Risk Factor Criteria

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The concept of the risk factor for chronic diseases, such as cardiovascular disorders, is derived from the application of epidemiological methods initially developed for infectious and nutritional deficiency diseases to chronic conditions to identify the factor(s) linked to the development of the chronic disease. Typically in infectious or nutritional deficiency conditions, a single causative agent or primary cause is identified. Thus, the cause of tuberculosis is the tubercle bacillus, and the cause of pellagra is niacin deficiency. However, for cardiovascular diseases, in which causes are usually complex and multifactorial, new concepts were required. For example, individuals with hypertension have a far greater risk for cardiovascular disease than those without hypertension, but many individuals with hypertension never have clinical sequelae, and many individuals with diagnosed cardiovascular diseases have no hypertension. One can also argue that many individuals who are exposed to the tubercle bacillus do not develop clinical tuberculosis, but the converse is not true; no one has tuberculosis without the tubercle bacillus. This provides a clear distinction between multifactorial diseases, such as coronary disease where the risk factor concept is paramount, and other health conditions.

The initial application of the risk factor concept was well developed long before the term was coined. Early in the previous century, insurance companies noted that individuals with high blood pressure were at higher risk for premature mortality and therefore would be accepted for life insurance with high blood pressure were at higher risk for premature mortality until later.

Although the underlying concept had been widely discussed and applied, the term “risk factor” was coined by Dr. William Kannel, one of the pioneers of the Framingham Heart Study. The term was used in the medical literature by 1961. Although the derivation of the word “factor” from the Latin (meaning doer) implies causality, from its initial use, the term risk factor included both causal and predictive factors (Table 1). Hypertension was perhaps the first well-established cardiovascular risk factor. Regardless of the underlying cause of high blood pressure (eg, renal artery stenosis, obesity, etc), hypertension directly contributes to cardiovascular disease risk and it predicts cardiovascular disease, according to findings from the Framingham Heart Study. Subsequent clinical trials showed that medications that lower blood pressure reliably reduce cardiovascular disease risk, thus documenting the causal link. In contrast, male sex and age are both also considered classical risk factors, yet these clearly are not causal in the same way as hypertension. Not only are they not amenable to treatment, they also contribute to risk in largely unknown and complex ways.

Typically, risk factors are surrogates for deeper causes (and better predictors) of cardiovascular disease. A good illustration of this concept is overweight. Body weight is correlated with height, so measures of weight adjusted for height, such as the body mass index (BMI), were developed to better reflect overweight. However, this is only partly a reflection of adiposity. Bone and muscle also contribute to weight; heavily muscled athletes can have a relatively high BMI without excess adiposity. Moreover, with older age, as both muscle and bone are lost, an individual could remain at the same weight and close to the same BMI, but attain a substantial increase in adiposity. Because weight is so easy and inexpensive to measure with great accuracy, it has been retained as a risk factor (adjusted for height), although related measures of adiposity, such as waist circumference, are gaining favor. Even adiposity itself may not be the true underlying factor, because fat depots in different parts of the body have varying degrees of metabolic activity, supporting the concept of abdominal obesity.

Identification of a risk factor does not have, necessarily, any immediate clinical implication. If a risk factor is associated with occurrence of disease but is not itself causal, then changing that factor may have no impact on the disease. The efficacy of specific interventions should be evaluated in randomized trials whenever feasible. Moreover, when possible, such trials should assess clinical end points, not merely the change in risk factor levels. Thus, assessment of a new antihypertensive medication should involve a randomized trial comparison against current known effective therapies with clinical outcomes (including side effects). Simply demonstrating efficacy for blood pressure reduction may not be sufficient. Another example is homocysteine, which has been found in some, but not all, studies to be an independent predictor of cardiovascular disease risk. Even if this associ-
TABLE 1. Selected Risk Factors and Biomarkers in Cardiovascular Disease

<table>
<thead>
<tr>
<th>Risk Factor/Biomarker</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Traditional risk factors</td>
<td>Smoking, hypertension, glucose intolerance, diabetes, hyperlipidemia (total cholesterol, LDL, HDL, triglycerides), low exercise levels, male gender, older age</td>
</tr>
<tr>
<td>Physical signs</td>
<td>Obesity, body mass index, ankle-brachial index, palmar/tuberoeruptive xanthomas, corneal arcus</td>
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<tr>
<td>Novel plasma-based biomarkers</td>
<td>Lipoprotein(a), apoA, apoB, particle size, particle density</td>
</tr>
<tr>
<td>Nontraditional lipid markers</td>
<td>hsCRP, SAA, IL-6, IL-18, TNF, cell adhesion molecules, CD40 ligand, MPO</td>
</tr>
<tr>
<td>Markers of hemostasis and thrombosis</td>
<td>Homocysteine, tPA/PAI-1, TAFI, fibrinogen, D-dimer</td>
</tr>
<tr>
<td>Markers of oxidation</td>
<td>ox-LDL, glutathione</td>
</tr>
<tr>
<td>Imaging-based biomarkers</td>
<td>Carotid intima-medial thickening, coronary calcification, magnetic resonance imaging angiography</td>
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<tr>
<td>Noninvasive</td>
<td>Coronary angiography, intravascular ultrasound</td>
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<tr>
<td>Invasive</td>
<td></td>
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<tr>
<td>Genetic biomarkers</td>
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<td>Proteomic biomarkers</td>
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Apo indicates apolipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LDL, low-density lipoprotein; MPO, myeloperoxidase; ox-LDL, oxidized low-density lipoprotein; PAI-1, plasminogen activator inhibitor; SAA, serum amyloid A; TAFI, thrombin activatable fibrinolysis inhibitor; TNF, tumor necrosis factor; tPA, tissue plasminogen activator.

lation were firmly established, one could not infer that homocysteine-lowering remedies would consequently lower risk of heart disease. Homocysteine-lowering interventions must be tested in randomized trials. Several such trials have been completed or are in progress.

It is important to distinguish between causal risk factors that directly reflect the underlying biology of the disease and risk factors that are used solely for prediction, to identify those at higher risk. All predictors of cardiovascular risk ultimately have some biological basis, of course. Sometimes, a predictor may simply reflect another, more proximal risk factor. For example, having yellow fingers might predict risk of myocardial infarction because it identifies heavy cigarette smokers. Sometimes risk predictors reflect a combination of biological factors. For instance, socioeconomic status is linked with risk of cardiovascular disease. Part of this association is attributable to differences in prevalence of cigarette smoking, degree of physical activity, dietary factors, and other behavioral determinants. One goal in risk factor research is to move ever closer to the proximal direct causes of disease. A complementary goal is to improve prediction to identify individuals who are more likely to develop cardiovascular disease and who therefore should be receiving more intensive interventions where possible. In this context, age is an important predictive risk factor. The reason that age is so strongly linked with cardiovascular disease is largely unknown and probably reflects a summation of a wide array of complex biological activities. However, despite our ignorance of the biological mechanisms, age is a critical predictive factor.

For clinical prediction models, a variety of criteria naturally arise for risk factors that might be useful and practical. First, the factor should actually predict the occurrence of disease. That is, those with the factor or with higher levels have higher rates of disease. The factor should be present and measurable before the clinical appearance of the outcome. In this context, a risk factor is usually validated from large epidemiological studies in which the factor is measured in a large cohort of individuals who are followed prospectively for development of the disease. To be useful in a clinical setting, the measurement of the factor must be sensitive, specific, and practical. A practical measure cannot be too expensive, uncomfortable, or dangerous. This implies that the factor being assessed must have a sufficient prevalence in the population. For example, a genetic polymorphism (hypothetical) in the gene encoding the low-density lipoprotein (LDL) receptor that confers a 2-fold increase in risk might be an important risk factor if it were common in the population, but not if it were present only in 1 in a million individuals. This issue underscores the importance of prospective large cohort studies, especially epidemiological population studies.

These criteria also imply that to be useful, the factor must be an independent predictor of risk. That is, it must improve the predictive power of other risk factors already identified and used for prediction. This typically might be shown in statistical models where the fit of the predictors to the outcome data are significantly better when the putative risk factor is included in the model, as compared with a model without that factor. Considerable weight has been given to the importance of the statistical independence of a risk factor. The independence of risk factors partly reflects the biology, but partly reflects other issues. For example, the biological directly important risk factor may not appear as independent if it is highly correlated with another factor that is measured with greater accuracy. Sometimes risk factors are highly correlated, and the one factor that emerges as independent may vary depending on the characteristics of the measurement and the population. For example, LDL cholesterol and apolipoprotein B (apo B) levels both strongly predict risk of myocardial infarction and are highly correlated because they largely reflect the same biological entity (LDL particles). Because of the high correlation, for prediction models, it usually will not matter a great deal which is chosen for inclusion, as long as the laboratory measurement is accurate.
of number of LDL particles as opposed to their lipid content, these issues loom larger.

The utility of a risk factor for practical application must be based on sound clinical judgment, not simply statistical tests. Risk factor assessments are useful only to the extent that they affect therapeutic decision making. That should remain the keystone for decisions regarding the utility of newly defined risk factors. A decision to make a recognized risk factor in part because of the ease with which it is measured. Thus, had a simple, inexpensive, and reliable assay for apo B been invented long ago, that may well have considered the risk factor to measure rather than LDL cholesterol.

A related example of a traditional risk factor that has been refined over the years is serum cholesterol. Total cholesterol is clearly a predictor of increased risk of coronary disease, but distinction of its component parts improves prediction dramatically. High-density lipoprotein (HDL) cholesterol is a strong predictor for decreased risk, whereas LDL strongly predicts increased risk. One may speculate that one reason for the delay in accepting HDL as a risk factor (for decreased risk) was that, unlike LDL, there was no immediate pharmacological intervention. The delay in recognizing the importance of HDL may, in part, stem from the difficulty in distinguishing risk factors as predictive markers, as opposed to precursors of disease that are readily amenable to treatment. Another example is high-sensitivity C-reactive protein (hsCRP). Strong evidence supports hsCRP as an independent predictor of coronary disease, but whether it is directly causal is uncertain. This issue is explored in greater detail in a section of this supplement on plasma-based biomarkers.

Another useful conceptual distinction is between risk factors and markers of early disease. Markers of early cardiovascular disease might include aortic calcification and carotid intima-media thickening. These markers can be predictors of the future occurrence of clinical outcomes, yet they typically are not considered risk factors, but rather are seen as reflections of the atherosclerotic disease process. In practice, this distinction may be difficult and unnecessary. Perhaps these markers can be considered risk factors if they are validated in large cohort studies and prove useful for routine population testing. At this time, such markers could potentially be useful in prediction to identify high-risk individuals for aggressive intervention. In addition, they may be informative for the biological progression of disease.

During the past 50 years since the term was coined by Dr. Kannel and used in cardiovascular epidemiology, the concept of a risk factor has been refined and developed. Established risk factors have enabled reasonably accurate assessment of risk among groups and individuals to provide guidance for management. In addition, risk factors have provided important clues to the biology of cardiovascular diseases. Despite advances, our ability to predict the occurrence of clinical events in individuals according to their risk factor status is limited. A case in point is that only 50% of patients with coronary artery disease have elevated serum cholesterol. As new risk factors emerge and are evaluated, it will be important to consider the distinctions and utility criteria described.

In a recent perspective on novel risk markers and clinical practice, Teri Manolio3 provided a thoughtful commentary listing 5 characteristics that should be evaluated to consider the routine applications of new markers for patient care (Table 2). First, the measure should add important independent information about risk of prognosis, beyond that which could be gleaned from current standard measures. Second, the measure should account for a large proportion of the risk associated with the given disease or condition. This is a function of a combination of the magnitude of the risk and the prevalence of the risk factor, as discussed earlier. However, for common conditions such as cardiovascular disease, accounting even for a modest proportion of risk could have important public health and clinical implications. Third, the measure should be reproducible, and fourth, as a diagnostic tool it should be sensitive and specific so as to provide a high predictive value. The fifth characteristic is that the test should be available and practical to implement. Careful consideration of these factors can guide the useful transition of new markers into clinical practice and improved patient care.

**References**


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