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## Identifying Patients at High Risk of a Cardiovascular Event in the Near Future:

### Current Status and Future Directions: Report of a National Heart, Lung, and Blood Institute Working Group

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### Abstract

The National Heart, Lung, and Blood Institute convened working group to provide basic and clinical research recommendations to the National Heart, Lung, and Blood Institute on the development of an integrated approach for identifying those individuals who are at high risk for cardiovascular event such as acute coronary syndromes (ACS) or sudden cardiac death in the “near term.” The working group members defined near-term as occurring within 1 year of the time of assessment. The participants reviewed current clinical cardiology practices for risk assessment and state-of-the-science techniques in several areas, including biomarkers, proteomics, genetics, psychosocial factors, imaging, coagulation, and vascular and myocardial susceptibility. This report presents highlights of these reviews and a summary of suggested research directions.

### Keywords

cardiovascular diseases; death, sudden; myocardial infarction; risk factors; risk prediction

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### Disclosures

None.

## Clinical Risk Assessment

### Near-Term Risk

The proper deployment of preventive strategies requires an accurate classification system that allows the physician to target intensive treatments to the highest-risk patients. A commonly recommended approach is a multivariable assessment such as the Framingham Risk Score (FRS).<sup>1</sup> Although the FRS is recommended in many guidelines on cardiovascular risk assessment,<sup>2</sup> it has some limitations. It does not include several factors of the metabolic syndrome (glucose intolerance, central obesity, and hypertriglyceridemia), nor does it include family history. Moreover, the FRS classifies risk over a period of 10 years rather than in the near term (within 1 year). Indeed, no algorithm has been developed that accurately predicts near-term risk across diverse populations.

The ability to forecast near-term risk of ACS or sudden cardiac death would represent an important advance in cardiovascular medicine because it would clarify which individuals are in most urgent need of intervention. It would help identify those rare asymptomatic, apparently healthy individuals who are in imminent danger of a cardiovascular event yet ordinarily would not receive therapy at all. In asymptomatic individuals judged to be at intermediate or high risk by the FRS, determining that they are at increased near-term risk could result in immediate (and perhaps temporary) intensification of therapy or other interventions. Among patients with known coronary artery disease and/or some degree of left ventricular dysfunction, those at high near-term risk would warrant the most aggressive level of treatment and monitoring.

### Post-ACS Risk Prediction

Tools to predict near-term cardiovascular risk after ACS are already available. For example, for patients presenting with ACS, the 7-point Thrombolysis in Myocardial Infarction (TIMI) risk score is an easy and valid tool for predicting risk of very-near-term events (eg, 14 to 30 days).<sup>3</sup> However, risk stratification developed from randomized trial populations may lack generalizability to patients seen in usual clinical practice.<sup>4</sup> The Global Registry of Acute Coronary Events (GRACE) risk score has been well validated as a risk prediction tool applicable for types of ACS patients encountered in clinical practice.<sup>4-6</sup> Additionally, multiple biomarkers have been shown to have prognostic value in the post-ACS setting, both individually and in combination.<sup>7</sup>

Many drugs have been proven to reduce near-term, post-ACS events in randomized trials (eg, angiotensin-converting enzyme inhibitors, aspirin and thienopyridines, supplements, aldosterone blockers, and statins). In some cases, interventions have been shown to be of particular value in patients at high short-term risk. For example, some studies have demonstrated improved post-ACS outcomes with the early intervention strategy compared with the early conservative strategy in patients presenting with high TIMI risk scores; no difference was seen among patients with low TIMI risk scores.<sup>8</sup> Similarly, enoxaparin provided improved outcomes compared with unfractionated heparin exclusively in individuals with high TIMI risk scores.<sup>3</sup> Thus, determination of near-term risk can help guide optimal therapy in post-ACS patients.

Although much work is needed to perfect near-term risk prediction in the post-ACS setting, there is a relative wealth of information compared with the scant data available for asymptomatic individuals. A major unmet need is the development of risk scores akin to the TIMI and GRACE scores to forecast near-term risk in the primary prevention setting.

## Candidate Areas for New Risk Assessment Tools

### Classic and Novel Risk Factors

Since the initial 4 risk factors underlying cardiovascular disease (CVD)—hypertension, hypercholesterolemia, left ventricular hypertrophy, and diabetes mellitus—were described in 1961 by Kannel et al.,<sup>9</sup> the list has grown to include many others. Additional clinical cardiovascular risk factors such as male gender, black race, advancing age, smoking, insufficient exercise, obesity, and family history are well recognized.<sup>10</sup> However, all of these are fixed or chronic conditions that are better suited to predicting long-term risk than near-term risk. What are needed are novel risk factors that reflect acute processes influencing atherosclerotic plaque rupture, atherothrombosis, and electric instability in the myocardium. Of most value would be novel, easy-to-measure biomarkers that would make it possible to screen large numbers of individuals for near-term risk.

Biomarkers are proteins or metabolites, individually or in combination, that correlate to pathological processes.<sup>11</sup> A clinically useful biomarker should have specificity to the disease process; should differ quantitatively from controls, with this difference being larger than technical and biological variation combined; should be stable in blood or other body fluids; and should present in sufficient amounts for easy clinical measurement.<sup>12</sup>

Some novel plasma-based biomarkers are associated with myocardial, renal, skeletal muscle, and brain involvement from atherosclerotic vascular disease, including brain natriuretic protein, bone morphogenic protein, transforming growth factor- $\beta$ , and neuroprotein D1. These biomarkers may be related to damage of “target organs” and thus are potential risk factors. However, care must be taken to distinguish those that are truly predictors of future events from those that are secondary, downstream markers reflecting a prior event and have no predictive value. For example, the plasma level of troponin, a marker for myocardial damage, has little prognostic value in the primary prevention setting, where the test is principally used as a diagnostic marker to determine whether a symptomatic patient has suffered a cardiovascular event. In the secondary prevention setting, however, troponin has been demonstrated to be a useful biomarker for determining near-term risk and is a component of the TIMI risk score.

Other biomarkers are associated with atherosclerosis, inflammation, endothelial cell dysfunction, plaque instability, thrombosis, and myocardial susceptibility and so are more likely to be causal risk factors. How these “new” biomarkers and “old” risk factors interrelate and how they might together help us define near-term risk require more study.

### Atherosclerosis and Inflammation Biology

The focus in the field of the pathophysiology of atherosclerosis has shifted from the concept of a lipid storage disease to that of a chronic inflammatory process. In the first phase, inflammatory cells such as monocytes join the arterial endothelial and smooth muscle cells of the normal artery to initiate an inflammatory response. Multiple adhesion molecules for leukocytes, chemoattractant cytokines, and activators of leukocyte function are operative in the atherogenic process.

Vascular cell adhesion molecule-1 mediates mononuclear cell adhesion to activated endothelial cells.<sup>13</sup> Bound leukocytes enter the arterial intima in response to chemokines such as monocyte chemoattractant protein-1.<sup>13</sup> Leukocyte activators such as macrophage colony-stimulating factor promote the maturation of monocytes into macrophage foam cells and stimulate their elaboration of multiple mediators of the atherosclerosis process.<sup>14</sup> Inflammatory mediators also participate in the progression of atherosclerotic disease.

The ultimate clinical expression of atherosclerotic pathology, atherothrombosis, causes the most dreaded clinical complications of this disease such as ACS. Inflammation sets the stage for the thrombotic complications of atherosclerosis not only by affecting the “solid state” of the lesion but also by hindering fibrinolysis and augmenting thrombosis and coagulability in the fluid phase of blood.<sup>15</sup>

The use of biomarkers of inflammation such as vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, and macrophage colony-stimulating factor in clinical medicine offers the potential to sharpen our ability to predict cardiovascular risk. Inflammatory markers relate to prospective risk of cardiovascular complications and show promise to potentially add relevant prognostic information. However, moving from general measures of inflammation to more transitory markers that may be associated with greatly heightened near-term risk requires further study.

### The Endothelium

Endothelial cells from arteries and veins display distinct phenotypes. Some of these site-specific properties are epigenetically predetermined during embryogenesis, whereas others are mediated by differences in the microenvironment, most notably hemodynamic forces. Changes in endothelial cells overlying atherosclerotic plaque include irregular orientation and altered gene/protein expression/activity (including proinflammatory transcription factors, hemostatic factors, cell adhesion molecules, and nitric oxide).<sup>16</sup> Atherosclerosis-associated endothelium displays abnormalities in vasomotor tone, increased leukocyte trafficking, and exaggerated apoptosis. Dysfunctional endothelium promotes oxidation of lipoproteins, inflammation, lipid accumulation, and smooth muscle cell proliferation.

Endothelial dysfunction, assayed by flow studies, measures endothelium-dependent vasodilation. Abnormalities have been correlated with atherosclerosis and risk for ACS.<sup>17,18</sup> However, these studies are highly operator dependent, and they measure only a single function of the endothelium. An important goal in vascular biology is to develop novel methods for diagnosing endothelial dysfunction and to use this information to predict plaque vulnerability. Such a diagnostic platform may ultimately include some combination of soluble mediators, cell-based assays, and molecular imaging. Dysfunctional endothelial cells release a number of soluble mediators into the blood, including endothelin-1, von Willebrand factor, tissue-type plasminogen activator, and soluble thrombomodulin.<sup>19</sup> Although few of these biomarkers are truly specific for the endothelium, circulating levels of one or another marker have been correlated with an increased risk for cardiovascular events. However, systematic analysis and comparison of available biomarkers are lacking.

Use of multiplex ELISAs and/or proteomics approaches to measure myriad endothelium-derived soluble mediators simultaneously may yield important diagnostic/prognostic information that is not available from single mediator assays. Cell-based assays include quantification and/or phenotyping of circulating endothelial cells, endothelium-derived microparticles, and endothelial progenitor cells.<sup>20–22</sup> Studies have demonstrated an association between the number of circulating cells or microparticles and coronary artery disease. The phenotype of cells and/or microparticles (eg, with fluorescence activated cell sorting) may provide valuable information about the vascular bed of origin and underlying disease status. The precise role for cell-based assays in diagnosing the vulnerable plaque in an individual patient remains to be determined.

Finally, molecular imaging holds promise. As an example, phage display has been used to identify a novel vascular cell adhesion molecule-1–specific cell-internalizing peptide that allows sensitive magnetic resonance imaging of atherosclerotic lesions in mice.<sup>23</sup> It appears likely that clinical events occur minutes, hours, days, or even weeks after initiation of

processes that are occurring at the endothelial level. Developing test strategies to identify these processes before their phenotypic expression has great potential.

### Triggers of Plaque Rupture and the Concept of Vulnerable Blood

The probability that an individual will suffer an acute cardiovascular event in the near term is likely determined both by her/his burden of atherosclerotic plaques at relevant locations (coronary, carotid, mesenteric, iliofemoral arteries, etc) and by the probability that each plaque will become disrupted and trigger thrombosis of a magnitude and persistence sufficient to critically narrow or occlude the vessel or to produce symptomatic emboli. Knowledge of the indexes of plaque burden, the frequency of plaque disruption in a given individual, and that individual's tendency toward thrombosis should together help predict near-term risk for cardiovascular events.

Assessing the frequency of subclinical plaque disruption might provide a direct and relevant measure of plaque activity. Plaque erosions and mural thrombi are relatively frequent incidental findings at autopsy, and plaques often show evidence of repeated rupture and healing.<sup>24</sup> Thus, clinically silent plaque disruption is common. Direct high-resolution anatomic imaging is 1 approach to detect disrupted plaques; molecular imaging to detect extracellular matrix proteins or other molecules or cells exposed by plaque disruption is another.

Platelets and the coagulation cascade have evolved so that they continuously interrogate vascular integrity. Autopsy and other studies suggest that platelets and fibrin are regularly incorporated into disrupted atheroma.<sup>25</sup> Imaging methods to visualize accumulation/incorporation of platelets and fibrin at sites of plaque disruption should be developed. An ability to follow platelet and fibrin accumulation acutely at sites of plaque disruption in vivo may be valuable for assessing risk of coronary exclusion and potentially for assessing interventions aimed at plaque stabilization.

Tissues supplied by arteries in which plaque disruptions occur are reporters of plaque activity, as is evident from transient ischemic attacks. It is conceivable that clinically silent plaque rupture could leave subtle signatures that might be detected. Approaches might include sensitive assays of brain- and heart-specific biomarkers that enter the circulation as a result of "microscopic" ischemia or infarcts or functional tests that reflect subtle alteration in function (exercise testing, heart rate variability/recovery, T-wave alternans). Such indexes of subclinical thromboembolic events in the coronary circulation offer potential to predict near-term risk of ACS.

Whether a given plaque disruption remains silent or gives rise to a symptomatic thrombus depends on both local (plaque and vessel geometry and the exact composition of what is exposed to blood) and systemic (platelet, endothelial, monocyte, and coagulation cascade) function. We need a better understanding of the molecular mechanisms by which plaque rupture causes thrombosis to develop sensitive assays to measure the likelihood of clinically important clot formation. Thus, future biomarker studies should include a focus on platelets and coagulation proteins.

### Myocardial Susceptibility

The observation that the clinical outcome of a given myocardial insult may be worse in certain individuals is called "susceptible myocardium," defined as myocardium altered so that the patient is at risk for near-term adverse events (eg, myocardial injury, infarction, heart failure, or arrhythmias). Susceptible myocardium may be associated with conditions resulting in altered myocardial function or structure (eg, ischemia, scarring, hypertrophy, infiltration, inflammation), altered sympathetic nervous system activity (eg, hyperactivity,

impaired reactivity), severe left ventricular outflow obstruction (eg, aortic stenosis, hypertrophic obstructive cardiomyopathy), selected electrophysiological disorders (eg, prolonged QT syndromes), and commotio cordis.<sup>26</sup>

At least half of the cases presenting with death or first myocardial infarction arise among subjects without known CVD. We know little about how to identify subjects without known CVD who may be at risk for susceptible myocardium and thus may be at high risk for near-term events. Although the conditions associated with susceptible myocardium summarized above may be identified with imaging and/or physiological testing, these tests are costly and impractical to apply to the asymptomatic population.

Early after acute ischemic injury, metabolic and/or inflammatory alterations of both myocytes and microvessels may predict early adverse outcomes, including ischemic events of greater severity.<sup>27-32</sup> New developments related to myocardial susceptibility include abnormalities in myocardial metabolism (eg, high-energy phosphate depletion), impaired flow in nonculprit arteries, and immunomediated ischemia-independent widespread coronary microvessel and/or myocardial inflammation with infarct-related artery patency.<sup>33</sup> In a sense, the myocardium may record or store signals (eg, metabolic,<sup>34-35</sup> electric,<sup>36</sup> or mechanical<sup>37</sup>) from subclinical events (eg, ischemia and necrosis) that may predict near-term clinical events. Further studies of individuals with past ischemic events could yield important clues for identifying mechanisms and detection algorithms that may be applied to subjects without known disease.

### Environmental Triggers

Studies abound demonstrating that environmental triggers predict an initial cardiovascular event in the near term.<sup>38-40</sup> Triggers include external stimuli (eg, natural disasters, air pollution, Mondays, morning rising, or ambient temperature), patient behavior (eg, cocaine use, intake of a high-saturated-fat meal, or atypically intense physical activity), and patient emotional reactions (extreme anger or anxiety).<sup>38,40</sup>

In a study of triggers for acute myocardial infarction,<sup>41</sup> heavy exertion was reported to precipitate 6% of the acute myocardial infarctions, with moderate physical activity being a precipitant in 29% of the myocardial infarction cases. Intense emotional stress immediately preceded myocardial infarction in  $\approx$ 7% of cases and eating in 8% of cases. More than 20% of the cases in these population-based studies occurred during sleep. Physical exertion (particularly in the poorly conditioned), emotional stress, anger, and extreme excitement all appear to act as triggers for an ACS<sup>40</sup> by increasing sympathetic tone and catecholamine release.<sup>38</sup> Studies of biomarkers and other readouts that reflect physiological responses to exercise, feeding, extreme emotion, and other external stimuli may yield clues as to who may be more susceptible to environmental triggers in the near term and how to protect against cardiovascular events in these individuals.

### Psychosocial Factors

Long-term psychosocial factors such as depression, anxiety, phobic symptoms, low socioeconomic status, work stress, and the absence of social support have been identified as independent risk factors in the prediction of first cardiovascular events.<sup>39</sup> However, the majority of long-term psychosocial ACS risk factors have not been tested for their ability to predict an ACS in the near term. Furthermore, long-term psychosocial factors that may be implicated in the development of CVD may be quantitatively or even qualitatively different from those psychosocial factors and triggers that identify a patient at imminent risk for an ACS.<sup>42</sup> Although tests exist to assess an individual's short-term psychological state such as the State Trait Anxiety Inventory,<sup>43</sup> they have not yet been widely applied to the study of

CVD, and it remains to be seen whether they might provide a means for discriminating patients at near-term risk.

## New Technologies

### Noninvasive Imaging Tests

The imaging tests most commonly used to assess prognosis are  $^{99m}\text{Tc}$ -sestamibi or thallium-201 stress single-photon emission computed tomography perfusion scans and stress echocardiography. Numerous studies have shown that stress imaging confers added predictive value over Duke treadmill scores for the diagnosis of coronary artery disease,<sup>44</sup> and coronary artery calcium scores have been shown to more accurately predict coronary event rates than FRS alone in intermediate-risk individuals.<sup>45</sup> However, to date, none of these tests have been shown to reliably predict events over a short interval of 1 year. Stress imaging identifies chronic abnormalities of coronary perfusion resulting from hemodynamically significant lesions and possibly the effect of impaired endothelial function but not the vulnerability of plaques most likely to trigger acute coronary events.

Coronary computed tomography angiography with the latest-technology scanners appears promising in diagnosing the presence of significant stenoses. However, approximately two thirds of myocardial infarctions arise from plaque rupture in coronary artery segments that previously had <50% stenosis.<sup>46</sup> Some measure of total plaque volume may be more helpful in predicting such events. It has been demonstrated that computed tomography angiography correlates well with intravascular ultrasonography for measuring coronary artery plaque area.<sup>47</sup> However, systematic longitudinal studies linking the extent of plaque and plaque morphology, as assessed by computed tomography angiography, with acute events are not yet available.

Plaques that ultimately rupture or erode, with superimposed thrombosis leading to ACS and other ischemic events, often do not limit flow, and current techniques cannot yet distinguish plaques that will remain silent from those that will trigger thrombosis and clinical events. Advances in anatomic imaging technologies may eventually allow an assessment of plaque architecture and composition. Future functional imaging approaches that assess, for example, the activities of plaque macrophages may also help identify plaques likely to trigger clinical events. More detailed studies of the mechanisms of plaque disruption and the cellular and biochemical events associated with this process are needed.

There has been progress in the development of new magnetic resonance imaging contrast agents that target various aspects of atherosclerosis and thrombosis.<sup>48</sup> They have potential to identify the vulnerable plaque, but their diagnostic accuracy and prognostic accuracy have not yet been established. New imaging approaches such as in vivo 2-photon microscopy<sup>49–51</sup> are being developed to provide new cell-level information on disease processes that should provide a whole new perspective on the remodeling of the vascular wall in vivo rather than inference from pathology, genomics, proteomics, or cell culture approaches.

### Genomics

The commonly assessed cardiovascular risk factors—lipid profile, hypertension, diabetes mellitus, homocysteine, lipoprotein (a), body mass index, small dense low-density lipoprotein particles, and fibrinogen level—are all inherited to some degree. Human genetics studies are now focusing on identifying sites in the genome, or loci, with variations associated with each of these quantitative factors. The list of loci implicated in these phenotypes and, by extension, for cardiovascular end points is growing.

Until recently, most studies of genetic predictors of vascular disease were largely unsuccessful because they considered too few candidate loci and/or too few functional variants in each locus. This has changed dramatically with the completion of the Human Genome Project, the continuing efforts of the International HapMap Project, and the availability of resources for deep sequencing of candidate genomic loci in large numbers of individuals.

The latest studies attempt to consider all common variations in the loci of interest through dense genotyping of single-nucleotide polymorphisms, consideration of all common haplotypes (sets of physically linked polymorphisms), or selection of representative single-nucleotide polymorphisms that act as proxies for all polymorphisms in a locus. Because the population impact of a disease-associated single-nucleotide polymorphism is a function of both the magnitude of the effect size and the frequency of the single-nucleotide polymorphisms, attention has initially focused on common variants. Whole-genome association studies, with  $\geq 500\,000$  single-nucleotide polymorphisms tested across the genome, are underway; however, these studies represent a starting point, with identification of a list of candidate loci, that then requires more conventional functional studies of the genes in or near the implicated loci.

Although it is intuitive that a genetic “chip” summarizing genotype data at many risk alleles may improve prediction of cardiovascular risk, it remains to be demonstrated that genetic studies will be useful for this purpose. Prior investigations have succeeded in finding highly penetrant, mendelian rare genetic variants that result in familial dyslipidemia disorders that cause premature CVD (eg, *LDLR*, *APOB*, *PCSK9*) or result in electrophysiological syndromes that predispose to sudden death (eg, *KCNQ1*, *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *ANK2*, *KCNE2*, and *KCNJ2* for long-QT syndrome; *KCNH2* and *KCNQ1* for short-QT syndrome; *SCN5A* for Brugada syndrome; *PRKAG2* for Wolff-Parkinson-White syndrome).<sup>52,53</sup> The more recent whole-genome association studies have identified common genetic variants that are associated with modestly increased cardiovascular risk (eg, chromosome 9p21 locus),<sup>54,55</sup> although the responsible genes remain to be identified. These common variants may explain much of the inherited basis of CVD and sudden death.

Although knowledge of these DNA variants may eventually be useful in improving risk prediction algorithms, they will most likely be relevant to predicting lifetime cardiovascular risk because the variants do not change over time and represent genetic “exposures” to which a given individual has been subjected while in utero; through infancy, childhood, and adolescence; and into adulthood. Thus, the variants themselves are unlikely to meaningfully predict risk in the time frame of months to years. However, an individual’s set of genetic variants may provide the milieu on which other risk factors may confer increased near-term cardiovascular risk. For example, an individual with a particular variant of a QT syndrome gene may have normal risk of ventricular arrhythmia at baseline but may be at severe risk of arrhythmia if given a QT-prolonging drug, whereas the same drug would promote little risk in a normal individual. As so-called “pharmacogenomic” information becomes available, there may be utility to its inclusion into near-term risk algorithms.

## Proteomics

Proteomics is the study of the proteome or the protein complement of a sample comprising all or part (subproteome) of cells, tissue, or a body fluid such as serum or plasma. Although proteomic analysis can provide insights into the molecular mechanisms of disease at the protein level, it also has the potential to identify specific disease biomarkers.

The 2 proteomic strategies for biomarker discovery include a broad-based “direct” approach, in which proteomic techniques are used to screen large numbers of proteins directly in



serum or plasma to identify those that correlate to a disease phenotype, and the candidate “indirect” biomarker approach, in which proteins are preselected on the basis of known biological assumptions or from prior discovery. Either way, all biomarkers must be validated, most often with immunobased assays on a series of large independent cohorts. This validation phase is critical in the cardiovascular system, in which biomarker identification is complicated by the fact that heart function is influenced by and influences many other organ systems, making identification of robust markers difficult without an understanding of this interplay. Hence, it is important to identify and eliminate biomarkers that are generic “illness markers” or that overlap with other potentially confounding disease origins (eg, diabetes mellitus).

In contrast to DNA variants, protein expression and activity in cells, tissue, and body fluids can be quite mutable over time, with fluctuations over time intervals as brief as minutes. Thus, it is more plausible for variations with proteins to be causative and predictive of near-term cardiovascular risk than variations in DNA. As such, proteomics approaches are much more likely than genomics approaches to identify novel factors that will improve near-term risk prediction algorithms.

### Gene Expression Studies

Although the genetic information encoded in the genome is stable and, for the most part, does not change over an individual’s lifetime, expression of the roughly 25 000 genes at the RNA level is highly variable and, like proteins, can readily reflect short-term physiological changes. Although it is not practical to obtain samples of most tissues to measure gene expression profiles, easily accessed cells may permit large clinical studies. For example, data from other fields of medicine suggest that gene expression data from whole blood or isolated mononuclear cells may have significant predictive power.<sup>56</sup> Blood gene expression profiling can classify individuals with atherosclerosis, heart failure, and early allograft rejection after cardiac transplantation.<sup>57–59</sup> Thus, gene expression analyses may offer a whole new class of biomarkers for use in near-term risk prediction and is an important area for future investigation.

### Integrative Approaches to Predict Risk

Coronary artery disease is a complex phenotype arising from the interplay of inherited genetic variants, fluctuations in protein expression and activity, and environmental exposures. Thus, individuals with coronary artery disease will likely have differing molecular manifestations of their disease despite having similar clinical phenotypes of atherosclerotic plaque and/or myocardial infarction. It is conceivable that future research on inflammation, endothelium, thrombosis, myocardium, environmental triggers, and psychosocial factors; imaging tests; and studies on genomics, proteomics, and gene expression will help unravel the complexity of coronary artery disease sufficiently to provide information on the risk of events for an individual patient and ideally to guide more precise and targeted therapies ultimately aimed at the individual.

There is a critical need to refine predictive models or to develop them de novo to predict events in the near term (ie, within a year or so). As described above, biomarker approaches, possibly supplemented by imaging and genomic analyses, are most likely to be relevant to near-term cardiovascular risk prediction, and future research should focus there. Because blood-based constituents are dynamic and can participate in atherosclerosis, the development of vulnerable plaques, and plaque rupture, a blood-based profile should yield significant predictive information for near-term events,<sup>60</sup> provided that data sets are collected that consist of clinical data, events, and outcomes of ACS, along with serum samples that can be used for proteomic and gene expression analyses.

To fully realize the clinical potential of these diverse sources of information requires a fundamental change in the way complex, large-scale data are viewed, analyzed, and used.<sup>61</sup> Today, the tradition of identifying 1 or a small number of biomarkers continues in the context of cardiovascular risk, but the 1-gene- or 1-protein-at-a-time approach to risk prediction is fraught with inefficiency and bias. This working group recognizes the paramount need for comprehensive, integrative methods of analysis that evaluate relevant biological pathway information and other factors and that fairly assess the combined prognostic implications of these data to refine near-term risk assessment and ultimately guide therapies.

## Recommendations for Scientific Investment

The working group recommends the following to develop an algorithm to assess “near-term” (within 1 year) risk:

- Establish adequately powered population cohorts for time-series studies in asymptomatic patients who are expected to have higher event rates than the general population compared with normal control subjects. Obtain comprehensive clinical and biological information, including cells, tissue, and body fluids, when feasible.
- Use these cohorts to develop novel biomarkers for the “high-risk patient” using large-scale “omics” technologies (eg, proteomics, gene expression studies) and other measures (eg, endothelial cell– based markers) as risk reporters. There is a need for the establishment of the early kinetics of these markers, their validation in the clinical setting, the development of informatics platforms, and prediction modeling. Unlike in traditional studies, this will require frequent monitoring of these biological “signatures,” at least annually, to discern which markers are perturbed before a clinical event and thus will be specifically useful for predicting near-term risk.
- Using the “high-risk patient” biomarker profiles, develop novel molecular imaging strategies for near-term risk prediction in these selected populations.
- Use molecular information from cohort studies to better understand the underlying pathogenic mechanisms, to discover reporters for those mechanisms, and to better understand both the environmental and biological determinants that may account for individual differences in plaque disruption, thrombus formation and propagation, and triggering mechanisms for acute cardiovascular events.
- Develop novel methods for data analysis and statistical and predictive modeling using multidimensional data sets.
- Develop and validate a “near-term Framingham score” that may include novel genetic, proteomic, and imaging markers, as well as environmental variables such as psychosocial factors. The scoring system should allow the addition of new variables as they become available. It would be used as a targeted screening tool for individuals deemed to be at intermediate or high 10-year cardiovascular risk by traditional risk scores such as the FRS to determine who would benefit from more intensive monitoring and therapeutic interventions in the near term.
- Develop programs to understand the barriers to the clinical implementation of such a risk assessment tool. Develop physician education and fellowship training incentives to encourage clinical acceptance and use of novel risk assessment methods.

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