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SUPPLEMENT

Biomarkers and Heart Disease

Michelle A. Albert, M.D., M.P.H.
Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

This review will focus on the evaluation of biomarkers and surrogate endpoints in chronic disease risk with a focus on cardiovascular disease. It provides an example of how identification of relevant biomarkers might be useful in sleep research and clinical care. Much of this review is derived from work performed by the Institute of Medicine (IOM) Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease (see footnote in the Acknowledgments).[1] This discussion will review the committee charge, definitions of biomarkers and other endpoints, biomarker evaluation framework, case studies of representative biomarkers, recommendations, and conclusions.

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What is the genesis of interest in biomarkers and disease risk? Biomarkers are very important because they can be used in research studies as surrogate endpoints to enable more rapid performance of clinical studies, predict disease risk, monitor disease status, and provide information that might be useful for life-saving or health-promoting interventions. For example, blood pressure is a biomarker as is body temperature. These are biomarkers or surrogate endpoints that you don't really think about. However, policy makers make decisions about health care based on information from clinical trials using such biomarkers.

In the last decade, there has been an explosion of biomarkers in the research arena particularly in the domains of cardiovascular disease and cancer, however many of these biomarkers are actually not yet clinically available. Consequently, the Federal Drug Administration (FDA) is concerned about the lack of clear guidance about the use of biomarkers as surrogate endpoints, particularly since it is almost impossible to equate most available biomarkers with actual disease outcome. Hence, the FDA funded a study by the Institute of Medicine (IOM) to provide guidance. Therefore, the IOM committee's charge was to: 1) evaluate risk biomarkers and surrogate endpoints in chronic diseases, using cancer and cardiovascular disease as prototypes; 2) use existing prototypes to develop a framework that can be employed by various entities including the National Institutes of Health, Congress, and the FDA to assess the utility of biomarkers as surrogates in particular disease processes.

Before progressing further, it is necessary to provide some definitions. A biomarker represents a normal biological or pathogenic process, or pharmacologic response to an intervention. An example of a surrogate biomarker is the association of cholesterol level with cardiovascular disease risk. *What is a surrogate endpoint?* A surrogate endpoint is, for example, a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit or harm, or lack of benefit or harm as a result of an intervention, or a period of observation. LDL cholesterol, for example, is commonly used to approximate the risk for cardiovascular disease. Blood pressure is used similarly. In fact, these are the two primary biomarkers that are actually qualified by the FDA as being able to act as surrogate endpoints although these biomarkers are less than ideal. *A clinical endpoint* is a characteristic or variable that reflects how a patient or consumer feels, functions, or survives. Often, survival is the primary clinical endpoint with relatively little importance placed on how a patient feels or functions. However, the issue of quality of life is of paramount importance. This is particularly true in cardiovascular disease, where the heart failure epidemic is a major source of morbidity or mortality. The core issue is: will quality of life and longevity be maximized by the use of surrogate biomarker endpoints? With respect to sleep disorders, there are important quality and quantity of life issues related to car crashes and sleepiness.

What are the Stakeholder Concerns?

There are many organizations, institutions and individuals who have a stake in identification and use of biomarkers. Patients, the public, clinicians, the FDA, healthcare policy, researchers, advocacy and regulators, the legal community, peers and insurance, pharmaceutical companies, and device companies all have a very strong interest in this arena.

Obviously, many stakeholders are concerned about public safety. They want to ensure that biomarker surrogate endpoints may be used to reduce disease burden. There is also a financial concern because of the need to contain healthcare costs; appropriate patient care innovation must be encouraged while minimizing discrimination. This is discrimination in both a scientific as well as a social sense. For example, if the police perform a traffic stop related to drowsiness, you need to have good criteria for determination of drowsiness since our country has a legacy of societal discrimination. And of course there is scientific discrimination related to statistical sensitivity and specificity of the biomarker. As a result, the surrogate endpoint would need to be a valid representation of disease for which it is a marker. Moreover, evidence that the surrogate endpoint approximates the disease in multiple populations based on geography and demographic characteristics is also critical. Furthermore, a well defined process for legal recourse related to privacy issues

must exist, a factor that may become increasingly important as genetic biomarkers of disease risk remains the rave.

Biomarker Examples

Ongoing challenges for biomarker identification include the need for objective assessment, measurement precision, meaningful replication (particularly important for genetic biomarkers) and reliability. Furthermore, it is extremely important that the biomarker captures disease course pathophysiology in order to reflect the correct disease outcome. The biomarker examples discussed in this review will focus primarily on cardiovascular disease.

Blood Pressure: One successful biomarker used as a surrogate endpoint for cardiovascular disease is blood pressure. However, blood pressure as a surrogate is only really robust for primary prevention of cardiovascular disease. It is associated with mortality from myocardial infarction, as it relates to use of diuretics and beta-blocker drugs. However, blood pressure is a poor surrogate for secondary endpoints of cardiovascular disease. For example, blood pressure changes after administration of alpha adrenergic blockers do not necessarily reflect in mortality improvement.

Premature Ventricular Contractions: Over two decades ago, the premature ventricular contraction (PVC) hypothesis was advocated. Investigators noted, particularly in the setting of the intensive care unit that post-myocardial infarction patients with more than 10 PVCs per hour were at increased risk for fatal arrhythmias and recurrent myocardial infarction. It was felt that PVCs represented a biomarker or surrogate endpoint for risk of sudden death, which could be reduced if the PVCs were suppressed with medication. Since many clinicians strongly felt that it was unethical to not give patients anti-arrhythmic therapies for PVCs, over 200,000 patients actually used these drugs. Thereafter, a pivotal randomized placebo-controlled clinical trial named the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that use of the anti-arrhythmic agents, ecainide and flecainide after myocardial infarction for PVC suppression actually increased the incidence of sudden death compared to placebo.[2] Other trials quickly followed demonstrating similar findings for other anti-arrhythmic agents. This is another example of where a putative biomarker or surrogate end-point did not accurately reflect the desired clinical end-point.

LDL Cholesterol: In contrast, LDL cholesterol is a much better example of a generic surrogate endpoint that generally reflects cardiovascular risk. In fact, national guidelines advocate lowering LDL cholesterol in order to help decrease cardiovascular risk.

In discussions about biomarkers and their relationship to chronic disease risk, it is important to ensure that the biomarker/surrogate is along the causal pathway of the clinical outcome. It is also important to realize that evaluation of biomarkers is a complex process. There can be multiple biomarkers and causal pathways as well as several different clinical outcomes. In some cases, a biomarker or surrogate endpoint may be correlated with a true clinical outcome as is often demonstrated in cross-sectional studies, but the surrogate endpoint might not be on the causal path of the clinical outcome. Consequently, "an associated biomarker" may not be actually measuring what you intend. Thus, when an intervention is given in relation to a biomarker/surrogate, that intervention may be affecting the pathway of the surrogate outcome but not the mechanism of the clinical outcome.

Why is the Investigation of Biomarkers Flourishing?

Utilizing biomarkers in research and clinical care is in part appealing because outcomes of randomized, controlled trials take a long time to occur and these trials are costly. By contrast, measurement of a biomarker level can be much quicker than an outcome-driven clinical trial.

Institute of Medicine Biomarker/ Surrogate Endpoint Framework

The core task of the IOM committee was to recommend a framework to evaluate biomarkers and surrogate endpoints in chronic disease. Three steps were proposed: 1) analytic validation; 2) qualification; and 3) utilization.

Analytic validation refers to whether a potential biomarker is reliable, reproducible across multiple laboratories and clinical settings, and maintains adequate sensitivity and specificity.

Qualification requires an evaluation of the nature and strength of evidence supporting whether a biomarker is on the causal pathway of a disease entity. However, different levels of evidence may be required depending on the disease process involved. The qualification process may be quite different if the disease process is pancreatic cancer versus hypertension in that the former might require lower levels of evidence. Another example specific to this conference might be evidence linking sleepiness to IL 6 or C-Reactive Protien (CRP), obstructive sleep apnea to apolipoprotein levels, and obstructive sleep apnea to different inflammatory biomarkers. However, caution is advised because many studies are small or cross-sectional and their results do not necessarily equate to disease risk. This lesson has been learned in both cardiology and oncology as both disciplines remain at the forefront of the biomarker explosion. The second component of qualification requires that the available evidence demonstrates that interventions targeting the biomarker impact the clinical endpoints of interest. One example is the use of "statin" therapy for lowering LDL cholesterol. In this case, it is necessary to assess the importance of the degree a "statin" drug lowers LDL cholesterol, and then consider whether the amount of reduction does or does not have a relationship to the clinical outcome, cardiovascular disease.

Utilization attests to the context within which the biomarker will be used and thus depends on the specific proposed use in addition to the strength of the available evidence. Therefore, utilization includes determination of whether the validation and qualification conducted provides sufficient support for the use proposed. Strong evidence and a compelling context are needed for the utilization of a biomarker as a surrogate endpoint.

Although the biomarker evaluation process appears to be three independent steps, it is not. These three steps are all inter-related in that you can't have qualification without analytic validation or utilization without qualification.

A Biomarker Case Study: High Sensitivity C-Reactive Protein (CRP) in Cardiovascular Disease

CRP is an acute phase reactant produced by the liver, strongly regulated by IL-6 concentrations. CRP is associated with

obesity because adipose tissue releases IL-6. CRP is also produced by the smooth muscles cells of coronary arteries. The assay for CRP has been validated and standardized. Studies associating CRP and disease risk date to the 1950s primarily in the gynecology literature. However, formerly the assays were not high-sensitivity, meaning that they measured CRP levels that were greater than 10 mg/liter. Today, CRP is measured with so-called high-sensitivity assays which measure levels within the normal range of CRP.

Multiple epidemiologic studies demonstrate that CRP is a risk predictor of cardiovascular outcomes. However, the pathophysiologic role of CRP is uncertain. Therefore, although it provides additive predictive information to both the lipid profile and the Framingham Cardiovascular Risk Score, whether it is part of the causal pathway engenders ongoing debate. Intervention trials show that it is possible to lower both LDL cholesterol and CRP with the use of a "statin" medication. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) shows that giving a "statin" compared to placebo resulted in not only lowering CRP, but decreased also cardiovascular event risk by 44%.[3]

In summary with respect to CRP and the framework proposed by the IOM, the analytic step is satisfied, the strength and association (qualification) step is also sound and you have at least one intervention step. Therefore, the IOM committee concluded that CRP is an independent predictor of future cardiovascular events, including myocardial infarction, ischemic stroke, peripheral vascular disease, and vascular death. In the qualification step of biomarker evaluation, evidence was found for CRP's prognostic value but not for use as a surrogate endpoint. Thus, although evidence from this large "statin" trial with over 16,000 participants demonstrates a 44% reduction in cardiovascular risk, it is not known whether the data can be translated to other interventional agents or behavioral interventions.

There are some other cautionary concerns with biomarker use to approximate disease risk. Is the biomarker useful in all demographic groups? What is the cost, both monetary and for some biomarkers psychologic cost to an individual/population? Are there factors that modify the usefulness of the biomarker? All of these are important issues to take into consideration when assessing the utility of a biomarker.

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CORRESPONDENCE

Address correspondence to: Michelle A. Albert, M.D., M.P.H., Cardiology, Tower 3B, 75 Francis St., Boston, MA 02115; E-mail: maalbert@partners.org

DISCLOSURE STATEMENT

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