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From Vulnerable Plaque to Vulnerable Patient

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On behalf of the vulnerable patient Consensus writing group*

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ABSTRACT

Atherosclerotic cardiovascular disease results in millions of sudden deaths annually, and coronary artery disease accounts for the majority of this toll. Despite major advances in the treatment of coronary artery disease, 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 in the field of cardiovascular medicine. This consensus 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,

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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 a 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. This chapter reports the consensus document created among experts on vulnerable plaque, vulnerable blood, and vulnerable myocardium, and provides an outline of the overall risk assessment of the vulnerable patient.

Key words: Atherosclerosis; Vulnerable plaque; Vulnerable blood; Vulnerable myocardium; Vulnerable patient; Plaque rupture

KEY POINTS

- Plaque rupture is the most common type of plaque complication, accounting for $\approx 70\%$ of fatal acute myocardial infarctions and/or sudden coronary deaths. However, rupture-prone plaques are not the only vulnerable plaques. All types of atherosclerotic plaques with a high likelihood of thrombotic complications and rapid progression should be considered as vulnerable plaques.
- 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.
- 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.
- The search for the vulnerable patient must follow a pyramid approach, the base of which would start from a comprehensive non-invasive, non-imaging assessment of vascular health along with risk factor measurement. The next step would be non-invasive imaging of atherosclerosis (structure and activity) followed by invasive procedures if risk of an eminent event is expected.
- Longitudinal natural study of vulnerable plaque and vulnerable patients are needed to compare the proposed pyramid-based approach versus the status quo.

INTRODUCTION

Cardiovascular disease has long been the leading cause of death in developed countries, and it is rapidly becoming the number one killer in the developing countries [1]. According to current estimates, 61,800,000 Americans have one or more types of cardiovascular disease [2].

Every year, more than 1 million people in the United States and more than 19 million others worldwide experience a sudden cardiac event (acute coronary syndromes and/or sudden cardiac death). A large portion of this population has no prior symptom [3]. There is considerable demand for diagnosis and treatment of the pathologic conditions that underlie these sudden cardiac events. This consensus document proposes new directions to prevent infarction and sudden cardiac events [4].

UNDERLYING CAUSES OF SUDDEN, FATAL AND NONFATAL CARDIAC EVENTS

Figure 1 delineates the underlying causes of acute cardiac events. The first branch point of the tree indicates patients who lack significant atherosclerosis or related myocardial damage, that is, those who have no ischemic heart disease (see section Nonischemic Vulnerable Myocardium). This leaves the patients with atherosclerosis, some of whom also have a hypercoagulable state (see section Vulnerable (Thrombogenic) Blood).

The next branch point involves the presence or absence of an occlusive or subocclusive thrombus. A thrombus identifies a culprit plaque that may be ruptured or nonruptured.

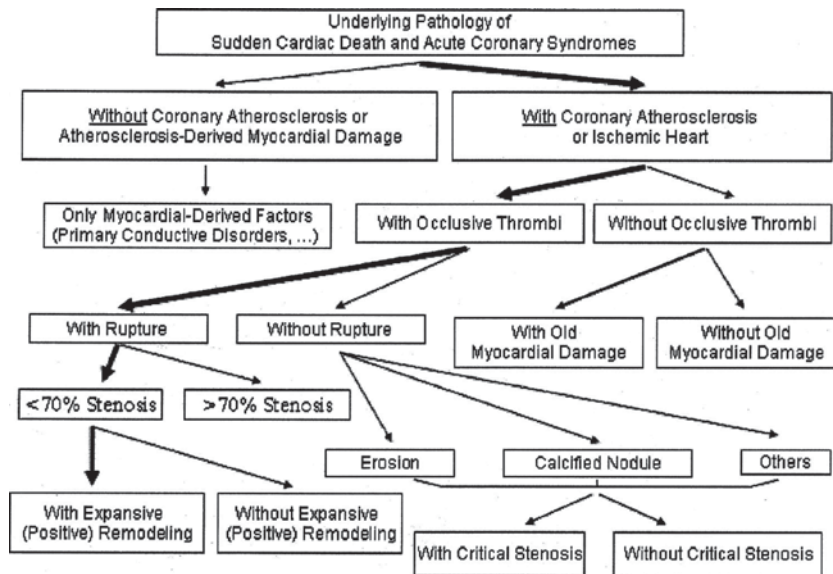


Fig. 1. Proposed diagram of the potential underlying pathology of acute coronary syndrome, (i.e., unstable angina, acute myocardial infarction and sudden cardiac death).

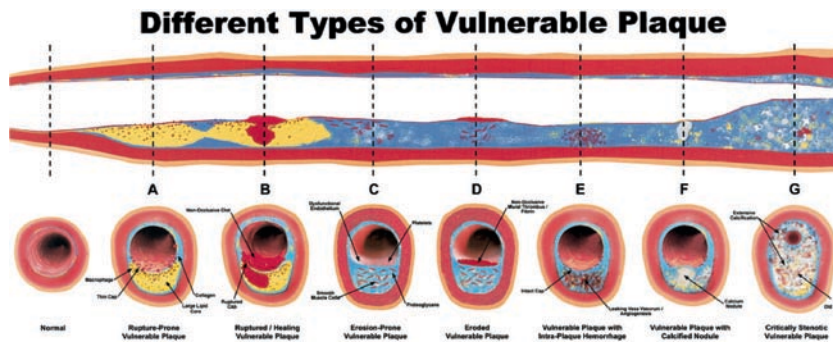


Fig. 2. Different types of vulnerable plaque as underlying cause of acute coronary events (ACS) and sudden cardiac death (SCD). (a) Rupture-prone plaque with large lipid core and thin fibrous cap infiltrated by macrophages. (b) Ruptured plaque with subocclusive thrombus and early organization. (c) Erosion-prone plaque with proteoglycan matrix in a smooth muscle cell-rich plaque. (d) Eroded plaque with subocclusive thrombus. (e) Intraplaque hemorrhage secondary to leaking vasa vasorum. (f) Calcific nodule protruding into the vessel lumen. (g) Chronically stenotic plaque with severe calcification, old thrombus, and eccentric lumen.

Plaque rupture is the most common type of plaque complication, accounting for ~70% of fatal acute myocardial infarctions and/or sudden coronary deaths (Fig. 2). Several retrospective autopsy series and a few cross-sectional clinical studies have suggested that thrombotic coronary death and acute coronary syndromes are caused by the plaque features and associated factors presented in Table 1 [5–7]. Most techniques for detecting and treating vulnerable plaque are devoted to rupture-prone plaque. This type of plaque has been termed a “thin-cap fibroatheroma” [8].

In some cases, a deep plaque injury cannot be identified despite a careful search. The thrombus appears to be superimposed on a de-endothelialized, but otherwise intact, plaque. This type of superficial plaque

Table 1
Underlying pathologies of “culprit” coronary lesions

Ruptured plaques (~70%)
Stenotic (20%)
Nonstenotic (50%)
Nonruptured plaques (~30%)
Erosion
Calcified nodule
Others/unknown

Adapted from Falk and associates [6], Davies [7], and Virmani et al. [5]

injury is called “plaque erosion” [9]. Other types of culprit plaques also exist (Fig. 2). In cases involving nonruptured plaques, plaque erosion or nodular calcification usually accompanies the luminal thrombus [5]. Other forms of thrombosis in nonruptured plaques may be described in the future. In all cases that involve a superimposed thrombus, the underlying lesion may be stenotic or nonstenotic. However, nonstenotic lesions are far more frequent than stenotic plaques and account for the majority of culprit ruptured plaques [10].

In cases of sudden cardiac death without thrombosis, we hypothesize that coronary spasm, emboli to the distal intramural vasculature, or myocardial damage related to previous injury may account for a terminal arrhythmic episode.

THE CHALLENGE OF TERMINOLOGY: CULPRIT PLAQUE VERSUS VULNERABLE PLAQUE

Culprit Plaque, a Retrospective Terminology

Interventional cardiologists and cardiovascular pathologists retrospectively describe the plaque responsible for coronary occlusion and death as a *culprit* plaque, regardless of its histopathologic features. For prospective evaluation, clinicians need a similar term for describing such plaques *before* an event occurs. Plaque rupture was reported sporadically by pathologists in the early twentieth century; it became a focus of attention of pioneering scientists in the 1960s (Table 2) and was later documented further by others [11–16].

Since the 1970s, scientists have been seeking the mechanisms responsible for converting chronic coronary atherosclerosis to acute coronary artery disease [11–15, 17]. As insights into this process have evolved, the relevant terminology has been continually updated. In the 1980s, Falk [11] and Davies and Thomas [15] used “plaque disruption” synonymously with “plaque rupture.” Later, Muller et al. [18, 19] used “vulnerable” to describe rupture-prone plaques as the underlying cause of most clinical coronary events. When this functional definition was proposed, the plaque considered responsible for acute coronary events (based on retrospective autopsy studies) had a large lipid pool, a thin cap, and macrophage-dense inflammation on or beneath its surface (Fig. 3).

Over the past several years, “vulnerable plaque” has been used sometimes to denote this concept and at other times to denote the specific histopathologic appearance of the above-described plaque. This dual usage is confusing, particularly as plaques can have other histologic features (see Fig. 2) that may also cause acute coronary events [5].

Table 2
Descriptions used by pioneers for culprit plaques [93, 94]

<i>Author</i>	<i>Year</i>	<i>Description used</i>
Olcott	1931	Plaque rupture
Leary	1934	Rupture of atheromatous abscess
Wartman	1938	Rupture-induced occlusion
Horn	1940	Plaque fissure
Helpern	1957	Plaque erosion
Crawford	1961	Plaque thrombosis
Gore	1963	Plaque ulceration
Byers	1964	Thrombogenic gruel
Chapman	1966	Plaque rupture
Constantinides	1966	Plaque rupture

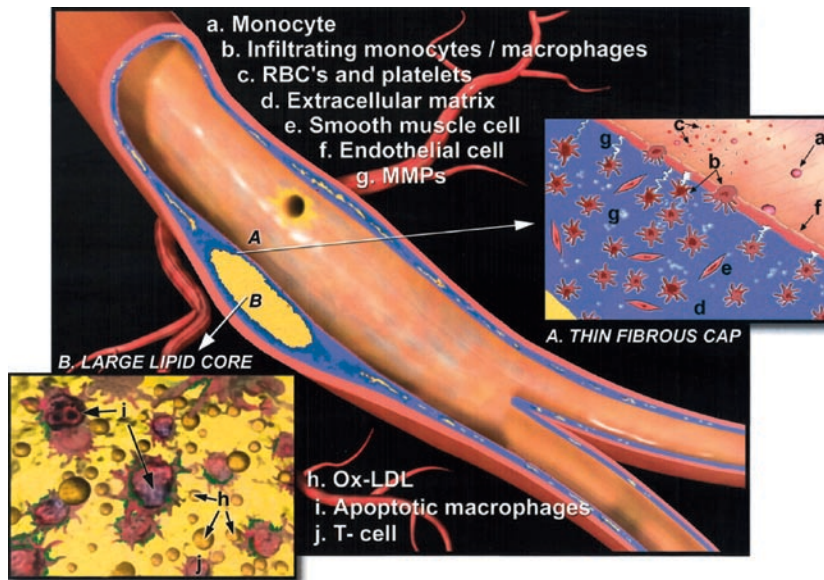


Fig. 3. Schematic figure illustrating the most common type of vulnerable plaque characterized by thin fibrous cap, extensive macrophage infiltration, paucity of smooth muscle cells, and large lipid core, without significant luminal narrowing.

Vulnerable Plaque, a Future Culprit Plaque

The term “vulnerable” is defined by English dictionaries as “susceptible to injury or susceptible to attack,” [20] as in “We are vulnerable both by water and land, without either fleet or army” (Alexander Hamilton). It denotes the likelihood of having an event in the future. The term “vulnerable” has been used in various reports in the medical literature, all of which describe conditions susceptible to injury. In this regard, the term “vulnerable plaque” is most suitable to define plaques susceptible to complications. An alternative term, “high-risk plaque,” has been proposed [18]. The term “high-risk” is often used to describe the high-risk patient groups with acute coronary syndromes. However, our intention is to provide a terminology to identify apparently healthy subjects at the risk of future events. Therefore,

the term vulnerable seems to be more appropriate. Also, because “vulnerable plaque” has already been widely adopted by investigators and clinicians, we recommend that the existing usage of this term be continued. We advise that the underlying morphological features be described broadly enough to include all dangerous plaques that involve a risk of thrombosis and/or rapid progression.

To provide a uniform language to help standardize the terminology, we recommend “vulnerable plaque” to identify all thrombosis-prone plaques and plaques with a high probability of undergoing rapid progression, thus becoming culprit plaques (Table 3). A proposed histopathologic classification for different types of vulnerable plaque is presented in Fig. 2. A list of proposed major and minor criteria for defining vulnerable plaques, based on autopsy studies (culprit plaques), is presented in Table 4.

A large number of vulnerable plaques are relatively uncalcified, relatively nonstenotic, and similar to type IV atherosclerotic lesions described in the American Heart Association classification [21]. However, as depicted in Fig. 3, different types of vulnerable plaques exist. Although Table 1 shows the relative distribution of ruptured and nonruptured culprit plaques, the exact prevalence of each type of vulnerable plaque is unknown and can only be determined in prospective studies.

Table 3
Interchangeable terms used to denote vulnerable plaque

<i>Acceptable but not recommended</i>	<i>Unacceptable^a</i>
High-risk plaque	Soft plaque
Dangerous plaque	Noncalcified plaque
Unstable plaque	AHA type IV plaque

AHA American Heart Association
^aThe term vulnerable plaque refers to all plaques at risk for thrombosis or rapid progression to become culprit lesions. A vulnerable plaque is not necessarily a soft plaque, a non-calcified plaque, an AHA type IV plaque, or a non-stenotic plaque [8, 21]

Table 4
Criteria for defining vulnerable plaque, based on the study of culprit plaques

Major criteria
Active inflammation (monocyte/macrophage and sometimes T-cell infiltration)
Thin cap with large lipid core
Endothelial denudation with superficial platelet aggregation
Fissured plaque
Stenosis >90%
Minor criteria
Superficial calcified nodule
Glistening yellow
Intraplaque hemorrhage
Endothelial dysfunction
Outward (positive) remodeling

Pan-Coronary Vulnerability

Several investigators have noted the presence of more than one vulnerable plaque in patients at risk of cardiovascular events. Mann and Davies [22] and Burke et al. [23] in cardiac autopsy specimens, Goldstein et al. [24] in angiography studies, Nissen [25] and Rioufol et al. [26] with intravascular ultrasound, and Buffon et al. [27] measuring neutrophil myeloperoxidase found multiple rupture-prone or ruptured plaques in a wide range of cardiovascular patient populations. A most recent series of publications on vulnerability reiterated the importance of going beyond a vulnerable plaque and called for evaluating the total arterial tree as a whole [28–30].

Silent-Plaque Rupture

Thrombotic complications that arise from rupture or fissure (small rupture) of a vulnerable plaque may be clinically silent, yet contribute to the natural history of plaque progression and ultimately luminal stenosis [31, 32].

BEYOND THE ATHEROSCLEROTIC PLAQUE

It is important to identify patients in whom disruption of a vulnerable plaque is likely to result in a clinical event. In these patients, other factors beyond plaque (i.e., thrombogenic blood and electrical instability of myocardium) are responsible for the final outcome (Fig. 4). We propose that such patients be referred to as “vulnerable patients.” In fact, plaques with similar characteristics may have different clinical presentations because of blood coagulability (vulnerable blood) or myocardial susceptibility to develop fatal arrhythmia (vulnerable myocardium). The latter may depend on a current or previous ischemic condition and/or a nonischemic electrophysiological abnormality.



Fig. 4. The risk of a vulnerable patient is affected by vulnerable plaque and/or vulnerable blood and/or vulnerable myocardium. A comprehensive assessment must consider all of the above.

DEFINITION OF A CARDIOVASCULAR VULNERABLE PATIENT

The term “cardiovascular vulnerable patient” is proposed to define subjects susceptible to an acute coronary syndrome or sudden cardiac death based on plaque, blood, or myocardial vulnerability (for example, 1-year risk $\geq 5\%$). Extensive efforts are needed to quantify an individual’s risk of an event according to each component of vulnerability (plaque, blood, and myocardium). Such a comprehensive risk-stratification tool capable of predicting acute coronary syndromes as well as sudden cardiac death would be very useful for preventive cardiology (Fig. 4).

DIAGNOSIS OF VULNERABLE PLAQUE/ARTERY

A number of issues have hampered the establishment of ideal criteria for defining vulnerable plaque: (1) the current body of evidence is largely based on cross-sectional and retrospective studies of culprit plaques; (2) robust prospective outcome studies based on plaque characterization have not been done (because of the lack of a reproducible, validated diagnostic technique); and (3) a lack of a representative animal model of plaque rupture and acute coronary syndrome/sudden death.

On the basis of retrospective evidence, we propose that the criteria listed in Tables 4 and 5 FX be used to define a vulnerable plaque. The sensitivity, specificity, and overall predictive value of each potential diagnostic technique need to be assessed before entering clinical practice.

Table 5
Markers of vulnerability at the plaque/artery level

Plaque
Morphology/structure
Plaque cap thickness
Plaque lipid core size
Plaque stenosis (luminal narrowing)
Remodeling (expansive vs. constrictive remodeling)
Color (yellow, glistening yellow, red, etc.)
Collagen content versus lipid content, mechanical stability (stiffness and elasticity)
Calcification burden and pattern (nodule vs. scattered, superficial vs. deep, etc.)
Shear stress (flow pattern throughout the coronary artery)
Activity/function
Plaque inflammation (macrophage density, rate of monocyte infiltration and density of activated T cell)
Endothelial denudation or dysfunction (local NO production, anti-/procoagulation properties of the endothelium)
Plaque oxidative stress
Superficial platelet aggregation and fibrin deposition (residual mural thrombus)
Rate of apoptosis (apoptosis protein markers, coronary microsatellite, etc.)
Angiogenesis, leaking vasa vasorum, and intraplaque hemorrhage
Matrix-digesting enzyme activity in the cap (MMPs 2, 3, 9, etc.)
Certain microbial antigens (e.g., HSP60, <i>C. pneumoniae</i>)
Pan-arterial
Transcoronary gradient of serum markers of vulnerability
Total coronary calcium burden
Total coronary vasoreactivity (endothelial function)
Total arterial burden of plaque including peripheral (e.g., carotid IMT)

MMP matrix metalloproteinase; *NO* nitric oxide; *IMT* intima-media thickness

Major Criteria

The following are proposed as major criteria for the detection of a vulnerable plaque. The presence of one or a combination of these factors may warrant higher risk of plaque complication. Techniques for detection of vulnerable plaque based on these criteria are briefly summarized here. A detailed discussion of advantages and disadvantages are reviewed elsewhere [33].

Active Inflammation

Plaques with active inflammation may be identified by extensive macrophage accumulation [13]. Possible intravascular diagnostic techniques [34, 35] include thermography (measurement of plaque temperature) [36, 37], contrast-enhanced (CE) MRI [38, 39], fluorodeoxyglucose positron emission tomography [33, 40], and immunoscintigraphy [41]. It has been shown that optical coherence tomography reflects the macrophage content of the fibrous cap [42]. Noninvasive options include MRI with superparamagnetic iron oxide [35, 36] and gadolinium fluorine compounds [43–45].

A Thin Cap With a Large Lipid Core

These plaques have a cap thickness of $<100\mu\text{m}$ and a lipid core accounting for $>40\%$ of the plaque's total volume [8]. Possible intravascular diagnostic techniques include optical coherence tomography (OCT) [46, 47], intravascular ultrasonography (IVUS) [48], high-resolution IVUS [49], elastography (palpography) [50, 51], MRI [52], angiography [53], near-infrared (NIR) spectroscopy [54–56], and radiofrequency IVUS analysis [57, 58]. The only noninvasive options are presently MRI and possibly CT [34, 35, 59–62].

Endothelial Denudation with Superficial Platelet Aggregation

These plaques are characterized by superficial erosion and platelet aggregation or fibrin deposition [5]. Possible intravascular diagnostic techniques include angiography with dye [63] and matrix-targeted/fibrin-targeted immune scintigraphy and OCT [46, 47]. Noninvasive options include fibrin/matrix-targeted contrast enhanced MRI [64], platelet/fibrin-targeted single photon emission computed tomography [41], and MRI [52].

Fissured/Injured Plaque

Plaques with a fissured cap (most of them involving a recent rupture) that did not result in occlusive thrombi may be prone to subsequent thrombosis, entailing occlusive thrombi or thromboemboli [5]. Possible intravascular diagnostic techniques include OCT [46, 47], IVUS, high-resolution IVUS [49], angiography, and MRI [34, 35]. A noninvasive option is fibrin-targeted CE-MRI [64, 65].

Severe Stenosis

On the surface of plaques with severe stenosis, shear stress imposes a significant risk of thrombosis and sudden occlusion. Therefore, a stenotic plaque may be a vulnerable plaque regardless of ischemia. Moreover, a stenotic plaque may indicate the presence of many nonstenotic or less stenotic plaques that can be vulnerable to rupture and thrombosis [24, 66] (Fig. 5). The current standard technique is invasive x-ray angiography [32]. Noninvasive options include multislice CT [67, 68], magnetic resonance angiography with or without a contrast agent, and electron-beam tomography angiography [59, 69–71].

Minor Criteria

For techniques that focus on the plaque level, minor criteria include the following features.

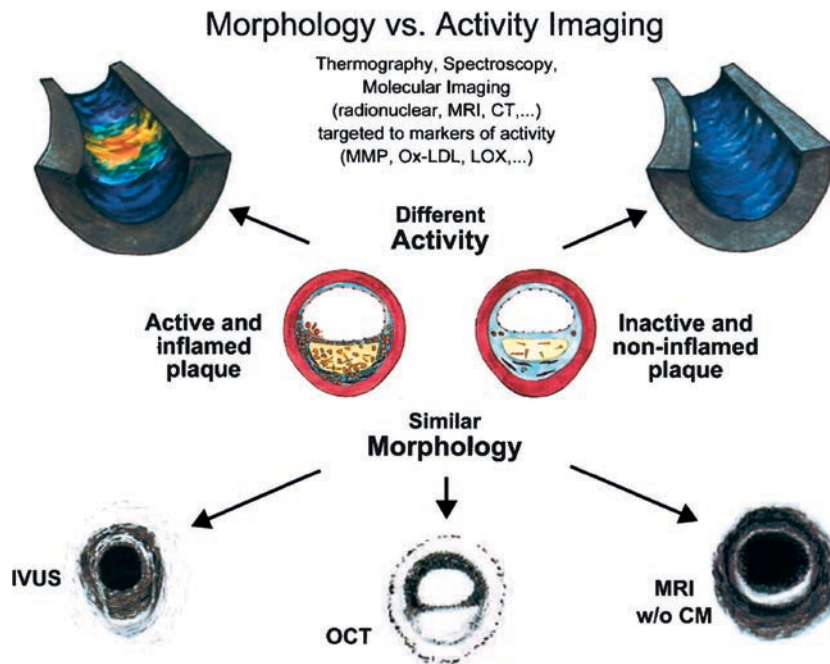


Fig. 5. Plaques with nearly similar morphology in terms of lipid core and fibrous cap (*middle panel*) may look similar with diagnostic imaging aimed at morphology only (*bottom panel*). However, they might look very different using diagnostic methods capable of detecting activity and physiology of the plaques. The *top left* plaque is hot (as evidenced in a thermography image), whereas the *top right* plaque is inactive and detected relatively as a cool plaque.

Superficial Calcified Nodules

These plaques have a calcified nodule within, or very close to, their cap, and this structure protrudes through and can rupture the cap. This event may or may not be associated with severe coronary calcification and a high calcium score [5]. Possible intravascular diagnostic techniques include OCT [46, 47], IVUS and elastography (palpography) [48]. Noninvasive options include electron-beam CT [72], multisession spiral CT [73], and MRI [34, 35].

Yellow Color (on Angioscopy)

Yellow plaques, particularly glistening ones, may indicate a large lipid core and thin fibrous cap, suggesting a high risk of rupture. However, because plaques in different stages can be yellow and because not all lipid-laden plaques are destined to rupture or undergo thrombosis, this criterion may lack sufficient specificity [53, 74]. Possible intravascular diagnostic techniques include angioscopy [73] and transcatheter colorimetry [75]. No diagnostic method has yet been developed for noninvasive angioscopy.

Intraplaque Hemorrhage

Extravasation of red blood cells, or iron accumulation in plaque, may represent plaque instability [76]. Possible intravascular diagnostic techniques include NIR spectroscopy [54, 55], tissue Doppler methods [77], and intravascular MRI. A noninvasive option is MRI [34, 35, 61].

Endothelial Dysfunction

Impaired endothelial vasodilator function occurs in a variety of acute and chronic disease states. Patients with cardiovascular risk factors have endothelial dysfunction. Endothelial dysfunction predicts CHD and stroke [89, 156]. Vulnerable plaques have sites of active inflammation and oxidative stress and are likely to be associated with impaired endothelial function. Possible diagnostic techniques are endothelium-dependent coronary artery dilatation (intravascular) [78] and measurement of flow-mediated dilatation by brachial artery ultrasonography and other emerging techniques (noninvasive) [79].

Expansive (Positive) Remodeling

Many of the nonstenotic lesions undergo “expansive,” “positive,” or “outward” remodeling, namely compensatory enlargement before impinging significantly on the vascular lumen. This phenomenon was considered as positive remodeling because the luminal area was not affected and stenosis was the only measure of risk. However, with the emphasis on plaque rupture in nonstenotic lesions, the so-called positive remodeling may not be truly positive and beneficial. Several studies have suggested that such remodeling is a potential surrogate marker of plaque vulnerability [80, 81]. In these studies, intravascular ultrasound was used to evaluate remodeling in coronary arteries. A recent study by Kim et al. [82] introduced a noninvasive method for the detection of expansive remodeling in coronary arteries by MRI. CT might also provide a noninvasive method for studying arterial remodeling.

Few of the above techniques have been tested in clinical trials showing ability to predict events. MRI and CT-based approaches are being developed. These technologies and strategies must also be evaluated with regard to their cost-effectiveness.

FUNCTIONAL VERSUS STRUCTURAL ASSESSMENT

A growing body of evidence indicates that different types of vulnerable plaque with various histopathology and biology exist. To evaluate plaque vulnerability, it is evident that a combined approach capable of evaluating structural characteristics (morphology) as well as functional properties (activity) of plaque may be more informative and may provide higher predictive value than a single approach. For instance, a combination of IVUS or OCT with thermography [80, 83] may provide more diagnostic value than each of these techniques alone. Such an arrangement can be useful for both intravascular as well as noninvasive diagnostic methods (Fig. 6). Autopsy [84] and IVUS studies [85] have shown that atherosclerotic lesions are frequently found in young and asymptomatic individuals. It is unclear what percentage of these lesions present morphologies of rupture-prone vulnerable plaques. Moreover, chronic inflammation [86] and macrophage/foam cell formation are an intrinsic part of the natural history of atherosclerosis. These data suggest that screening only based on plaque morphology and/or chronic markers of inflammation may not provide satisfactory predictive value for detection of vulnerable patients.

PAN-ARTERIAL APPROACH

Diagnostic and therapeutic methods may focus on the total burden of coronary artery disease [27]. The coronary calcium score is a good example of using CT for this purpose [72]. The total burden of calcified atherosclerotic plaques in all coronary arteries is identified by ultrafast CT. Extensive efforts are underway to improve image quality, signal processing, and interpretation of detailed components of coronary arteries that lend hope of a new calcium scoring and risk stratification technique based on

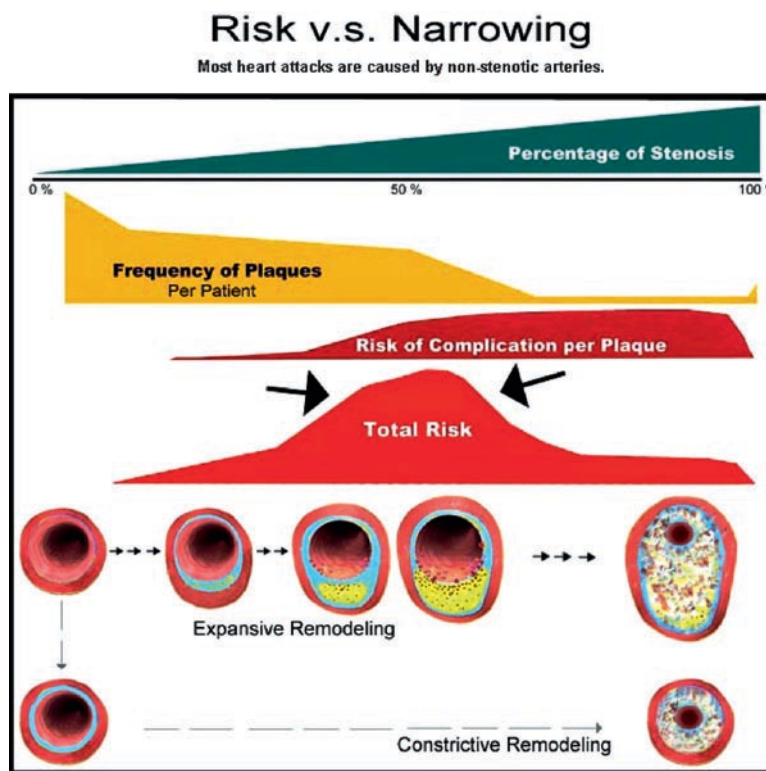


Fig. 6. Correlation between frequency of plaques, degree of stenosis, and risk of complication per plaque as a function of plaque progression. Although the average absolute risk of severely stenotic plaques may be higher than the average absolute risk of mildly stenotic plaques, there are more plaques with mild stenoses than plaques with severe stenoses.

CT information [87]. Like systemic indexes of inflammation (e.g., high sensitive CRP), endothelial dysfunction as measured by impaired flow-mediated vasodilation in the brachial artery can aid in the detection of pan-arterial vulnerability and may serve as a screening tool [88, 89].

Another emerging technique is the measurement of the transcoronary gradient (difference in concentration between coronary ostium and coronary sinus, or between proximal and distal segments of each coronary segment) of various factors, including cytokines [90], adhesion molecules [91], temperature, etc.

It will be important in the future to identify plaques that are on a trajectory of evolution toward a vulnerable state, to find out how long they will stay vulnerable, and to be able to target interventions to those plaques most likely to develop thrombosis. Similarly, factors that protect plaques from becoming vulnerable also need to be identified. It is likely that local hemodynamic factors and three-dimensional morphology may provide insight regarding the temporal course of an evolving plaque.

New studies are unraveling the role of the adventitia and periadventitial connective and adipose tissue in vulnerability of atherosclerotic plaques [92]. Further studies are needed to define the importance of these findings in the detection and treatment of vulnerable plaques.

VULNERABLE (THROMBOGENIC) BLOOD

Serum Markers of Atherosclerosis and Inflammation

Serum markers may predict a patient’s risk of acute cardiovascular complications (Table 6). C-reactive protein (CRP) is an independent risk factor and a powerful predictor of future coronary events in the asymptomatic population [154, 155] 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 [96, 97].

Circulating interleukin-6 levels, which are elevated in patients with acute coronary syndromes, also predict the risk of future coronary events in such patients [98]. Investigators have shown that high plasma concentrations of soluble CD40 ligand may indicate an increased vascular risk in apparently healthy women [99]. Likewise, Hwang et al. [100] 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 [101]. Pregnancy-associated plasma protein A (PAPP-A) is present in unstable plaques, and its circulating levels are elevated in patients with acute coronary syndromes [102]. Increased serum levels of PAPP-A may reflect instability of atherosclerotic plaques [103].

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 [104]. The tools and knowledge base, made possible by the Human Genome Project, allow the field

Table 6
Serological markers of vulnerability (reflecting metabolic and immune disorders)

Abnormal lipoprotein profile (e.g., high LDL, low HDL, abnormal LDL and HDL size density, lipoprotein [a], etc.)
Nonspecific markers of inflammation (e.g., 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 (e.g., diabetes or hypertriglyceridemia)
Specific markers of immune activation (e.g., anti-LDL antibody, anti-HSP antibody)
Markers of lipid peroxidation (e.g., ox-LDL and ox-HDL)
Homocysteine
PAPP-A
Circulating apoptosis marker(s) (e.g., Fas/Fas ligand, not specific to plaque)
ADMA/DDAH
Circulating nonesterified fatty acids (e.g., NEFA)

hsCRP 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; *NEFA* nonesterified fatty acids

to move beyond one or a few single-nucleotide polymorphisms in a priori candidate genes. Genome-wide linkage analyses have been carried out for coronary artery calcification [105], and genome-wide association studies for myocardial infarction are already a reality [106]. 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 reemphasized by Karnicki et al. [107] 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 [108]. 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 7).

Some platelet polymorphisms, such as glycoprotein IIIa P1(A2) [109], Ib agene-5T/C Kozak [110], high factor V and factor VII clotting [111], have been reported as independent risk factors for myocardial infarction. Reiner et al. [112] 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 [113]. 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 [114, 115].

Table 7
Blood markers of vulnerability (reflecting hypercoagulability)

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

t-PA tissue plasminogen activator; PAI-1 type 1 plasminogen activator inhibitor

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. The main antibodies of this syndrome are the anticardiolipin antibody, the lupus anticoagulant, and the IgG antibodies against prothrombin and b₂-glycoprotein [116, 117].

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 [118].

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 [119, 120].

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 [121]. Similarly, metabolic factors, such as postprandial metabolic changes, are associated with increased blood coagulability [122]. Likewise, estrogen replacement therapy can lead to a hypercoagulable state [123].

Finally, plasma viscosity, as well as fibrinogen and white blood cell counts, is positively associated with CHD events as shown by Koenig et al. [124] Furthermore, Junker et al. [125] 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 [126, 127]. 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 [122, 128, 129]. Susceptibility of the myocardium to acute ischemia was reviewed by Airaksinen [130], 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 ischemic myocardium may impair the arterial baroreflex and lead to hemodynamic instability [131].

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, b-blockade, and gender seem to affect autonomic reactions and the risk of fatal ventricular arrhythmias [130, 132, 133]. Recent studies have documented a hereditary component for autonomic function, and genetic factors may also modify the clinical presentation of acute coronary occlusion [134, 135]. Table 8 depicts conditions and markers associated with myocardial vulnerability.

Table 8
Conditions and markers associated with myocardial vulnerability

With atherosclerosis-derived myocardial ischemia as shown by
ECG abnormalities
During rest
During stress test
Silent ischemia (e.g., 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
Commotio cordis
Anomalous origination of a coronary artery
Myocarditis
Myocardial bridging

MSCT multislice computed tomography; *PET* positron emission tomography; *SPECT* single-photon emission computed tomography

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 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 [136]. 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 8). Circulating nonesterified fatty acids are another risk factor for sudden death in middle-aged men, as is elevated serum concentration of CRP; serum measurements may help screening for vulnerable myocardium [137].

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 [138].

Table 9 provides electrophysiological diagnostic criteria and techniques for the 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 the development of CHD in a large group of cases (25% [139] to 50% [3, 140, 141]). 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 pioneering studies by Ridker et al. [95] who noted a greater impact of an inflammatory marker such as serum CRP than LDL levels, is of interest. Several risk factor assessment models (e.g., Framingham [142], Sheffield [143, 144], New Zealand [145, 146], Canadian [147], British [148], European [149], Dundee [150], Munster [PROCAM] [151], and MONICA [152]) 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 (i.e., 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 the 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.

Table 9
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

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 (e.g., 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 [153].

The information used for developing such risk stratification in the future is likely to come from a combination of smaller prospective studies (e.g., from new imaging techniques) and retrospective cohort studies (e.g., 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 [94, 154].

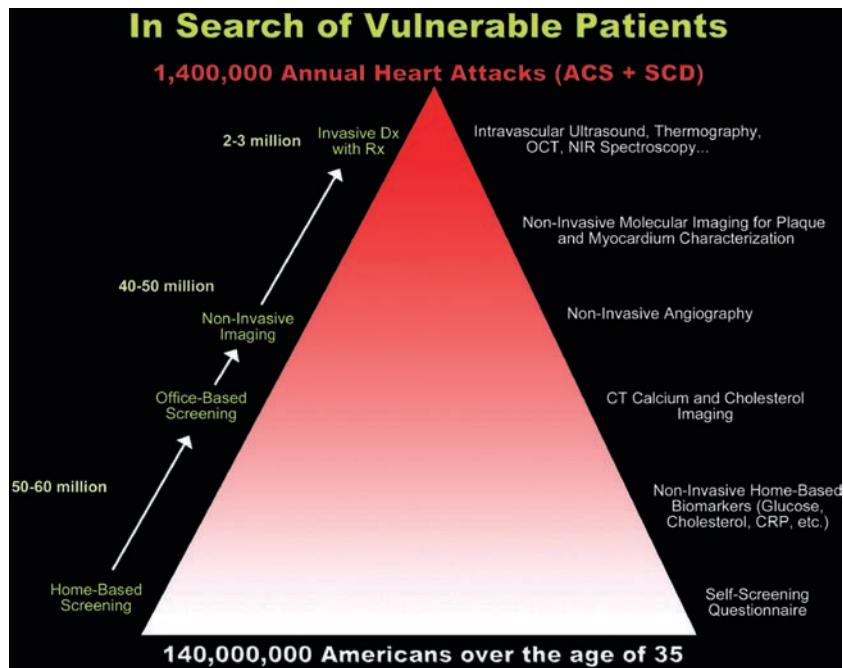


Fig. 7. The Vulnerable Patient Pyramid. This pyramid illustrates a speculative roadmap in search of vulnerable patients (numbers represent population in the United States). The major need is to develop noninvasive, relatively inexpensive, readily available, and accurate screening/diagnostic tools allowing multistep screening of an apparently healthy population and those with known atherosclerosis but whose risks for acute events are uncertain.

In Search of the Vulnerable Patient

The ideal method for screening vulnerable patients should be (1) inexpensive, (2) relatively non-invasive, (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 (Fig. 7).

The Vulnerable Patient 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.

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