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From Vulnerable Plaque to Vulnerable Patient—Part III

A New Paradigm for the Prevention of Heart Attack: Identification and Treatment of the Asymptomatic Vulnerable Patient

Executive Summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force Report

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Foreword

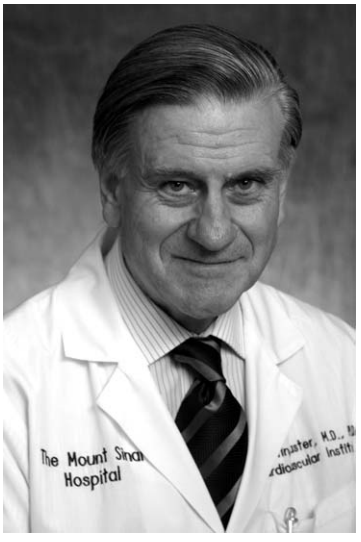
Valentin Fuster, MD, PhD

It is a pleasure to provide this Foreword to the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. The contributors to the SHAPE initiative must be congratulated for their original, ambitious, and provocative approach to the number 1 problem in the cardiovascular field, a problem that affects millions of lives annually. Since the landmark Framingham Heart Study introduced the concept of cardiovascular risk factors, prediction and prevention of adverse cardiac events have been based primarily on the identification and treatment of these risk factors. Nonetheless, atherosclerotic cardiovascular disease has remained the primary cause of mortality and morbidity in most countries. It is now obvious that new strategies are needed to fight the growing epidemic of atherosclerotic cardiovascular disease. In my view, early detection and treatment of high-risk subclinical atherosclerosis is a leading candidate to fulfill that role.

Early observations in the 1980s sparked the concept of the vulnerable or high-risk plaque, and generated the search for the immediate underlying cause of acute coronary events. Subsequent advances in the field of cardiology constitute a long list of major developments that are likely to change the practice of cardiology. I believe that advances in noninvasive imaging head this list. The notion of the vulnerable or high-risk plaque is rightly evolving into the more comprehensive concept of the "vulnerable patient," as evidenced by the plurality of vulnerable plaques and the total burden of atherosclerotic disease. In addition, other sources of vulnerability from thrombogenic blood and ischemic or arrhythmogenic myocardium must be considered.

Despite questions regarding the feasibility and practicality of such an ambitious proposal, the SHAPE Guideline is a worthy and timely effort that goes beyond traditional risk assessment and has the potential to transform the field of preventive cardiology.

The driving passion and commitment of the members of the SHAPE Task Force is commendable. It serves as an example to all of us who wish to stop and reverse the epidemic of atherosclerotic cardiovascular disease. I will certainly feel proud to contribute to the SHAPE initiative's call for future studies that will validate and accelerate the adoption of screening for subclinical atherosclerosis as proposed by the SHAPE Guideline.



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Introduction

Erling Falk, MD, PhD,[a] Morteza Naghavi, MD,[b,*] and Prediman K. Shah, MD[c]

In the second half of the 20th century significant advances were made in the primary prevention of atherosclerotic cardiovascular disease. This progress was a result of the discovery of atherosclerotic risk factors and implementation of population-based risk assessment and risk reduction strategies. Nonetheless, cardiovascular disease has remained the number 1 killer in most developed countries, and it is increasingly threatening populations in the developing world. More specifically, little progress has been made in the identification of high-risk asymptomatic individuals who could benefit from aggressive preventive therapies but who are unaware of the presence and the severity of their disease. The hidden nature of the disease has made the battle against heart attack and stroke much more difficult than the fight against other diseases.

Fortunately, new developments in the detection of subclinical atherosclerosis are now providing us with unprecedented opportunities to identify asymptomatic individuals with the highest risk (the "vulnerable patient") and to implement aggressive preventive strategies tailored to each individual. The Association for Eradication of Heart Attack (AEHA), a grassroots organization comprised of cardiovascular specialists, was created to take advantage of these new opportunities and has led the effort to create expert consensus guidelines in the field. The definitions of *vulnerable plaque* and the *vulnerable patient* have been addressed previously. The Screening for Heart Attack Prevention and Education (SHAPE) Task Force was recently organized to address the identification and treatment of the vulnerable patient.

On behalf of the SHAPE Task Force, we are pleased to introduce you to the SHAPE Guideline for prevention of cardiovascular disease. We hope this effort will help advance the practice of preventive cardiology and will be welcomed by national healthcare policymakers. The Task Force will continue to monitor new developments in the field and will update the SHAPE Guideline in the future as new information becomes available.

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From Vulnerable Plaque to Vulnerable Patient—Part III: Executive Summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force Report

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Screening for early-stage asymptomatic cancers (eg, cancers of breast and colon) to prevent late-stage malignancies has been widely accepted. However, although atherosclerotic cardiovascular disease (eg, heart attack and stroke) accounts for more death and disability than all cancers combined, there are no national screening guidelines for asymptomatic (subclinical) atherosclerosis, and there is no government- or healthcare-sponsored reimbursement for atherosclerosis screening. Part I and Part II of this consensus statement elaborated on new discoveries in the field of atherosclerosis that led to the concept of the "vulnerable patient." These landmark discoveries, along with new diagnostic and therapeutic options, have set the stage for the next step: translation of this knowledge into a new practice of preventive cardiology. The identification and treatment of the vulnerable patient are the focuses of this consensus statement.

In this report, the Screening for Heart Attack Prevention and Education (SHAPE) Task Force presents a new practice guideline for cardiovascular screening in the asymptomatic at-risk population. In summary, the SHAPE Guideline calls for noninvasive screening of all asymptomatic men 45–75 years of age and asymptomatic women 55–75 years of age (except those defined as very low risk) to detect and treat those with subclinical atherosclerosis. A variety of screening tests are available, and the cost-effectiveness of their use in a comprehensive strategy must be validated. Some of these screening tests, such as measurement of coronary artery calcification by computed tomography scanning and carotid artery intima–media thickness and plaque by ultrasonography, have been available longer than others and are capable of providing direct evidence for the presence and extent of atherosclerosis. Both of these imaging methods provide prognostic information of proven value regarding the future risk of heart attack and stroke. Careful and responsible implementation of these tests as part of a comprehensive risk assessment and reduction approach is warranted and outlined by this report. Other tests for the detection of atherosclerosis and abnormal arterial structure and function, such as magnetic resonance imaging of the great arteries, studies of small and large artery stiffness, and assessment of systemic endothelial dysfunction, are emerging and must be further validated. The screening results (severity of subclinical arterial disease) combined with risk factor assessment are used for risk stratification to identify the vulnerable patient and initiate appropriate therapy. The higher the risk, the more vulnerable an individual is to a near-term adverse event. Because <10% of the population who test positive for atherosclerosis will experience a near-term event, additional risk stratification based on reliable markers of disease activity is needed and is expected to further focus the search for the vulnerable patient in the future. All individuals with asymptomatic atherosclerosis should be counseled and treated to prevent progression to overt

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clinical disease. The aggressiveness of the treatment should be proportional to the level of risk. Individuals with no evidence of subclinical disease may be reassured of the low risk of a future near-term event, yet encouraged to adhere to a healthy lifestyle and maintain appropriate risk factor levels. Early heart attack care education is urged for all individuals with a positive test for atherosclerosis. The SHAPE Task Force reinforces existing guidelines for the screening and treatment of risk factors in younger populations.

Cardiovascular healthcare professionals and policymakers are urged to adopt the SHAPE proposal and its attendant cost-effectiveness as a new strategy to contain the epidemic of atherosclerotic cardiovascular disease and the rising cost of therapies associated with this epidemic. **(Am J Cardiol 2006;98[suppl]:2H–15H)**

Atherosclerosis is a common and dangerous disease of the arteries of the heart, brain, and periphery. It is by far the most frequent underlying cause of angina, heart attack, and peripheral arterial disease and is responsible for many cases of stroke. Thus, atherosclerosis and its thrombotic complications are currently the most deadly and disabling diseases in affluent countries and in the near future will be so in the entire world.[1,2] Yet many individuals, even those with severe atherosclerosis, are unaware of their risk, because they have no symptoms. In 30%–50% of these individuals, the first indicator of atherosclerosis is an acute heart attack, which often is fatal.[3–5]

Although easily measured, potentially modifiable risk factors account for >90% of the risk of an initial acute myocardial infarction (MI).[1,6,7] Moreover, although effective risk-lowering therapies exist, MI or sudden unexpected death remain all too common first manifestations of coronary atherosclerosis. These attacks often occur in patients who are not receiving the benefits of preventive therapies of proven efficacy because their arterial disease was unrecognized (asymptomatic) and/or they had been misclassified by conventional risk factors and assigned a treatment goal at odds with their actual burden of atherosclerosis.

Many pharmacologic and nonpharmacologic therapies have been shown to prevent atherosclerotic events and prolong survival. Therefore, early detection of atherosclerosis itself before symptoms occur can provide a major opportunity to prevent many cardiovascular events. Because screening to identify subclinical or asymptomatic atherosclerosis could confer great public health benefit, it may seem surprising that it has not yet been incorporated into national and international clinical guidelines. Therapeutic strategies targeted to at-risk vulnerable patients can reduce the heavy economic burden of symptomatic and end-stage care for cardiovascular disease (CVD). There have been 2 primary reasons for this conservative strategy. First, there has been a perception that more data are needed to demonstrate that screening for subclinical atherosclerosis improves the risk assessment beyond that provided by traditional risk factors such as smoking, hypertension, hypercholesterolemia, and diabetes mellitus. Second, the appropriate tools for the detection of subclinical atherosclerosis have not been widely available to clinicians. However, recent developments have provided us with the requisite data and the necessary technology, as well as highly effective and safe therapies.

Burden of Atherosclerotic Cardiovascular Disease

Atherosclerosis is responsible for nearly all cases of coronary heart disease (CHD), intermittent claudication and

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critical limb ischemia, and many cases of stroke. CHD alone is the single greatest killer of men and women in the United States (479,300 CHD deaths in 2003), causing >1 of every 5 deaths.[3] In 2006, an estimated 875,000 individuals in the United States will have a first heart attack, and 500,000 will have a recurrent attack.[3] Because the risk of CHD increases markedly with age, and because women tend to live longer than men, almost as many women as men ultimately die of CHD.[3]

In the United States, approximately 700,000 individuals will have a stroke this year; stroke is the number 3 cause of death in the country and it is a leading cause of severe, long-term disability.[3] In 2002, 657,054 persons in the United States died of heart attacks and stroke compared with 557,264 deaths due to cancers.[8,9] Despite the greater magnitude of CVD, screening for occult breast and colorectal cancers has become a widely adopted public policy strategy, whereas screening for subclinical atherosclerosis in at-risk adults to prevent heart attack and stroke is not currently recommended.[10]

The cost of clinical care during and after an acute heart attack is growing rapidly, and the number of patients with heart failure after heart attack has been escalating in the past 2 decades.[11,12] There is therefore an imperative to develop a new paradigm to screen for subclinical atherosclerosis and prevent its transition to deadly and costly clinical and symptomatic stages.

Risk Factors, Susceptibility, and Vulnerability

Atherosclerosis begins to develop early in life and progresses with time, but the speed of progression is, to a large extent, unpredictable and differs markedly among seemingly comparable individuals. At every level of risk factor exposure, the amount of established atherosclerosis and the vulnerability to acute events varies greatly, probably because of genetic variability in an individual's susceptibility to atherosclerosis and propensity to arterial thrombosis ("vulnerable blood") and ventricular arrhythmias ("vulnerable myocardium"). Comparative studies of prospective trials with clinical follow-up have revealed that the observed event rate may differ severalfold among populations predicted to have similar risk by risk factor scoring.[13–26]

In the United States, the prevalence of ≥1 major risk factor (aside from age) is very high among persons aged ≥40 years who develop CHD.[27] However, it is also high among those who do not develop CHD, illustrating that when risk factors are almost universally present in a population, they do not predict the development of disease very well in individuals.[28–32] Based on recently published data from 3 influential prospective epidemiologic studies,[27] Weissler[32] highlighted this failure by using likelihood ratio analysis. A likelihood ratio ≤2.0 denotes low predictive power and a likelihood ratio ≥9.0 denotes high predictive power. Remarkably low predictive power (likelihood ratio <1.4) was found for ≥1 risk factor in predicting death from CHD and/or nonfatal MI, despite the high frequency of this risk profile in the population with CHD events. The relation between cigarette smoking and lung cancer provides a reasonable analogy: When almost everyone in a given population smokes, smoking itself fails to predict the risk of cancer.

The limitations of the traditional risk factors to identify at-risk individuals constitute the foundation behind the "polypill" strategy in which people with known CVD or over a specified age would be treated with a single daily pill containing 6 components to reduce events and prolong survival, regardless of what current risk assessment algorithms predict.[33] Age is the most discriminatory screening factor in apparently healthy individuals; 96% of deaths from CHD or stroke occur in people aged ≥55 years.[33]

Current Guidelines in Primary Prevention

The current guidelines in primary prevention recommend initial assessment and risk stratification based on traditional risk factors (eg, the Framingham Risk Score in the United States and the Systemic Coronary Risk Evaluation [SCORE] in Europe), followed by goal-directed therapy when necessary.[19,34–36] Although this approach may identify persons at very low or very high risk of a heart attack or stroke within the next 10 years, the majority of the population belongs to an intermediate-risk group in which the predictive power of risk factors is low. Most heart attacks occur in this group. Consequently, many individuals at risk will not be properly identified and will not be treated to appropriately individualized goals. Others will be erroneously classified as high risk and will be unnecessarily treated with drug therapy for the rest of their lives. This strategy is neither cost-effective nor representative of good medical practice.

The limitations of current guidelines are recognized by the American Heart Association (AHA), the National Cholesterol Education Program (NCEP) Expert Panel, and by the European Third Joint Task Force.[19,34,36] Therefore, these organizations recommended the use of noninvasive screening tests that identify abnormal arterial structure and function as an option for advanced risk assessment in appropriately selected persons, particularly in those with multiple risk factors who are judged to be at intermediate (or indeterminate) risk. These tests include carotid intima–media thickness (CIMT) measured by ultrasound, coronary artery calcification score (CACS) determined by computed tomography (CT), endothelial vasomotor dysfunction evaluated by ultrasound, ankle–brachial blood pressure ratio (ABI), and magnetic resonance imaging (MRI) techniques.[19,34,36]

CHD risk equivalents: Patients who already have developed clinical atherosclerotic disease, whether cerebral

(transient ischemic attack or stroke of carotid origin) or peripheral (claudication or abdominal aortic aneurysm), have declared themselves to be at continued high risk (ie, vulnerable).[37] Current American and European guidelines also recognize groups of asymptomatic patients who are at similar high risk.[19,34,36] These include patients with diabetes, as well as asymptomatic patients in whom atherosclerosis and/or its consequences have been demonstrated by noninvasive testing. For example, the presence of myocardial ischemia appropriately identified by stress testing qualifies as a diagnosis of CHD. Moreover, carotid or iliofemoral atherosclerosis is considered a CHD risk equivalent and should be treated aggressively; atherosclerosis in a vascular bed predicts atherosclerosis in other vascular beds. In addition, patients with ≥2 risk factors with a 10-year risk for CHD >20% are considered a CHD risk equivalent. However, existing guidelines do not recognize severe nonobstructive coronary atherosclerosis as a CHD risk equivalent even though most heart attacks originate from nonobstructive coronary plaques.

Screening for subclinical atherosclerosis: In a recent scientific statement, the American Cancer Society (ACS), the AHA, and the American Diabetes Association (ADA) announced a new collaborative initiative to create a national commitment to prevention and early detection of cancer, CVD, and diabetes.[38] The ACS recommends the following screening ages: age 20 years for breast cancer, with mammography starting at age 40 (at least annually); age 21 for cervical cancer (Pap test); age 50 for colorectal cancer (several options); and age 50 for prostate cancer (prostate-specific antigen test and digital rectal examination annually).[38]

The AHA recommends that assessment of cardiovascular risk begin at age 20 years, to be repeated at regular intervals, preferentially by calculating the Framingham risk score.[38] In contrast to cancer, early detection of CVD by screening with the best available technology is not mentioned, despite the >500,000 deaths per year from atherosclerosis, compared with ~57,000 from colorectoanal cancer, ~42,000 from breast cancer, and ~31,000 from prostate cancer.[8,9] The current focus on breast cancer overlooks the much greater threat to young and middle-aged women posed by CVD.

We believe, therefore, that the time has come to replace the traditional, imprecise risk factor approach to individual risk assessment in primary prevention with an approach largely based on noninvasive screening for the disease itself (subclinical atherosclerosis). The Screening for Heart Attack Prevention and Education (SHAPE) Task Force has developed a model to identify individuals who are susceptible to atherosclerosis and its thrombotic and arrhythmogenic complications (vulnerable patients) and initiate appropriate care to prevent the sequelae of CVD, and to avoid unnecessarily intensive treatment.

New Paradigm for the Prevention of Heart Attack

In search of the vulnerable patient: Parts I and II of this consensus statement elaborated on new discoveries in the field of atherosclerosis that led to the concept of the vulnerable patient.[39,40] This focus on the identification and aggressive treatment of the previously unrecognized very-high-risk population neglected the majority of the population who are not in the very-high-risk category. To rectify this major omission, the SHAPE report introduces a new paradigm to stratify the entire US population at risk and to tailor recommendations accordingly. Almost all vulnerable individuals have detectable subclinical atherosclerosis, and we now possess the tools to identify it with sufficient predictive power. It is therefore proposed that all apparently healthy men 45–75 years of age and women 55–75 years of age with no known history of CHD and who are considered not to be at very low risk undergo screening for atherosclerosis. Of the 61,163,000 US individuals in the SHAPE age range, 3,951,000 have known CHD. The size of the very-low-risk population is difficult to ascertain but is probably around 5%–10% based on data from large US cohort studies.[7] This population, and those who have already undergone CACS or CIMT assessment, are excluded from the SHAPE-eligible population. Because an exact number is not available, 50 million has been chosen as the approximate number of persons who will require SHAPE evaluation. Based on a 50% compliance rate for SHAPE screening over 10 years, and a 5-year reexamination cycle, the number of persons required to undergo annual screening after a decade will decrease to 5–6 million per year.

In the United States, an estimated 875,000 persons annually experience a first heart attack, and 175,000 of these attacks are "silent."[3] Because approximately 500,000 of the total will occur in the 50 million persons in the SHAPE-eligible population (the peak of the pyramid in Figure 1), a screening ratio of 1:100 (500,000:50,000,000) is anticipated. Almost all of the events will occur in the ~50% of the eligible population who have a positive atherosclerosis test; these individuals therefore have ~2% annual risk, consistent with the high-risk classification used in the existing US guidelines. However, according to the SHAPE classification, in those with positive tests the annual risk escalates as the burden of atherosclerosis increases, as illustrated in Figure 1. Those with the highest burden of atherosclerosis are the most vulnerable patients. A major advantage of the SHAPE Guideline over the existing guidelines is that in the existing guidelines the low-risk and intermediate-risk population account for the majority of heart attacks; <20% of the total results from cardiac events in the high-risk population. In the SHAPE Guideline, the majority of heart attacks occur in the high-risk population.

Criteria for recommended screening tests: Several factors are used in selecting individual tests as part of a screening program. These factors include (1) the abundance

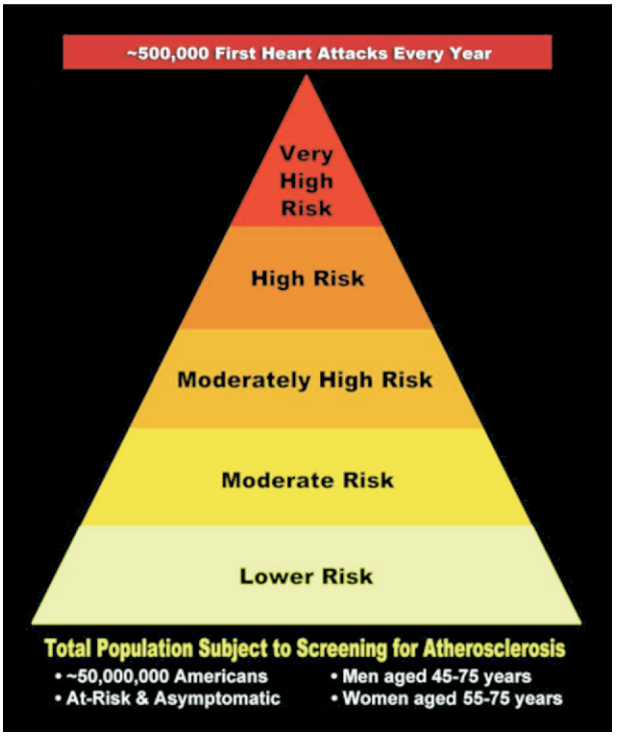

Figure 1. In search of the vulnerable patient: the Screening for Heart Attack Prevention and Education (SHAPE) paradigm calls for screening all apparently healthy (ie, with no prior diagnosis of coronary heart disease) men 45–75 years of age and women 55–75 years of age who are not considered very low risk. This population accounts for approximately 50 million people in the United States.

of evidence for the predictive value of the test in the recommended population over and above that available from standard office-based risk assessment tools (incremental value), (2) availability, (3) reproducibility, (4) complementary value with respect to the concept of the vulnerable patient, and/or (5) cost-effectiveness relative to the status quo.

Figure 2 illustrates the array of available diagnostic tests, including traditional risk factor–based tests and tests that more directly evaluate the presence or effect of atherosclerosis. The atherosclerosis screening methods selected as those that currently best fulfill the above criteria are (1) CACS determined by CT and (2) CIMT and plaque determined by ultrasonography. The evidence behind this selection[41–75] and further support can be found in the full SHAPE Report on the Association for the Eradication of Heart Attack's (AEHA) Web site (www.aeha.org).

The First SHAPE Guideline

A conceptual flow chart illustrating the principles of the new paradigm is shown in Figure 3.

In contrast to the existing traditional risk factor–based guidelines, this new strategy is primarily based on noninvasive screening for subclinical atherosclerosis using 2 well-established noninvasive imaging modalities: CT for measurement of CACS and B-mode ultrasound for measurement of CIMT and carotid plaque.[41–75] This strategy is driven by the data-supported principle that the major determinant of risk for atherosclerotic CVD in asymptomatic adults is the presence of the underlying disease itself, ie, subclinical atherosclerosis. Early detection of atherosclerosis will permit more widespread and effective prevention strategies to be implemented through accurate risk stratification and tailoring the intensity of therapy to the underlying CAD risk in a cost-effective manner.

The screening strategy for risk assessment and the associated treatment algorithm of the First SHAPE Guideline are summarized in Figure 4. Briefly, all asymptomatic men 45–75 years of age and women 55–75 years of age who do not have very-low-risk characteristics or a documented history of CVD are encouraged to undergo screening for atherosclerosis. The *very-low-risk* group is characterized by the absence of any traditional cardiovascular risk factors (see Figure 4).

Individuals with negative tests for atherosclerosis (defined as CACS = 0, or CIMT <50th percentile without carotid plaque) are classified as *lower risk* (those without conventional risk factors) or *moderate risk* (those with established risk factors), and treated as recommended in the NCEP Adult Treatment Panel III (ATP III) guidelines, with low-density lipoprotein (LDL) cholesterol targets of <160 mg/dL (<4.14 mmol/L) and <130 mg/dL (<3.37 mmol/L), respectively.[35] Reassessment is recommended within 5–10 years unless otherwise indicated.

Those who test positive for atherosclerosis (CACS ≥1, or CIMT ≥50th percentile or presence of carotid plaque) are further stratified according to the magnitude of atherosclerotic burden into the following risk categories:

- *Moderately high risk:* CACS <100 (but >0) and <75th percentile, or a CIMT <1 mm and <75th percentile (but ≥50th percentile) without discernible carotid plaque. Treatment includes lifestyle modifications and a LDL cholesterol target of <130 mg/dL (<3.37 mmol/L); targeting to <100 mg/dL (<2.59 mmol/L) is optional.
- *High risk:* CACS 100–399 or >75th percentile, or a CIMT ≥1 mm or >75th percentile or a carotid plaque causing <50% stenosis. Treatment calls for aggressive lifestyle modifications and a LDL cholesterol target of <100 mg/dL (<2.59 mmol/L); targeting to <70 mg/dL (<1.82 mmol/L) is optional.
- *Very high risk:* CACS >100 and >90th percentile or a CACS ≥400, or carotid plaque causing ≥50% stenosis. Treatment includes aggressive lifestyle modification and a LDL cholesterol target of <70 mg/dL (<1.82 mmol/L). Additional testing for myocardial ischemia is recommended for this group, and, depending on the extent of the ischemia, those who test

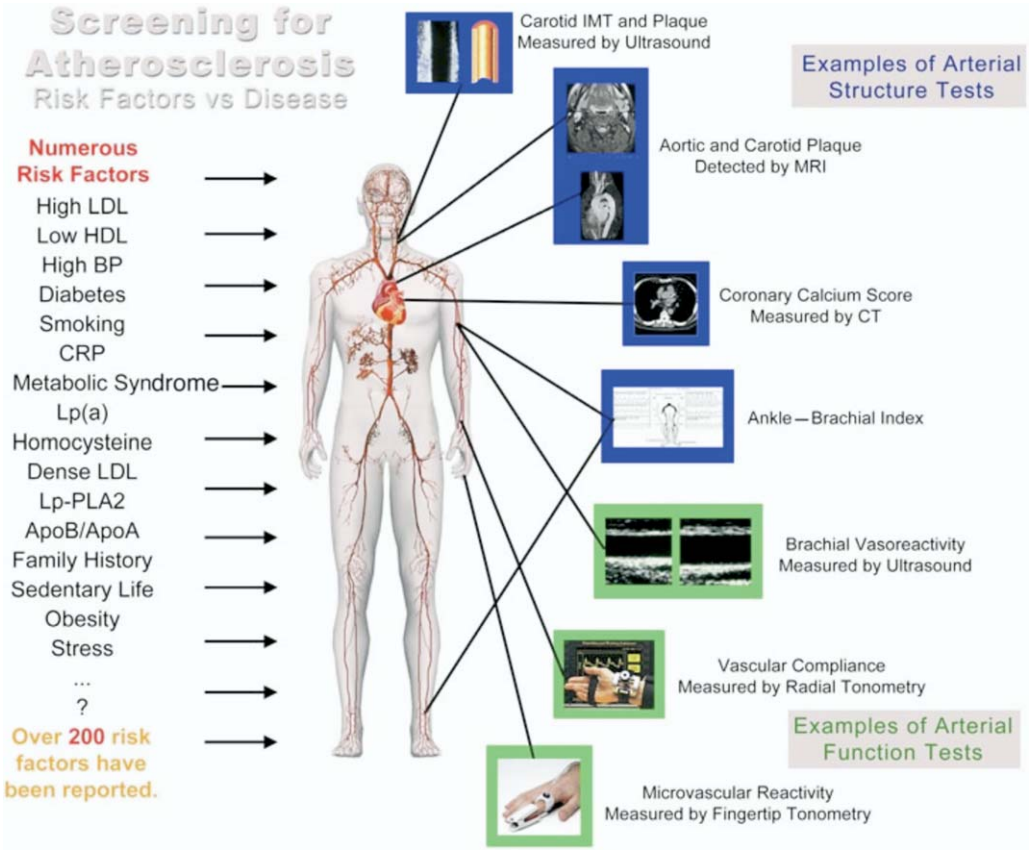

Figure 2. The new Screening for Heart Attack Prevention and Education (SHAPE) paradigm: screening directly for the presence and severity of atherosclerosis by structure and function testing (*right*) versus the traditional approach in which the likelihood of atherosclerotic disease is estimated indirectly by evaluating risk factors for the disease (*left*). Apo = apolipoprotein; BP = blood pressure; CRP = C-reactive protein; CT = computed tomography; HDL = high-density lipoprotein; IMT = intima–media thickness; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); Lp-PLA2 = lipoprotein-associated phospholipase A_2; MRI = magnetic resonance imaging.

positive for ischemia should be considered for angiography.

Thus, the First SHAPE Guideline emphasizes titrating the intensity of risk factor modification and treatment goals proportional to the risk.

Important considerations: The importance of lifestyle modifications recommended by existing guidelines applies to all categories of SHAPE as follows[19,34–36]:

- Although arguments could be made for applying the paradigm to persons aged >75 years, the cost-effectiveness of such an approach is questionable.[33] Consequently, the most reasonable path is to apply high-risk treatment to those in this group, in view of the high likelihood of significant subclinical atherosclerosis with increasing age.
- Other tests may be considered for optional use. For example, a high C-reactive protein (CRP) value may confer higher risk than lower values,[76–78] as does an ABI <0.6 versus 0.6–0.9.[34,79,80] The SHAPE Guideline flow chart suggests how these tests may be used to upgrade an individual to a higher risk category.
- An ABI <0.9 suggests significant peripheral atherosclerosis and is associated with a high risk of heart attack because of the high likelihood of coexisting coronary atherosclerosis.[34,35] Aggressive therapy against atherothrombosis should be mandated in such patients.
- Diabetes is not considered a CHD risk equivalent in the absence of subclinical atherosclerosis.[81] If, however, subclinical atherosclerosis is present, diabetes is accorded high-risk status; an increased propensity to arterial thrombosis (vulnerable blood) may be contributory.[82,83]
- The presence of left ventricular hypertrophy is also considered a high-risk state because of the increased risk of ventricular arrhythmias and sudden cardiac death (vulnerable myocardium).[84]
- Additional functional and structural tests, such as MRI of the aorta and carotid arteries,[85,88] studies of small and large artery stiffness,[89,90] and assessment of endothelial dysfunction[91–94] have been shown to predict events. However, the additive value of these tests to the sensitivity and specificity of detection of subclinical disease requires further validation.

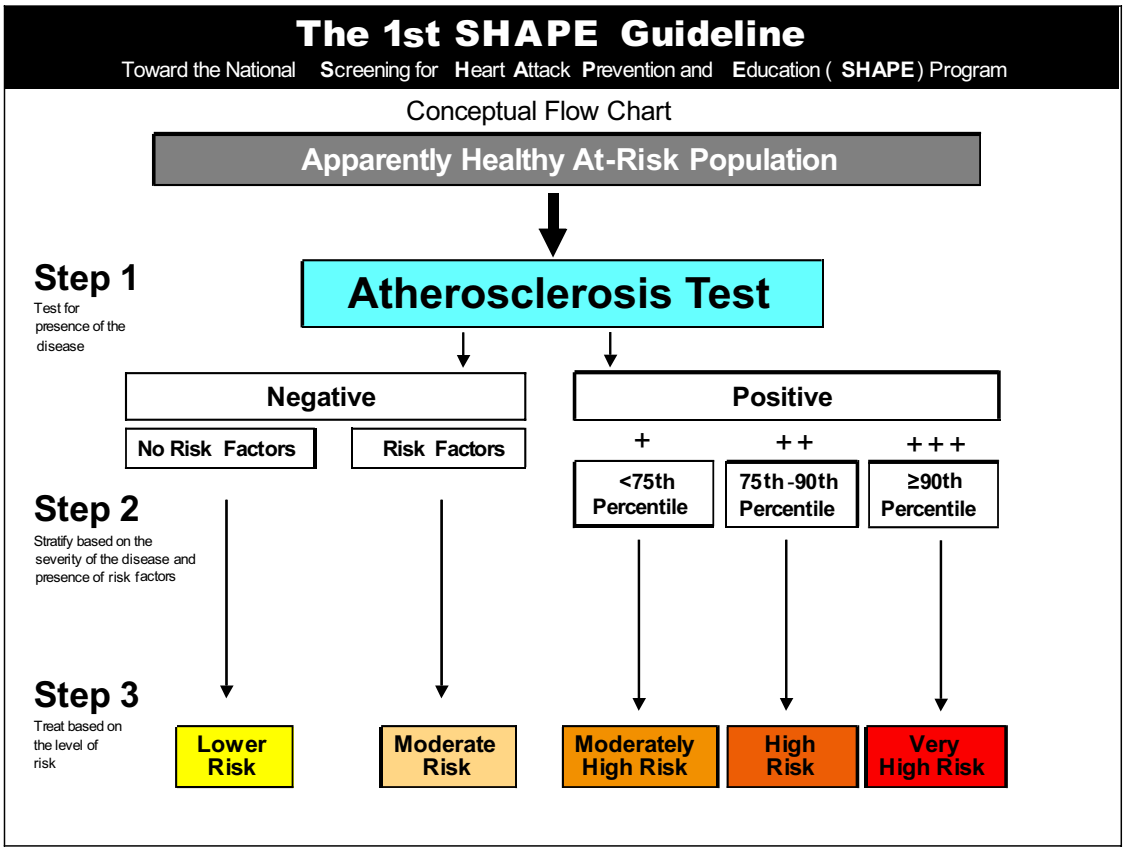

Figure 3. Conceptual flow chart illustrating the principles of the new Screening for Heart Attack Prevention and Education (SHAPE) algorithm.

- With the advancement of noninvasive and intravascular imaging techniques aimed at detailed characterization of coronary atherosclerotic plaque, it might become possible to screen for vulnerable plaques.[94–100] However, it is the search for the vulnerable patients and their aggressive treatment that remain the focus of the SHAPE Guidelines.
- Reassessment in those with negative atherosclerosis is recommended every 5–10 years. In those with a positive atherosclerosis test, reassessment is recommended within 5 years unless otherwise indicated. In this context, one may consider factors associated with a higher rate of progression of the disease in individuals within the same level of risk (burden of the disease). For example, patients with diabetes, autoimmune disorders such as rheumatoid arteritis, lupus, and those with renal failure may be on a faster trajectory.[101,102]
- All individuals in the high-risk categories (the atherosclerosis-positive SHAPE subpopulation) and their closest relatives should be offered early heart attack care education, focusing on early warning signs and reducing delay time in seeking medical assistance after the onset of symptoms.[103,104]

Adherence to treatment: Despite significant and consistent data on the benefits of lipid-lowering agents to reduce cardiovascular events, adherence and utilization of these agents remains low. It is important, therefore, that a recent study demonstrated that adherence to 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) treatment increased from 44% over 3 years to >90% in those with baseline calcium scores in the top 75th percentile for age and sex ($p < 0.001$).[105] In multivariable analysis, after adjusting for cardiovascular risk factors, age, and sex, higher baseline CACS scores were strongly associated with adherence to statin therapy. Thus, in addition to risk stratification, actually seeing their coronary artery can improve patients' adherence to treatments such as lipid-lowering therapy.

Cost-effectiveness of SHAPE Guideline versus existing preventive guidelines: In this era of limited healthcare resources, proof of cost-effectiveness is a prerequisite for inclusion of CACS and CIMT in national guidelines on screening to prevent CHD. The SHAPE Guideline maintains that shifting of CHD care to subclinical arterial disease (atherosclerosis), particularly to the most vulnerable individuals who bear the highest risk for a near-future heart attack, has the potential to circumvent the downstream economic burden of symptomatic CHD and to alleviate the heavy and rising cost of providing care to patients with CHD in the United States.

The cost-effectiveness analysis in this report is based on comparing competing choices for screening to prevent CHD, with the result being the incremental price of an additional outcome for a given strategy as compared with an

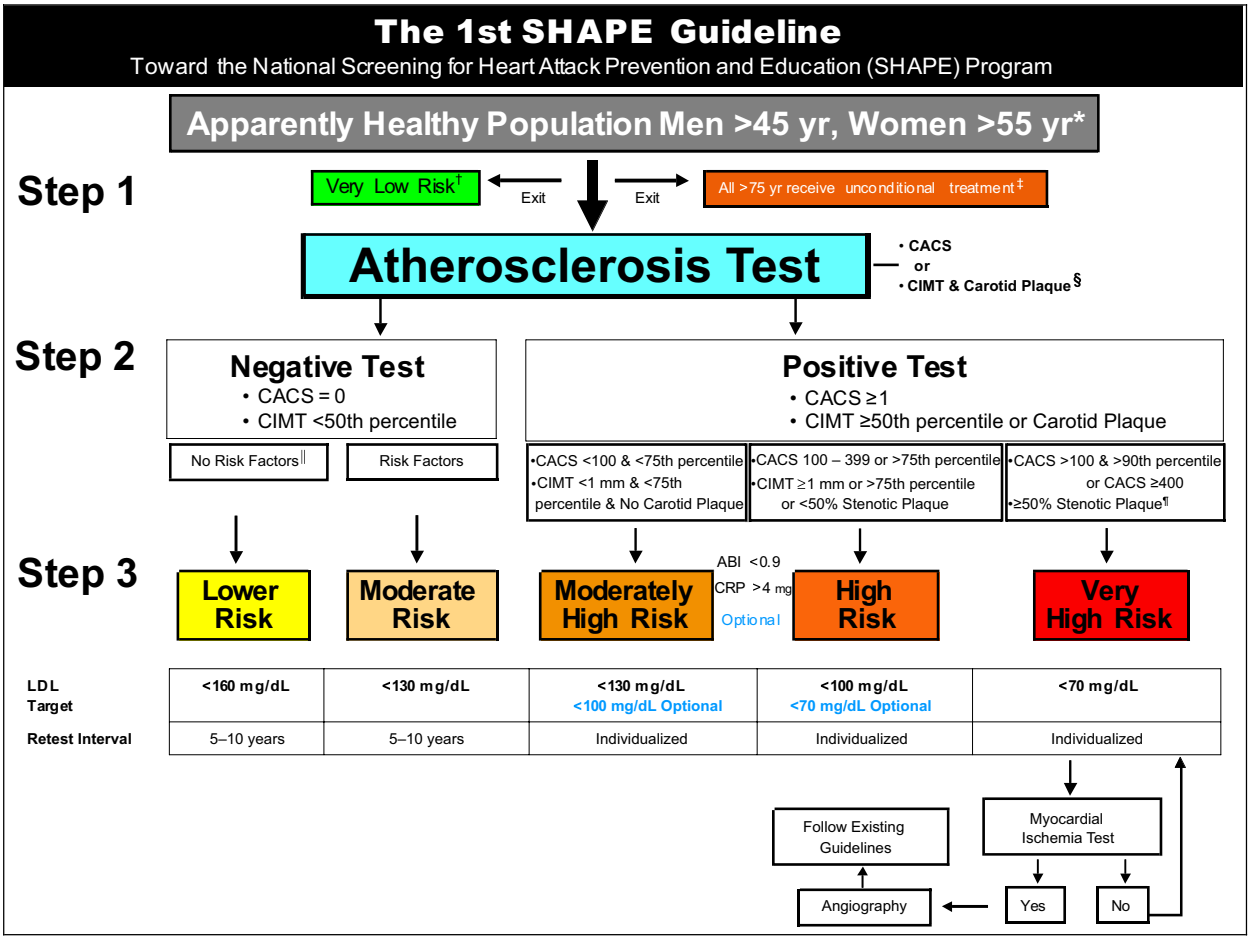

Figure 4. Flow chart of the First Screening for Heart Attack Prevention and Education (SHAPE) Guideline. ABI = ankle–brachial index; CACS = coronary artery calcium score; CIMT = carotid intima–media thickness; CRP = C-reactive protein; LDL = low-density lipoprotein. *No history of angina, heart attack, stroke, or peripheral arterial disease. †Population aged >75 years is considered high risk and must receive therapy without testing for atherosclerosis. ‡Must not have any of the following: total cholesterol level 200 mg/dL (5.18 mmol/L), blood pressure >120/80 mm Hg, diabetes mellitus, smoking, family history of coronary heart disease (CHD), or the metabolic syndrome. §Pending the development of standard practice guidelines. ¶High cholesterol, high blood pressure, diabetes, smoking, family history of CHD, or the metabolic syndrome.‖ For stroke prevention, follow existing guidelines.

alternative approach. The initial economic models examined the cost-effectiveness of treating selected at-risk adults (ie, men aged 45–75 years and women aged 55–75 years) with evidence of subclinical atherosclerosis compared with the existing guideline (based on screening for risk factors using the Framingham risk score).

We have also compared the SHAPE Guideline with the usual preventive screening care using exercise electrocardiography. For our cost-effectiveness analysis, we devised the following model:

$$\frac{\text{Costs of Screening} - \text{Costs Averted}}{\text{Net Effectiveness}}$$

We devised our decision models to examine the burden of CHD, including the prevalence of CHD, years of life lost prematurely to CHD, disability or changes in quality of life, and the current economic burden of CHD.[106] This, in total, comprised the burden of the disease and was incorporated into a single measure of both mortality and morbidity from CHD. When compared with the existing guideline (screening based on risk factors), the SHAPE model shows that the use of screening for subclinical atherosclerosis is cost-effective, consistently resulting in cost-effectiveness ratios <$50,000 per year of life saved.

Based on evidence that a high percentage of patients are missed by Framingham risk scores,[107,108] ~25 million men and ~20 million women would be treated with statins based on evidence of high-risk subclinical atherosclerosis, resulting in a 50%–65% increase in the statin-eligible population. Given a relative risk reduction with treatment of 35%, treatment of patients with high-risk subclinical disease resulted in an average 0.58 year of life saved.

Because our economic model attempted to identify costs that may be averted with treatment, we used the current costs of CHD burden and used sensitivity analyses to evaluate potential costs averted in our SHAPE analysis. Table 1[3,109] details the results of this analysis, including an estimated US$21.5 billion each year in care for patients with CHD that

Table 1
Cost-effectiveness of the First Screening for Heart Attack Prevention and Education (SHAPE) Guideline

	Number (per year)	Estimated Impact of SHAPE (Sensitivity Analysis Range)	Estimated Change in Cost*
CVD deaths	910,600	↓ 10% (5%–25%)	($1.2 b)
MI (prevalence)	7,200,000	↓ 25% (5%–35%)	($18.0 b)
Chest pain symptoms (ER visits)	6,500,000	↓ 5% (2.5%–25%)	($4.1 b)
Hospital discharge for primary diagnosis of CVD	6,373,000	↑ 10% (5%–25%)	$3.8 b
Hospital discharge for primary diagnosis of CHD	970,000	↓ 10% (5%–25%)	($9.9 b)
Cholesterol-lowering therapy	—	↑ 50% (50%–65%)	$8.00 b
CV imaging	8,700,000	↑ 10% (5%–25%)	$358 m
Angiography	6,800,000	↑ 15%–CTA (2.5%–25%)	$600 m
PCIs per yr	657,000	↓ 10% (5%–50%)	($580 m)
CABGs per yr	515,000	↓ 5% (2.5%–50%)	($672 m)
Total Δ in Cost	—		($21.5 b)

b = billion; CABGs = coronary artery bypass grafts; CHD = coronary heart disease; CTA = computed tomography angiography; CV = cardiovascular; CVD = cardiovascular disease; ER = emergency room; m = million; MI = myocardial infarction; PCI = percutaneous coronary intervention; ↑ = increase; ↓ = decrease.

*Costs in parentheses are negative costs or reductions in cost (US dollars).

Adapted from *Heart Disease and Stroke Statistics–2006 Update.*[3]

may be offset by the use of subclinical disease screening with CACS or CIMT.

It should be noted that decision models do not replace evidence gathered from randomized clinical trials comparing screening for subclinical atherosclerosis with usual care or other strategies. However, given the high cost of such a clinical trial on screening to prevent CHD, and given that currently no such study is planned for the next 3–5 years, the current evidence based on the SHAPE cost models can be considered as estimated state-of-the-art economic evidence. Thus, we believe that the application of the SHAPE model, using high-quality prognostic and economic evidence, can aid in the targeting of preventive screening strategies that may result in more dramatic declines in CHD mortality and avert the presentation of symptomatic CHD in thousands of patients every year.

Future Directions

Genetic, structural, and functional assessment: Serum markers that can accurately identify the vulnerable individual with both high sensitivity and specificity might be derived from a thorough proteomic survey of blood samples collected from heart attack victims within a few months before the event.[110] The incremental predictive value of genes over existing and emerging nongene predictors will need careful scientific and economic evaluation.[111,112] Noninvasive screening tests for subclinical atherosclerosis are rapidly advancing, and include MRI detection of plaque inflammation, contrast-enhanced CT for assessment of noncalcified plaques, and positron-emission tomography–CT for combined assessment of plaque burden and activity of the plaques.[113–120] Other innovative tests for the assessment of vascular structure and function are undergoing development and clinical testing. These include noninvasive molecular imaging tests and noninvasive nonimaging tests such as molecular pulsewave analysis and endothelial function assessment.[89–93,121] In addition, new serum biomarkers of inflammation and oxidative stress in the arterial wall, eg, lipoprotein-associated phospholipase A_2 and myeloperoxidase, are being actively researched.[122,123] These emerging tools have the potential to advance the SHAPE Guideline and may significantly determine how the Guideline will be updated in the future. Combinations of tests may offer great promise. An ideal scenario would be a combination of a very-low-cost, noninvasive, nonimaging test or serum marker (such as endothelial function tests and serum markers of arterial inflammation or oxidation) with an accurate, inexpensive, and widely available imaging tool capable of imaging plaque burden and activity. Such molecular imaging techniques may enable us to accurately identify the site of vulnerable plaques based on markers of inflammation, oxidation, angiogenesis, apoptosis, and matrix degradation. The future direction of screening will also be greatly influenced by new developments in therapeutic modalities. The balance between new noninvasive systemic drug therapies capable of rapid stabilization of vulnerable plaques, and new invasive focal therapies without long-term adverse effects, will have an impact on the future of diagnostic screening. Needless to say, in the present outcome-oriented era, analysis of the cost-effectiveness of the SHAPE Guideline will be crucial to its continued implementation.

Mission: ERADICATING HEART ATTACK. In view of the widespread epidemic of heart attack inherited from the 20th century, it is difficult for most people to imagine a future in which heart attack is no longer a threat. However, this goal may be achieved by the end of the 21st century. New therapeutic opportunities such as highly effective prophylactic polypills, immune modulation and vaccination thera-

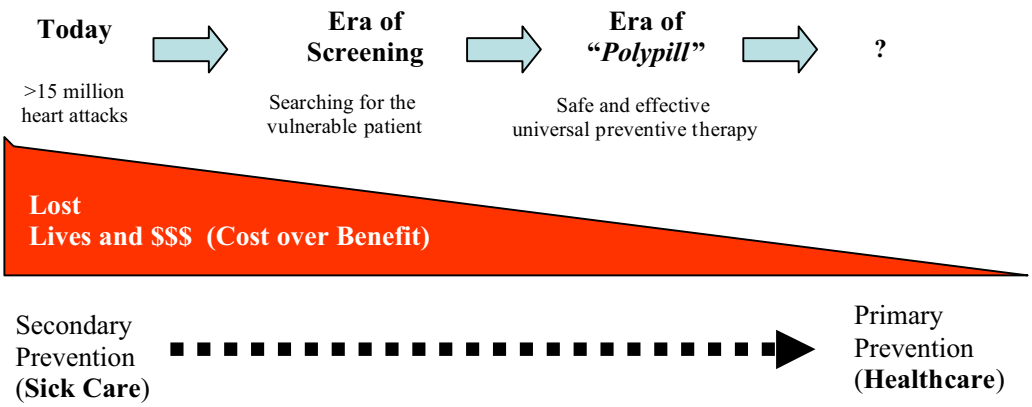

Figure 5. A path toward eradicating heart attack.

pies may expedite this achievement.[124,125] A potential path to the future is illustrated in Figure 5.

Conclusion

The SHAPE Task Force strongly recommends screening of the at-risk asymptomatic population (men 45–75 years of age and women 55–75 years of age) for subclinical atherosclerosis to more accurately identify and treat patients at high risk for acute ischemic events, as well as to identify those at lower risk who may be treated more conservatively. The Task Force reinforces the existing guidelines for screening and treatment of atherosclerosis risk factors in the younger, very-low-risk population.

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Appendix

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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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Many of the authors of this work, in addition to their research activities, have served as consultants to and/or employees of pharmaceutical, medical equipment, and other related companies.

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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[1–3] 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.[4,5]

Circulating interleukin-6 levels, which are elevated in patients with acute coronary syndromes, also predict the risk of future coronary events in such patients.[6] Recently, investigators have shown that high plasma concentrations of soluble CD40 ligand may indicate an increased vascular risk in apparently healthy women.[7] Likewise, Hwang et al[8] 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.[9] Pregnancy-associated plasma protein A (PAPP-A) is present in unstable plaques, and its circulating levels are elevated in patients with acute coronary syndromes.[10] Increased serum levels of PAPP-A may reflect instability of atherosclerotic plaques.[11]

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.[12] 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,[13] and genome-wide association studies for myocardial infarction are already a reality.[14] 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,[15] 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.[16] 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),[17] Ib α gene-5T/C Kozak,[18] high factor V and factor VII clotting,[19] have been reported as independent risk factors for myocardial infarction. Reiner et al[20] 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.[21] 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.[22,23]

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.[24,25] The main antibodies of this syndrome are the anticardiolipin antibody, the lupus anticoagulant, and the IgG antibodies against prothrombin and β_2-glycoprotein.[24,25]

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.[26]

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.[27,28]

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.[29] Similarly, metabolic factors, such as postprandial metabolic changes, are associated with increased blood coagulability.[30] Likewise, estrogen replacement therapy can lead to a hypercoagulable state.[31]

Finally, plasma viscosity, as well as fibrinogen and white blood cell counts, is positively associated with CHD events as shown by Koenig et al.[32] Furthermore, Junker et al[33] 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.[34,35] 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.[30,36,37] Susceptibility of the myocardium to acute ischemia was reviewed by Airaksinen,[38] 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
Commotio 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.

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

ischemic myocardium may impair the arterial baroreflex and lead to hemodynamic instability.[39]

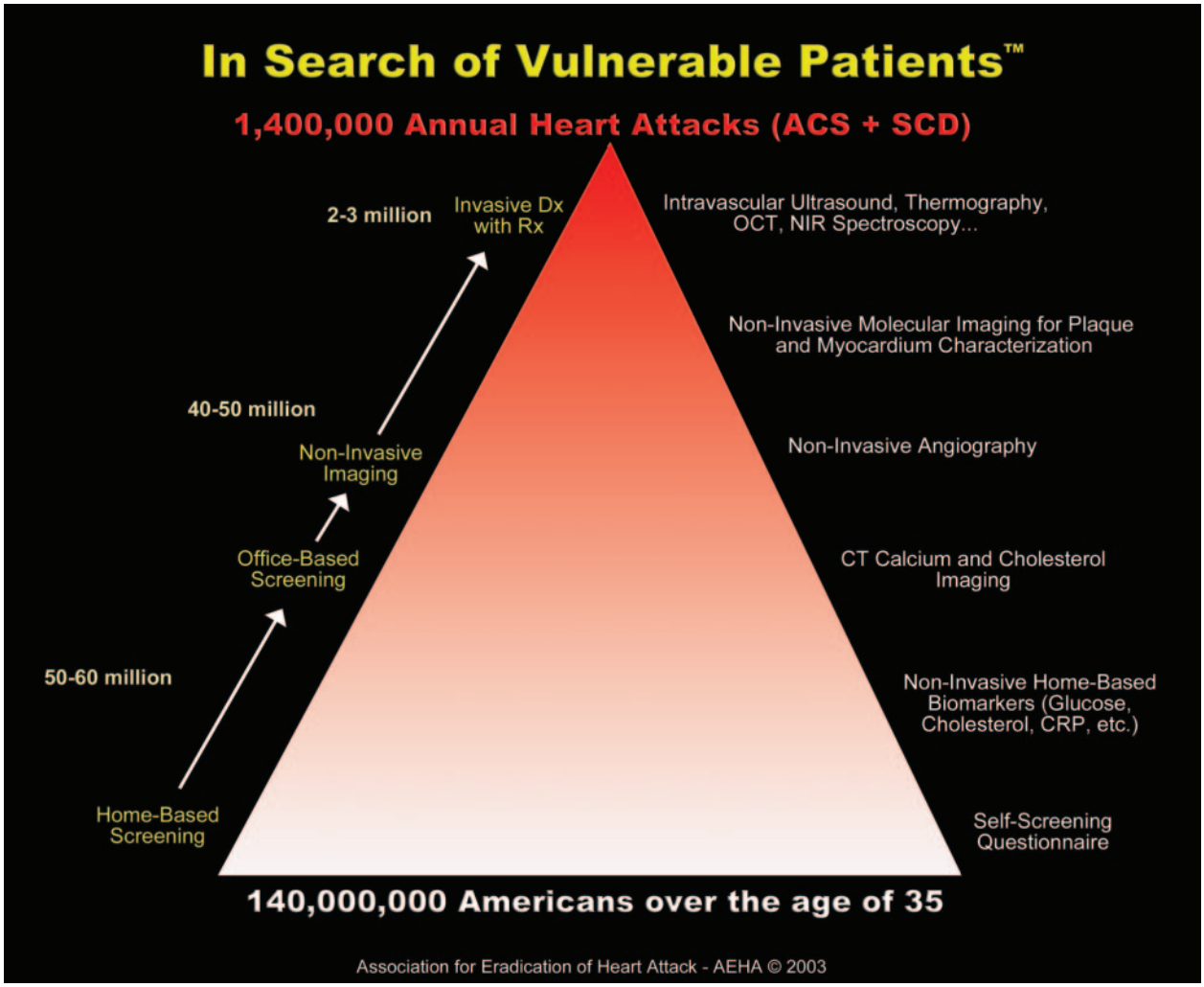
There seems to be a wide interindividual variation in the type and severity of autonomic reactions during the early phase of abrupt coronary occlusion, a critical period for out-of-hospital cardiac arrest. The pre-existing severity of a coronary stenosis, adaptation or preconditioning to myocardial ischemia, habitual physical exercise, β-blockade, and gender seem to affect autonomic reactions and the risk of fatal ventricular arrhythmias.[38,40,41] Recent studies have documented a hereditary component for autonomic function, and genetic factors may also modify the clinical presentation of acute coronary occlusion.[42,43] 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 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.[44] 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.[45]

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.[46]

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%[47] to 50%[3,48,49]). 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,[3] 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,[50] Sheffield,[51,52] New Zealand,[53,54] Canadian,[55] British,[56] European,[57] Dundee,[58] Munster [PROCAM],[59] and MONICA[60]) 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.[61]

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.[2,62]

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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From Vulnerable Plaque to Vulnerable Patient

A Call for New Definitions and Risk Assessment Strategies: Part I

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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

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opportunity 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, 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 focuses 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;108:1664-1672.)**

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

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, >1 million people in the United States and >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 The Nonischemic Vulnerable Myocardium). This leaves the patients with atherosclerosis, some of whom also have a hypercoagulable state (see Vulnerable 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.

Plaque rupture is the most common type of plaque complication, accounting for ≈70% of fatal acute myocardial infarctions and/or sudden coronary deaths (Figure 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]

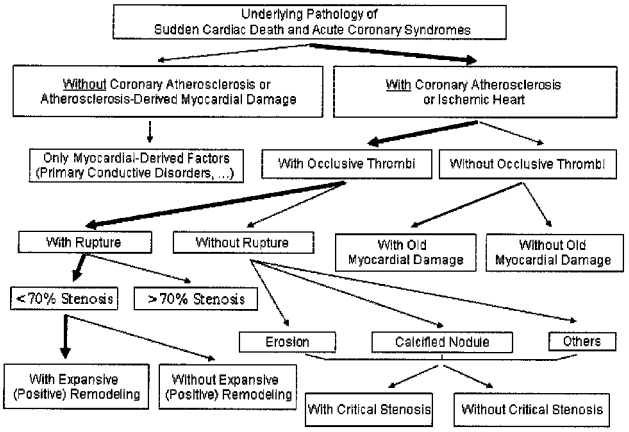

Figure 1. Proposed diagram of the potential underlying pathology of acute coronary syndrome, (ie, unstable angina, acute myocardial infarction and sudden cardiac death).

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 injury is called "plaque erosion."[9] Other types of culprit plaques also exist (Figure 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.

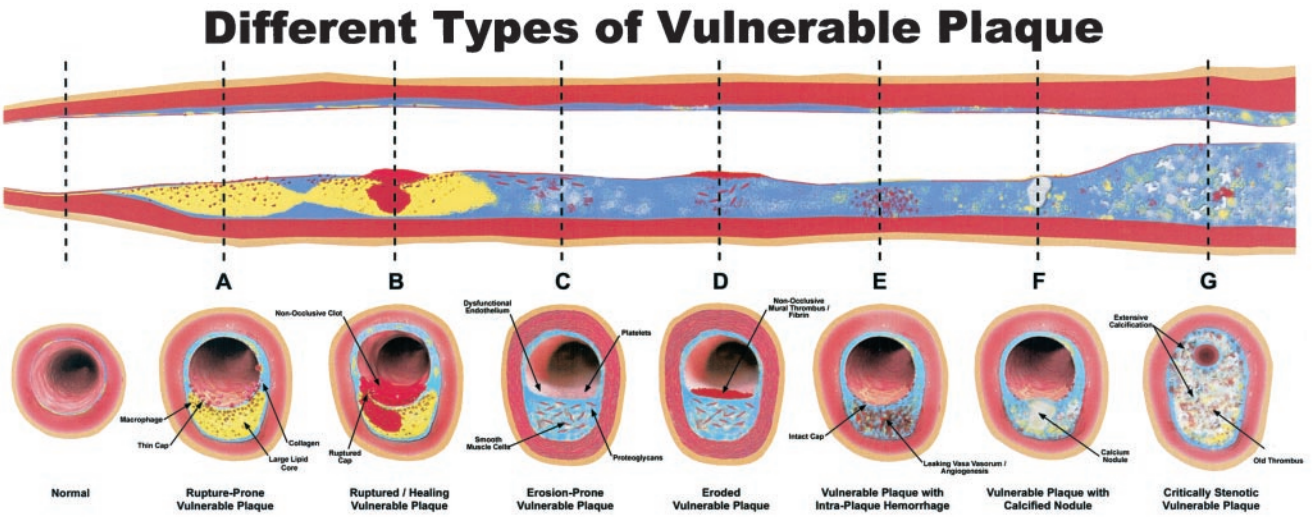

Figure 2. Different types of vulnerable plaque as underlying cause of acute coronary events (ACS) and sudden cardiac death (SCD). A, Rupture-prone plaque with large lipid core and thin fibrous cap infiltrated by macrophages. B, Ruptured plaque with subocclusive thrombus and early organization. C, Erosion-prone 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.

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 20th century; it became a focus of attention of pioneering scientists in the 1960s (Table 2) and was later documented further by others.[11–15]

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 and colleagues[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 (Figure 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 Figure 2) that may also cause acute coronary events.[5]

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 recently proposed.[18] The term "high-risk" is often used to describe the

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 and colleagues.[7]

TABLE 2. Descriptions Used by Pioneers for Culprit Plaques[93,94]

Author	Year	Description Used
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

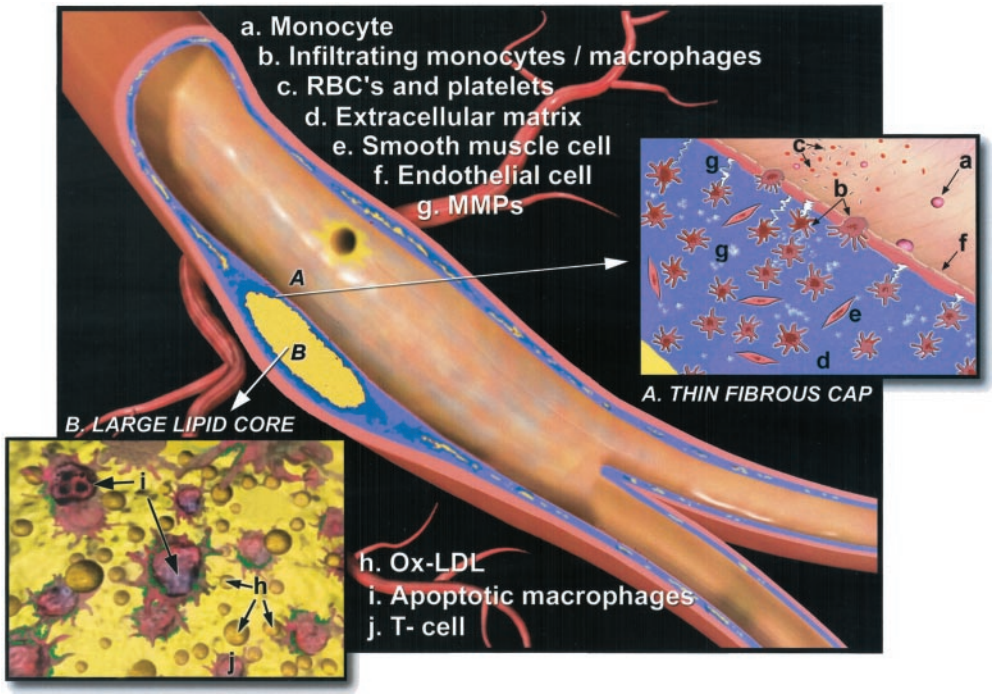

Figure 3. Schematic figure illustrating the most common type of vulnerable plaque characterized by thin fibrous cap, extensive macrophage infiltration, paucity of smooth muscle cells, and large lipid core, without significant luminal narrowing.

high-risk patient groups with acute coronary syndromes. However, our intention is to provide a terminology to identify apparently healthy subjects at 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 Figure 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 Figure 3, different types of vulnerable plaque 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

Acceptable But Not Recommended	Unacceptable*
High-risk plaque	Soft plaque
Dangerous plaque	Noncalcified plaque
Unstable plaque	AHA type IV plaque

AHA indicates American Heart Association.

*The 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 noncalcified plaque, an AHA type IV plaque, or a nonstenotic plaque.[8,21]

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

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

Figure 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.

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 (ie, thrombogenic blood and electrical instability of myocardium) are responsible for the final outcome (Figure 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.

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 ≥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 (Figure 4).

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 (eg, HSP60, *C. pneumoniae*)

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 (eg, carotid IMT)

MMP indicates matrix metalloproteinase; NO, nitric oxide; and IMT, intima medial thickness.

Diagnosis of Vulnerable Plaque/Artery

A number of issues have hampered 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 (due to 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 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.

Major Criteria

The following are proposed as major criteria for 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]

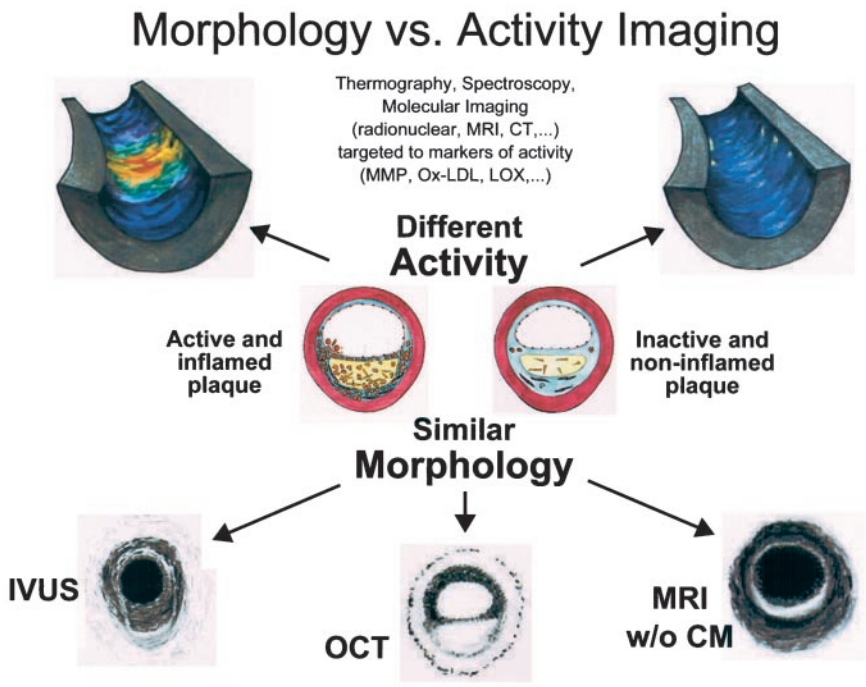

Figure 5. Plaques with nearly similar morphology in terms of lipid core and fibrous cap (middle panel) may look similar with diagnostic imaging aimed at morphology only (bottom panel). However, they might look very different using diagnostic methods capable of detecting activity and physiology of the 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.

1. 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 recently 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]

2. A Thin Cap With a Large Lipid Core

These plaques have a cap thickness of <100 μm 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] angioscopy,[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]

3. 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 angioscopy 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]

4. 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] angioscopy, and MRI.[34,35] A noninvasive option is fibrin-targeted CE-MRI.[64,65]

5. 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] (Figure 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.

1. 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] multisection spiral CT,[73] and MRI.[34,35]

2. 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 in-

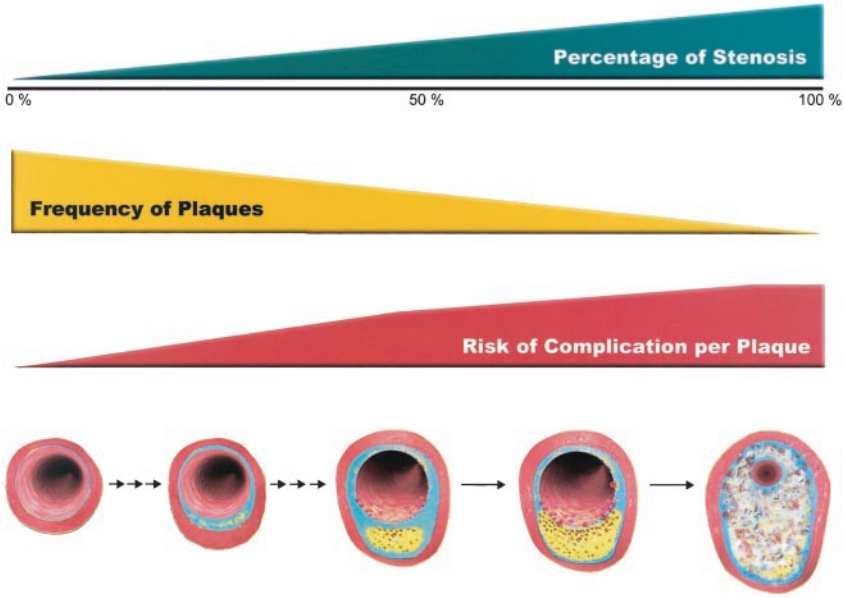

Figure 6. Correlation between frequency of plaques, degree of stenosis, and risk of complication per plaque as a function of plaque progression. Although the average absolute risk of severely stenotic plaques may be higher than the average absolute risk of mildly stenotic plaques, there are more plaques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

clude angioscopy[73] and transcatheter colorimetry.[75] No diagnostic method has yet been developed for noninvasive angioscopy.

3. 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]

4. 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.[89,95] 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]

5. 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 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 (Figure 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 CT information.[87] Like systemic indexes of inflammation (eg, 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 3-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.

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