European Atherosclerosis Society Screening Recommendations for Lipoprotein(a) and High-Sensitivity C-Reactive Protein: Double Standard or Failure of Evidence-Based Medicine?

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While remaining silent on the role of high sensitivity C-Reactive Protein (hsCRP), the European Atherosclerosis Society (EAS) has issued a new consensus statement endorsing routine measurement of lipoprotein(a) \([\text{Lp}(a)]\) among patients at moderate to high risk of cardiovascular disease \((1)\). The EAS took an even larger step in this consensus document and recommended prescription of niacin therapy \((1–3 \text{ g})\) to lower \([\text{Lp}(a)]\) concentrations to less than 50 mg/dL. This recommendation is exceptionally broad, because as many as 1 in 5 adults may have an \([\text{Lp}(a)]\) concentration that exceeds 50 mg/dL. Therefore, the EAS recommendations urging healthcare providers to screen for high concentrations of \([\text{Lp}(a)]\) and advising treatment of high concentrations with niacin mark radical changes in policy.

The role of \([\text{Lp}(a)]\) as an independent biomarker of vascular risk has been investigated for more than 20 years. Problems with standardization and reporting of \([\text{Lp}(a)]\) assays have persisted without resolution. Therefore, it is reasonable to inquire what new evidence has emerged to explain this seismic shift in thinking and to justify these new and far-reaching recommendations for screening and treatment in the field of cardiovascular disease prevention.

Surprisingly, the impetus and rationale for these changes stem largely from recent observational studies using the techniques of mendelian randomization, which refers to the random assortment of gene variants passed from parents to offspring. Mendelian randomization is a method used by some epidemiologists in an attempt to understand causal pathways for intermediate phenotypes. With regard to \([\text{Lp}(a)]\), results of 2 recently reported studies demonstrated that polymorphism in the lipoprotein, \([\text{Lp}(a)]\) \((\text{LPA})\) gene is associated both with plasma \([\text{Lp}(a)]\) concentrations and with subsequent vascular risk \((2, 3)\). Proponents have suggested that these data define a causal relationship between \([\text{Lp}(a)]\) and cardiovascular disease \((4)\). However, the technique of mendelian randomization is itself highly controversial, and its use to infer a causal relationship in observational epidemiology has been challenged \((5, 6)\).

Regardless of controversy about causality, the EAS recommendations fail to adhere to the longstanding criteria by which biomarkers have traditionally been evaluated for clinical use. As noted recently in a scientific statement by the American Heart Association (AHA) \((7)\), risk markers should demonstrate independence in multiple prospective cohort studies, must demonstrate incremental information beyond usual risk factors (i.e., improvement in discrimination, calibration, and reclassification over traditional risk schemes such as the Framingham risk score), must demonstrate that assessment leads to clinical benefit with regard to patient outcomes, and should be proven cost-effective.

For \([\text{Lp}(a)]\), results of prospective epidemiologic studies have generally supported a modest association with vascular risk. However, virtually none of the other standard criteria used to evaluate a biomarker for clinical use have been applied or evaluated for \([\text{Lp}(a)]\).

The knowledge base for \([\text{Lp}(a)]\) is limited. In marked contrast, all of the AHA criteria have been fulfilled for hsCRP, an inflammatory biomarker, and this evaluation process has advanced the field of cardiovascular prevention. First, as demonstrated in a recent metaanalysis of 54 prospective cohort studies, hsCRP is not only strongly and linearly associated with future vascular risk, but the magnitude of risk associated with a 1-SD increase in hsCRP is actually larger than that associated with a similar increase in cholesterol, non-HDL cholesterol, or blood pressure \((8)\). Second, in contrast to \([\text{Lp}(a)]\), for which multiple commercial assays provide varying results on the same plasma sample, a standardized assay for hsCRP has been developed and validated by the CDC. Consequently, all laboratories worldwide now provide similar hsCRP data and
similar reporting practices. Third, several major studies have found that hsCRP adds to clinical reclassification (9–11). Simple algorithms such as the Reynolds Risk Score for the use of hsCRP along with traditional factors have been developed and validated in women (12) and in men (13). Fourth, the use of hsCRP in intermediate-risk groups has been endorsed by the CDC and the AHA (14), and a recent comprehensive review of novel risk markers from the National Academy of Clinical Biochemistry found hsCRP to be the only emerging risk marker with appropriate characteristics for clinical use (15).

Most importantly, however, as demonstrated in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), patients who were identified to be at high risk owing to increased hsCRP concentrations benefited from a therapy they otherwise would not have received (16). Specifically, JUPITER investigators enrolled 17 802 men and women who had LDL cholesterol concentrations that would otherwise disqualify them from treatment with a statin [<130 mg/dL (<3.37 mmol/L)], but who were identified as being at high risk owing to hsCRP ≥2 mg/L. The primary outcome was occurrence of a first major cardiovascular event—myocardial infarction (MI), stroke, hospitalization for unstable angina, arterial revascularization, or confirmed cardiovascular death. Patients who were randomly assigned to receive rosuvastatin 20 mg had a 55% reduction in MI, a 48% reduction in stroke (17), a 46% reduction in need for bypass surgery or angioplasty, and a 20% reduction in all-cause mortality (16).

The risk reduction in cardiovascular events was similar in men and women (18). There was a 43% reduction in symptomatic deep-vein thrombosis and pulmonary embolism in the rosuvastatin group (19).

The use of rosuvastatin was associated with reduction in cardiovascular events in all subgroups evaluated. In particular, black and Hispanic populations benefited as well as white participants.

The findings in JUPITER contrast markedly to those of investigations of Lp(a), for which no hard endpoint data exist to support the use of niacin among patients with increased Lp(a) concentrations. Given this situation, readers might wonder whether a double standard exists at the EAS for evaluating Lp(a) vs hsCRP or whether this new recommendation for widespread Lp(a) screening marks a failure of evidence-based medicine. It is important to point out that neither the authors nor the editorialists of the new Lp(a) reports endorse a call for wide-scale Lp(a) screening, but instead are appropriately careful in their interpretations. For example, Kamstrup et al (3) stated that “final proof of causality still requires randomized clinical trials demonstrating reduced MI risk in response to lipoprotein(a)-lowering therapy.” The accompanying editorial (20) concludes: “At present, the clinical implications remain quite limited. These results do not provide the necessary evidence that genetic testing of the LPA locus or measurement of plasma Lp(a) have a role in cardiovascular risk stratification or decisions regarding lipid-lowering therapy.” Similarly, although Clarke et al (2) suggest that the data “provide support for a causal role of Lp(a),” they do not endorse screening. The accompanying editorial from Kathiresan (4) correctly notes that “a therapeutic intervention that selectively lowers the plasma Lp(a) concentration will need to be tested in a randomized clinical trial”.

Based on available evidence, it appears that the EAS took too large a leap by endorsing widespread screening for Lp(a). The additional EAS consensus recommendation to treat patients with niacin for Lp(a) increases is especially questionable because there are no randomized trials to support this new practice guideline.

With respect to EAS consensus guideline recommendations, there appears to be a double standard for Lp(a) compared with the inflammatory biomarker hsCRP. Reports by Clarke et al (2) and Kamstrup et al (3) support the hypothesis that increased Lp(a) concentrations are associated with an increased risk of MI. But the hypothesis remains controversial and unproven. Nevertheless, Lp(a) screening and treatment garnered rapid support from the EAS. This backing is based solely on the results of several observational studies but no randomized trials.

By contrast, the JUPITER data provided evidence that statin therapy lowers LDL cholesterol concentrations, reduces hsCRP concentrations, and reduces cardiovascular death and disability. In addition, results of prospective outcomes studies included in PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy trial) (21), A to Z (“A” Aggrastat to “Z” Zocor trial) (22), and JUPITER (23) all demonstrated that therapeutic interventions that lower hsCRP and those that lower LDL cholesterol both contribute to improved outcomes in patients on statin therapy. Whereas evidence supporting screening for high concentrations of Lp(a) is weak and evidence favoring treatment is virtually nonexistent, hsCRP screening and treatment with statin therapy have a robust foundation in clinical science.

The double standard favoring Lp(a) over hsCRP for screening and treatment is difficult to understand, unwise for patient care, costly for public policy, and impossible to defend if guidelines are to be evidence based rather than opinion based. It is time to adopt an even-handed approach to assessing the clinical utility of using cardiac biomarkers for preventive screening and to judge the efficacy of therapies used to normalize elevated concentrations of these biomarkers. The relevant question physicians must ask when evaluating a
new test is ultimately rather simple: “Is there evidence that individuals identified by the biomarker of interest will benefit from an intervention or therapy they otherwise would not have received?” For hsCRP, the answer is a solid “yes,” and for Lp(a), a solid “no”.

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