

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

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

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

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

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

Atherosclerosis is a common and dangerous disease of the arteries of the heart, brain, and periphery. It is by far the most frequent underlying cause of angina, heart attack, and peripheral arterial disease and is responsible for many cases of stroke. Thus, atherosclerosis and its thrombotic complications are currently the most deadly and disabling diseases in affluent countries and in the near future will be so in the entire world.^{1,2} Yet many individuals, even those with severe atherosclerosis, are unaware of their risk, because they

have no symptoms. In 30%–50% of these individuals, the first indicator of atherosclerosis is an acute heart attack, which often is fatal.^{3–5}

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

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

Burden of Atherosclerotic Cardiovascular Disease

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

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

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

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

Risk Factors, Susceptibility, and Vulnerability

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

In the United States, the prevalence of ≥ 1 major risk factor (aside from age) is very high among persons aged ≥ 40 years who develop CHD.²⁷ However, it is also high among those who do not develop CHD, illustrating that when risk factors are almost universally present in a population, they do not predict the development of disease very well in individuals.^{28–32} Based on recently published data from 3 influential prospective epidemiologic studies,²⁷ Weisler³² highlighted this failure by using likelihood ratio analysis. A likelihood ratio ≤ 2.0 denotes low predictive power and a likelihood ratio ≥ 9.0 denotes high predictive power. Remarkably low predictive power (likelihood ratio

< 1.4) was found for ≥ 1 risk factor in predicting death from CHD and/or nonfatal MI, despite the high frequency of this risk profile in the population with CHD events. The relation between cigarette smoking and lung cancer provides a reasonable analogy: When almost everyone in a given population smokes, smoking itself fails to predict the risk of cancer.

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

Current Guidelines in Primary Prevention

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

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

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

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

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

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

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

New Paradigm for the Prevention of Heart Attack

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

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

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

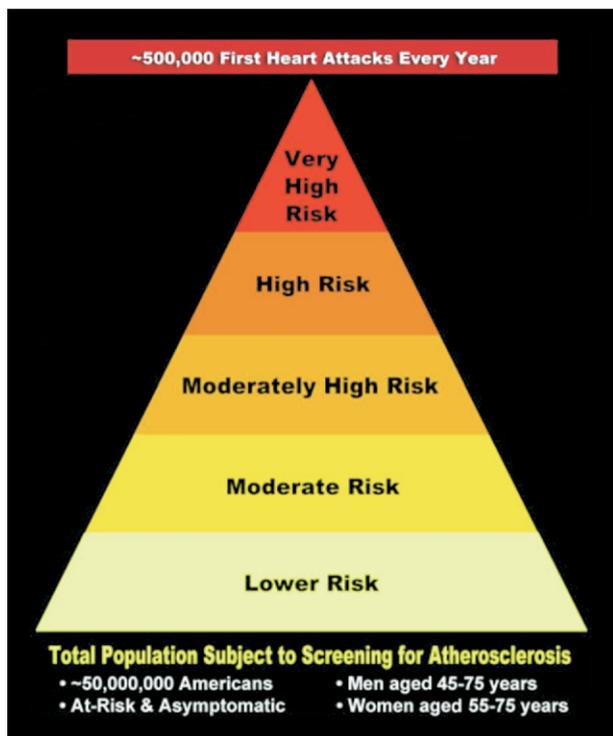


Figure 1. In search of the vulnerable patient: the Screening for Heart Attack Prevention and Education (SHAPE) paradigm calls for screening all apparently healthy (ie, with no prior diagnosis of coronary heart disease) men 45–75 years of age and women 55–75 years of age who are not considered very low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

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

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

The First SHAPE Guideline

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

In contrast to the existing traditional risk factor–based guidelines, this new strategy is primarily based on nonin-

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

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

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

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

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

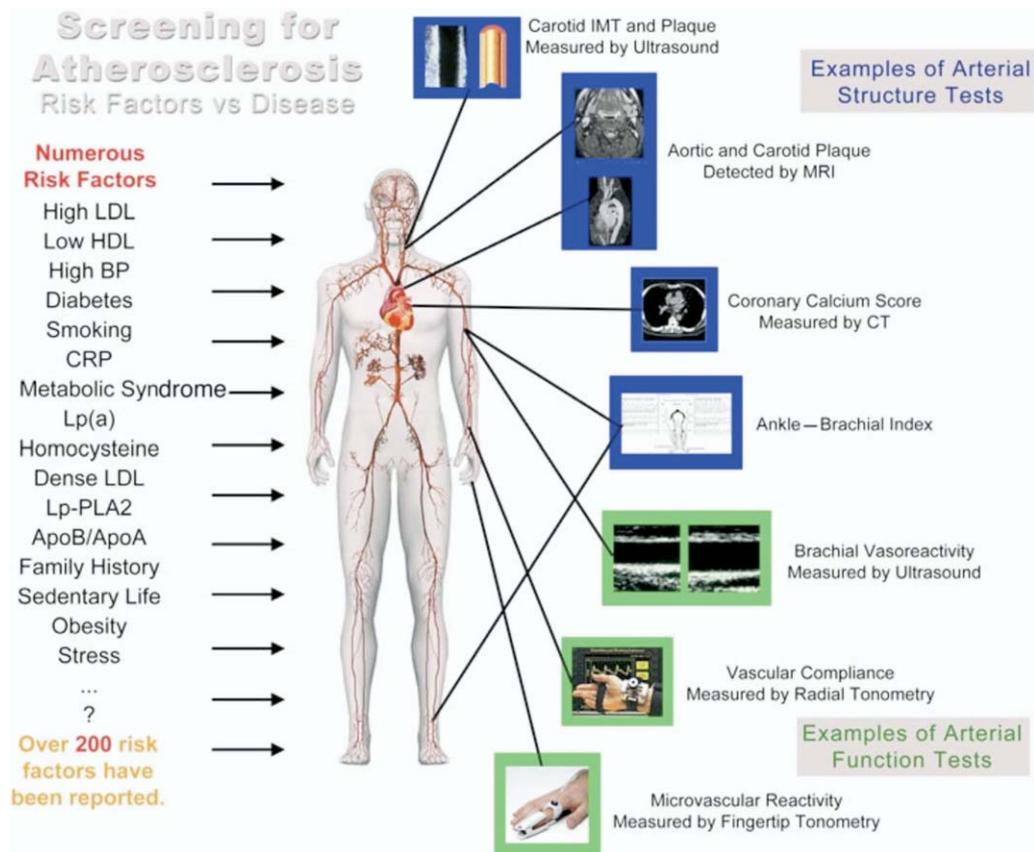


Figure 2. The new Screening for Heart Attack Prevention and Education (SHAPE) paradigm: screening directly for the presence and severity of atherosclerosis by structure and function testing (*right*) versus the traditional approach in which the likelihood of atherosclerotic disease is estimated indirectly by evaluating risk factors for the disease (*left*). Apo = apolipoprotein; BP = blood pressure; CRP = C-reactive protein; CT = computed tomography; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); Lp-PLA2 = lipoprotein-associated phospholipase A₂; MRI = magnetic resonance imaging.

positive for ischemia should be considered for angiography.

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

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

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

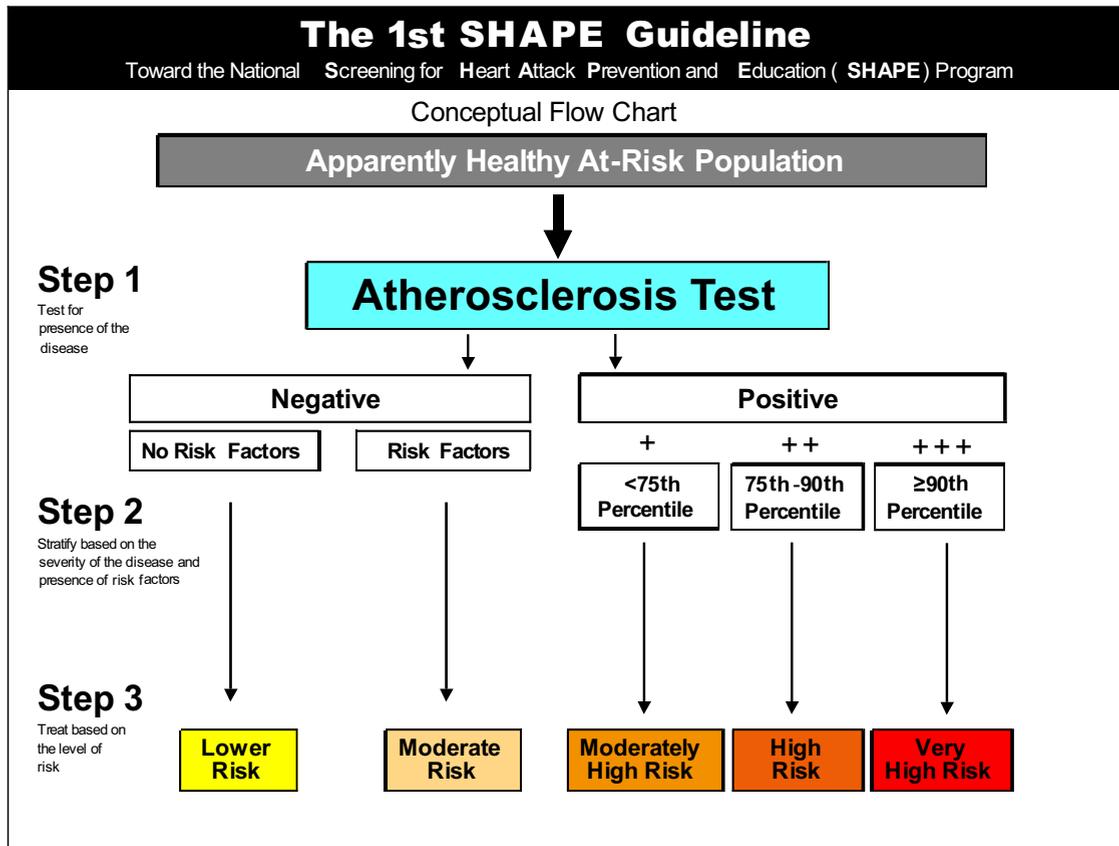


Figure 3. Conceptual flow chart illustrating the principles of the new Screening for Heart Attack Prevention and Education (SHAPE) algorithm.

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

Adherence to treatment: Despite significant and consistent data on the benefits of lipid-lowering agents to reduce cardiovascular events, adherence and utilization of these agents

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

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

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

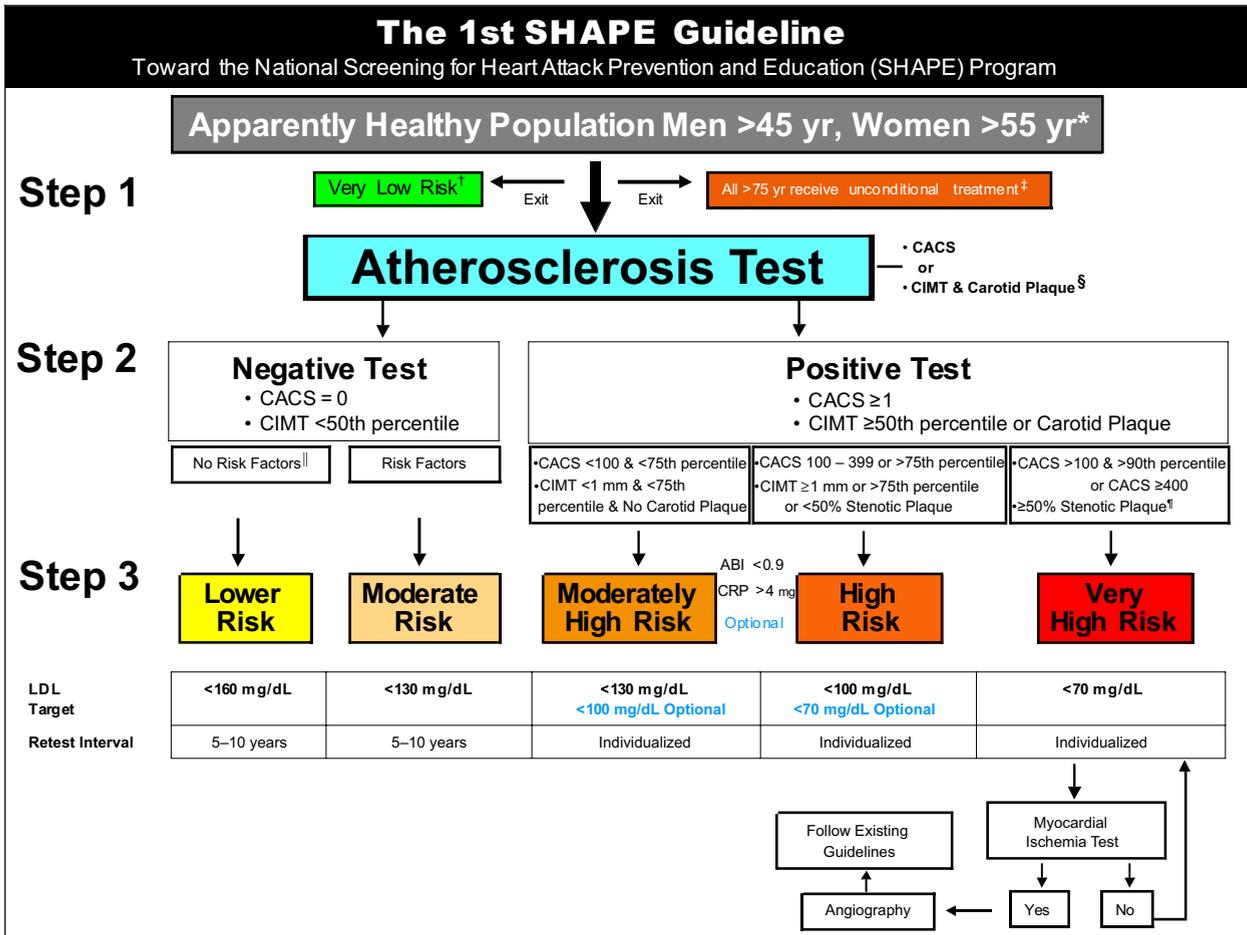


Figure 4. Flow chart of the First Screening for Heart Attack Prevention and Education (SHAPE) Guideline. ABI = ankle-brachial index; CACS = coronary artery calcium score; CIMT = carotid intima-media thickness; CRP = C-reactive protein; LDL = low-density lipoprotein. *No history of angina, heart attack,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

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

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

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

We devised our decision models to examine the burden of CHD, including the prevalence of CHD, years of life lost prematurely to CHD, disability or changes in quality of life, and the current economic burden of CHD.¹⁰⁶ This, in total, comprised the burden of the disease and was incorporated into a single measure of both mortality and morbidity from

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

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

Because our economic model attempted to identify costs that may be averted with treatment, we used the current costs of CHD burden and used sensitivity analyses to evaluate potential costs averted in our SHAPE analysis. Table 13.109 details the results of this analysis, including an estimated US\$21.5 billion each year in care for patients with CHD that

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

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

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

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

Adapted from *Heart Disease and Stroke Statistics—2006 Update*.³

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

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

Future Directions

Genetic, structural, and functional assessment: Serum markers that can accurately identify the vulnerable individual with both high sensitivity and specificity might be derived from a thorough proteomic survey of blood samples collected from heart attack victims within a few months before the event.¹¹⁰ The incremental predictive value of genes over existing and emerging nongene predictors will need careful scientific and economic evaluation.^{111,112} Noninvasive screening tests for subclinical atherosclerosis are rapidly advancing, and include MRI detection of plaque inflammation, contrast-enhanced CT for assessment of non-calcified plaques, and positron-emission tomography–CT for combined assessment of plaque burden and activity of the plaques.^{113–120} Other innovative tests for the assessment of vascular structure and function are undergoing development and clinical testing. These include noninvasive molec-

ular imaging tests and noninvasive nonimaging tests such as molecular pulsewave analysis and endothelial function assessment.^{89–93,121} In addition, new serum biomarkers of inflammation and oxidative stress in the arterial wall, eg, lipoprotein-associated phospholipase A₂ and myeloperoxidase, are being actively researched.^{122,123} These emerging tools have the potential to advance the SHAPE Guideline and may significantly determine how the Guideline will be updated in the future. Combinations of tests may offer great promise. An ideal scenario would be a combination of a very-low-cost, noninvasive, nonimaging test or serum marker (such as endothelial function tests and serum markers of arterial inflammation or oxidation) with an accurate, inexpensive, and widely available imaging tool capable of imaging plaque burden and activity. Such molecular imaging techniques may enable us to accurately identify the site of vulnerable plaques based on markers of inflammation, oxidation, angiogenesis, apoptosis, and matrix degradation. The future direction of screening will also be greatly influenced by new developments in therapeutic modalities. The balance between new noninvasive systemic drug therapies capable of rapid stabilization of vulnerable plaques, and new invasive focal therapies without long-term adverse effects, will have an impact on the future of diagnostic screening. Needless to say, in the present outcome-oriented era, analysis of the cost-effectiveness of the SHAPE Guideline will be crucial to its continued implementation.

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

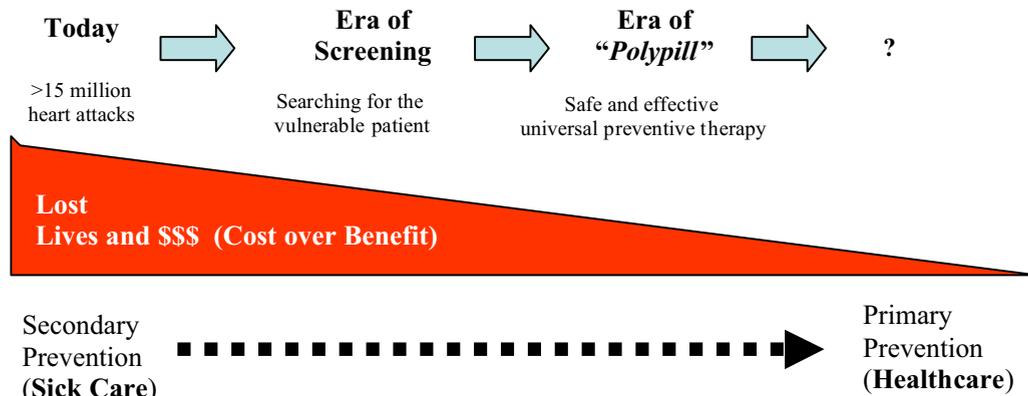


Figure 5. A path toward eradicating heart attack.

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

Conclusion

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

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