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Screening Asymptomatic Subjects for Subclinical Atherosclerosis

Can We, Does It Matter, and Should We?

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Unheralded vaso-occlusive cardiovascular events (myocardial infarction, sudden death, and stroke) are common manifestations of atherothrombotic vascular disease, and accurate identification of individuals at risk of such events is highly desirable. Risk factor assessment and management have been the cornerstones of preventive strategies but are constrained by less than desirable accuracy and less than optimal compliance, respectively. In selected populations, noninvasive imaging using carotid ultrasound and/or coronary calcium score can incrementally refine risk assessment and may allow for improved adherence and better matching of preventive interventions to the magnitude of risk. Further refinements in the future may also be possible with novel biomarkers and measures of plaque phenotype. (J Am Coll Cardiol 2010;56:98–105) © 2010 by the American College of Cardiology Foundation

Burden of Cardiovascular Disease

Recently, I heard the famous author Dr. Deepak Chopra state on television: "We are all on death row; the only uncertainty is the length of reprieve and the method of execution" (1). As physicians, we strive to prolong life by delaying death and improving quality of life; any references to preventing death are obviously illusory because the only thing certain after birth is death. Atherosclerotic cardiovascular disease leading to coronary heart disease and stroke continue to be the leading causes of morbidity and mortality in much of the world (2). Cardiovascular disease accounts for nearly one-third of all deaths worldwide (17 million in 1999 and projected to be 25 million in 2020). In the U.S., cardiovascular disease and stroke cause 1 death every 33 to 37 s and cumulatively cause more annual deaths than cancer, respiratory disease, accidents, and diabetes combined (2). About 16 million Americans have coronary heart disease, and each year nearly 800,000 have a first acute myocardial infarction, 430,000 have a recurrent myocardial infarction, and nearly 800,000 have a first or recurrent stroke (2). Cardiovascular disease was estimated to have cost the U.S. health care system more than $400 billion in 2008. During the past several decades, we have witnessed significant gains against cardiovascular disease, with a significant decline in age-adjusted mortality; however, with the aging baby boomers and continually rising trends in obesity and metabolic syndrome/diabetes, we are likely to see a reversal of these gains within the coming decades with disastrous human and fiscal implications. Therefore, prevention of atherosclerotic cardiovascular events (myocardial infarction, sudden death, and stroke) remains a major imperative for health care professionals.

The process of atherosclerosis, now considered to be a chronic immunoinflammatory disease of medium- and large-sized arteries, often begins in childhood and adolescence and frequently remains clinically dormant until plaque rupture or plaque erosion leads to abrupt thrombosis triggering acute clinical events (3). In 2008, the sudden cardiac death of Tim Russert, a journalistic icon, brought focus on the value and limitations of current strategies for preventing unheralded cardiovascular events in asymptomatic subjects. Approximately 40% to 60% of major occlusive atherosclerotic cardiovascular events (myocardial infarction, sudden death) occur as the first manifestation (unheralded events), accounting for >700,000 such events annually in the U.S. (2). The identification of subjects at risk of such events is obviously important, if identification leads to implementation of and compliance with effective preventive measures that reduce such risk. Stress testing to detect a flow-limiting coronary stenosis among asymptomatic subjects is unlikely to identify a significant majority of at-risk individuals because nearly 70% of acute coronary events result from coronary lesions that are not hemodynamically significant or flow limiting before the event (4).

Framingham Risk Score (FRS) and Cardiovascular Events: Good but Not Good Enough

The Framingham study provided critical and extremely valuable information regarding risk factors associated with the development of atherosclerotic cardiovascular disease (5–7). The INTERHEART study demonstrated that nearly 90% to 95% of population-attributable risk of myocardial

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infarction is related to 9 potentially modifiable risk factors (smoking, apoprotein B/apoprotein A1 ratio, hypertension, diabetes, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol intake, and regular physical activity) that apply to men and women, old and young, and in all regions of the world (8). Thus, risk factor inventory–based prediction models> using the FRS have been recommended as the cornerstone for risk stratification of asymptomatic subjects and matching intensity of preventive interventions (specifically, lipid-lowering drug therapy and cholesterol targets) to the magnitude of the predicted risk, as suggested by the National Cholesterol Education Program (NCEP) and the Adult Treatment Panel III (ATP III) (9,10). Assessment of a few readily available clinical and laboratory variables such as age, sex, total cholesterol level, high-density lipoprotein cholesterol level, smoking status, and systolic blood pressure are used to calculate a 10-year risk of cardiovascular events. According to the NCEP/ATP III guidelines, subjects are considered to be at low risk if the estimated 10-year event rate is <10%, at high risk if the 10-year event rate is >20%, and at intermediate risk if the 10-year event rate is between 10% and 20%. Based on this scheme of risk stratification, NCEP guidelines suggest cholesterol goals for each of the subsets (9,10). In 2003, the American College of Cardiology Bethesda Conference on Atherosclerosis Imaging suggested that low risk should be defined as a 10-year risk of ≤5% and intermediate risk defined as a 10-year risk of 6% to 20%. Although FRS and NCEP/ATP III guidelines are relatively simple, inexpensive, and useful, they are not good enough by themselves (11). Limitations of the FRS and NCEP/ATP III guidelines include a substantial underestimation of lifetime risk, especially in women when only a 10-year risk model is used, misclassification of high-risk subjects as low or intermediate risk, and misclassification of very low-risk subjects into higher strata of risk (11). Karim et al. (12) showed that in an ethnically diverse group of 498 asymptomatic men and women, 312 (63%) had a low FRS, and of these, 214 (69%) had noninvasive imaging evidence of subclinical atherosclerosis in ≥1 of the 3 vascular beds (coronary, aortic, and carotid). In the same study, of the 68 subjects with subclinical atherosclerosis in all 3 vascular beds, 35% had a low-risk FRS, 41% had an intermediate-risk FRS, and only 23% had a high-risk FRS (12). Furthermore, Akosah et al. (13) pointed out the shortcomings of the FRS in a study of 222 patients (men younger than 55 and women younger than 65 years of age) presenting with their first acute myocardial infarction over a 3-year period who were asymptomatic before the acute event. Based on their FRS, 75% of these patients would have been considered ineligible for statin use under the current NCEP guidelines that match intensity of treatment to the baseline FRS (13). A minority of patients with coronary heart disease have none of the traditional risk factors, but, more importantly, in a large proportion of patients with ≥1 risk factors, coronary heart disease does not develop (14). Furthermore, there is considerable variation in the severity of atherosclerotic burden at any given level of risk factor exposure, presumably attributable to additional known or unknown genetic and environmental risk factors and risk modifiers. The FRS also places a substantial number of women in the low-risk category using 10-year risk estimates even though they have a high lifetime risk; thus, very few women will reach the threshold for initiation of lipid-lowering or aspirin therapy (11,15). The FRS does not incorporate family history and many of the components of metabolic syndrome, both of which are important risk factors for coronary heart disease. A substantial number (>60% to 70%) of unheralded cardiovascular events occur in "low" and "intermediate" risk categories (16). Nasir et al. (17) showed that 79% of young men and women with significant coronary atherosclerotic burden displayed by coronary calcification were not eligible for pharmacotherapy based on current NCEP-ATP III guidelines. Although groups of patients can be placed in risk categories, many patients at risk would not be recommended for lipid-modifying therapy, and many patients in whom an event will not develop would be needlessly targeted for aggressive medical management (11). Thus, FRS and NCEP/ATP III guidelines, although reasonable for populations, remain suboptimal for individual subjects. In 2007, Ridker et al. (18) introduced the Reynolds Risk Score (RRS) for risk assessment in women, which, in addition to traditional risk factors, also incorporated high-sensitivity C-reactive protein (hsCRP) and family history of premature coronary artery disease. The RRS reclassified 30% of women estimated to be in the intermediate-risk group by the traditional FRS into a higher or lower risk category with improved accuracy. Subsequently, the RRS was tested in 10,724 initially healthy nondiabetic men age 50 years or older from the Physicians Heath Study who were followed for 10.8 years (19). The RRS was shown to be superior to the traditional FRS in predicting risk. Despite improved risk assessment with RRS compared with the traditional FRS, neither scheme is sufficiently accurate for individual risk assessment and, unlike the FRS, the RRS has not yet been fully validated outside the Women's Health Study and Physicians Health Study participants.

Abbreviations and Acronyms

CCS = coronary calcium score

CIMT = carotid artery intima-media thickness

CT = computed tomography

FRS = Framingham risk score

hsCRP = high-sensitivity C-reactive protein

NCEP = National Cholesterol Education Program

RRS = Reynolds Risk Score

Unconditional Treatment of All: Why Bother Screening for Risk? Why Not Treat Everyone?

Widespread application of preventive interventions (lifestyle, medications) without previous risk stratification (i.e., unconditional interventions for all) would be most appropriate if

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Table 1 Standard Risk Factor-Adjusted Coronary Event Rates in 4 Racial/Ethnic Groups of Asymptomatic Subjects Based on Coronary Calcium Score (Multi-Ethnic Study of Atherosclerosis)

Calcium Score	Hazard Ratio	Annual Number and Rate of Coronary Events
0 (n = 3,409)	1	15 (0.10%)
1–100 (n = 1,728)	3.6	39 (0.59%)
101–300 (n = 752)	7.73	41 (1.43%)
>300 (n = 833)	9.67	67 (2.87%)

Note that 90% of all events occurred in subjects with coronary calcification, and nearly 50% of the subjects had no coronary calcification. Adapted from Detrano et al. (24).

interventions were safe, inexpensive, easily implemented, highly effective, and associated with high compliance and low discontinuation rate. Unfortunately, in the real world, there is no such thing as universally effective, safe, and inexpensive prevention that carries a high degree of compliance. Lifestyle modification, although clearly important and effective, is difficult to implement on a wide scale because of social, cultural, and economic factors; drug therapy, specifically lipid-modifying therapy, although effective is limited by cost, need for lifelong use, intolerance because of nuisance type, and less commonly, more serious side effects, and overall resistance of many subjects to lifelong use, thereby limiting long-term compliance. Furthermore, drug therapy, specifically statin therapy, only addresses about 30% to 50% of the risk, leaving a considerable amount of residual risk.

Therefore, we must continue to search for better ways of identifying at-risk individuals so that aggressive preventive measures can be targeted to this population while sparing those who are at no or extremely low risk the cost and side effects of protracted and potentially lifelong drug therapy. Unfortunately, FRS only partially fulfills the need, and the currently available biomarkers, specifically hsCRP and lipoprotein-associated phospholipase A2, provide statistically significant but clinically modest incremental prognostic value and thus are not sufficiently precise to markedly improve the discriminant value of FRS. Because we are primarily talking about atherothrombotic cardiovascular disease, it is logical to ask the question: instead of simply measuring risk factors that at best have only a modest relationship to the presence and extent of atherosclerosis and cardiovascular events (high sensitivity but low specificity), can we actually detect the disease itself (i.e., atherosclerosis) before it causes catastrophic events? After all, detection of subclinical atherosclerosis identifies the biological substrate for all but the rarest forms of ischemic cardiovascular disease, and detecting subclinical atherosclerosis provides an integrated view of cumulative exposure to known and unknown risk factors and risk modifiers.

Can We Detect Subclinical Atherosclerosis Noninvasively, and Does It Matter?

There are multiple noninvasive imaging techniques that can identify subclinical atherosclerosis in various vascular beds, including ultrasonography, coronary Ca^{2+} assessment by computed tomography (CT), noninvasive CT angiography, and magnetic resonance imaging. Although all of these methods have their relative advantages and drawbacks, imaging of coronary arteries to identify coronary calcium, a validated measure of atherosclerotic plaque, by computed tomography without contrast and use of B-mode ultrasonography to detect carotid intima-media thickness and carotid plaque have been most extensively studied and have the potential to be suitable screening tools for the detection of subclinical atherosclerosis.

Coronary calcium score (CCS). Coronary calcium detection by CT has been shown to identify atherosclerotic plaque and to quantitatively assess coronary calcium; using the Agatston CCS, a surrogate for plaque burden, has been shown to provide powerful prognostic information in multiple studies involving both sexes and multiple ethnic groups (20–35). Furthermore, CCS has been shown to provide prognostic information that is independent of and substantially incremental to that provided by the FRS and hsCRP (20–35) (Table 1). The CCS can provide individual risk assessment and can reclassify the low and particularly intermediate Framingham risk cohort into lower- and higher-risk strata, as shown by Preis et al. (36) in a study involving 3,529 asymptomatic subjects from the Framingham Offspring Cohort (Table 2). Absence of coronary calcium (CCS = 0), while not excluding the presence of noncalcified plaque, virtually excludes significant coronary atherosclerosis, but more importantly is associated, in an asymptomatic population, with an extremely low risk of cardiovascular events in the ensuing 5 to 10 years ranging from annual event rates of 0% to 0.6% (32). The higher event rates reported in subjects with a 0 coronary calcium score by Greenland et al. (25) came from a study that used 6-mm thick slices, which is known to result in data loss compared with 3-mm slices. In an observational cohort of 35,765 asymptomatic subjects from published studies, 16,106 (45%) had zero coronary calcium; their annual event rate was only 0.027% (32). Blaha et al. (37) reported from an asymptomatic cohort of 44,052 subjects referred for coronary calcium scanning that 19,898 of these subjects (45% of the total cohort) had a CCS of 0 and a 10-year all-cause

Table 2 Reclassification of Framingham Risk by Coronary Calcium Score in the Framingham Offspring and Third-Generation Cohort

	FRS + Coronary Calcium Score		
FRS	Low	Intermediate	High
Low (n = 2,410)	89% (92%)	11% (8%)	22% (39%)
Intermediate (n = 595)	25% (25%)	53% (35%)	
High (n = 245)			100% (100%)

Coronary calcium score criterion was either the ≥90th percentile value or absolute score ≥100; data using the absolute coronary calcium score is shown in parentheses. Note that in the FRS intermediate group, coronary calcium score reclassified 25% of subjects into a lower risk stratum and 22% to 39% into a higher risk stratum. Eight percent to 11% of those at low risk FRS level were upgraded to intermediate risk level with the addition of coronary calcium score. Data adapted from Preis et al. (36).

FRS = Framingham risk score.

mortality rate of 1%; the mortality rate was 2-fold higher in subjects with minimal coronary calcification with a CCS of 1 to 10 and nearly 9-fold higher with a CCS >10 (37). In a systematic review of 13 published studies involving 64,873 asymptomatic subjects undergoing coronary calcium assessment and prognostic evaluation, 25,903 subjects (45% of cohort) with zero coronary calcium were identified whose cardiovascular event rate was 0.56% during a 4.25-year follow-up (38). In another registry study involving >25,000 subjects, Budoff et al. (23), in a follow-up extending up to 12 years, demonstrated a mortality rate of 0.4%. These observations highlight the fact that asymptomatic subjects with a CCS of 0 have an extremely low 5- to 10-year risk of cardiovascular and all-cause mortality and that such patients are unlikely to benefit from lipid-lowering therapy and any additional downstream tests for vaso-occlusive disease. Interestingly, in a cohort of 900 subjects with diabetes, a CCS of 0 was associated with a 5-year survival rate of 98.8%, and the survival of diabetic and nondiabetic patients with a CCS of 0 was remarkably similar (98.8% vs. 99.4%) (30). In another prospective study of patients with type 2 diabetes, a CCS <10 was associated with a zero event rate at 2 years of follow-up (39). Such very low-risk individuals constitute 40% to 50% of asymptomatic cohorts (23), are unlikely to benefit from aggressive preventive interventions, and may be recommended only to follow a healthy lifestyle and could well be spared the cost and side effects of aggressive lipid-lowering therapy. It is, however, important to point out that in a symptomatic population with clinical evidence of myocardial ischemia, absence of coronary calcium is not totally reassuring and may be associated with a higher event rate (annual event rate of 3.6%) (40–42). This is consistent with recent observations from noninvasive contrast CT coronary angiography revealing that 6% to 11.6% of subjects may have only noncalcified plaque, which would be missed on coronary calcium scoring (43,44). The major drawbacks of this CT-based technique include exposure to a small amount of radiation, which may be particularly undesirable in young subjects, especially women, and the very rare but definite instance in which a subject with only a noncalcified plaque is labeled as normal (43,44); such an eventuality is quite rare in asymptomatic subjects. When a coronary event occurs in a subject with a CCS of 0, besides a noncalcified culprit plaque, one must also consider other unpredictable reasons for cardiovascular events that have nothing to do with atherosclerosis such as acute myocarditis simulating myocardial infarction, coronary embolism, coronary dissection presenting as an acute coronary syndrome, and stress-induced acute myocardial syndrome in women. None of these relatively uncommon nonatherosclerotic events could be predicted by any known tests.

B-mode ultrasonography. B-mode ultrasound imaging of carotid arteries provides yet another noninvasive, simple, and relatively inexpensive modality for the detection of subclinical atherosclerosis or pre-atherosclerosis as measured by a thickened intima-media (carotid artery intima-media thickness [CIMT]); this technique is safe and, unlike coronary calcium scanning, carries no risk of radiation exposure (45,46). Several prospective studies, including the MESA (Multi-Ethnic Study of Atherosclerosis), of asymptomatic subjects demonstrated that increased CIMT over 75th percentile for a person's age, sex, and race (using nomograms from large population-based studies) is associated with future risk of myocardial infarction, stroke, and death from coronary heart disease that in most studies was independent of traditional risk factors (45,46). Furthermore, several large studies have shown that the presence of carotid plaque on ultrasonography (defined as focal thickening of the carotid wall that is at least 50% greater than that of surrounding wall or as a focal region with CIMT >1.5 mm that is distinct from adjacent boundary and protrudes into the lumen) in asymptomatic subjects is associated with increased risk of cardiovascular events that is comparable to or better than that of increased CIMT (46). A recent meta-analysis by Lorenz et al. (47) reported significant relative risks of coronary heart disease of 1.26 for myocardial infarction and 1.32 for stroke for each 1-SD increment of CIMT.

Comparative prognostic value of coronary calcium scanning versus carotid ultrasonography. Although atherosclerosis is generally considered to be a diffuse or at least multifocal process and both carotid ultrasonography as well as coronary calcium scanning can detect subclinical atherosclerosis, CIMT and CCS are only modestly correlated in individual subjects, with some patients exhibiting a CCS of 0 in the context of abnormal CIMT or carotid plaque and some patients with an abnormal CCS exhibiting normal CIMT and no carotid plaque. Two recent prospective studies compared the incremental prognostic value of CIMT and coronary calcium scanning in initially asymptomatic subjects (48,49). Newman et al. (48) found that in adults older than 70 years, CIMT and CCS similarly predicted cardiovascular disease and coronary heart disease, but CIMT was a better predictor of stroke. However, Folsom et al. (49) reported the results of MESA and showed that the CCS was a stronger predictor of cardiovascular events than CIMT. For cardiovascular events, the traditional risk factor-adjusted hazard increased 2.1-fold for each SD greater level of log-transformed CCS versus 1.3-fold for each SD greater maximum CIMT; comparable differences in relative risk were noted for coronary heart disease (49). That CIMT was modestly better than CCS in predicting stroke reflects a closer correlation between stroke and the relevant vascular territory. These results were further supported by receiver-operator characteristic analysis in which adding CCS to risk factor analysis significantly improved the area under the curve, whereas CIMT provided little additional value (49).

Imaging of Subclinical Atherosclerosis: We Can and It Matters, but Should We?

It is abundantly clear that subclinical atherosclerosis in 2 major consequential vascular beds (coronary and carotid) can be detected by noninvasive imaging and such assessment can clearly refine Framingham risk assessment in individual patients and do it better than biomarkers such as hsCRP and lipoprotein-associated phospholipase A2. Large-scale screening for subclinical atherosclerosis would be useful if it is simple, easily available, relatively safe and effective, adds value to prediction leading to better selection of subjects for aggressive treatment and sparing very low-risk subjects unlikely to benefit, and improves compliance and adherence to risk-modifying interventions. The CCS and CIMT fulfill many but not all of these requirements; in particular, the added value of imaging-guided management in improving patient outcomes has not yet been proven using randomized, controlled clinical trials, and therefore, in that sense, to a purist the "jury" is still out. However, we must acknowledge that FRS-based management using NCEP guidelines has also not been subjected to similar rigorous clinical trials and yet is accepted as a reasonable strategy for risk detection and modification based on purely observational data. Holding noninvasive imaging to a different standard even when its prognostic value has been unequivocally demonstrated to be significantly incremental to FRS, especially among low- and intermediate-risk categories, is indicative of a double standard (50). Despite the lack of randomized clinical trial evidence, the totality of observational evidence supports imaging-guided management because: 1) detecting disease the consequences of which we are trying to prevent is likely better than simply identifying risk factors that have only a modest specificity and a highly variable relationship to the development of disease; 2) imaging can reclassify intermediate- and low-risk FRS subjects into higher-risk strata for which more aggressive medical therapy and lower cholesterol targets would be recommended, thereby tangibly altering therapy while at the same time identifying a very low-risk cohort that could avoid aggressive drug therapy because of a lack of likely near-term benefit; and 3) imaging-based identification of at-risk subjects may improve compliance and adherence to risk-modifying interventions; this is particularly germane because long-term compliance with effective preventive therapy results in better outcomes, making adherence a surrogate for outcomes. A random-effects meta-analysis of 5 recent trials involving 52,319 patients showed that adherence to statin therapy averaged only 65% (51). In a study involving 505 subjects on statin therapy followed for 3 years, Kalia et al. (51) showed that the overall statin compliance was lowest (44%) among those with a CCS in the first quartile (0 to 30), whereas 91% of individuals with a baseline CCS in the fourth quartile adhered to statin therapy. Multivariable analysis, after adjusting for cardiovascular risk factors, age, and sex, showed that a higher baseline CCS score was strongly associated with adherence to statin therapy (51). Taylor et al. (52) recently reported on the association of the CCS detected on a screening examination with subsequent use of statins and aspirin in 1,640 asymptomatic men 40 to 50 years of age. In this prospective cohort followed for up to 6 years, the presence of coronary calcification was associated with a 3-fold greater likelihood of statin and aspirin use that was independent of NCEP risk variables and baseline medication use. These findings from a community-based nonreferred study population provide strong evidence of a significant and incremental impact of subclinical atherosclerosis detection, over and above FRS-NCEP risk assessment, on patient management, thus supporting the use of such an approach to refine cardiovascular risk assessment (52). It should be noted that an earlier small randomized trial from the same group reported no effect of coronary calcium detection on improvement in FRS; however, this study was limited by the small number of subjects with coronary calcification (only 66 of 450 subjects) and the overall very low-risk nature of the cohort that had a predicted a mean 10-year Framingham risk of only 5.8% (53). Favorable results were also reported by Orakzai et al. (54) from a study of 980 individuals who were followed for a mean of 3 ± 2 years after an initial coronary calcium scan in which multivariate analysis showed that a greater baseline CCS was strongly associated with initiation of aspirin therapy, dietary changes, and increased exercise. Wong et al. (55) showed that potentially important risk-reducing behaviors are reinforced by the knowledge of a positive coronary calcium scan independent of pre-existing coronary risk factors. In another small study, motivation for smoking cessation and cessation rates were higher in cigarette smokers shown to have carotid plaque compared with those without plaque (56).

Therefore, the recommendations of the SHAPE (Screening for Heart Attack Prevention and Education) Task Force, although based on a wealth of published observational data but not randomized, controlled trials, represent a reasonable blueprint for an imaging-augmented strategy for risk assessment and management (57). The SHAPE Task Force recommended noninvasive atherosclerosis imaging of all asymptomatic men (age 45 to 75 years) and women (age 55 to 75 years), except those at very low risk, to augment conventional cardiovascular risk assessment algorithms (57). Recent observations from 2,611 participants 30 to 65 years of age from the Dallas Heart Study provided evidence in favor of the SHAPE algorithm because SHAPE recommendations resulted in bidirectional reclassification of eligibility for lipid-lowering therapy in the participants (58). Application of imaging according to the SHAPE guidelines to the Dallas Heart Study Cohort reclassified 35% to 48% of the cohort into a higher-risk stratum, making them eligible for lipid-lowering therapy, and the number needed to reclassify 1 individual as newly eligible (or no longer eligible) for lipid-lowering therapy ranged from 4.1 to 7.8, depending on the coronary calcium score threshold used (58).

An important consideration in any recommendation for large-scale screening is the cost-effectiveness of such an approach. Diamond and Kaul (59) recently compared the costs and effectiveness of unconditional treatment of all risk factor–based treatment recommended by the NCEP and imaging-based treatment recommended by the SHAPE Task Force while making certain assumptions regarding costs of imaging and treatment with statins. The Diamond and Kaul (59) analysis supported cost-effectiveness of the SHAPE algorithm over the NCEP strategy, as also found by the SHAPE Task Force analysis (57), but suggested that unconditional treatment was most cost-effective. However, Diamond and Kaul (59) were quick to point out that if the SHAPE algorithm improves adherence to preventive therapy, its cost-effectiveness could surpass unconditional treatment. Similarly, Hecht (50) pointed out that reducing imaging costs to $100, instead of the $400 assumed by Diamond and Kaul (59), would make imaging-based treatment the most cost-effective option. Although potential risks associated with radiation exposure are of concern, the actual radiation exposure with coronary calcium scanning is small (0.6 to 1.0 mSv for electron-beam CT and 0.9 to 2.0 mSv for multidetector CT), although it can vary by 10-fold depending on many technical factors; these can be optimized and standardized to reduce the actual amount of radiation exposure. A recent analysis suggested that there could be a small increase in lifetime risk of cancer with the radiation exposure entailed in a coronary CT examination delivering a median radiation exposure of 2.3 mSv; however, the authors acknowledge that depending on the methodology used to predict risk, the estimated cancer risk could be higher or lower by a factor of 2 (60). Thus, there is considerable uncertainty about the true magnitude of cancer risk posed by coronary calcium scanning, especially when the very young are excluded.

We must also be clear that although detecting subclinical atherosclerosis is a logical first step after Framingham risk assessment to improve prognostic value, the answer to the question "plaque present or absent?" cannot be the final solution because the amount/extent of plaque (plaque burden) and the composition of plaque are likely to contribute additional important prognostic information and can further improve the sensitivity and specificity of noninvasive imaging for risk prediction. Adding some measures beyond arterial structure, specifically addressing arterial function (arterial compliance and vasodilator function) (61), plaque phenotype as an index of vulnerability to acute thrombotic events will likely further improve imaging-based risk prediction. Such approaches might include assessing plaque composition/configuration (inflammation, lipid core, thin cap, increased plaque neovascularity, outward remodeling, intraplaque hemorrhage), circulating biomarker reflective of biological processes relevant to plaque rupture (proteomics/metabolomics/circulating biomarkers), and genotypes that are predictive of risk. Such a comprehensive multimodality approach is currently under way in the High Risk Plaque Initiative, which is likely to provide valuable new information in the near future (62).

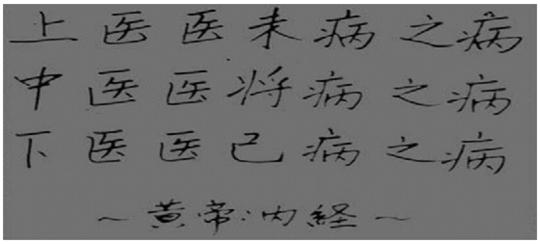

Figure 1 **Huang Dee: Nai-Ching (2600 BC, First Medical Text)**

Translation: superior doctors prevent the disease; mediocre doctors treat the disease before evident; inferior doctors treat the full-blown disease.

Conclusions

Although randomized, controlled prospective data to prove the efficacy of imaging-guided risk assessment in improving clinical outcomes are not available and such studies should be encouraged, the large amount of observational cohort and prospective longitudinal data support selective use of imaging-based risk assessment, especially in intermediate-risk groups identified by the FRS (Fig. 1) (63). Therefore, the answer to the question (screening asymptomatic subjects for subclinical atherosclerosis: can we, does it matter, and should we?) is yes, we can, it matters, and we should in selected subjects because: 1) a large body of published evidence supports incremental value of noninvasive imaging-guided risk assessment over and above that of FRS, especially among intermediate- and possibly low-risk cohorts; 2) imaging-based bidirectional reclassification of patients into different strata of risk has tangible clinical value and implications for better matching of intensity of prevention to expected risk; and 3) despite earlier reports, new evidence is accumulating that imaging may improve adherence to and compliance with risk-modifying interventions. Although data support the superior relative prognostic value of coronary calcium scanning relative to carotid ultrasonography as a preferred screening strategy, a reasonable alternative strategy for imaging might involve first using carotid ultrasonography (since it is safe and radiation free), and if carotid plaque or markedly thickened CIMT is discovered, no further screening is needed; however, if carotid ultrasonography is normal, a coronary calcium scan might be reasonable because some patients with normal findings on carotid ultrasonography may actually have coronary atherosclerosis.

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