Biomarkers and Cardiovascular Disease: Determining Causality and Quantifying Contribution to Risk Assessment

Svati H. Shah; James A. de Lemos


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Determining Causality and Quantifying Contribution to Risk Assessment

Svati H. Shah, MD, MHS
James A. de Lemos, MD

Personalized medicine aims to use individual biological signals to improve disease detection, risk stratification, and therapeutic selection. Such a strategy holds great appeal to practitioners, who are increasingly disillusioned with the “one size fits all” approach that characterizes contemporary medicine. Key to achieving these goals is integration of genetics and biomarkers with currently available clinical data. While the model of personalized medicine is appealing, many questions remain about which markers are diagnostic, prognostic, or pathologic.

Studies combining genetics and biomarkers may help establish causality of a biomarker with disease. This may have particular clinical relevance when the biomarker is potentially modifiable, in which case a biomarker-guided targeted treatment strategy may be feasible. To establish this causal link, investigators have traditionally used observational data showing an association between biomarker and outcome. However, it is often unclear which associated variable is cause and which is effect. Further, the association may be confounded by unobserved variables. If a genetic variant is related to the biomarker but is not otherwise associated with outcome, then the relationship of genotype with outcome can be exploited to assess the causal relationship between biomarker and outcome. Specifically, if the relationship between biomarker and outcome is causal, then genotype should associate with outcome, with the magnitude predicted by the association of genotype and biomarker. This concept, termed mendelian randomization, is premised on the random assignment of genotype at meiosis, and hence is independent of confounding factors.1,2

C-reactive protein (CRP) is a well-established inflammatory and coronary heart disease (CHD) biomarker, but studies have been inconclusive regarding a causal role in CHD.3 In this issue of JAMA, Elliott and colleagues4 use a powerful multistaged study design to further evaluate this hotly debated topic. Using a genome-wide association study (GWAS) to identify genetic variants associated with CRP levels in several combined populations, they identified a single-nucleotide polymorphism (SNP) in the CRP gene strongly associated with CRP levels, with each minor allele associated with a 21% decrease in CRP level. A systematic review of 35 observational studies predicted that CHD risk would be reduced by 6% for this degree of CRP reduction. However, in the mendelian randomization experiment, this SNP was not associated with CHD in pooled studies, nor were 2 other CRP SNPs associated with CHD in separate meta-analyses.4

Mendelian randomization may be particularly helpful when direct intervention studies are not feasible due to the absence of a specific inhibitor of the biomarker. In the case of CRP, intervention trials to date have used drugs that affect multiple other risk factors such as lipids, body weight, and glucose metabolism and thus cannot definitively link lowering CRP levels to outcomes. The current findings from the study by Elliot et al.,4 considered together with prior mendelian randomization studies,5-7 strongly challenge a causal effect of CRP levels on CHD. Importantly, the strengths of the current study include its large sample size due to a remarkable international collaboration that facilitated multiple combined GWAS and CRP studies. These large sample sizes are required to generate sufficiently precise effect estimates to refute a causal effect using mendelian randomization.8

Three core conditions of mendelian randomization must be in place to ensure accurate inferences: (1) genotype is independent of confounding between biomarker and outcome, (2) genotype is associated with the biomarker (the stronger the association the better), and (3) genotype is independent of outcome except as mediated through the biomarker.2 In the case of CRP, Elliott et al confirmed these conditions. However, inferences about causality using mendelian randomization can also be influenced by linkage disequilibrium (CRP gene resides near another gene that causes CHD), pleiotropy (CRP SNPs influence other biomarkers that cause or prevent CHD), gene-gene interactions (false-negative conclusion due to failure to account for a second gene that modifies CRP levels),9 and canalization (compensa-
soratory changes in other systems counterbalance genetic elevations in CRP levels). Although none of these factors appears to be at play regarding CRP, unrecognized influences remain possible given the heterogeneous populations used in this study. Nevertheless, based on this and other studies, it is likely that CRP does not cause CHD and that reported associations between CRP and CHD are either confounded by other risk factors or represent reverse causality.

These results lead to an important question: does it matter whether CRP is a risk marker instead of a risk factor? The answer is both yes and no. Certainly, these null findings make it much less likely that therapies specifically altering CRP levels alone will prove beneficial. However, the study does not negate the role of inflammation as causal in CHD, nor does it exclude a potential biological interaction between drugs acting on other inflammatory pathways and CRP levels. If CRP increases in response to other inflammatory triggers, it may still be a useful tool for personalizing selection of anti-inflammatory therapies, including statins. Alternatively, CRP may emerge as one of several actuarial tools to help identify individuals with sufficiently high risk of CHD for whom statins or other preventive therapies will have favorable risk-benefit and cost-benefit profiles.

Another study in this issue of JAMA by Melander and colleagues focuses on the incremental value of CRP and other markers in quantitative risk assessment. Studying a low-risk population, the investigators found that 5 of 6 biomarkers studied were independently associated with coronary and cardiovascular events, yet these associations were quantitatively modest (adjusted hazard ratio, 1.12-1.37 per standard deviation increment) and failed to substantially improve model discrimination or risk reclassification beyond traditional demographics and risk factors. The largely null conclusions of this study are consistent with some but in sharp distinction to other population-based studies. The divergent results likely reflect several factors: (1) study population: the current study was generally low risk and biomarkers perform less well in such populations; (2) end points: many biomarkers (including those tested in the current article) are better predictors of mortality and heart failure than of nonfatal ischemic events and stroke; (3) reference model: incremental performance is more difficult to demonstrate over a data-derived risk factor model than a prespecified algorithm (ie, Adult Treatment Panel III); and (4) number and quality of biomarkers evaluated.

What are the implications of these 2 important studies? Ideally, biomarkers would also be risk factors and could be used for both risk assessment and to individualize specific therapies. Large collaborative investigations incorporating GWAS and mendelian randomization as highlighted by Elliott et al offer a blueprint for definitive evaluation of the causal role of intermediate traits such as biomarkers. Similarly, studies such as that by Melander et al exemplify the necessity of comprehensive appraisal of the value of novel biomarkers, including CRP, beyond standard risk factors in specific populations. Studies such as these will help determine which biomarkers are likely to be useful as specific drug targets but also whether they have a potential role in risk assessment or even therapeutic selection. In the future, better biomarkers and more creative strategies for combining them will be needed, along with comprehensive statistical and functional evaluation of causality, to fulfill the promise of biomarkers for personalized medicine.

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