Markers of Malign Across the Cardiovascular Continuum
Interpretation and Application

Cardiovascular disease is the consequence of a complex series of events that begins with one or more homeostatic imbalances initiated by abnormal gene environment interaction(s). Factors or agents that induce biochemical or physical stress/injury can elicit pathophysiological responses that include molecular, cellular, tissue, and/or integrative processes. Accordingly, the responses may be of a systemic, circulating, or local nature. In genetically susceptible individuals, these pathophysiologic responses can result in tissue damage, ultimately leading to impaired tissue function, target organ failure, clinical events, or death.

Physicians are challenged with predicting which individual is at risk for developing disease, identifying causal factors, assessing the presence of underlying disease processes, ascertaining whether early target organ damage already exists, and evaluating the effect of the prescribed therapy. In the clinic, these issues are very difficult. More than 50 years ago, William Kannel first popularized the concept of cardiovascular disease risk factors for clinicians and clinical epidemiologists. Risk factors, in his initial broad definition, were used as predictors of cardiovascular disease. Thus, the presence of one or more risk factor predicted the increased likelihood of the later development of cardiovascular clinical events. Although not all risk factors cause disease, some, such as hypertension and hypercholesterolemia, undoubtedly are also causal factors. The establishment of a factor as causative for disease requires extensive experimental studies and, importantly, clinical interventional trials that clearly document that reducing the level of the factor prevents or attenuates disease development and/or clinical events. There is little question that identification of causal factors will yield the greatest benefit in terms of prevention or intervention. However, much is still unknown of the factors that cause cardiovascular disease. Debate exists on the contribution of infectious agents, immunological processes, nutritional factors, and environmental agents. Indeed, in patients with coronary heart disease, up to 50% do not have elevated serum cholesterol or other traditional risk factors. Thus, the presence of risk factors helps us to identify those who are in need of early or aggressive treatment.

The evaluation of disease process or target organ response/damage in patients has traditionally involved difficult and cumbersome methods that are frequently time consuming, insensitive, and expensive. With improvement in the understanding of pathophysiology and the development of sensitive, specific, and simpler technologies, the notion of early detection and monitoring has become increasingly attractive. Thus, the concept of markers has been introduced in the last several years. A marker is a measurable variable that can be a substance found in an available biological sample, such as blood or urine, or can be detected in tissue imaging, such as aortic calcium deposits using electron-beam computed tomography (EBCT). The relationship of markers to the disease process also varies. A marker might reflect underlying disease pathophysiology, predict future events, or indicate the presence of disease or damage to an organ. A marker could also be measured to assess the progress of treatment. Occasionally, such a marker may function as a causative factor. However, validation and qualification of a marker as a causative or predictive factor is a complex process potentially requiring large prospective clinical trials. An established method of measurement of a marker and guidelines for interpretation of the results of the measurement must be available for it to have diagnostic value.

The measurement of markers has proven to be valuable in determining the extent of the burden of cardiovascular disease, both in an individual patient and in populations. The assessment of markers has increased the understanding of the pathophysiology of disease at both the organ and cellular levels. An example is the identification of cytokines and chemoattractants that mediate inflammation as markers of atherosclerotic vascular disease. In addition, recent evidence indicates that blood levels of C-reactive protein, which is involved with the inflammatory response, have the potential to predict future cardiovascular disease.

Although a clinical outcome is the strongest indicator of disease, identification and measurement of disease markers are desirable for several reasons. Markers can be useful as sensitive detectors of early target organ damage. For example, microalbuminuria is one of the most sensitive measures of kidney disease. Markers may be used as monitors of disease progression, as well as of the effect of treatment in arresting disease progression. Although clinical events/outcomes are undoubtedly the most valuable end points in evaluating a specific treatment, these involve large-scale, multi-year, expensive clinical trials. Surrogate markers of clinical outcome have been proposed as alternative end points instead of clinical events for trials. Currently, much debate exists as to the general acceptability of this approach to evaluate treatment outcome.

Advances in technology play an important role in the effort to identify markers. The development of specific and sensitive methods for reproducible measurement of substances in biological samples and of physiological functions is impor-
tant to the clinical value of markers. Progress in the understanding of the mechanisms of various cardiovascular diseases at the molecular level forecasts a future where differences in both circulating proteins and gene expression are measured. With the complete sequencing and mapping of the human genome, we now have the capacity to study the differential expression of thousands of genes in diseased versus normal tissues, and to identify genetic variations that influence disease susceptibility and individual variances in response to therapy. The ability to measure variations in gene expression associated with disease phenotypes using rapid, high-throughput protein and genomics and proteomic techniques will lead to the identification of novel markers. The findings of basic research on molecular mechanisms and gene expression analyses must then make the transition to clinical application. Genetic markers will be valuable not only in predicting an individual’s susceptibility to disease, but also in improving outcomes through individualized therapy.

In recent literature, there is a proliferation of reports on new markers and factors that are variously called novel risk factors, biomarkers, surrogate markers, etc. Much of these data have provided new and useful information and new avenues of research. However, some have created confusion in their use of terms, definition, and clinical impact. To that end, this supplement to Circulation represents the collective efforts of expert clinicians and scientists in the field to review our current understanding of risk factors, biomarkers, surrogate markers, and genetic markers. In each article, there is an emphasis on the definition of terms, and the evolution of the terminology is included to describe how individual factors were identified and categorized. A table of available markers that attempts to be inclusive is provided where appropriate. Each article is not intended to be a comprehensive review of each category; rather, selective factors and markers are discussed in more detail to exemplify the utility and value of each marker in particular and the category in general. Atherothrombosis is the specific disease process predominantly used, because it is the most prevalent cardiovascular disease in the population. However, because atherothrombosis is not the only form of cardiovascular disease, other conditions are discussed when appropriate.

It is acknowledged that some of the presented material is controversial and may reflect more the opinion of the author of that section. To mitigate this situation, explanations are given as to the rationale for choosing a particular marker for discussion, including evidence of the clinical utility. Areas of controversy are included because one of the purposes of this supplement is to recognize that there are differences of opinions on a topic. Disagreements and unresolved topics are the basis of the discussions included at the end of each section. Another purpose is to inform the reader of how to use the information in the clinic. Although research is the basis for identification of markers, the contributors have been diligent in making clear the clinical relevance of the topics.

In addition to exploring emerging areas in the development of factors and markers, an overall goal of this supplement is to describe unmet needs and to propose prospective studies that have the potential to meet these needs. The intention of this supplement is to address some of these important issues and develop a consensus agreement on definitions of the terminology and use, leading to an increased understanding of the clinical value of risk factor, biomarkers, surrogate markers, and genetic factors. Furthermore, this supplement is not intended to be all-inclusive but illustrative; not encyclopedic, but to bring into focus the resolved and unresolved aspects of this important area of cardiovascular diseases. Finally, these articles represent a starting point for future discussions in an expanding, evolving field.

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