overestimation of actual risk in various populations and thus must be adapted to the true background risk of the population. As a consequence of these issues and others, acceptance of the use of these scores in general practice is rather low. Although this situation does not invalidate the concept of traditional risk factors, it highlights some of the inherent problems of the global risk assessment approach.

Global risk assessment brings about yet another problem. Application of these algorithms yields an estimation of absolute 10-year risk, which for Framingham Risk Score is considered to be high when higher than 20% and low when it is lower than 6%–10%. For either high- or low-risk individuals, recommendations in the guidelines are clear: reevaluate those at very low risk after 3–5 years, advise lifestyle changes, and eventually prescribe a statin to those at high risk. This leaves an intermediate-risk group, comprising approximately 25%–40% (3) of the total population, for whom there is no guidance regarding what to do.

The Potential Role of Biomarkers to Refine Risk Stratification for CVD

The gap in our preventive strategy has prompted the search for novel biomarkers of cardiovascular risk to help improve risk prediction. Potentially useful biomarkers include various blood biomarkers relevant to the pathophysiology of atherothrombosis, such as markers of inflammatory response, coagulation, platelet aggregation, and lipoproteins or lipid-related variables and genetic markers. Markers of subclinical disease, such as coronary calcium and carotid intima media thickness, may also aid in improved risk prediction. A large panel of blood biomarkers have been shown to be associated with CVD in prospective studies, but most of them are not yet applicable in routine clinical practice (4, 5). A reason for the delay in clinical application is that the clinical utility of a biomarker must be demonstrated by additional criteria beyond relative risk in association studies to determine whether the marker provides incremental information above and beyond global risk assessment. Processes involved in biomarker investigation include discrimination, calibration, and reclassification. Until recently we have desperately tried to demonstrate a significant increase in the area under the curve in ROC analyses for various markers, and we must admit that by and large we have failed for various reasons. Few studies using reclassification strategies have been reported, but their results look promising (6). Thus, debate is ongoing regarding the clinical value of various emerging biomarkers, including C-reactive protein (CRP) measured with high-sensitivity methods (hsCRP).

THE PARTICULAR ROLE OF hsCRP
Among emerging biomarkers, one of the largest databases exists for hsCRP, the classical acute-phase protein. The hsCRP measurement procedure is well standardized and automated, and high-sensitive assays with sufficient imprecision are available. On the basis of substantial evidence of a contribution of inflammation to atherothrombosis, a recent American Heart Association/CDC consensus report has recommended the measurement of hsCRP in asymptomatic individuals at intermediate risk for future coronary events (10-year risk of 10%–20%). As mentioned above, however,

the decision on the clinical utility of hsCRP is still pending.

The JUPITER Trial

Posthoc analyses from the Air Force /Texas Coronary Atherosclerosis Prevention Study of more than 6605 hyperlipidemic men and women with particularly low HDL-cholesterol (HDL-C) have shown that the therapeutic benefit of lovastatin was seen not only in individuals with high LDL-C [higher than the median of 4.12 mmol/L (159 mg/dL)] and normal or increased hsCRP (higher than the median of 1.62 mg/L) but also in those with increased hsCRP but an LDL-C below the median. By contrast, no effect was seen in those with both LDL-C and hsCRP below the median. These data form the basis of the scientific rationale for the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (7) to test the hypothesis that daily treatment with 20 mg rosuvastatin compared to placebo would decrease the rate of first major cardiovascular events in individuals with LDL-C <3.37 mmol/L (130 mg/dL), who were thus below the current treatment threshold for a statin, and signs of a low-grade inflammatory response indicated by an hsCRP ≥2 mg/L after repeat measurements. JUPITER was an investigator-initiated study conducted in 17 802 apparently healthy persons from 1315 sites in 26 countries. The study included men age ≥50 years and women age ≥60 years without a prior history of CVD. Main baseline data showed an average LDL-C of 2.80 mmol/L (108 mg/dL) and an hsCRP of 4.2 mg/L. The study population was 38% women; 71% were white and 29% were either black, hispanic, or of other ethnicity. More than 40% had metabolic syndrome. Participants showed the lowest LDL-C values and the highest HDL-C values among all studies in primary prevention. JUPITER was designed to provide 90% power to detect a 25% reduction in hazard for the occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure, or confirmed cardiovascular death. Secondary endpoints included components of the primary endpoints individually, and all-cause-mortality. The trial was halted prematurely on March 31, 2008, owing to unequivocal evidence of benefit after a median follow-up of only 1.9 years. Rosuvastatin reduced LDL-C by 50% and hsCRP by 39%, achieving an LDL-C of 1.42 mmol/L (55 mg/dL) and an hsCRP of 1.8 mg/L. The main composite endpoint was reduced by 44% compared to placebo (rate per 100 person-years: 0.77 versus 1.36). The occurrence of myocardial infarction was reduced by 54%, stroke by 48%, and revascularization and unstable angina by 47%. Finally, a reduction in total mortality of 20% was seen in the absence of myopathy and cancer. Importantly, groups typically assumed to be at low risk also benefited: non-smokers and individuals of normal weight, those without metabolic syndrome, and those with a Framingham Risk Score of 10% or less.

WHAT MESSAGE CAN WE TAKE FROM JUPITER?

There are several important lessons to learn from JUPITER. First, in this population LDL-C was safely decreased to 1.42 mmol/L (55 mg/dL) without an increase in adverse events, in particular no increased incidence of myopathy. There was also no increase in cancer incidence, but we have to keep in mind the relatively short follow-up period. Second, JUPITER included 38% women, the largest number in any primary prevention trial, and thus will provide reliable data on treatment efficacy in women. Third, for traditional risk factors, the JUPITER study population had the lowest risk profile among all primary prevention trials (lowest LDL-C, highest HDL-C, no prior CVD, no history of diabetes, low percentage of smokers and of positive family history, and low prevalence of hypertension). Nevertheless, increased hsCRP >2 mg/L identified a group of individuals who clearly benefited from statin therapy despite the fact that they were not candidates according to current National Cholesterol Education Program guidelines. Surprisingly, the benefit was larger than that observed in any previous primary prevention trial. The JUPITER selection criterion, which differed from prior statin trials, was hsCRP rather than LDL-C, and provides a possible explanation for the unexpected results. Such robust reductions in vascular risk have 2 possible interpretations: hsCRP must be considered as a marker that integrates the risk of traditional risk factors, because many of those are correlated with hsCRP, albeit moderately, and/or the modest increase in hsCRP represents an increased inflammatory response carrying its own risk. That the reduction in vascular risk was larger than one would have expected from the lowering of LDL-C alone (20% for each 38.7 mg/dL or 1.00 mmol/L of LDL-C) supports the latter argument.

Returning to the initial question, should we measure hsCRP in clinical practice? Certainly, we do not need to measure hsCRP if a patient is a candidate for statin therapy on the basis of an LDL-C >3.37 mmol/L (130 mg/dL). But in individuals with lower LDL-C, hsCRP measurement may well make sense. The fact that rosuvastatin showed similar efficacy in various subgroups, including those with a Framingham Risk Score ≤10%, raises the provocative question of whether global risk assessment is useful, especially in light of its low acceptance rate, and whether or not

increased hsCRP might serve as a diagnostic criterion to initiate statin treatment. JUPITER has a randomized, controlled, state-of-the-art trial design, and a number needed to treat of 25 for the primary endpoint projected for 5 years is being considered acceptable. More data are needed, however, to prove that this treatment strategy is cost-effective.

Conclusions

JUPITER provides provocative data not only from a public health perspective but also from the pathophysiological point of view. In the context of existing guidelines regarding statin treatment, the conclusions may be as follows: if the patient has coronary heart disease, treat; if the patient is diabetic, treat; if the patient has an LDL-C >4.14 mmol/L (160 mg/dL), treat; and if the patient has none of the above but has hsCRP >2 mg/L, then also treat. Discussions on whether or not to use hsCRP to identify at-risk individuals who would benefit from treatment with a statin will continue, but JUPITER has revitalized the discussion and will make it more difficult in the future to neglect the evidence built around hsCRP and cardiovascular risk. The story will continue . . . .

References

1. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European Society of Cardiology. American Heart Association. American College of Cardiology. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). Atherosclerosis 2004;173:381–91.

2. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290:898–904.

3. Greenland P, Smith SC Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. Circulation 2001;104:1863–7.

4. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation 2006;113:2335–62.

5. Koenig W, Khuseyinova N. Biomarkers of atherosclerotic plaque instability and rupture. Arterioscler Thromb Vasc Biol 2007;27:15–26.

6. Zethelius B, Berglund L, Sundström J, Ingelsson E, Basu S, Larsson A, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. N Engl J Med 2008;358:2107–16.

7. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al., on behalf of the JUPITER Trial Study Group. Rosuvastain for vascular prevention among men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.