Introduction to Surrogate Markers

The clinical complications of atherosclerosis and atherothrombotic disease represent the major causes of morbidity and mortality in the United States and worldwide. The disorders that shorten life expectancy include myocardial infarction and ischemia, heart failure, stroke, renal failure, peripheral vascular disease, sudden death, and dementia, in all of which atherothrombotic disease is the most common cause. Efforts to delay or prevent these morbid events have been the focus of all clinical trials aimed at documenting the efficacy of therapeutic interventions. Furthermore, these events have served as the definition of disease used to establish population risk and risk factors.

The underlying disease that eventuates in these morbid events begins in the arterial wall and progresses through well-known mechanisms that include endothelial dysfunction, inflammation, plaque formation, plaque rupture, and thrombosis. Risk factors are markers that are statistically related to the risk of morbid events, presumably because they identify or contribute to one or more of the vascular processes that lead to these events, but they do not necessarily identify the disease itself. New insights and expanding technology now make it possible to identify and track the progression of the arterial wall or end-organ disease instead of relying on the statistically related risk factors. The availability of reliable markers for the disease might ultimately allow disease progression to replace end-point events as a guide to the risk of disease and its response to therapy. Such a shift in emphasis would allow more precise assessment of factors associated with disease progression, could encourage smaller and shorter intervention trials, and would facilitate the study of earlier phases of disease not likely to precipitate short-term morbid events.

The traditional term used to describe these markers for disease progression is “surrogate.” The conventional view is that a surrogate, to be a reliable substitute for a morbid event end point, must track with the frequency of the end point both as an epidemiologic marker and as a therapeutic responder. But certain caveats must be recognized regarding both the end points and the surrogates. The morbid cardiovascular events cited above represent the complications of cardiovascular disease that reduce duration and quality of life and consume health care expenditures, but not all such events are consequences of atherosclerotic or atherothrombotic disease that may be associated with identified risk factors and markers of vascular disease. For example, cardiomyopathies, valvular heart disease, and genetic vascular disorders all may contribute to morbid events. Furthermore, the difficulty in assigning mechanism of deaths means that deaths not related to cardiovascular disease may often be included among the events attributed to atherothrombotic disease in a population.

Surrogate markers may take several forms. Demonstrable structural abnormalities of the arteries or heart appear to be direct markers of the cardiovascular disease process that, in the absence of effective therapy, would be expected to progress with time. Effective therapy could halt or slow the trajectory of progression. Coronary angiography and intravascular coronary ultrasound invasively measure the status of the coronary tree and, as such, cannot be considered surrogates for the presence of disease. On the other hand, several noninvasive methods that do not directly measure coronary disease are nonetheless commonly used as surrogates for the presence of cardiovascular disease, of which coronary disease is one manifestation. We have chosen to focus on two noninvasive vascular and cardiac assessments, carotid artery wall thickness and left ventricular mass, as examples of structural surrogate markers.

Functional surrogates are more complex. Some are markers, although imperfect, for the underlying structural cardiovascular disease. Some may also contribute to the structural disease itself. With some, amelioration of the surrogate may be expected to reduce the risk of a morbid event, but with others it is less certain that response of the surrogate is a prerequisite for a benefit on the disease process. In the latter instance, the surrogate may be a sensitive marker for the likelihood of disease but not a useful therapeutic target. In the section entitled “Functional Surrogate Markers” we will explore blood pressure, endothelial dysfunction, arterial wall compliance or stiffness, and albuminuria. These have all been demonstrated to be useful markers for underlying vascular disease.

In dealing with mortality or morbidity end points versus surrogate markers for the underlying disease process it is important to distinguish between therapeutic efficacy and safety. A treatment may slow progression of disease as assessed by so-called surrogate markers, but concomitant adverse effects (eg, electrolyte disturbances, arrhythmias, hypotension) might cause deaths. Thus, end points may not allow distinction between efficacy and safety. If a treatment is designed to slow progression of vascular or cardiac disease, structural or functional surrogates may better track efficacy on the disease process, whereas mortality and morbidity end points are needed to assess the net benefit on outcome. Indeed, such an approach would be necessary to develop strategies (eg, defibrillators) to counteract adverse effects of an intervention that might otherwise be efficacious.

The fact that morbidity and mortality events do not serve as a sensitive or specific guide to disease progression renders surrogate markers an important potential contributor to understanding the natural history of disease and its response to therapeutic intervention. Some potential surrogate markers progress with time; therefore, an alteration in the surrogate may be a slowing of the time-dependent progression rather
than necessarily a normalization of the surrogate. This concept of progression and the trajectory of time-dependent structural or functional measures as predictors of subsequent events are critical in understanding the value of certain surrogate markers.

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