Can Biomarkers Improve Prediction of Future Cardiovascular Events in Heart Disease Patients?

Shlipak MG, Ix JH, Bibbins-Domingo K, et al. Biomarkers to predict recurrent cardiovascular disease: the Heart and Soul Study. Am J Med 2008;121:50–7.

Study Overview

Objective. To evaluate the ability of 6 biomarkers to improve prediction of cardiovascular events among persons with established coronary artery disease (CAD).

Design. Prospective cohort study.

Setting and participants. Participants with CAD enrolled in the Heart and Soul Study. Participants were included if they had a prior myocardial infarction (MI), angiographic evidence of > 50% stenosis in ≥ 1 coronary vessels, exercise-induced ischemia as measured by treadmill or nuclear testing, or prior coronary revascularization. Data on clinical risk factors and laboratory tests were obtained at the time of enrollment. Biomarkers evaluated were N-terminal prohormone brain natriuretic peptide (Nt-proBNP), cystatin C, albumin/creatinine ratio, C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen.

Main outcome measures. Time to CAD death, nonfatal MI, and stroke.

Main results. Of 979 participants, 82% were men, 60% were white, and the mean age was 67 years. 142 participants experienced a cardiovascular event during an average follow-up of 3.7 years, including 87 MIs, 26 strokes, and 50 deaths from coronary heart disease. Among the 6 biomarkers evaluated, 5 were associated with cardiovascular events independent of clinical risk factors such as diabetes and hypertension. For these 5 biomarkers, the risk of cardiovascular events in the highest quartile (vs. the other 3 quartiles) was as follows: Nt-proBNP (hazard ratio [HR], 2.1 [95% confidence interval {CI}, 1.4–3.2]), CRP (HR, 2.0 [95% CI, 1.4–2.9]), IL-6 (HR, 1.8 [95% CI, 1.1–2.7]), cystatin C (HR, 1.7 [95% CI, 1.1–2.7]), and albuminuria (HR, 1.7 [95% CI, 1.2–2.5]). In a multivariable model evaluating all 6 biomarkers, Nt-proBNP, albuminuria, and CRP remained independent predictors.

Conclusion. Readily available biomarkers can help identify high-risk individuals in a cohort of patients with preexisting CAD. These biomarkers, which reflect comorbidities such as kidney damage and systemic inflammation, may be useful adjuncts for aggressive management and for reducing morbidity and mortality due to CAD.

Commentary

Although cardiovascular disease remains the leading killer of Americans, substantial progress has been made in reducing morbidity and mortality from this disease. The widespread use of therapies such as statins, β blockers, and angiotensin receptor blockers among patients with established CAD has lead to important improvements in survival. However, more remains to be done. Patients with CAD continue to die at alarmingly high rates. There are effective therapies, but they are not without side effects. Clinicians are often caught between wanting to avoid undertreating higher-risk patients and overtreating lower-risk patients.

Until recently, it has been difficult to identify which

patients with established coronary heart disease are at high risk. Traditional risk factors, such as smoking and hypertension, are helpful for identifying which patients will develop heart disease but are less helpful in patients with preexisting heart disease [1]. This is why biomarkers are potentially useful. If clinicians can use simple, readily available laboratory tests (beyond cholesterol levels) to predict which patients are at high risk for subsequent coronary events, they can more aggressively treat those with concerning biomarker profiles and back off on others.

This study by Shlipak and colleagues is a helpful step on the long journey of using biomarkers to guide clinical management. Six biomarkers were evaluated, 5 of which added substantial information (identifying which patients will have recurrent cardiac events) beyond what was available using standard cardiovascular risk factors (eg, diabetes, smoking, cholesterol, or blood pressure). Further, the effect size for these biomarkers was impressive. For instance, patients who had Nt-proBNP values within the highest quartile had more than twice the risk of having a cardiovascular event. Finally, even when the biomarkers were evaluated simultaneously, 3 of them (Nt-proBNP, albuminuria, CRP) continued to add important prognostic value in identifying patients at high risk.

Although this study adds important insights, caution is needed before these biomarkers are used for this purpose in clinical practice. First, the biomarkers were evaluated at the time of study enrollment, and we do not know whether they were elevated just prior to a cardiovascular event. If the levels of these biomarkers fluctuate significantly or normalize before an event, it can lead to a significant number of false-positive and false-negative results. Second, and more importantly, we do not know if aggressively treating patients with elevated biomarkers reduces their risk of future events. It is possible that elevated biomarkers identify sicker patients who are fated to have more cardiovascular events, and therefore more aggressive therapy will not lower this risk. Only a clinical trial that uses biomarkers to segregate and differentially treat patients can answer this question. Finally, the study examined a predominantly male population with preexisting heart disease. Whether these biomarkers are useful in women or in those without known heart disease is unclear.

Applications for Clinical Practice

The use of biomarkers is an increasingly promising approach to identifying high-risk patients. However, before biomarkers are widely used, we need to better understand whether they are stable over time, useful in women, and helpful among patients without known heart disease. Most importantly, we need to know whether aggressively treating patients with elevated biomarkers leads to improvements in morbidity and mortality.

—Review by Ashish K. Jha, MD, MPH

Reference

1. Vittinghoff E, Shlipak MG, Varosy PD, et al; Heart and Estrogen/progestin Replacement Study Research Group. Risk factors and secondary prevention in women with heart disease: the Heart and Estrogen/progestin Replacement Study. Ann Intern Med 2003;138:81–9.