

## From Vulnerable Plaque to Vulnerable Patient

### A Call for New Definitions and Risk Assessment Strategies: Part II

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**Abstract**—Atherosclerotic cardiovascular disease results in >19 million deaths annually, and coronary heart disease accounts for the majority of this toll. Despite major advances in treatment of coronary heart disease patients, a large number of victims of the disease who are apparently healthy die suddenly without prior symptoms. Available screening and diagnostic methods are insufficient to identify the victims before the event occurs. The recognition of the role of the vulnerable plaque has opened new avenues of opportunity in the field of cardiovascular medicine. This consensus

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document concludes the following. (1) Rupture-prone plaques are not the only vulnerable plaques. All types of atherosclerotic plaques with high likelihood of thrombotic complications and rapid progression should be considered as vulnerable plaques. We propose a classification for clinical as well as pathological evaluation of vulnerable plaques. (2) Vulnerable plaques are not the only culprit factors for the development of acute coronary syndromes, myocardial infarction, and sudden cardiac death. Vulnerable blood (prone to thrombosis) and vulnerable myocardium (prone to fatal arrhythmia) play an important role in the outcome. Therefore, the term “vulnerable patient” may be more appropriate and is proposed now for the identification of subjects with high likelihood of developing cardiac events in the near future. (3) A quantitative method for cumulative risk assessment of vulnerable patients needs to be developed that may include variables based on plaque, blood, and myocardial vulnerability. In Part I of this consensus document, we cover the new definition of vulnerable plaque and its relationship with vulnerable patients. Part II of this consensus document will focus on vulnerable blood and vulnerable myocardium and provide an outline of overall risk assessment of vulnerable patients. Parts I and II are meant to provide a general consensus and overviews the new field of vulnerable patient. Recently developed assays (eg, C-reactive protein), imaging techniques (eg, CT and MRI), noninvasive electrophysiological tests (for vulnerable myocardium), and emerging catheters (to localize and characterize vulnerable plaque) in combination with future genomic and proteomic techniques will guide us in the search for vulnerable patients. It will also lead to the development and deployment of new therapies and ultimately to reduce the incidence of acute coronary syndromes and sudden cardiac death. We encourage healthcare policy makers to promote translational research for screening and treatment of vulnerable patients. (*Circulation*. 2003;108:1772-1778.)

**Key Words:** coronary disease ■ plaque ■ myocardial infarction ■ atherosclerosis ■ death, sudden

In Part I of this consensus document, we have introduced the concept of vulnerable patient as defined by plaque, blood, and myocardial vulnerability. Vulnerable plaque was extensively discussed in Part I. Here we discuss the definition of vulnerable blood and vulnerable myocardium and present an outline for overall risk assessment of vulnerable patients.

### Vulnerable (Thrombogenic) Blood

#### Serum Markers of Atherosclerosis and Inflammation

Serum markers may predict a patient's risk of acute cardiovascular complications (Table 1). C-reactive protein (CRP) is an independent risk factor and a powerful predictor of future coronary events in the asymptomatic population<sup>1-3</sup> and in patients with stable and unstable disease. Although CRP is a nonspecific marker of systemic inflammation, it activates endothelium and accumulates in the plaque, suggesting an important role in plaque inflammation.<sup>4,5</sup>

Circulating interleukin-6 levels, which are elevated in patients with acute coronary syndromes, also predict the risk of future coronary events in such patients.<sup>6</sup> Recently, investigators have shown that high plasma concentrations of soluble CD40 ligand may indicate an increased vascular risk in apparently healthy women.<sup>7</sup> Likewise, Hwang et al<sup>8</sup> showed in a large population-based sample of individuals that circulating levels of soluble intracellular adhesion molecule were predictive of future acute coronary events.

Markers of systemic inflammation, such as soluble adhesion molecules, circulating bacterial endotoxin, soluble human heat-shock protein 60, and antibodies to mycobacterial heat-shock protein 65, may predict an increased risk of atherosclerosis.<sup>9</sup> Pregnancy-associated plasma protein A (PAPP-A) is present in unstable plaques, and its circulating levels are elevated in patients with acute coronary syndromes.<sup>10</sup> Increased serum levels of PAPP-A may reflect instability of atherosclerotic plaques.<sup>11</sup>

With major advances in high-throughput genomics and proteomics research, future studies will undoubtedly identify new risk and protective factors and biomarkers that can be used for screening purposes. A recent study suggested an association between several genetic polymorphisms and clinical outcomes, some of which can be possibly related to plaque, blood, and myocardial vulnerability.<sup>12</sup> The tools and knowledge base made possible by the Human Genome Project allow the field to move beyond one or a few single-nucleotide polymorphisms in a priori candidate genes. Genome-wide linkage analyses have been

**TABLE 1. Serological Markers of Vulnerability (Reflecting Metabolic and Immune Disorders)**

- Abnormal lipoprotein profile (eg, high LDL, low HDL, abnormal LDL and HDL size density, lipoprotein [a], etc)
- Nonspecific markers of inflammation (eg, hsCRP, CD40L, ICAM-1, VCAM-1, P-selectin, leukocytosis, and other serological markers related to the immune system; these markers may not be specific for atherosclerosis or plaque inflammation)
- Serum markers of metabolic syndrome (eg, diabetes or hypertriglyceridemia)
- Specific markers of immune activation (eg, anti-LDL antibody, anti-HSP antibody)
- Markers of lipid peroxidation (eg, ox-LDL and ox-HDL)
- Homocysteine
- PAPP-A
- Circulating apoptosis marker(s) (eg, Fas/Fas ligand, not specific to plaque)
- ADMA/DDAH
- Circulating nonesterified fatty acids (eg, NEFA)

hsCRP indicates high-sensitivity CRP; CD40L, CD40 ligand; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; MMP, matrix metalloproteinases; TIMP, tissue inhibitors of MMPs; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HSP, heat shock protein; ADMA, asymmetric dimethylarginine; ADMA, dimethylarginine dimethylaminohydrolase; and NEFA, nonesterified fatty acids.

**TABLE 2. Blood Markers of Vulnerability (Reflecting Hypercoagulability)**

- Markers of blood hypercoagulability (eg, fibrinogen, D-dimer, and factor V Leiden)
- Increased platelet activation and aggregation (eg, gene polymorphisms of platelet glycoproteins IIb/IIIa, Ia/IIa, and Ib/IX)
- Increased coagulation factors (eg, clotting of factors V, VII, and VIII; von Willebrand factor; and factor XIII)
- Decreased anticoagulation factors (eg, proteins S and C, thrombomodulin, and antithrombin III)
- Decreased endogenous fibrinolysis activity (eg, reduced t-PA, increased PAI-1, certain PAI-1 polymorphisms)
- Prothrombin mutation (eg, G20210A)
- Other thrombogenic factors (eg, anticardiolipin antibodies, thrombocytosis, sickle cell disease, polycythemia, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia)
- Increased viscosity
- Transient hypercoagulability (eg, smoking, dehydration, infection, adrenergic surge, cocaine, estrogens, postprandial, etc)

t-PA indicates tissue plasminogen activator; PAI, type 1 plasminogen activator inhibitor.

carried out for coronary artery calcification,<sup>13</sup> and genome-wide association studies for myocardial infarction are already a reality.<sup>14</sup> Further studies are needed to address the relationship between single-nucleotide polymorphisms in components of each of the plaque, blood, and myocardial vulnerabilities and future outcomes (acute coronary syndromes and sudden cardiac death). However, ongoing proteomic research on serum samples of vulnerable patients collected from prospective studies before the onset of symptoms is most promising.

### Coagulation/Anticoagulation System

The importance of the coagulation system in the outcome of plaque complications was recently reemphasized by Karnicki et al,<sup>15</sup> who in a porcine model demonstrated that the role assigned to lesion-bound tissue factor was not physically realistic and that blood borne factors must have a major role in thrombus propagation. A hematologic disorder is rarely the sole cause of coronary thrombosis and myocardial infarction. Inflammation promotes thrombosis and vice versa.<sup>16</sup> Extensive atherosclerosis may be associated with increased blood thrombogenicity, but the magnitude of thrombogenicity varies from patient to patient, and unstable plaques are much more thrombogenic than stable ones (Table 2).

Some platelet polymorphisms, such as glycoprotein IIIa P1(A2),<sup>17</sup> Ib  $\alpha$  gene-5T/C Kozak,<sup>18</sup> high factor V and factor VII clotting,<sup>19</sup> have been reported as independent risk factors for myocardial infarction. Reiner et al<sup>20</sup> recently reviewed the associations of known and potential genetic susceptibility markers for intermediate hemostatic phenotypes with arterial thrombotic disease.

Other conditions that lead to a hypercoagulable state are diabetes mellitus, hypercholesterolemia, and cigarette smoking. High levels of circulating tissue factor may be the

mechanism of action responsible for the increased thrombotic complications associated with the presence of these cardiovascular risk factors.<sup>21</sup> Acute coronary syndromes are associated with proinflammatory and prothrombotic conditions that involve a prolonged increase in the levels of fibrinogen, CRP, and plasminogen activator inhibitor.<sup>22,23</sup>

A number of blood abnormalities, including antithrombin III deficiency, protein C or S deficiency, and resistance to activated protein C (also known as factor V Leiden), have been implicated as causes of venous thrombosis. The risk of arterial thrombosis is only modestly increased in these conditions, but these abnormalities are thought to interact with traditional risk factors for arterial thrombosis.

Venous and arterial thromboses are prominent features of the antiphospholipid syndrome.<sup>24,25</sup> The main antibodies of this syndrome are the anticardiolipin antibody, the lupus anticoagulant, and the IgG antibodies against prothrombin and  $\beta_2$ -glycoprotein.<sup>24,25</sup>

In the nephrotic syndrome, proteinuria results in abnormal concentration and activity of coagulation factors. Moreover, the associated hypoalbuminemia, thrombocytosis, and hypercholesterolemia may induce arterial and venous thrombosis.<sup>26</sup>

The importance of the coagulation/fibrinolytic system is highlighted by several autopsy studies that have shown a high prevalence of old plaque disruptions without infarctions. Therefore, an active fibrinolytic system may be able to prevent luminal thrombosis in some cases of plaque disruption.<sup>27,28</sup>

A transient shift in the coagulation and anticoagulation balance is likely to be an important factor in plaque-blood interaction, resulting in an acute event. "Triggers" such as exercise and smoking, which are associated with catecholamine release, may increase the risk of plaque thrombosis.<sup>29</sup> Similarly, metabolic factors, such as postprandial metabolic changes, are associated with increased blood coagulability.<sup>30</sup> Likewise, estrogen replacement therapy can lead to a hypercoagulable state.<sup>31</sup>

Finally, plasma viscosity, as well as fibrinogen and white blood cell counts, is positively associated with CHD events as shown by Koenig et al.<sup>32</sup> Furthermore, Junker et al<sup>33</sup> showed a positive relationship between plasma viscosity and the severity of coronary heart disease (CHD).

### Vulnerable Myocardium

#### Ischemic Vulnerable Myocardium Without Prior Atherosclerosis-Derived Myocardial Damage

Abrupt occlusion of a coronary artery is a common cause of sudden death. It often leads to acute myocardial infarction or exacerbation of chest pain.<sup>34,35</sup> Extensive studies in experimental animals and increasing clinical evidence indicate that autonomic nervous activity has a significant role in modifying the clinical outcome with coronary occlusion.<sup>30,36,37</sup> Susceptibility of the myocardium to acute ischemia was reviewed by Airaksinen,<sup>38</sup> who emphasized the key role of autonomic tone in the outcome after plaque rupture. Sympathetic hyperactivity favors the genesis of life-threatening ventricular tachyarrhythmias, whereas vagal activation exerts an antifibrillatory effect. Strong afferent stimuli from the

**TABLE 3. Conditions and Markers Associated With Myocardial Vulnerability**

With atherosclerosis-derived myocardial ischemia as shown by:

ECG abnormalities:

During rest

During stress test

Silent ischemia (eg, ST changes on Holter monitoring)

Perfusion and viability disorder:

PET scan

SPECT

Wall motion abnormalities

Echocardiography

MR imaging

X-ray ventriculogram

MSCT

Without atherosclerosis-derived myocardial ischemia:

Sympathetic hyperactivity

Impaired autonomic reactivity

Left ventricular hypertrophy

Cardiomyopathy (dilated, hypertrophic, or restrictive)

Valvular disease (aortic stenosis and mitral valve prolapse)

Electrophysiological disorders:

Long-QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome, sinus and atrioventricular conduction disturbances, catecholaminergic polymorphic ventricular tachycardia, T-wave alternans, drug-induced torsades de pointes

Comotio cordis

Anomalous origination of a coronary artery

Myocarditis

Myocardial bridging

MSCT indicates multislice computed tomography; PET, positron emission tomography; and SPECT, single-photon emission computed tomography.

ischemic myocardium may impair the arterial baroreflex and lead to hemodynamic instability.<sup>39</sup>

There seems to be a wide interindividual variation in the type and severity of autonomic reactions during the early phase of abrupt coronary occlusion, a critical period for out-of-hospital cardiac arrest. The pre-existing severity of a coronary stenosis, adaptation or preconditioning to myocardial ischemia, habitual physical exercise,  $\beta$ -blockade, and gender seem to affect autonomic reactions and the risk of fatal ventricular arrhythmias.<sup>38,40,41</sup> Recent studies have documented a hereditary component for autonomic function, and genetic factors may also modify the clinical presentation of acute coronary occlusion.<sup>42,43</sup> Table 3 depicts conditions and markers associated with myocardial vulnerability.

### Ischemic Vulnerable Myocardium With Prior Atherosclerosis-Derived Myocardial Damage (Chronic Myocardial Damage)

Any type of atherosclerosis-related myocardial injury, such as ischemia, an old or new myocardial infarction, inflammation, and/or fibrosis, potentially increases the patient's vulnerability to arrhythmia and sudden death. In

**TABLE 4. Available Techniques for Electrophysiological Risk Stratification of Vulnerable Myocardium**

Diagnostic criteria:

Arrhythmia

QT dispersion

QT dynamics

T-wave alternans

Ventricular late potentials

Heart rate variability

Diagnostic techniques:

Noninvasive

Resting ECG

Stress ECG

Ambulatory ECG

Signal-averaged ECG

Surface high-resolution ECG

Invasive

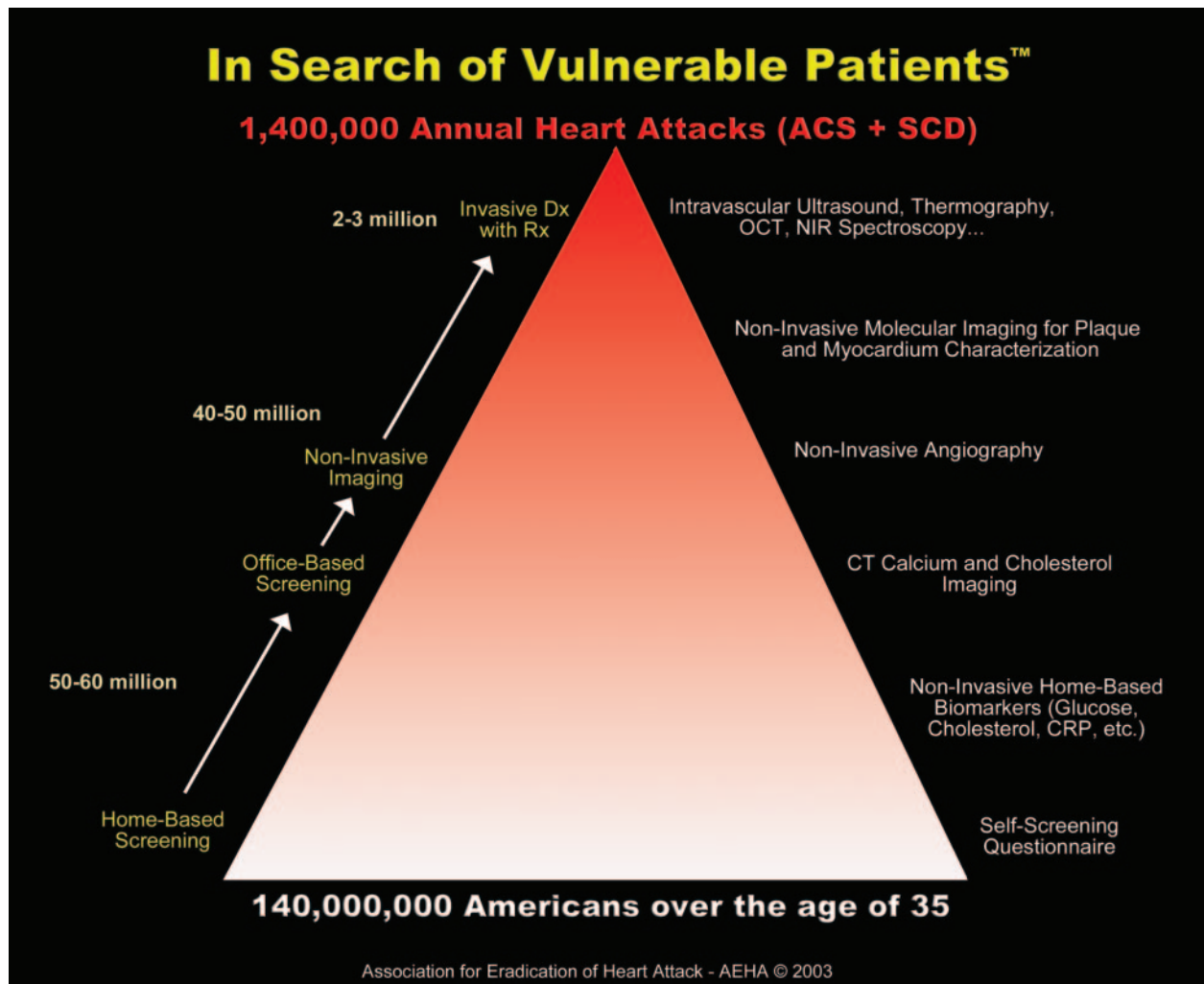
Programmed ventricular stimulation

Real-time 3D magnetic-navigated activation map

the past few decades, a number of diagnostic methods have been developed for imaging cardiac ischemia and for assessing the risk of developing a life-threatening cardiac arrhythmia. In patients with a history of ischemic heart disease, ischemic cardiomyopathy is the ultimate form of myocardial damage. With the advent of new, effective treatments for hypertension and more efficient management of acute myocardial infarction, deaths resulting from stroke and acute myocardial infarction have steadily decreased.<sup>44</sup> More patients are now surviving acute events, but some develop heart failure or ischemic cardiomyopathy later with the potential for fatal arrhythmias. It is also important to remember that in a significant number of patients, sudden cardiac death is the first manifestation of underlying heart disease, and it is still responsible for >450 000 deaths annually in the United States.

### Nonischemic Vulnerable Myocardium

A smaller subset of patients experience fatal arrhythmia as a result of diseases other than coronary atherosclerosis. The various forms of cardiomyopathy (dilated, hypertrophic, restrictive, and right ventricular) account for most noncoronary cardiac deaths. Other underlying pathological processes include valvular heart disease, such as aortic stenosis and primary electrical disturbances (long-QT syndromes, Brugada syndrome, Wolff-Parkinson-White syndrome, sinus and atrioventricular conduction disturbances, catecholaminergic polymorphic ventricular tachycardia, and congenital and drug-induced long QT syndromes with torsades de pointes), and, infrequently, commotio cordis from chest trauma. Less common pathological conditions include anomalous origin of a coronary artery, myocarditis, and myocardial bridging (Table 3). Circulating nonesterified fatty acids are another risk factor



The "VP Pyramid." This pyramid illustrates a speculative roadmap in search of vulnerable patients (numbers represent population in the United States). The major need is to develop noninvasive, relatively inexpensive, readily available, and accurate screening/diagnostic tools allowing multistep screening of an apparently healthy population and those with known atherosclerosis but whose risks for acute events are uncertain. Modified with permission from the AEHA.

for sudden death in middle-aged men, as is elevated serum concentration of CRP; serum measurements may help screening for vulnerable myocardium.<sup>45</sup>

Recently, the Task Force on Sudden Cardiac Death, organized by the European Society of Cardiology, issued a report that includes detailed diagnostic and therapeutic recommendations for a large number of cardiomyopathic conditions capable of causing sudden cardiac death.<sup>46</sup>

Table 4 provides electrophysiological diagnostic criteria and techniques for detection of myocardial vulnerability.

### Risk Assessment for Vulnerable Patients

#### Traditional Risk Assessment Strategies

Despite extensive studies and development of several risk prediction models, traditional CHD risk factors fail to predict development of CHD in a large group of cases (25%<sup>47</sup> to 50%<sup>3,48,49</sup>). Risk prediction models developed on the basis of data from long-term population-based follow-up studies may not be able to predict short-term risks for individual persons. The recent report by Ridker et al,<sup>3</sup> who noted a greater impact

of an inflammatory marker such as serum CRP than LDL levels, is of interest. Several risk factor assessment models (eg, Framingham,<sup>50</sup> Sheffield,<sup>51,52</sup> New Zealand,<sup>53,54</sup> Canadian,<sup>55</sup> British,<sup>56</sup> European,<sup>57</sup> Dundee,<sup>58</sup> Munster [PROCAM],<sup>59</sup> and MONICA<sup>60</sup>) have been developed. However, all of them are based on the traditional risk factors known to contribute to the chronic development of atherosclerosis. Addition of emerging risk factors, particularly those indicative of the activity of the disease (ie, plaque inflammation), may allow individualized risk assessments to be made.

The traditional risk assessment has been shown to predict long-term outcome in large populations. However, they fall short in predicting near-future events particularly in individual clinical practice. For example, a high Framingham Risk Score, although capable of forecasting an adverse cardiovascular event in 10 years, clearly falls short in accurately predicting events in individual patients and cannot provide a clear clinical route for cardiologists to identify and treat, to prevent near future victims of acute coronary syndromes and sudden death. The same is true for

coronary evaluations using electrocardiography, myocardial perfusion tests, and coronary angiography. A positive test for coronary stenosis or reversible perfusion defect (ischemia), although considered as a major risk factor, must be coupled in the future with emerging methods of risk assessment for detection of vulnerable patients to predict more accurately the near-future outcome and prognosis. Those who have no indication of coronary stenosis or myocardial ischemia and who may even lack traditional risk factors may benefit from the techniques now under development that evaluate plaque biology and inflammation.

### New Risk Assessment Strategies

We propose a Cumulative Vulnerability Index based on the following:

- Vulnerable plaque/artery
- Vulnerable blood (prone to thrombosis)
- Vulnerable myocardium (prone to life-threatening arrhythmia)

This proposal is by no means intended to disregard the predictive value of traditional risk assessment strategies that have been proven in predicting long-term outcome but instead to strengthen their value in providing higher accuracy, especially for near-term outcomes.

Atherosclerosis is a diffuse and multisystem, chronic inflammatory disorder involving vascular, metabolic, and immune systems with various local and systemic manifestations. Therefore, it is essential to assess total vulnerability burden and not just search for a single, unstable coronary plaque. A composite risk score (eg, a vulnerability index), that comprises the total burden of atherosclerosis and vulnerable plaque in the coronaries (and aorta and carotid, femoral, etc, arteries), and that includes blood and myocardial vulnerability factors, should be a more accurate method of risk stratification. Such a vulnerability index would indicate the likelihood that a patient with certain factors would have a clinical event in the coming year. Use of the state-of-the-art bioinformatics tools such as neural networks may provide substantial improvement for risk calculations.<sup>61</sup>

The information used for developing such risk stratification in the future is likely to come from a combination of smaller prospective studies (eg, from new imaging techniques) and retrospective cohort studies (eg, for serum factors) in which the risks for near future cardiovascular events can be quantitatively calculated. A few such studies have been conducted or are underway.<sup>2,62</sup>

### In Search of the Vulnerable Patient

The ideal method for screening vulnerable patients should be (1) inexpensive, (2) relatively noninvasive, (3) widely reproducible, (4) readily applicable to an asymptomatic population, and (5) capable of adding predicted value to measurements of established risk factors. Such a method should provide a cost-effective, stepwise approach designed to further stratify risk and provide reliable diagnosis and pathways for monitoring therapy. Obviously, these goals are hard to achieve with today's tools. However, it is well within our

reach, if academia and industry in the field of cardiovascular medicine undertake a coordinated effort to embark on developing new screening and diagnostic techniques to identify vulnerable patients (Figure).

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