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

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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, hypertention, 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), Weissler 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 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 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 unrecognised 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 underogone 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.

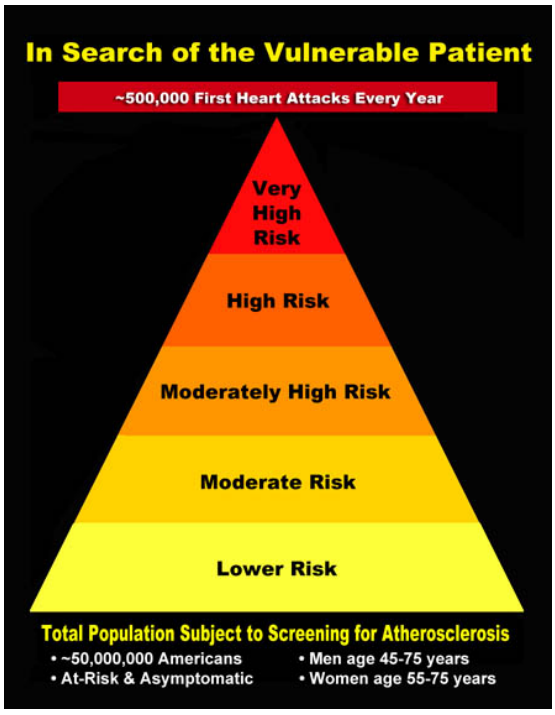


Figure 1. The SHAPE paradigm calls for screening all apparently healthy (with no prior diagnosis of CHD) men 45-75 years of age and women 55-75 years of age who are not considered very-low-risk. This population accounts for approximately 50 million people in the US.

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.

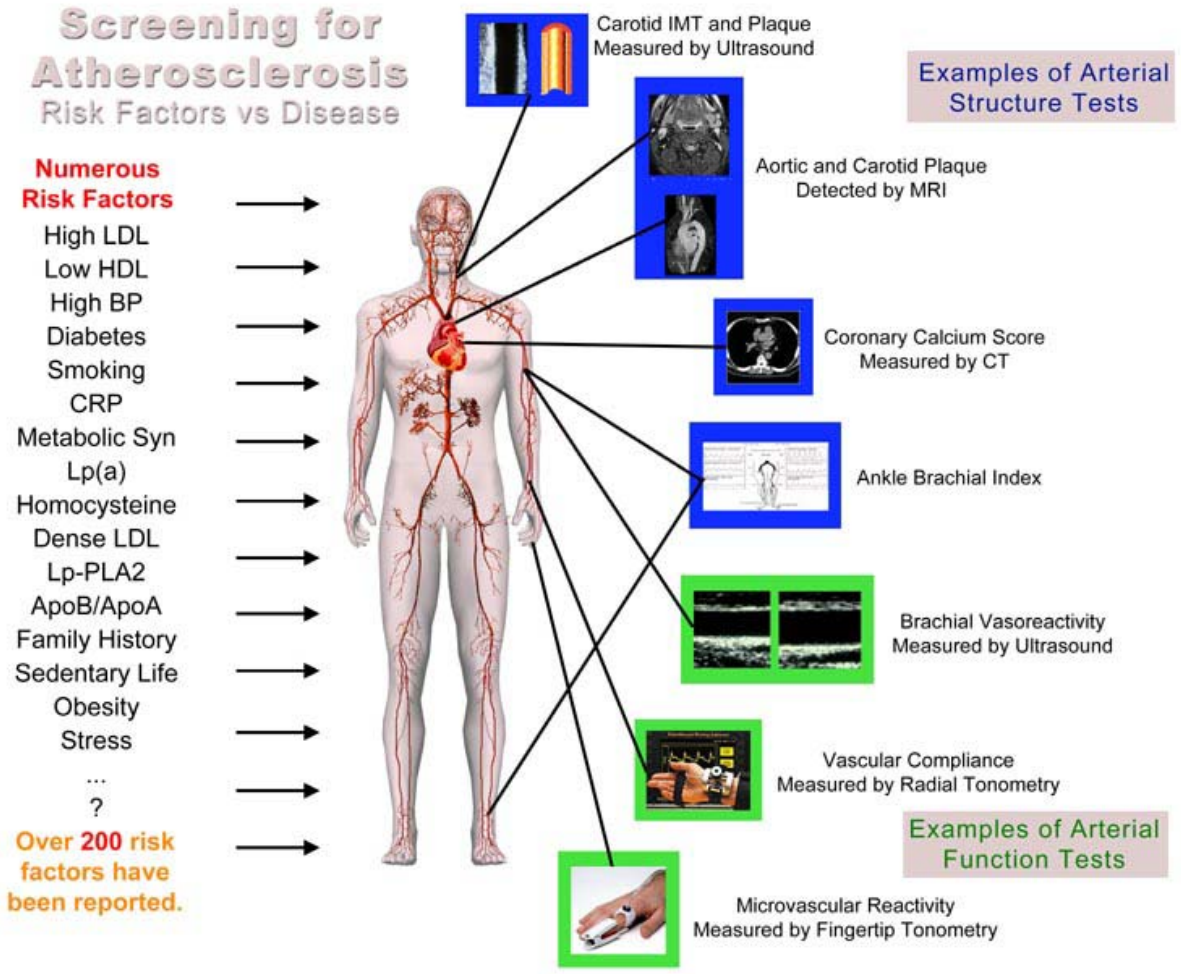


Figure 2. The new SHAPE paradigm: screening *directly* for the presence and severity of atherosclerosis by structure and function testing (right), versus the traditional approach in which the likelihood of atherosclerotic disease is estimated *indirectly* by evaluating risk factors for the disease (left).

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 1st SHAPE Guideline have accumulated in recent years (41-75), and further support can be found in the full SHAPE Report (www.aeha.org).

The 1st SHAPE Guideline

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

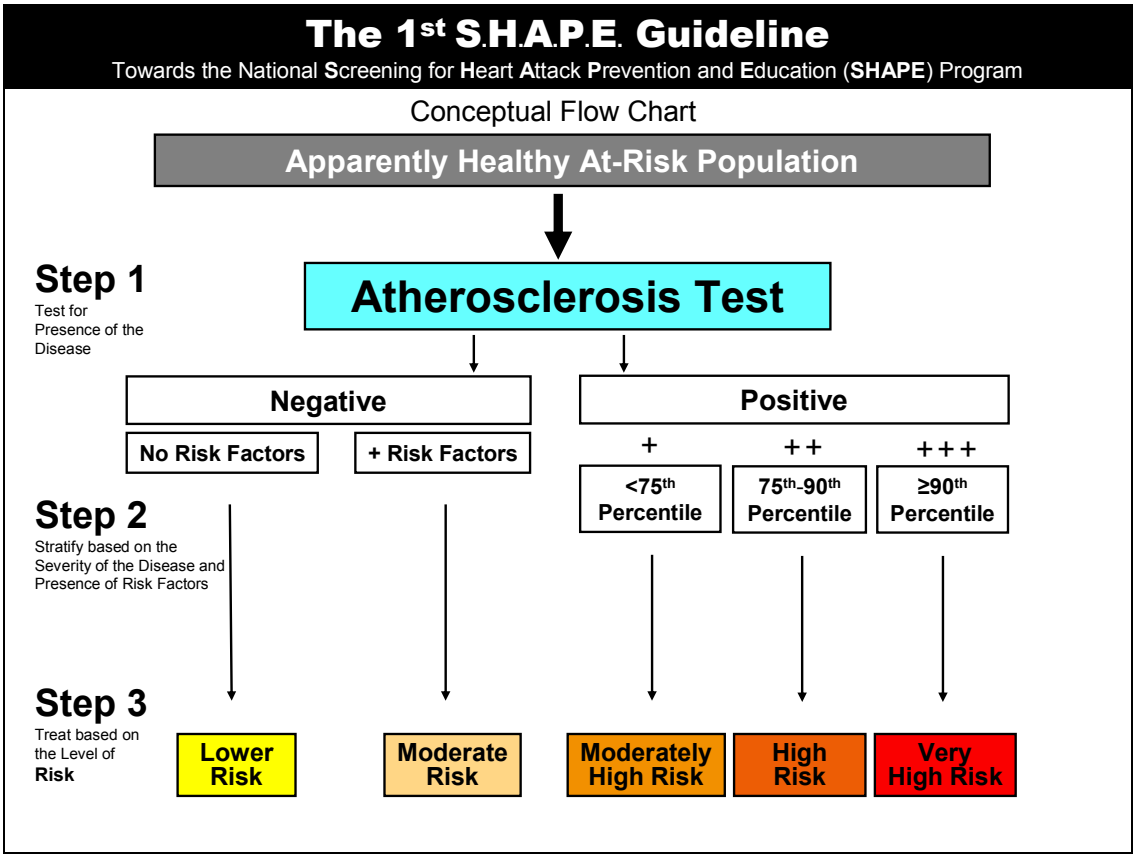
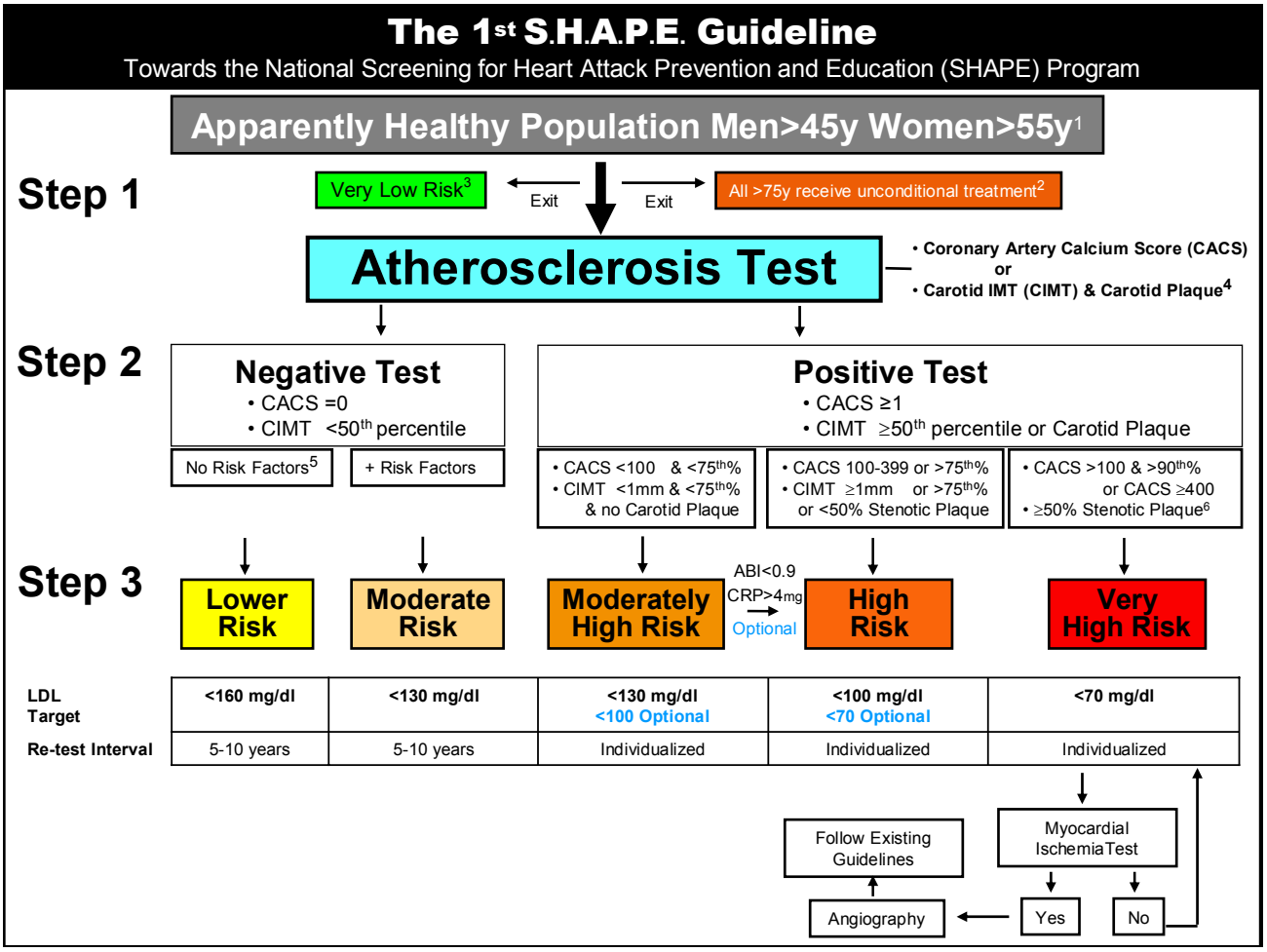


Figure 3. Conceptual flow chart illustrating the principles of the new algorithm.

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 1st 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 <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 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 ≥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 <1mm and <75th (but ≥50th) 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 >75th percentile, or a CIMT ≥1mm or >75th 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 >90th percentile or a CACS ≥400, or carotid plaque causing ≥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 1st 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 exisiting 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 (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
PCI (percutaneous coronary interventions per year)	657,000	↓ 10% (5%-50%)	($580 m)
CABS (coronary artery bypass surgeries per year)	515,000	↓ 5% (2.5%-50%)	($672 m)
Total Δ in Cost			($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

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

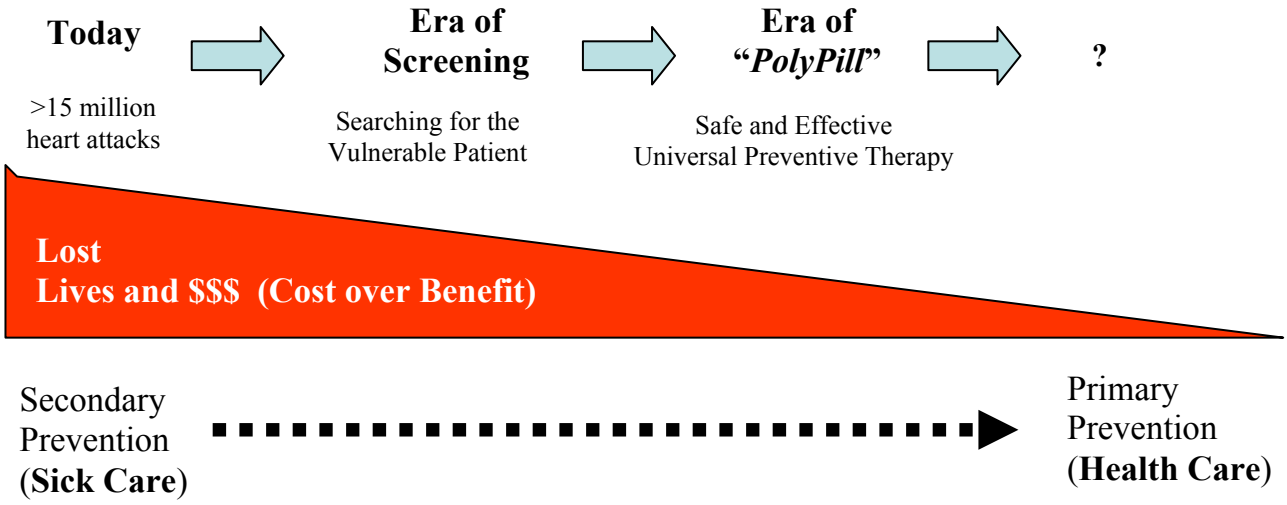
Serum markers that can accurately identify the vulnerable individual with both high sensitivity and specificity might be derived from a thorough proteomic survey of blood samples collected from heart attack victims within a few months prior to the event (109). The incremental predictive value of genes 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 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 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



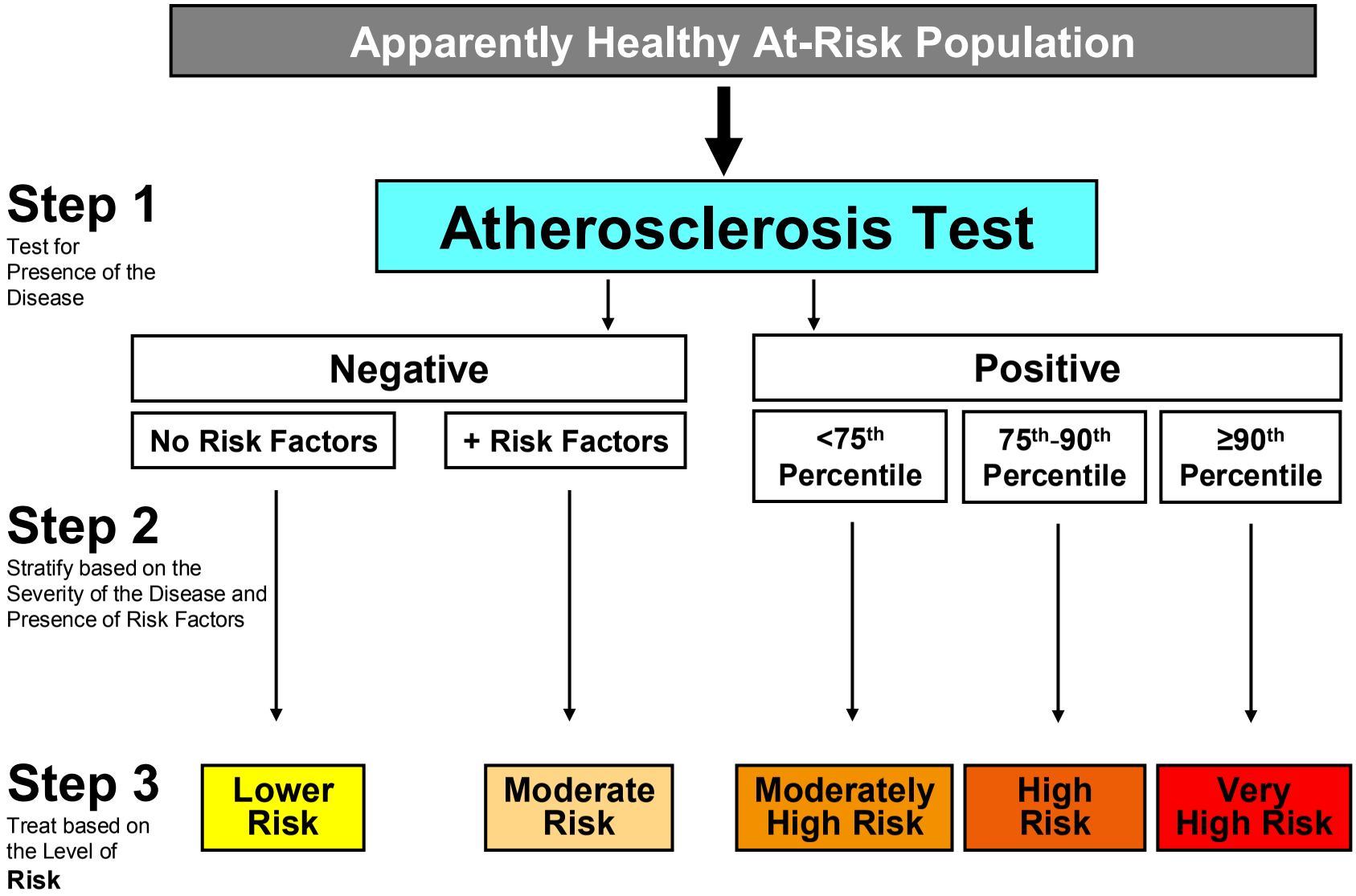
Conclusion

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.

The 1st S.H.A.P.E. Guideline

Towards the National **S**creening for **H**eart **A**ttack **P**revention and **E**ducation (**SHAPE**) Program

Conceptual Flow Chart



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