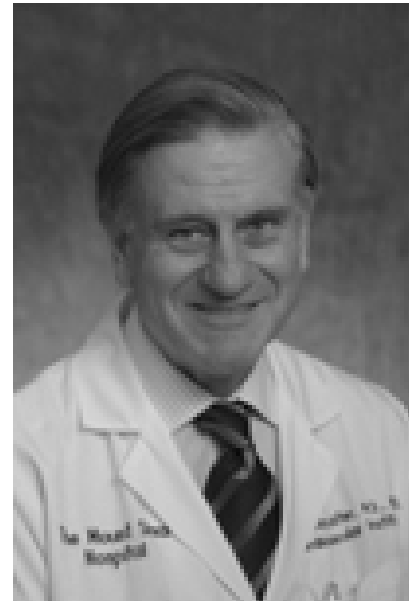


Please obtain the published version of this document from the American Journal of Cardiology [www.ajconline.org](http://www.ajconline.org)

A note from the guest editor:

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



Early observations by our group and others 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. Subsequently, the field of cardiology has witnessed a list of major developments that are likely to change the practice of cardiology. I believe advances in noninvasive imaging lead the 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 SHAPE Task Force individuals is commendable. It serves as an example for 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 in their call for future studies that will validate and accelerate the adoption of screening for subclinical atherosclerosis as proposed by the SHAPE guideline.

Valentin Fuster, M.D., Ph.D.

Director of the Cardiovascular Institute and  
Center for Cardiovascular Health  
Mount Sinai Medical Center – New York, NY  
President of the World Heart Federation  
Past President of the American Heart Association



Dear Colleague,

In the second half of the 20<sup>th</sup> century significant progress was made in the primary prevention of atherosclerotic cardiovascular disease, due to the discovery of atherosclerosis risk factors and implementation of population based risk assessment and risk reduction strategies. Nonetheless, it has remained the number one killer in most developed countries and is increasingly threatening 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 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 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 the 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 previously addressed. 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. We hope this effort will help advance the practice of preventive cardiology and will be welcomed by the 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.

Sincerely yours,

Erling Falk, M.D., Ph.D.

Morteza Naghavi, M.D.

P.K. Shah, M.D.

# **From Vulnerable Plaque to Vulnerable Patient – Part III**

## **Introducing a New Paradigm for the Prevention of Heart Attack; Identification and Treatment of the Asymptomatic Vulnerable Patient**

### **Screening for Heart Attack Prevention and Education (SHAPE) Task Force Report**

#### **Executive Summary**

##### **Authors**

Morteza Naghavi, MD, Erling Falk, MD, PhD, Harvey S. Hecht, MD, Michael J Jamieson, MD, Sanjay Kaul, MD, MPH, Daniel Berman, MD, Zahi Fayad, PhD, Matthew J. Budoff, MD, John Rumberger, MD, PhD, Tasneem Z. Naqvi, MD, Leslee J. Shaw, PhD, Ole Faergeman, MD, Jay Cohn, MD, Raymond Bahr, MD, Wolfgang Koenig, MD, PhD, Jasenka Demirovic, MD, PhD, Dan Arking, PhD, Victoria L.M. Herrera, MD, Juan Badimon, PhD, James A. Goldstein, MD, Yoram Rudy, PhD, Juhani Airaksinen, MD, Robert S. Schwartz, MD, Ward A. Riley, PhD, Robert. A. Mendes, MD, Pamela Douglas, MD, Prediman K. Shah, MD

## The SHAPE Task Force

**Chairman:** Morteza Naghavi, M.D.

**Editorial Committee:** Prediman K. Shah, M.D. (Chief); (alphabetic order): Raymond Bahr, M.D., Daniel Berman, M.D., Roger Blumenthal, M.D., Matthew J. Budoff, M.D., Jay Cohn, M.D., Erling Falk, M.D., Ph.D., Ole Faergeman, M.D., Zahi Fayad, Ph.D., Harvey S. Hecht, M.D., Michael J Jamieson, M.D., Wolfgang Koenig, M.D., Ph.D., Daniel Lane, M.D., Ph.D., Morteza Naghavi, M.D., John Rumberger, M.D., Ph.D., Allen J. Taylor, M.D.

**Writing Group:** Erling Falk, M.D., Ph.D. (Coordinator); (alphabetic order): Juhani Airaksinen, M.D., Dan Arking, Ph.D., Juan Badimon, Ph.D., Raymond Bahr, M.D., Daniel Berman, M.D., Matthew J. Budoff, M.D., Jay Cohn, M.D., Jasenka Demirovic, M.D., Ph.D., George A. Diamond, M.D., Pamela Douglas, M.D., Ole Faergeman, M.D., Zahi Fayad, Ph.D., James A. Goldstein, M.D., Harvey S. Hecht, M.D., Victoria L.M. Herrera, M.D., Michael J Jamieson, M.D., Sanjay Kaul, M.D., M.P.H., Wolfgang Koenig, M.D., Ph.D., Robert A. Mendes, M.D., Morteza Naghavi, M.D.; Tasneem Z. Naqvi, M.D., Ward A. Riley, Ph.D., Yoram Rudy, PhD, John Rumberger, M.D., Ph.D., Leslee Shaw, Ph.D., Robert S. Schwartz, M.D., Arturo G. Touchard, M.D.

**Advisors** (alphabetic order): Arthur Agagston, M.D., Stephane Carlier, M.D., Ph.D., Raimund Erbel, M.D., Chris deKorte, Ph.D., Craig Hartley, Ph.D., Ioannis Kakadiaris, Ph.D., Roxana Mehran, M.D., Daniel O'Leary, M.D., Jan Nilsson, M.D., Gerard Pasterkamp, M.D., Ph.D., Paul Schoenhagen, M.D., Henrik Sillesen, M.D., Ph.D.

**Guest Editor:** Valentin Fuster, M.D., Ph.D.

**Acknowledgement:** AEHA would like to thank the following for their administrative support to the SHAPE Task Force: (alphabetic order): Asif Ali, M.D., Lori Cantu, Suzanne Ekblad, M.P.H., Uzma Gul, and Daniel Jamieson.

**Special Thanks to:** Khawar Gul, M.D., Lisa Brown, Craig Jamieson, Bryan Jenkins, Mark Johnson, Daniel Keeney, and Kelly Papinchak.

The financial disclosure of the SHAPE Task Force is available on [www.aeha.org](http://www.aeha.org)

The publication of this report was funded by Pfizer Inc.

**Note:** Only the Executive Summary of the SHAPE Task Force report is published in the July edition of American Journal of Cardiology.

# **Contents**

## **Section I: Executive Summary**

**Abstract**

**Introduction**

**Burden of Atherosclerotic Cardiovascular Disease**

**Risk Factors, Susceptibility, and Vulnerability**

**Current Guidelines in Primary Prevention**

**CHD Risk Equivalents**

**Screening for Subclinical Atherosclerosis**

**New Paradigm for the Prevention of Heart Attack**

**In Search of the Vulnerable Patient**

**Criteria for Recommended Screening Tests**

**The 1<sup>st</sup> SHAPE Guideline**

**Important Considerations**

**Compliance with Treatment**

**Cost-Effectiveness of SHAPE Guideline vs Existing Preventive Guidelines**

**Future Directions**

**Genetic, Structural and Functional Assessment**

**Eradicating Heart Attack**

**Conclusion**

## **Section II: Scientific Background and Supportive Documents**

### **IIa. Risk Factors, Vulnerability, and Disease**

**Introduction**

**Burden of Diseases Caused by Atherosclerosis**

**Risk Factors vs Susceptibility vs Vulnerability**

**Current Guidelines in Primary Prevention**

**Screening for Silent Disease to Prevent Deadly Disease**

**The Time Has Come**

**Noninvasive Assessment of Atherosclerosis**

### **IIb. Scientific Foundations**

**Duty-Bound: Philosophical Foundations of Clinical Strategies for Prevention of Cardiovascular Events**

*George A. Diamond and Sanjay Kaul*

**Epidemiology of Sudden Cardiac Death**

*Jasenka Demirovic*

**Cost Effective Screening for Atherosclerosis**

*Leslee J Shaw*

**Role of Risk Factors in the Proposed Strategy**

*Ole Faergeman*

**Iic. Available Technologies**

**Coronary Artery Calcium**

*Harvey S. Hecht*

**Carotid Intima-Media Thickness**

*Tasneem Z. Naqvi and Pamela Douglas*

**Carotid Intima-Media Thickness: Clinical implementation in Individual Risk Assessment**

*Ward A. Riley*

**Magnetic Resonance Imaging**

*Zahi Fayad*

**Endothelial Dysfunction**

*Jay Cohn*

**Vascular Compliance**

*Jay Cohn*

**Angiography for Detection of Complex and Vulnerable Atherosclerotic Plaque**

*James A. Goldstein*

**Non-Invasive Coronary Angiography: CT and MRI**

*John A. Rumberger*

**Silent and Stress-Induced Myocardial Ischemia**

*Dan Berman*

**Ankle-Brachial Index**

*Matthew Budoff*

**Systemic Markers of Atherosclerosis**

*Wolfgang Koenig*

**Section III: Future Directions**

**Introduction**

**Dynamic Changes in Risk as the Basis for Therapeutic Triage**

*George A. Diamond and Sanjay Kaul*

**Nuclear Imaging/Molecular Imaging**

*Dan Berman*

**Targeted MRI of Molecular Components in Atherosclerotic Plaque**

*Zahi A. Fayad*

**Vulnerable Blood**

*Juan Badimon*

**Vulnerable Myocardium**

*Juhani Airaksinen*

**Electrocardiographic Imaging (ECGI):**

**Possible Application in Noninvasive Screening of the Vulnerable Patient**

*Yoram Rudy*

**Integration of Markers of Endothelial Activation in**

**Mechanism-based Management of Coronary Artery Disease**

*Victoria L. M. Herrera*

**Detecting Vulnerable Plaque Using Invasive Methods**

*Arturo G. Touchard and Robert S. Schwartz*

**Genetic Screening and Sudden Cardiac Death**

*Dan Arking*

**Acute Prevention Through Early Intervention During Heart Attack**

*Raymond D. Bahr*

**“Polypill”, “CardioPill” and Other Multi-Constituent Cardiovascular Pills**

*Michael J Jamieson*

**The SHAPE Guideline – Why Primary Care Physicians Should Embrace It**

*Robert Mendes*

**Towards the Mission of Eradicating Heart Attack**

*Morteza Naghavi*

## Abstract

Screening for early-stage asymptomatic cancers (e.g. breast and colon) to prevent late-stage malignancies has been widely accepted. However, although atherosclerotic cardiovascular disease (e.g. 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. 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. These landmark discoveries, along with the 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 focus 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 need to 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. Since less than 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 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 life style 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.

## **Introduction**

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 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 over 90 percent of the risk of an initial acute myocardial infarction (MI) (1,6,7). Although effective risk-lowering therapies exist, moreover, 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 non-pharmacologic 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. Since 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 two 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. Second, the appropriate tools for the detection of subclinical atherosclerosis have not been widely available to clinicians. However, recent developments have provided us with both 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 critical limb ischemia, and many cases of strokes. CHD alone is the single largest killer of American males and females (479,300 in 2003), causing more than 1 of every 5 deaths (3). This year, an estimated 875,000 Americans 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 women live longer than men, almost as many women ultimately die of CHD as men (3).

About 700,000 Americans will have a stroke this year. Stroke is the number 3 killer and a leading cause of severe, long-term disability (3). In 2002, 657,054 people succumbed in the United States to heart attacks and stroke compared to 557,264 deaths to cancers (8,9). Despite the greater magnitude of CVD, screening for occult breast and colorectal cancer has become a widely adopted public policy strategy, while 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 two 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 several fold among populations predicted to have similar risk by risk factor scoring (13-19).

The prevalence of one or more major risk factors (beyond age) is very high among Americans aged 40 years and above 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 data recently published from three influential prospective epidemiological studies (27), Weessler highlighted this failure by using likelihood ratio (LR) analysis (32). An LR of 2.0 or less denotes low predictive power and an LR of 9.0 or more denotes high predictive power. Remarkably low predictive power (LR<1.4) was found for 1 or more risk factors in predicting CHD death and/or nonfatal MI, despite the high frequency of this risk profile in the population with CHD events. The relationship 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 and over (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 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 appropriate “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 good medicine. (20-26)

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 (CAC) determined by computed tomography (CT), endothelial vasomotor dysfunction (evaluated by ultrasound, pulse wave velocity, or other emerging techniques), ankle/brachial blood pressure ratio (ABI), and magnetic resonance imaging (MRI) techniques (19,34,36) See Fig 2.

### **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 (vulnerable) (37). Current American and European guidelines also recognize groups of asymptomatic patients who are at similar high risk (19,33,36). They include patients with diabetes, as well as asymptomatic patients in whom atherosclerosis and/or its consequences have been demonstrated by non-invasive testing. For example, the presence of myocardial ischemia appropriately identified by stress testing qualifies as a diagnosis of CHD. Moreover, carotid or ilio-femoral atherosclerosis is considered a CHD risk equivalent and should be treated aggressively; atherosclerosis in one vascular bed predicts atherosclerosis in other vascular beds. In addition, patients with 2 or more 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 announced a new collaborative initiative to create a national commitment to the prevention and early detection of cancer, CVD, and diabetes (38). The ACS recommends the following screening ages: 20 for breast cancer with mammography from age 40 (at least annually), 21 for cervical cancer (Pap test), 50 for colorectal cancer (several options), and 50 for prostate cancer (prostate-specific antigen test and digital rectal examination annually) (38).

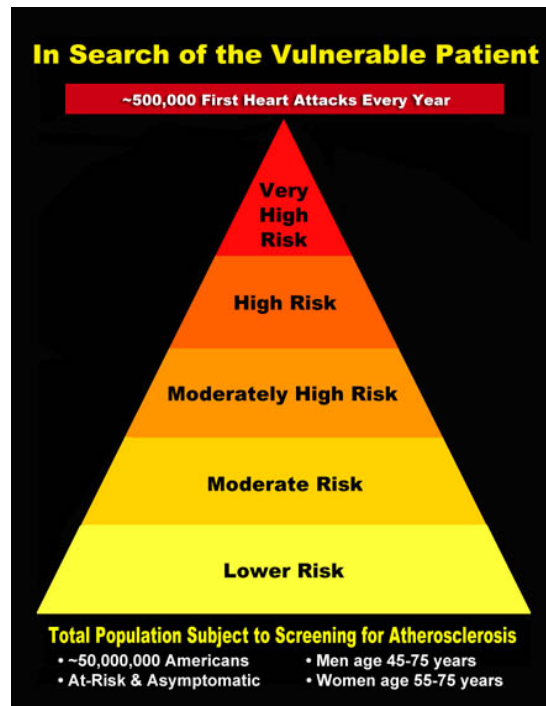
The AHA recommends that assessment of cardiovascular risk begin at age 20, to be repeated at regular intervals, preferentially by calculating the Framingham Risk Score (38). In contrast to cancer, early detection of CVD by screening with the best available technology is not mentioned, despite the more than 500,000 deaths per year from atherosclerosis, compared to ~57,000 from colorectal 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 those 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 U.S. 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 CHD and who are considered *not* to be at very-low-risk (footnoted under Figure 4) - undergo screening for atherosclerosis. Of the 61,163,000 US population 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. Since an exact number is not available, 50 million has been chosen as the approximate number who will require SHAPE evaluation. Based on a 50% compliance rate for SHAPE screening over 10 years, and a 5-year re-examination cycle, the number of people required to annual screening after a decade will decrease to 5-6 million per year.



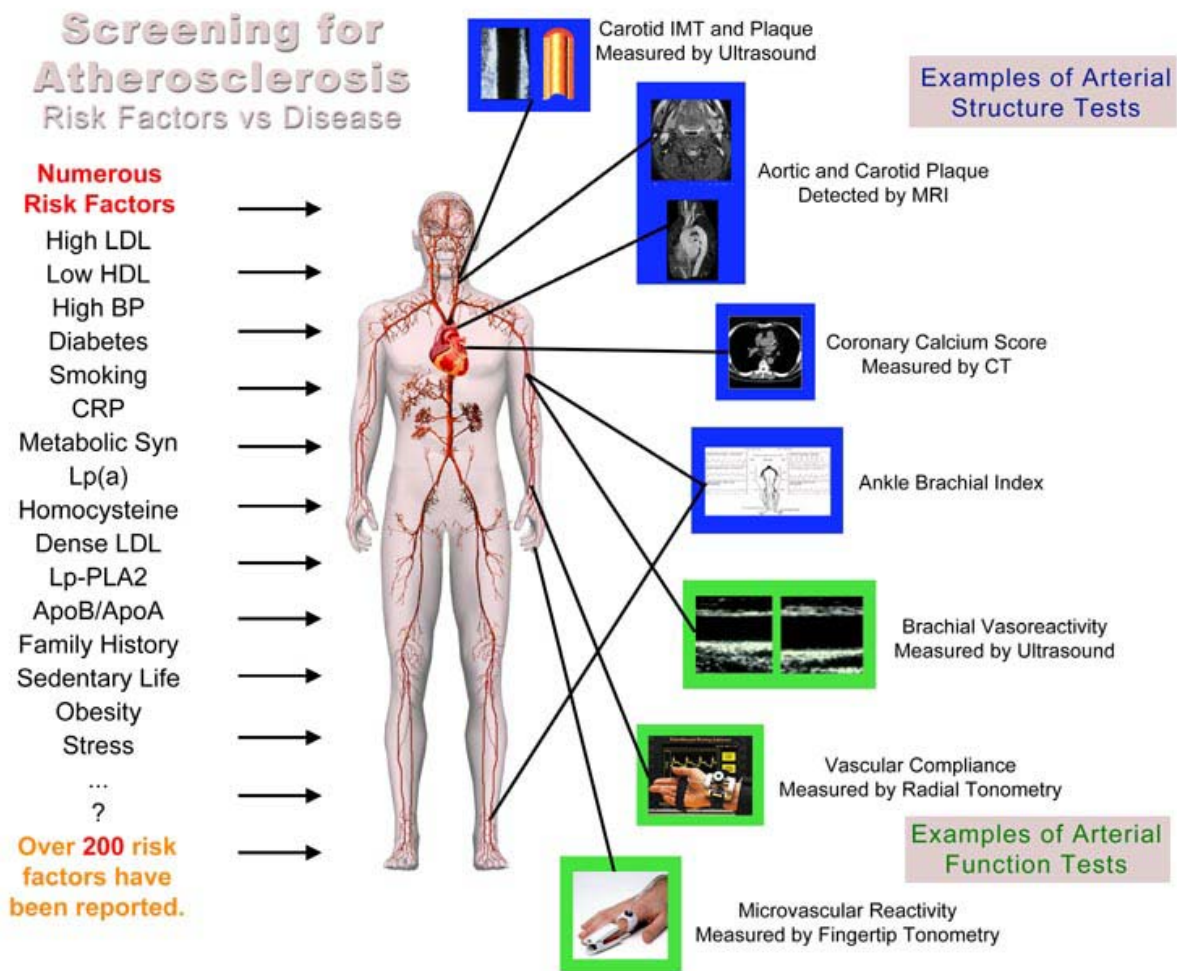
**Figure 1.** The SHAPE paradigm calls for screening all apparently healthy (with no prior diagnosis of CHD) men 45-75 years of age and women 55-75 years of age who are not considered very-low-risk. This population accounts for approximately 50 million people in the US.

An estimated 875,000 Americans annually experience a first heart attack of which 175,000 are silent heart attacks (3). Since approximately 500,000 of the total will occur in the 50 million 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. They, 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 demonstrated 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, and only less than 20% of the total number of the events results from the high-risk population, whereas in the SHAPE guideline, the majority of heart attacks happens 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 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 and tests that more directly evaluate the presence or effect of atherosclerosis.



**Figure 2.** The new 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).

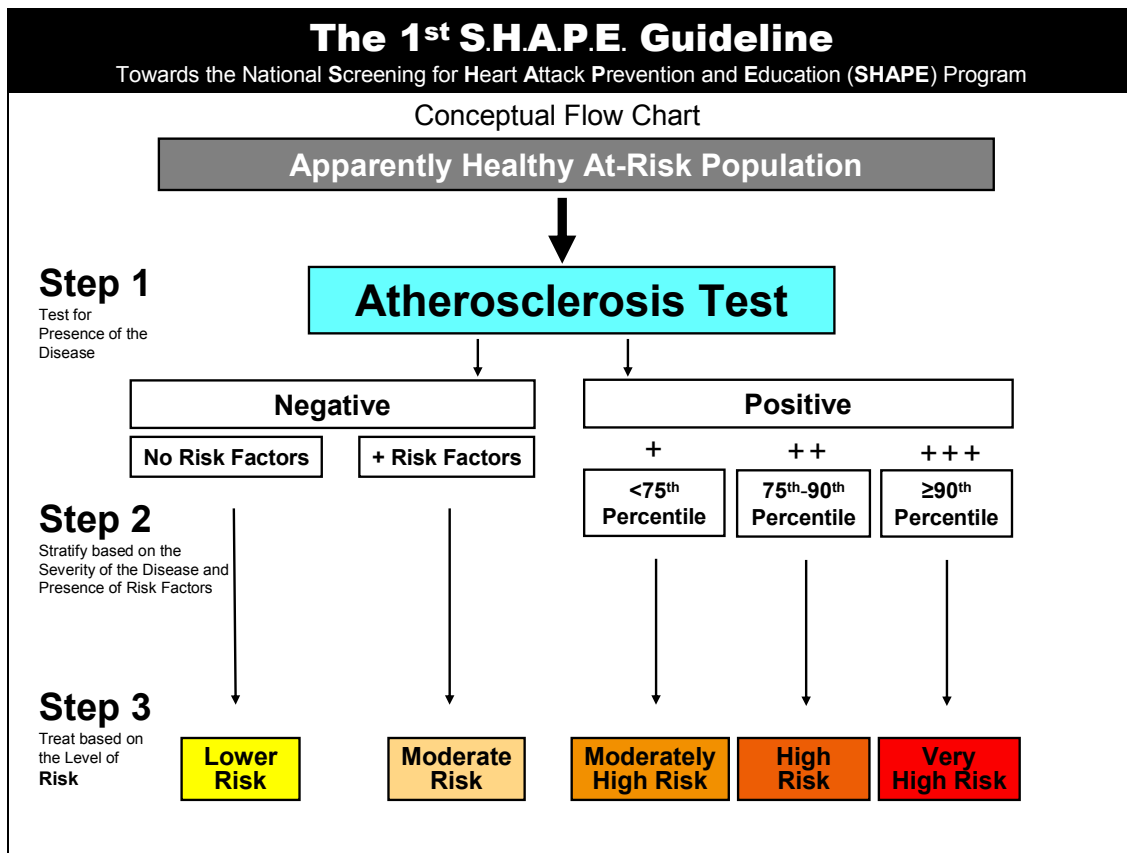
The following atherosclerosis screening methods were selected as those that currently best fulfill the above criteria:

- Coronary artery calcium (CAC) determined by CT
- Carotid intima-media thickness (CIMT) and plaque determined by ultrasonography

The evidence behind this selection and the suggested threshold values in the 1<sup>st</sup> SHAPE Guideline have accumulated in recent years (41-75), and further support can be found in the full SHAPE Report ([www.aeha.org](http://www.aeha.org)).

### The 1<sup>st</sup> SHAPE Guideline

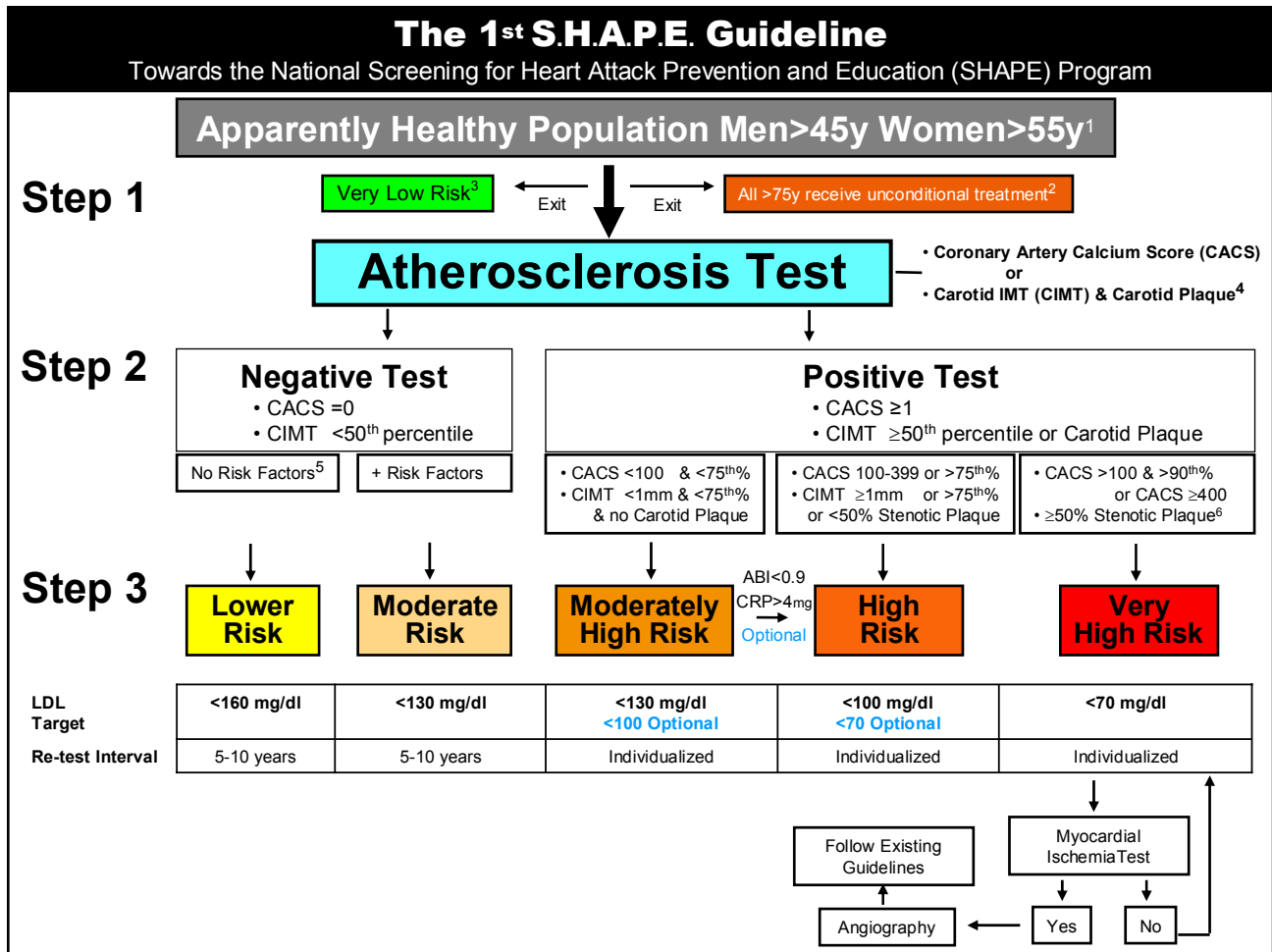
A conceptual flow chart illustrating the principles of the new paradigm is shown in Figure 3.



**Figure 3.** Conceptual flow chart illustrating the principles of the new algorithm.

In contrast to the existing traditional risk factor based guidelines, this new strategy is primarily based on noninvasive screening for subclinical atherosclerosis using two 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, i.e, 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 CHD risk in a cost-effective manner.

The screening strategy for risk assessment and the associated treatment algorithm of the 1<sup>st</sup> SHAPE Guideline are summarized in Figure 4.



- 1: No history of angina, heart attack, stroke, or peripheral arterial disease.
- 2: Population over age 75y is considered high risk and must receive therapy without testing for atherosclerosis.
- 3: Must not have any of the following: Chol > 200 mg/dl, blood pressure > 120/80 mmHg, diabetes, smoking, family history, metabolic syndrome.
- 4: Pending the development of standard practice guidelines.
- 5: High cholesterol, high blood pressure, diabetes, smoking, family history, metabolic syndrome.
- 6: For stroke prevention, follow existing guidelines.

**Figure 4.** The SHAPE Guideline Flow Chart.

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 cardiovascular disease are encouraged to undergo screening for atherosclerosis. The **very-low-risk** group is characterized by the absence of any traditional cardiovascular risk factors (footnoted under Figure 4).

Individuals with negative tests for atherosclerosis (defined as CACS = 0, or CIMT < 50<sup>th</sup> 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 ATP III guidelines with low density lipoprotein cholesterol (LDL-C) targets of <160 mg/dL and <130 mg/dL, respectively (35). Reassessment is recommended within 5-10 years unless otherwise indicated.

Those who test positive for atherosclerosis (CACS  $\geq 1$ , or CIMT  $\geq 50^{\text{th}}$  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 <75<sup>th</sup> percentile, or a CIMT <1mm and <75<sup>th</sup> (but  $\geq 50^{\text{th}}$ ) percentile without discernable carotid plaque. Treatment includes lifestyle modifications and a LDL-C target of <130 mg/dL; <100 mg/dL is optional.
- **High Risk:** CACS 100 - 399 or >75<sup>th</sup> percentile, or a CIMT  $\geq 1$ mm or >75<sup>th</sup> percentile or a carotid plaque causing <50% stenosis. Treatment calls for aggressive lifestyle modifications and a LDL-C target of <100 mg/dL; <70 mg/dL is optional.
- **Very High Risk:** CACS >100 and >90<sup>th</sup> percentile or a CACS  $\geq 400$ , or carotid plaque causing  $\geq 50\%$  stenosis. Treatment includes aggressive lifestyle modification and a LDL-C target of <70 mg/dL. Additional testing for myocardial ischemia is recommended for this group, and those who test positive for ischemia should be considered for angiography depending on the extent of the ischemia.

Thus, the 1<sup>st</sup> 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 (19,27-29).
- Although arguments could be made for applying the paradigm to those above 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.
- ABI below 0.9 suggests significant peripheral atherosclerosis and is associated with a high heart attack risk because of the high likelihood of co-existing 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 (LVH) 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 magnetic resonance imaging 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.
- 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 sub-population) and their closest relatives should be offered Early Heart Attack Care (EHAC) education, focusing on early warning signs and reducing delay time in seeking medical assistance after the onset of symptoms (103-104).

### **Compliance with 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 statin compliance increased from 44% over 3 years to over 90% in those with baseline calcium scores in the top 75th percentile for age and gender ( $p < 0.001$ ) (105). In multivariable analysis, after adjusting for cardiovascular risk factors, age and gender, higher baseline CAC scores were strongly associated with adherence to statin therapy. Thus, in addition to risk stratification, actually seeing their coronary artery can improve patients compliance to treatments such as lipid-lowering therapy.

### **Cost-Effectiveness of SHAPE Guideline vs Existing Preventive Guideline**

In this era of limited health care 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 CHD patients in this country.

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

The initial economic models examined the cost effectiveness of treating selective at-risk adults (i.e., men 45-75 years and women 55-75 years) with evidence of subclinical atherosclerosis compared to 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 EKG test.

For our cost effectiveness analysis, we devised a model comparing:

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

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 incorporated into a single measure both mortality and morbidity of CHD.

From the SHAPE model, when compared with the existing guideline (screening based on risk factors), the use of screening for subclinical atherosclerosis is cost effective, consistently resulting in cost effectiveness ratios <\$50,000 per life year saved.

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

As our economic model attempted to identify costs that may be averted with treatment, we utilized the current costs of CHD burden and used sensitivity analyses to evaluate potential costs averted in our SHAPE analysis. The table below details the results of this analysis including an estimated \$21.5 billion dollars each year in care for CHD patients that may be offset by the use of subclinical disease screening with CACS or CIMT.

|  | Number<br>(per year) | Estimated Impact<br>of SHAPE<br>(Sensitivity<br>Analysis Range) | Estimated<br>Change<br>in Cost |
|--|----------------------|---|--------------------------------|
| CVD Deaths   | 910,600              | ↓ 10%<br>(5%-25%)   | (\$1.2 b)                      |
| MI (prevalence)                                    | 7,200,000            | ↓ 25%<br>(5%-35%)   | (\$18.0 b)                     |
| Chest Pain Symptoms (ER visits)                    | 6,500,000            | ↓ 5%<br>(2.5%-25%)  | (\$4.1 b)                      |
| Hospital Discharge for Primary Diagnosis of CVD    | 6,373,000            | ↑ 10%<br>(5%-25%)   | \$3.8 b                        |
| Hospital Discharge for Primary Diagnosis of CHD    | 970,000              | ↓ 10%<br>(5%-25%)   | (\$9.9 b)                      |
| Cholesterol Lowering Therapy                       |                      | ↑ 50 %<br>(50%-65%)   | 8.00 b                         |
| CV Imaging   | 8,700,000            | ↑ 10%<br>(5%-25%)   | \$358 m                        |
| Angiography  | 6,800,000            | ↑ 15% - CTA<br>(2.5%-25%)                                       | \$600 m                        |
| PCI (percutaneous coronary interventions per year) | 657,000              | ↓ 10%<br>(5%-50%)   | (\$580 m)                      |
| CABS (coronary artery bypass surgeries per year)   | 515,000              | ↓ 5%<br>(2.5%-50%)  | (\$672 m)                      |
| <b><i>Total Δ in Cost</i></b>                      |                      |   | (\$21.5 b)                     |

Costs in parentheses are negative costs or reductions in cost. m= Millions, b = Billions

Source: <http://www.americanheart.org/presenter.jhtml?identifier=3000090>  
[http://www.acc.org/advocacy/word\\_files/2005ProposedPhysicianPmtRulev3%20web.xls](http://www.acc.org/advocacy/word_files/2005ProposedPhysicianPmtRulev3%20web.xls)

It should be noted that decision models do not replace evidence gathered from randomized clinical trials comparing screening for subclinical atherosclerosis to usual care or other strategies. However, given the high cost of such a clinical trial on screening to prevent CHD and that no such study is planned during the next 3-5 years, the current evidence based upon 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 for thousands of patients every year.

## Future Directions

### Genetic, Structural and Functional Assessment

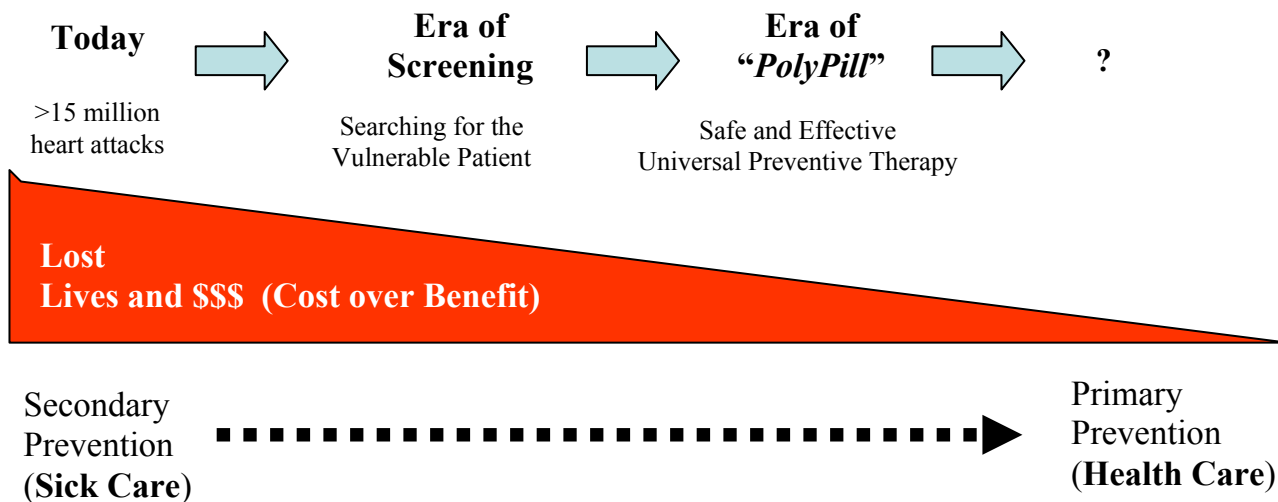
Serum markers that can accurately identify the vulnerable individual with both high sensitivity and specificity might be derived from a thorough proteomic survey of blood samples collected from heart attack victims within a few months prior to the event (109). The incremental predictive value of genes over existing and emerging non-gene predictors will need careful scientific and economic evaluation (110-111). Noninvasive screening tests for subclinical atherosclerosis are rapidly advancing, and include MRI detection of plaque inflammation, contrast-enhanced CT for assessment of noncalcified plaques, PET-CT for combined assessment of plaque burden and activity of the plaques (112-119). Other innovative tests for the assessment of vascular structure and function are under development and clinical testing. These include noninvasive molecular imaging tests and noninvasive nonimaging tests such as pulsewave analysis and endothelial function assessment (89-93,120). In addition, new serum biomarkers of inflammation and oxidative stress in the arterial wall, e.g., LP-PLA2 and myeloperoxidase, are being actively researched (121-122). These emerging tools have the potential to advance the SHAPE guideline and may significantly determine how the Guideline in the future will be updated. 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/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 impact the future of diagnostic screening. Needless to say, in this 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 20<sup>th</sup> 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 21<sup>st</sup> century. New therapeutic opportunities such as highly effective prophylactic Polypils, immune modulation and vaccination therapies may expedite this achievement. (123-124). The following illustrates a potential path to the future:

### A Path Towards Eradicating Heart Attack



### **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.

## References

1. Mackay J, Mensah G. The Atlas of Heart Disease and Stroke. World Health Organization and US Centers for Disease Control and Prevention, 2004. Available at [http://www.who.int/cardiovascular\\_diseases/resources/atlas/en/](http://www.who.int/cardiovascular_diseases/resources/atlas/en/)
2. A Race Against Time. The Challenge of Cardiovascular Disease in Developing Economies. Columbia University, New York, 2004. Available at [http://www.earth.columbia.edu/news/2004/images/raceagainsttime\\_FINAL\\_0410404.pdf](http://www.earth.columbia.edu/news/2004/images/raceagainsttime_FINAL_0410404.pdf)
3. American Heart Association. Heart Disease and Stroke Statistics – 2006 Update. Dallas, TX: AHA, 2006. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=3000090>
4. Zipes DP, Wellnes HJJ. Sudden cardiac death. *Circulation* 1998;98:2334-2351.
5. Zheng ZJ, Croft JB, Giles WH, Ayala CI, Greenlund KJ, Keenan NL, Neff L, Wattigney WA, Mensah GA. State-specific mortality from sudden cardiac death--United States, 1999. *MMWR* 2002;51:123–126. Available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5106a3.htm>.
6. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-52.
7. Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglius ML, Garside D, Dyer AR, Liu K, Greenland P. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA*. 1999;282:2012-8.
8. American Heart Association. Heart Disease and Stroke Statistics – 2005 Update. Dallas, TX: AHA, 2005.
9. United States Cancer Statistics. 2002 Incidence and Mortality. U.S. Department of Health and Human Services. Available at: <http://www.cdc.gov/cancer/npr/uscs/>
10. U.S. Preventive Services Task Force. Screening for Coronary Heart Disease, 2004. Available at <http://www.ahcpr.gov/clinic/uspstf/uspacad.htm>
11. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106:3068-72.
12. Young JB. The global epidemiology of heart failure. *Med Clin North Am*. 2004;88:1135-43, ix.
13. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180-7.
14. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med*. 2004;350:1387-97.
15. Cooper JA, Miller GJ, Humphries SE. A comparison of the PROCAM and Framingham point-scoring systems for estimation of individual risk of coronary heart disease in the Second Northwick Park Heart Study. *Atherosclerosis*. 2005;181:93-100.

16. Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA*. 2004;291:2591-9.
17. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol*. 2005;46:158-65.
18. Grundy SM. The changing face of cardiovascular risk. *J Am Coll Cardiol*. 2005;46:173-5. Editorial.
19. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D; Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2003;24:1601-10. Full text available at: [http://www.escardio.org/NR/rdonlyres/A0EF5CA5-421B-45EF-A65C-19B9EC411261/0/CVD\\_Prevention\\_03\\_full.pdf](http://www.escardio.org/NR/rdonlyres/A0EF5CA5-421B-45EF-A65C-19B9EC411261/0/CVD_Prevention_03_full.pdf)
- 20) Akosah K, Schaper A., Cogbil C., Schoenfeld, P., Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? *J Am Coll Cardiol*. 2003 May 7;41(9):1475-9.
- 21) Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, Ebrahim S. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ*. 2003 Nov 29;327(7426):1267
- 22)Empana JP, Ducimetiere P, Arveiler D, Ferrieres J, Evans A, Ruidavets JB, Haas B, Yarnell J, Bingham A, Amouyel P, Dallongeville J; PRIME Study Group. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. *Eur Heart J*. 2003 Nov;24(21):1903-11
- 23) Neuhauser HK, Ellert U, Kurth BM. A comparison of Framingham and SCORE-based cardiovascular risk estimates in participants of the German National Health Interview and Examination Survey 1998. *Eur J Cardiovasc Prev Rehabil*. 2005 Oct;12(5):442-50.
- 24) Bastuji-Garin S, Deverly A, Moyse D, Castaigne A, Mancia G, de Leeuw PW, Ruilope LM, Rosenthal T, Chatellier G; Intervention as a Goal in Hypertension Treatment Study Group. The Framingham prediction rule is not valid in a European population of treated hypertensive patients. *J Hypertens*. 2002 Oct;20(10):1973-80.
- 25) Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA*. 2004 Jun 2;291(21):2591-9.
- 26) Kuller LH. Prevention of coronary heart disease and the National Cholesterol Education Program. *Circulation*. 2006 Feb 7;113(5):598-600
27. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290:891-7.
28. Wald NJ, Law M, Watt HC, Wu T, Bailey A, Johnson AM, Craig WY, Ledue TB, Haddow JE. Apolipoproteins and ischaemic heart disease: implications for screening. *Lancet* 1994;343:75-9.
29. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ*. 1999;319:1562-5.

30. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ*. 2002;324:1570-6.
31. Law MR, Wald NJ, Morris JK. The performance of blood pressure and other cardiovascular risk factors as screening tests for ischaemic heart disease and stroke. *J Med Screen*. 2004;11:3-7.
32. Weissler AM. Traditional risk factors for coronary heart disease. *JAMA*. 2004;291:299-300. Letter.
33. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ*. 2003;326:1419-
34. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-421.  
Available at <http://circ.ahajournals.org/cgi/reprint/106/25/3143>
35. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-39.
36. Smith SC Jr, Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: executive summary. *Circulation*. 2000;101:111-6.
37. Law MR, Watt HC, Wald NJ. The underlying risk of death after myocardial infarction in the absence of treatment. *Arch Intern Med*. 2002;162:2405-10.
38. Eyre H, Kahn R, Robertson RM, Clark NG, Doyle C, Hong Y, Gansler T, Glynn T, Smith RA, Taubert K, Thun MJ. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation*. 2004;109:3244-55.
39. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhater MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003;108:1664-72. Review.
40. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, Fayad Z, Stone PH, Waxman S, Raggi P, Madjid M, Zarrabi A, Burke A, Yuan C, Fitzgerald PJ, Siscovick DS, de Korte CL, Aikawa M, Airaksinen KE, Assmann G, Becker CR, Chesebro JH, Farb A, Galis ZS, Jackson C, Jang IK, Koenig W, Lodder RA, March K, Demirovic J, Navab M, Priori SG, Rekhater MD, Bahr R, Grundy SM, Mehran R, Colombo A, Boerwinkle E, Ballantyne C, Insull W Jr, Schwartz RS, Vogel R, Serruys PW, Hansson GK, Faxon DP, Kaul S, Drexler H, Greenland P, Muller JE, Virmani R, Ridker PM, Zipes DP, Shah PK, Willerson JT. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation*. 2003;108:1772-8. Review.
41. Hoff JA, Chomka EV, Krainik AJ, et al. Age and Gender Distributions of Coronary Artery Calcium Detected by Electron Beam Tomography in 35,246 Adults. *Am J Cardiol* 2001; 87:1335.
42. Arad Y, Spadaro L, Goodman K, et al.: Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000; 36:1253-1260.
43. Park, R, Detrano R, Xiang M, et al. Combined use of computed tomography coronary calcium scores and C-reactive protein levels in predicting cardiovascular events in non-diabetic individuals. *Circulation* 2002; 106:2073-2077.

44. Raggi P, Callister TQ, Cooil B, et al.: Identification of patients at increased risk of first unheralded acute myocardial infarction by electron beam computed tomography. *Circulation* 2000; 101:850-885.
45. Wong ND, Hsu JC, Detrano RC, et al: Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000; 86:495-498.
46. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. NIH Publication No. 02-5215. September 2002.
47. Vliegenthart R, Oudkerk M, Song B. The Rotterdam Coronary Calcification Study. Coronary calcification detected by electron-beam computed tomography and myocardial infarction *Eur Heart J* 2002 23, 1596–1603.
48. Kondos GT, Hoff JA, Sevrukov A, et al. Coronary Artery Calcium and Cardiac Events Electron-Beam Tomography Coronary Artery Calcium and Cardiac Events: A 37-Month Follow-Up of 5,635 Initially Asymptomatic Low to Intermediate Risk Adults. *Circulation* 2003; 107:2571-2576.
49. DeBacker G, Ambrosioni E, Borch-Johnson K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third joint task force of European and other countries in cardiovascular disease in clinical practice. *Eur J Rehab Prev* 2003;10(suppl 1):S1-S78.
50. Greenland P, Gaziano JM. Clinical practice. Selecting asymptomatic patients for coronary computed tomography or electrocardiographic exercise testing. *N Engl J Med.* 2003;349:465-73. Review.
51. Shaw LJ, Raggi P, Schisterman E, et al. Prognostic Value of Cardiac Risk Factors and Coronary Artery Calcium Screening for All-Cause Mortality. *Radiology* 2003; 28:826–833.
52. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med.* 2004;164:1285-92.
53. Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004; 291:210-215.
54. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women Expert Panel/Writing Group. *Circulation.* 2004;109:672– 693
55. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary Calcification Improves Cardiovascular Risk Prediction in the Elderly. *Circulation.* 2005;112:572-577.
56. Taylor AJ, Bindeman J, Feuerstein I, et al. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) Project. *J Am Coll Cardiol* 2005;46:807–14.
57. Berman DS, Wong ND, Gransar H, Miranda-Peats R, Dahlbeck J, Hayes SW, Friedman JD, Kang X, Polk D, Hachamovitch R, Shaw L, Rozanski A. Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *JACC* 2004;44:923-30.
58. Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA: Non-Invasive Definition of Anatomic Coronary Artery Disease by Ultrafast CT: A Quantitative Pathologic Study. *J Am Coll Cardiol* 1992; 20: 1118-26

59. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS: Coronary Artery Calcium Areas by Electron Beam Computed Tomography and Coronary Atherosclerotic Plaque Area: A Histopathologic Correlative Study. *Circulation* 1995;92:2157-2162
60. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS: Arterial Calcification and Not Lumen Stenosis is Highly Correlated with Atherosclerotic Plaque Burden in Humans: A Histologic Study of 723 Coronary Artery Segments using Non-Decalcifying Methodology. *J Am Coll Cardiol* 1998;31:126-33
61. Chambless LE, Heiss G, Folsom AR, et al.: Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study. 1987-1993. *Am J Epidemiol* 1997, 146:483-494.
62. Chambless LE, Folsom AR, Clegg LX, et al.: Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J. Epidemiol* 2000, 151:478-487.
63. Bonithon-Kopp C, Scarabin P, Taquet A, Touboul P, Malmejac A, Guize L. Risk factors for early carotid atherosclerosis in middle-aged French women. *Arterioscler Thromb*. 1991;11:966-72.
64. Prevention Conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerosis burden: Writing Group III. *Circulation* 2000;101:e16.
65. Belcaro G, Nicolaides AN, Laurora G, Cesarone MR, De Sanctis M, Incandela L, Barsotti A. Ultrasound morphology classification of the arterial wall and cardiovascular events in a 6-year follow-up study. *Arterioscler Thromb Vasc Biol* 1996;16:851-6.
66. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Desvarieux M, Ebrahim S, Fatar M, Hernandez Hernandez R, Kownator S, Prati P, Rundek T, Taylor A, Bornstein N, Csiba L, Vicaut E, Woo KS, Zannad F; Advisory Board of the 3rd Watching the Risk Symposium 2004, 13th European Stroke Conference. Mannheim intima-media thickness consensus. *Cerebrovasc Dis*. 2004;18:346-9.
67. Stork S, van den Beld AW, von Schacky C, Angermann CE, Lamberts SW, Grobbee DE, Bots ML. Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study. *Circulation*. 2004;110:344-8.
68. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999;340:14-22.
69. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998; 128:262-9.
70. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* 1997;96:1432-7.
71. Hollander M, Hak AE, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Witteman JC, Breteler MM. Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. *Stroke*. 2003;34:2367-72.
72. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. *Circulation*. 2004;109:1089-94.
73. Brook RD, Bard RL, Patel S, Rubenfire M, Clarke NS, Kazerooni EA, Wakefield TW, Henke PK, Eagle KA. A Negative Carotid Plaque Area Test Is Superior to Other Noninvasive Atherosclerosis Studies for Reducing the Likelihood of Having Underlying Significant Coronary Artery Disease. *Arterioscler Thromb Vasc Biol*. 2005 Dec 15; [Epub ahead of print]

74. Riley, WA: Cardiovascular risk assessment in individual patients from carotid intimal-medial thickness measurements. *Curr Athero Reports* 2004;6:225-231.
75. Bots ML, Evans GW, Riley WA, Grobbee DE: Carotid intimal-medial thickness measurements in intervention studies: design options, progression rates, and sample size considerations: a point of view. *Stroke* 2003, 34:2985-2994.
76. Van Der Meer IM, De Maat MP, Hak AE, Kiliaan AJ, Del Sol AI, Van Der Kuip DA, Nijhuis RL, Hofman A, Witteman JC. C-reactive protein predicts progression of atherosclerosis measured at various sites in the arterial tree: the Rotterdam Study. *Stroke*. 2002;33:2750-5.
77. Khera A, de Lemos JA, Peshock RM, Lo HS, Stanek HG, Murphy SA, Wians FH Jr, Grundy SM, McGuire DK. Relationship between C-reactive protein and subclinical atherosclerosis: the Dallas Heart Study. *Circulation*. 2006;113:38-43.
78. Koenig W. Predicting risk and treatment benefit in atherosclerosis: the role of C-reactive protein. *Int J Cardiol*. 2005;98:199-206.
79. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW; Framingham Study. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. *Arch Intern Med*. 2003;163:1939-42.
80. Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, Yusuf S; HOPE study investigators. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J*. 2004;25:17-24.
81. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol*. 2004;43:1663-9.
82. Sobel BE, Schneider DJ. Cardiovascular complications in diabetes mellitus. *Curr Opin Pharmacol*. 2005;5:143-8.
83. Schneider DJ. Abnormalities of coagulation, platelet function, and fibrinolysis associated with syndromes of insulin resistance. *Coron Artery Dis*. 2005;16:473-6.
84. Tin LL, Beevers DG, Lip GY. Hypertension, left ventricular hypertrophy, and sudden death. *Curr Cardiol Rep*. 2002;4:449-57.
85. Lipinski MJ, Fuster V, Fisher EA, Fayad ZA. Technology insight: targeting of biological molecules for evaluation of high-risk atherosclerotic plaques with magnetic resonance imaging. *Nat Clin Pract Cardiovasc Med*. 2004;1:48-55.
86. Fuster V, Fayad ZA, Moreno PR, Poon M, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: Part II: approaches by non-invasive computed tomographic/magnetic resonance imaging. *J Am Coll Cardiol*. 2005;46:1209-18.
87. Takaya N, Yuan C, Chu B, Saam T, Polissar NL, Jarvik GP, Isaac C, McDonough J, Natiello C, Small R, Ferguson MS, Hatsukami TS. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. *Circulation*. 2005;111:2768-75.
88. Yuan C, Hatsukami TS, Cai J. MRI plaque tissue characterization and assessment of plaque stability. *Stud Health Technol Inform*. 2005;113:55-74.
89. Cohn JN, Quyyumi AA, Hollenberg NK, Jamerson KA. Surrogate markers for cardiovascular disease: Functional markers. *Circulation*. 2004;109(suppl IV):IV31-IV46. Review.
90. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005;25:932-43.

91. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol.* 2003;23:168-75. Review.
92. Ganz P, Vita JA. Testing endothelial vasomotor function: nitric oxide, a multipotent molecule. *Circulation.* 2003;108:2049-53. Review.
93. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol.* 2003;42:1149-60. Review
94. Madjid M, Zarrabi A, Litovsky S, Willerson JT, Casscells W. Finding vulnerable atherosclerotic plaques: is it worth the effort? *Arterioscler Thromb Vasc Biol.* 2004;24:1775-82.
95. MacNeill BD, Bouma BE, Yabushita H, Jang IK, Tearney GJ. Intravascular optical coherence tomography: cellular imaging. *J Nucl Cardiol.* 2005;12:460-5.
96. Carlier S, Kakadiaris IA, Dib N, Vavuranakis M, O'Malley SM, Gul K, Hartley CJ, Metcalfe R, Mehran R, Stefanadis C, Falk E, Stone G, Leon M, Naghavi M. Vasa vasorum imaging: a new window to the clinical detection of vulnerable atherosclerotic plaques. *Curr Atheroscler Rep.* 2005;7:164-9.
97. Fujii K, Carlier SG, Mintz GS, Wijns W, Colombo A, Bose D, Erbel R, de Ribamar Costa J Jr, Kimura M, Sano K, Costa RA, Lui J, Stone GW, Moses JW, Leon MB. Association of plaque characterization by intravascular ultrasound virtual histology and arterial remodeling. *Am J Cardiol.* 2005;96:1476-83.
98. Chen JW, Wasserman BA. Vulnerable plaque imaging. *Neuroimaging Clin N Am.* 2005;15:609-21.
99. Baldewsing RA, Schaar JA, Mastik F, Oomens CW, van der Steen AF. Assessment of vulnerable plaque composition by matching the deformation of a parametric plaque model to measured plaque deformation. *IEEE Trans Med Imaging.* 2005;24:514-28.
100. Schoenhagen P, Nissen SE. Assessing coronary plaque burden and plaque vulnerability: atherosclerosis imaging with IVUS and emerging noninvasive modalities. *Am Heart Hosp J.* 2003;1:164-9.
101. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation.* 2003;108:2957-63.
102. Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum.* 2005;35:8-17.
103. Joseph AJ, Cohen AG, Bahr RD. A formal, standardized and evidence-based approach to Chest Pain Center development and process improvement: the Society of Chest Pain Centers and Providers accreditation process. *J Cardiovasc Manag.* 2003;14:11-4.
104. Luepker RV, Raczynski JM, Osganian S, Goldberg RJ, Finnegan JR Jr, Hedges JR, Goff DC Jr, Eisenberg MS, Zapka JG, Feldman HA, Labarthe DR, McGovern PG, Cornell CE, Proschan MA, Simons-Morton DG. Effect of a community intervention on patient delay and emergency medical service use in acute coronary heart disease: The Rapid Early Action for Coronary Treatment (REACT) Trial. *JAMA.* 2000;284:60-7.
105. Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. *Atherosclerosis.* 2005 Jul 25; [Epub ahead of print]
106. Mark DB, Shaw LJ, Lauer MS, O'Malley P, Heidenreich P. 34<sup>th</sup> Bethesda Conference: Task force #5 - Is atherosclerotic imaging cost effective? From the 34<sup>th</sup> Bethesda Conference on Atherosclerotic Imaging. *J Am Coll Cardiol.* 2003;41:1906-17.

107. Fedder DO, Koro CE, L'Italien GJ. New National Cholesterol Education Program III guidelines for primary prevention lipid-lowering drug therapy: projected impact on the size, sex, and age distribution of the treatment-eligible population. *Circulation*. 2002;105:152-6.
108. Nasir K, Michos ED, Blumenthal RS, Raggi P. Detection of high-risk young adults and women by coronary calcium and National Cholesterol Education Program Panel III guidelines. *J Am Coll Cardiol*. 2005;46:1931-6.
109. Vivanco F, Martin-Ventura JL, Duran MC, Barderas MG, Blanco-Colio L, Darde VM, Mas S, Meilhac O, Michel JB, Tunon J, Egido J. Quest for novel cardiovascular biomarkers by proteomic analysis. *J Proteome Res*. 2005;4:1181-91.
110. Humphries SE, Ridker PM, Talmud PJ. Genetic testing for cardiovascular disease susceptibility: a useful clinical management tool or possible misinformation? *Arterioscler Thromb Vasc Biol*. 2004;24:628-36.
111. Topol EJ. Simon Dack Lecture. The genomic basis of myocardial infarction. *J Am Coll Cardiol*. 2005;46:1456-65.
112. Kooi ME, Cappendijk VC, Cleutjens KBJM, Kessels AGH, Kitslaar PJEHM, Borgers M, Frederik PM, Daemen MJAP, van Engelshoven JMA. Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging. *Circulation*. 2003;107:2453-8.
113. Trivedi RA, U-King-Im JM, Graves MJ, Cross JJ, Horsley J, Goddard MJ, Skepper JN, Quartey G, Warburton E, Joubert I, Wang L, Kirkpatrick PJ, Brown J, Gillard JH. In vivo detection of macrophages in human carotid atheroma: temporal dependence of ultrasmall superparamagnetic particles of iron oxide-enhanced MRI. *Stroke*. 2004;35:1631-5.
114. Cyrus T, Winter PM, Caruthers SD, Wickline SA, Lanza GM. Magnetic resonance nanoparticles for cardiovascular molecular imaging and therapy. *Expert Rev Cardiovasc Ther*. 2005;3:705-15.
115. Davies JR, Rudd JH, Weissberg PL. Molecular and metabolic imaging of atherosclerosis. *J Nucl Med*. 2004;45:1898-907. Review.
116. Kietselaer BLJH, Reutelingsperger CPM, Heidendal GAK, Daemen MJAP, Mess WH, Hofstra L, Narula J. Noninvasive detection of plaque instability with use of radiolabeled annexin A5 in patients with carotid-artery atherosclerosis. *New Engl J Med* 2004;350:1472-3.
117. Davies JR, Rudd JH, Fryer TD, Graves MJ, Clark JC, Kirkpatrick PJ, Gillard JH, Warburton EA, Weissberg PL. Identification of culprit lesions after transient ischemic attack by combined 18F fluorodeoxyglucose positron-emission tomography and high-resolution magnetic resonance imaging. *Stroke*. 2005;36:2642-7.
118. Dunphy MP, Freiman A, Larson SM, Strauss HW. Association of vascular 18F-FDG uptake with vascular calcification. *J Nucl Med*. 2005;46:1278-84.
119. Leber AW, Knez A, Becker A, Becker C, Reiser M, Steinbeck G, Boekstegers P. Visualising noncalcified coronary plaques by CT. *Int J Cardiovasc Imaging*. 2005;21:55-61.
120. Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr, Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *J Am Coll Cardiol*. 2004;44:2137-41.
121. Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. *Arterioscler Thromb Vasc Biol*. 2005;25:923-31.
122. Schwartz RS, Bayes-Genis A, Lesser JR, Sangiorgi M, Henry TD, Conover CA. Detecting vulnerable plaque using peripheral blood: inflammatory and cellular markers. *J Interv Cardiol*. 2003;16:231-42.

123. Shah PK, Chyu KY, Fredrikson GN, Nilsson J. Immunomodulation of atherosclerosis with a vaccine. *Nat Clin Pract Cardiovasc Med.* 2005;2:639-46.

124. Naghavi, M. The Mission of the Association for Eradication of Heart Attack. Available at <http://www.aeha.org/mission.html>