

# Noninvasive Assessment of Cardiovascular Risk: From Framingham to the Future

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*Risk assessment and risk factor modification have become essential tools in the management of cardiovascular disease. While the risk assessment defined by the Framingham Study researchers was a great leap forward, the search for additional and more precise markers of cardiovascular risk continues. Markers of thrombosis, abnormal endothelial function, plaque formation, and other events in atherosclerosis development are being evaluated. Some of the most promising for population screening are high-sensitivity C-reactive protein tests, degree of arterial stiffness (measured directly or as pulse pressure), and ankle-brachial index. [Rev Cardiovasc Med. 2000;1(1):34-42, 54]*

**Key words:** Cardiovascular disease • Risk factors

The assessment of cardiovascular risk is one of the most important tasks in medicine, for 3 reasons.<sup>1-5</sup> First, cardiovascular disease (CVD) is the leading cause of death in the United States, accounting for 42% of all deaths. The World Health Organization has projected that CVD will become the greatest cause of morbidity and mortality in the world by the year 2025. Second, stable angina is the presenting symptom for coronary heart disease (CHD) in only 25% of men and 47% of women.<sup>6</sup> Unstable angina, myocardial infarction (MI), urgent need for revascularization, and sudden death make up the majority of initial presentations, leaving little opportunity to initiate preventive measures. Third, recent advances in the management of risk factors, such as hypercholesterolemia, hypertension, and diabetes, have proved especially successful in reducing subsequent cardiovascular events in both primary and secondary prevention populations.

Early attempts at the noninvasive assessment of CVD were focused on the diagnosis of coronary artery disease (CAD). In recent years, the focus has shifted to the assessment of cardiovascular risk—that is, predicting the yearly incidence of cardiovascular events. This shift occurred because we have learned that coronary events are predominantly caused by plaque rupture or erosion, which is most common in intermediate, rather than high-grade, stenoses.<sup>7</sup> These vulnerable plaques are characterized by large, confluent lipid pools covered by thin, fibrous caps; re-

duced plaque collagen; increased numbers of foam cells and T lymphocytes; and active inflammation. While noninvasive tests for myocardial ischemia have proved useful for pinpointing patients who might benefit from coronary revascularization, these approaches are neither reliable nor cost-effective for screening asymptomatic populations.

### Traditional Risk Factors

The Framingham Heart Study, ongoing since 1948, has contributed substantially to our understanding of cardiovascular risk. More than 1000 papers have been published on this longitudinal study of 5209 initially asymptomatic men and women.<sup>8</sup> The Framingham Heart Study has established that 9 risk factors account for about 50% of cardiovascular event risk: age, gender, family history of premature coronary disease, cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, cigarette smoking, diabetes mellitus, and left ventricular hypertrophy.

Table 1 summarizes a clinically useful cumulative point-scale estimate of 10-year cardiovascular risk based on the Framingham data.<sup>9</sup> Using the traditional risk factors, this simple model assigns men and women yearly risk ranging from 0.1% to 5%. By comparison, patients with stable angina have a mean yearly mortality of about 2%, and patients following MI have a mean yearly mortality of about 2.5%. The Framingham Heart Study has yielded 2 important lessons:

- The presence of 1 risk factor increases the likelihood of other risk factors. The frequent association of insulin resistance, dyslipidemias, hypertension, and central obesity make up the dysmetabolic syndrome (syndrome X),

**Table 1**  
**Framingham Heart Study:**  
**10-Year Coronary Event Risk for Men (M) and Women (F)**

Variable	M	F	Variable	M	F
<b>Age</b>			<b>BP</b>		
30 - 34	-1	-9	< 120/< 80	0	-3
35 - 39	0	-4	120 - 129/80 - 84	0	0
40 - 44	1	0	130 - 139/85 - 89	1	0
45 - 49	2	3	140 - 159/90 - 99	2	2
50 - 54	3	6	≥ 160/≥ 100	3	3
60 - 64	5	8			
65 - 69	6	8			
70 - 74	7	8			
<b>TC</b>			<b>LDL-C</b>		
< 160	-3	-2	< 100	-3	-2
160 - 199	0	0	100 - 129	0	0
200 - 239	1	1	130 - 159	0	0
240 - 279	2	1	160 - 190	1	2
≥ 280	3	3	> 190	2	2
<b>HDL-C</b>			<b>Smoker</b>		
< 35	2	5		2	2
35 - 44	1	2			
45 - 49	0	1			
50 - 59	0	0			
≥ 60	-1	-3			
<b>DM</b>					
	2	4			

Add points for age, BP, TC or LDL-C, HDL-C, smoking, and DM.

Total points: < -2 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 >17

% Risk (M): 1 2 2 3 4 4 5 7 8 10 13 17 21 26 32 38 46 54 →

% Risk (F): 1 1 2 2 2 3 3 4 5 6 7 8 9 11 12 14 16 20 22 25 30

BP, blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus.

Adapted with permission from Wilson PW et al. *Circulation*. 1998.<sup>9</sup>

which is associated with endothelial dysfunction and frequently leads to cardiovascular disease.<sup>10</sup>

- The presence of any of the traditional risk factors multiplies the risk of any other factor.

Several nontraditional risk factors as well as noninvasive imaging and arterial assessment techniques are

currently being evaluated to determine whether they increase the accuracy of risk assessment. These are listed in Table 2 and are the focus of the remainder of this article.

### LDL Phenotype

Two low-density lipoprotein (LDL) subgroups, LDL phenotype and li-

**Table 2**  
**Traditional and Emerging Risk Factors and**  
**Arterial Assessment Techniques**

Traditional risk factors	Emerging risk factors	Arterial assessment techniques
Age	LDL phenotype	Pulse pressure
Gender	Lipoprotein(a)	Arterial stiffness
Family history	Homocysteine	Ankle-brachial index
Cholesterol	hs-CRP	Endothelial function
HDL cholesterol	<i>Chlamydia</i> titer	Carotid artery IMT
Blood pressure	ACE genotype	EBCT
Cigarette smoking	Fibrinogen	MRA
Diabetes mellitus		
LV hypertrophy		

HDL, high-density lipoprotein; LV, left ventricular; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; ACE, angiotensin-converting enzyme; IMT, intima-media thickness; EBCT, electron beam CT; MRA, magnetic resonance angiography.

poprotein(a) (Lp[a]), offer potentially better risk stratification than that afforded by standard LDL levels. Variation in LDL particle size appears to be an important determinant of both atherogenic potential and response to lipid-lowering therapy. Persons with small-dense LDL (phenotype B), often associated with the dysmetabolic syndrome, have an approximately 3-fold increase in cardiovascular risk, compared with those with large-buoyant LDL (phenotype A).<sup>11</sup> The increased cardiovascular risk associated with small-dense LDL is greatest in the presence of increased LDL levels.

Small-dense LDL, produced in part by hepatic lipase, is more easily oxidized and enters macrophages more rapidly than does large-buoyant LDL. Associations with endothelial dysfunction have been reported. Phenotypes A and B are generally associated with triglyceride levels below 100 mg/dL and above 200 mg/dL, respectively. The phenotype is indeterminate at intermediate triglyceride levels. LDL

phenotyping is performed by either gradient gel electrophoresis or magnetic resonance (MR) spectroscopy.<sup>12</sup> These assays currently cost about \$400 and \$100, respectively.

Several studies have demonstrated greater reductions in coronary atherosclerosis and cardiovascular events in patients with small-dense LDL than in patients with phenotype A undergoing lipid-lowering therapy. A controversy exists regarding the preferred method of lowering levels of small-dense LDL. Whereas niacin and fibrates predominantly reduce the small-dense LDL fraction, statins lower the level of all LDL particles.

HDL particle size may also be a determinant of cardiovascular risk. Large particles containing apolipoprotein A-I (apoA-I) are more protective than are smaller particles containing apoA-I/II. Except for the expense and lack of widespread availability of LDL and HDL phenotype assays, lipoprotein particle size appears to be a useful addition to risk stratification.

### Lipoprotein(a)

Lp(a) is a subtype of LDL containing the variably large apoprotein(a), which has homology to plasminogen.<sup>13</sup> As such, it is believed to be a link between atherosclerosis and thrombosis. Lp(a) levels are genetically determined and range from 0 to 200 mg/dL. Levels above 30 mg/dL are associated with a 3-fold increased cardiovascular risk. The increased risk associated with elevated Lp(a) levels depends on the presence of an LDL cholesterol level greater than 130 mg/dL.

Lp(a) levels are lowered by niacin and estrogen. Alternatively, associated increased risk is lowered by reducing levels of LDL cholesterol. Since the latter should be routinely accomplished as part of general risk modification, the value of measuring Lp(a) in risk stratification remains unclear.

### *Chlamydia pneumoniae*

There has been an explosion of literature published within the past several years on investigations into the possible causal role of infectious pathogens, particularly *Helicobacter pylori*, cytomegalovirus, and *C pneumoniae*, in the development of atherosclerosis.<sup>14,15</sup> Seroepidemiologic studies and various means of identification of organisms within atheroma (polymerase chain reaction, immunocytochemistry, electron microscopy) have provided stronger evidence for a relationship between *Chlamydia* and atherosclerosis than for *H pylori* or cytomegalovirus.

*Chlamydia* has been clearly demonstrated within plaque, can infect endothelial cells and induce smooth muscle proliferation, and can induce expression of adhesion molecules followed by adhesion and migration of monocytes into subintimal layers. In vitro, *Chlamydia* can promote both

oxidation of LDL and foam cell formation; up-regulate the expression of matrix metalloproteinases and inflammatory markers, such as interleukin-6 and tumor necrosis factor  $\alpha$ ; and induce expression of tissue factor and plasminogen activator-inhibitor. All of these processes may be important in the formation of atheroma and in the progression of plaque instability.

Numerous observational studies have shown a higher rate of *Chlamydia* seropositivity in coronary disease patients. Despite this well-established relationship with atherosclerosis, however, it is not clear whether *Chlamydia* plays a causal role. If a causal relationship could be demonstrated, then screening for this infectious agent and subsequent specific treatment might alter cardiovascular risk.

While 1 small secondary prevention trial suggested that such antibiotic therapy substantially reduces risk, other trials<sup>14</sup> have largely failed to show a benefit. A meta-analysis of existing data from 3 small studies showed a nonsignificant 30% decrease in cardiovascular events with antibiotic therapy. Several large-scale antibiotic trials are currently under way (Azithromycin and Coronary Events Study [ACES], Weekly Intervention with Zithromax for Atherosclerosis and Its Related Disorders [WIZARD], Croatian Azithromycin in Atherosclerotic Disease [CROAATS]), but until such studies are completed, generalized screening for infectious pathogens as part of cardiac risk assessment cannot be advocated.

### C-Reactive Protein

Inflammation is an integral part of the atherosclerotic process. It appears to be accelerated in unstable plaques and in regions of plaques likely to rupture.<sup>16</sup>

In light of this inflammatory process, it is interesting to note that epidemiologic studies have consistently linked an elevated white blood cell count with increased risk of MI.

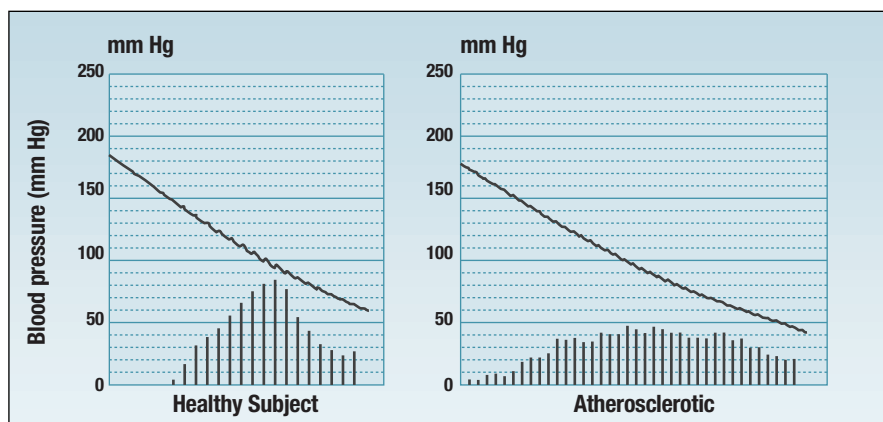
Ridker and associates<sup>17</sup> reported that a nonspecific circulating marker of inflammation, C-reactive protein (CRP), correlated with cardiovascular risk in a group of low-risk men with no history of CVD (Physician's Health Study). The risk of a first MI was 3-fold higher in men with baseline levels in the highest quartile than in men in the lowest quartile. This risk was not modified by smoking and was independent of other conventional cardiac risk factors, including lipid levels. Furthermore, the risk associated with an elevated CRP level appeared to be additive to the risk associated with hyperlipidemia. Similar associations between CRP and cardiovascular risk have been reported from the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg trial and the Women's Health Initiative. An elevated CRP level appears to predict benefit from aspirin and hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy, both of

which lower CRP levels.<sup>18</sup>

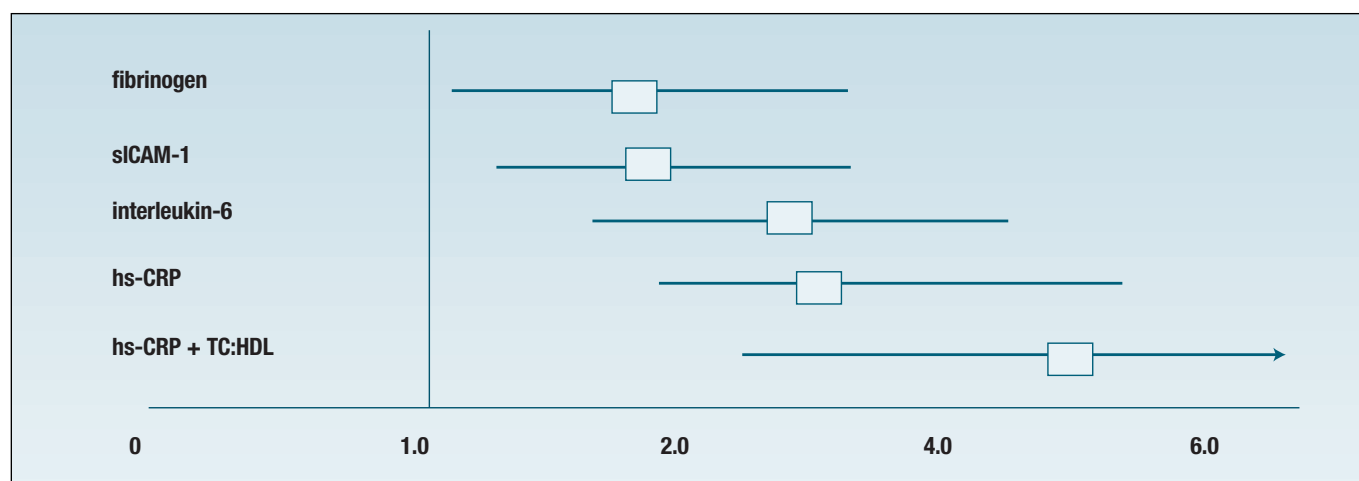
The assay for CRP is difficult to perform accurately, and the currently preferred test is high-sensitivity CRP (hs-CRP). Since elevated CRP levels have been repeatedly linked to an increased risk of a first cardiovascular event, and since their detection can lead to a change in treatment that may modify that risk, it seems prudent to include this test in our standard preventive cardiac evaluation. Figure 1 compares the risk ratio discrimination of traditional and inflammatory markers, including hs-CRP.

### Homocysteine

It has long been recognized that children and adults with congenital homocystinuria from cystathionine  $\beta$ -synthase deficiency experience frequent atherosclerotic (especially peripheral artery disease [PAD]) and thrombotic events. Recently, a clear correlation has been recognized between less markedly elevated serum homocysteine levels and the prognosis of CHD patients.<sup>19</sup> Most, but not all, studies have found homocysteine to be a risk factor in primary prevention populations. *continued*



**Figure 1.** Examples of computerized oscillometric assessment of brachial artery stiffness using an automated blood pressure cuff (CardioVision®, International Medical Device Partners, Inc, Las Vegas). The steep-sided curve (left) was obtained from a healthy subject and the rounded curve (right), from a person with multidistribution atherosclerosis.



**Figure 2.** Relative risks of future myocardial infarction for healthy middle-aged men (Physicians' Health Study) according to baseline markers of inflammation, coagulation, and lipids. (sICAM-1, soluble intercellular adhesion molecule-1; hs-CRP, high-sensitivity C-reactive protein; TC, total cholesterol; HDL, high-density lipoprotein cholesterol.) (Adapted with permission from Libby P, Ridker PM. *Circulation*. 1999.<sup>16</sup>)

Abnormal endothelial function is associated with elevated homocysteine levels (greater than 13  $\mu\text{mol/L}$ ), and a reduction in flow-mediated brachial artery vasoreactivity can be demonstrated in young, healthy people following oral methionine loading. The clinical value of methionine load testing is currently unclear.

Homocysteine levels can be lowered with folic acid, 0.4 to 1 mg/d, in most patients, but some patients require higher folic acid dosages and/or pyridoxine and vitamin B<sub>12</sub>, depending on specific enzyme deficiencies. In the United States, the supplementation of grains and breads with folic acid is lowering the homocysteine level in the general population. Reducing homocysteine levels is known to improve endothelial function, but the effect on cardiovascular risk is unknown. Trials are currently under way in both the United States and Europe to evaluate the effects on cardiovascular outcome of lowering serum homocysteine levels. Although B vitamin supplementation is inexpensive and probably harmless, the

American Heart Association has emphasized that decisions regarding screening and treatment of patients for elevated serum homocysteine levels should await the results of these trials.

### Angiotensin-Converting Enzyme Genotype

Angiotensin II promotes vasoconstrictor and oxygen free radical production as well as smooth muscle cell growth, all of which are important factors in atherosclerosis. On average, the angiotensin-converting enzyme (ACE) deletion/deletion (D/D) genotype is associated with a 1.3-fold increase in cardiovascular risk, compared with either the ACE insertion/insertion (I/I) genotype or the D/I genotype.<sup>20</sup> The ACE D/D genotype is associated with increased carotid intima-media thickness (IMT) and probably with increased restenosis after angioplasty. Risk ratios above 2 have been variably reported in both low-risk men and men with elevated cholesterol levels. At present, ACE genotype does not appear to be of significant value in risk stratification.

### Fibrinogen

An elevated fibrinogen level is associated with increased cardiovascular risk in population studies.<sup>21</sup> In addition, specific polymorphisms of fibrinogen, platelet glycoproteins, and factor VII may predict higher cardiac risks. Other hemostatic factors, such as von Willebrand factor, plasminogen activator-inhibitor levels, plasma viscosity, and soluble thrombomodulin, have also been implicated as potential markers for cardiovascular risk. While these studies contribute greatly to our understanding of the atherosclerotic process, markers of thrombosis cannot be easily integrated into risk stratification at this time.

### Arterial Stiffness, Pulse Pressure, Ankle-Brachial Index, and Endothelial Function

Several arterial assessments improve risk stratification. Three of the most cost-effective parameters are pulse pressure, arterial stiffness, and the ankle-brachial index.

Pulse pressure (systolic minus diastolic blood pressure) is an index of

generalized arterial stiffness, reflecting arterial thickening, fibrosis, and calcification. Pulse pressure was found to be a better predictor of cardiovascular events in the Framingham Heart Study than was either systolic or diastolic blood pressure and remained predictive at every blood pressure level.<sup>22</sup> Pulse pressure greater than 60 mm Hg is suggestive of generalized atherosclerosis, which is rarely limited to a single vascular bed.

Arterial stiffness can be directly measured by 3 noninvasive techniques: computerized oscillometry, tonometry, and ultrasonography. Computerized oscillometry uses an automated blood pressure cuff, which senses brachial artery volumetric changes under varying loading conditions (cuff pressure above, equal to, and below mean blood pressure). Nonatherosclerotic arteries have very nonlinear elastic properties, with high elasticity under unloaded conditions. Oscillometric curves for elastic and stiff arteries are shown in Figure 2.

We have compared the parameters of pulse pressure, arterial stiffness measured by computerized oscillometry, and brachial artery flow-mediated vasodilation (an index of endothelial function; see following discussion) in 30 patients with and without CVD. In this preliminary study, the diagnostic accuracies of the 3 techniques were as follows: arterial stiffness, 85%; pulse pressure, 71%; and endothelial function, 58%. Other approaches to measurement of arterial stiffness employ tonometric wave form analysis.

Using an approach based on ultrasonography, researchers found that carotid artery stiffness predicts coronary risk, although not as accurately as IMT (see following discussion).<sup>23</sup> The ankle-brachial index has also been

found to be an effective predictor of cardiovascular risk. Indexes of less than 0.9 suggest PAD, which is usually associated with coronary and cerebrovascular disease. Since arterial stiffness, pulse pressure, and ankle-brachial index are cost-effective measures of established atherosclerotic burden, it appears prudent to add 1 or more of them to the traditional risk assessment.

Endothelial dysfunction is an early process in the development of atherosclerosis and is associated with all traditional and evolving risk factors.<sup>24</sup> Endothelial dysfunction is associated with platelet aggregation, vasoconstriction, smooth muscle cell proliferation, monocyte adherence, thrombogenicity, inflammation, and

oxidative stress, which are all components of atherosclerosis.

Endothelial function can be determined noninvasively by high-frequency ultrasonographic assessment of brachial artery diameter changes in response to a blood pressure cuff-induced hyperemic stimulus (flow-mediated vasodilation). This index of nitric oxide availability has provided considerable insight into the interactions between risk factors and endothelial function. It has been variably shown to correlate with the presence of CVD.<sup>25</sup>

Measurement of brachial artery flow-mediated vasodilation, however, requires great technical skill. Endothelial function varies rapidly with changes in smoking, exercise, and di-

**Table 3**  
**Calcium Score Nomogram for 9728 Consecutive Subjects**

Patient age (y)	Calcium score (percentile)			
	25th	50th	75th	90th
<b>Men</b>				
35 - 39	0	0	2	21
40 - 44	0	0	11	64
45 - 49	0	3	44	176
50 - 54	0	16	101	320
55 - 59	3	41	187	502
60 - 64	14	118	434	804
65 - 70	28	151	569	1178
<b>Women</b>				
35 - 39	0	0	0	4
40 - 44	0	0	0	9
45 - 49	0	0	0	23
50 - 54	0	0	10	66
55 - 59	0	0	33	140
60 - 64	0	4	87	310
65 - 70	0	24	123	362

Adapted with permission from Grundy SM. *Am J Cardiol.* 2000.<sup>4</sup>

**Table 4**  
**Adjusting Framingham Age Points for Coronary Calcium Score**

Percentile of calcium score	Point adjustment*
0 - 24th	-2
25th - 49th	-1
50th - 74th	+1
75th - 89th	+2
> 90th	+3

\*The adjustment shown should be substituted for the age score of a given man or woman.

Adapted with permission from Grundy SM. *Am J Cardiol.* 2000.<sup>4</sup>

etary habits and with reductions in cholesterol levels. At present, this assessment, while effective, is exclusively a research tool.

### Carotid Ultrasonography

Easy to visualize by ultrasonography, the carotid arteries reflect the generalized process of atherosclerosis. Autopsy studies have shown close correlations between coronary and carotid atherosclerosis. Carotid IMT is a good indicator of the presence, extent, and progression of coronary atherosclerosis, as shown in observational and interventional studies.<sup>23</sup> In the Atherosclerosis Risk in Communities (ARIC) study of subjects initially free of CAD followed for 4 to 7 years, each 0.19-mm increase in IMT was associated with a 38% increase in coronary events in women and a 17% increase in men.<sup>26</sup>

In a long-term follow-up of subjects participating in the Cholesterol-Lowering Atherosclerosis Study, absolute carotid IMT and progression of thickening predicted the risk of coronary events better than did lipid level measurements.<sup>27</sup> In this study, each 0.33-mm increase in IMT was associated with a 2.2-fold increased risk of fatal MI over 2 years.

Although considerable technical precision is required, quantitative IMT has been used successfully to follow the impact of risk factor modification in several trials. Despite a strong correlation between carotid IMT and CAD in populations, the predictiveness in individuals is only modest. IMT values must be interpreted in the context of age-determined ranges, and the presence or absence of CAD can be best predicted in individuals if IMT values are, respectively, very high or low. Carotid ultrasonographic determination of IMT appears to provide additional value for cardiovascular risk stratification, the magnitude of which needs further clarification.

### Electron Beam CT

One of the most controversial risk stratification techniques is electron beam CT (EBCT). John Hunter first described an association between coronary artery calcification and coronary death in 1775. Nearly 200 years later, Blankenhorn and associates demonstrated that fluoroscopically detected coronary calcification was associated with atherosclerosis. The presence of coronary calcifications is predictive of coronary events, but the fluoroscopic approach to corona-

ry calcification detection is not useful as a general population risk assessment technique.

Nevertheless, the concept of non-invasive detection of coronary calcification for predicting coronary events has been furthered by the development of EBCT and, to a lesser degree, double-helical CT.<sup>28</sup> In contrast to the mechanical x-ray beam rotation used in conventional CT, EBCT rotates multiple x-ray beams electronically, permitting much more rapid, multi-slice image acquisition. Although slower in image acquisition than EBCT, helical CT, especially double-helical CT, is faster than conventional CT and overlaps image slices, making it more sensitive for the detection of coronary calcification.

Coronary calcification is accurately detected by EBCT. Close correlations with postmortem histology and radiography have been demonstrated. Although overall coronary stenosis burden correlates with cumulative calcium score (cumulative calcium density  $\times$  volume), the site of high-grade stenoses cannot be predicted by EBCT.

The predictive value of EBCT-determined coronary calcification is greatly dependent on patient age and gender. Coronary calcification increases dramatically with advanced age. Given this fact, it is not surprising that the sensitivity of EBCT to detect luminal stenosis increases with advanced age, while the specificity drops. Coronary arteries calcify earlier in men than in women. While the sensitivity of EBCT to predict coronary stenosis in men younger than 60 years remains high, in women younger than 60 years, it drops to about 50%. In contrast, almost all older men and many older women have coronary calcification, making this test useful in older age

groups only for exclusion of disease.

With these issues in mind, it is necessary to compare individual patient calcium scores with age- and gender-specific thresholds (Table 3). The predictive value of EBCT also greatly depends on the calcium score cut-point employed. Application of a higher calcium score cut-point increases specificity but lowers sensitivity. Double-helical CT-determined coronary calcification has generally the same diagnostic accuracy as does EBCT, but motion artifact may limit its ability to detect small areas of calcification that are detectable by the faster EBCT.

Although the association between coronary stenosis and calcification is valid, considerable debate remains regarding the ability of EBCT to risk-stratify patients better than the Framingham traditional risk factor approach can. Studying 1173 asymptomatic patients with coronary risk factors who underwent EBCT, Arad and coworkers<sup>29</sup> reported that patients with coronary calcification had odds ratios for a coronary event of 20 to 35 over a 19-month follow-up period. By contrast, the odds ratios for the individual conventional risk factors were all less than 2.5.

The Framingham and EBCT data were compared by area under the receiver-operator characteristic (ROC) curve, by which a score of 1.0 denotes a perfect diagnostic test. In comparison with an area under the ROC curve for National Cholesterol Education Program guidelines of 0.74 for the prediction of coronary events, Arad's team reported a remarkable ROC curve area for EBCT of 0.91, suggesting that EBCT offers improved prediction of coronary events over that of traditional risk factor assessment.

### Main Points

- Modification of risk factors, such as hypercholesterolemia, hypertension, and diabetes, can substantially reduce the morbidity and mortality associated with cardiovascular disease.
- Traditional risk factors, as defined by the Framingham researchers, provide reasonable stratification of cardiovascular risk.
- Determining low-density lipoprotein (LDL) phenotype offers potentially better risk stratification than does standard LDL determination, but phenotyping is expensive and is not widely available.
- The significance and value of determining *Chlamydia* seropositivity; angiotensin-converting enzyme genotype; and levels of lipoprotein(a), serum homocysteine, and fibrinogen remain unclear.
- Newer imaging techniques, such as carotid ultrasonographic determination of intima-media thickness, electron-beam CT, and magnetic resonance coronary angiography, may be useful for cardiovascular risk assessment, but only in selected populations.
- High-sensitivity C-reactive protein tests, arterial stiffness (measured directly or as pulse pressure), and ankle-brachial index are the most promising of the proposed new indicators of risk for population screening.

Detrano and colleagues<sup>30</sup> recently compared the ability of both the Framingham risk model and EBCT to predict coronary events in 1196 asymptomatic high-risk subjects for 41 months. These researchers reported ROC curve areas of 0.69 and 0.64, respectively, demonstrating a failure of EBCT calcium score to add significant incremental value to traditional risk factor assessment. The differences in the results of these studies may be owing (in part) to length of follow-up, the overall low number of cardiac events in these studies, and the relative insensitivity of EBCT to detect the soft, noncalcified plaque that is most vulnerable to rupture. The EBCT calcium score can be substituted for the age point score in the Framingham risk assessment approach (Table 4).

The use of EBCT as a screening and risk assessment technique remains expensive—about \$400—compared with other population-relevant measures (except stress testing and scintigra-

phy). In several regions of the country, EBCT has taken on a highly commercial aspect and is marketed to the wrong population. A limited value for EBCT may be to convince high-risk patients of the need for aggressive risk factor modification, but it should not be used to dissuade such patients from treatment if calcification scores are low. Coronary calcification is reduced by aggressive cholesterol lowering with statins, suggesting a value for following the results of treatment.

The American Heart Association has published a position paper on the role of EBCT in risk assessment. It states that “there is no role at present for use of the test to screen populations of young (less than 40 years old), healthy individuals with no risk factors.”<sup>31</sup>

### Magnetic Resonance Coronary Angiography

Coronary magnetic resonance angiography (MRA) is a rapidly developing



technique that promises to provide noninvasive visualization of the coronary arteries without ionizing radiation. Imaging techniques under investigation to improve coronary artery visualization include breath-holding or respiratory gating, fast imaging sequences, and coadministration of MR contrast agents.

In a preliminary study of 30 patients, coronary MRA had a 100% sensitivity and an 83% specificity for the detection of greater-than-70% stenosis of the distal left main and the proximal to mid-left anterior descending coronary arteries.<sup>32</sup> This high level of accuracy has not been universally reported. An early study of the diagnostic accuracy of MRA for left anterior descending coronary stenosis reported a 50% sensitivity and a 91% specificity.<sup>33</sup> These studies have not been extended to the detection of lesser stenoses and smaller arteries.

Good correlation has been demonstrated between MRA-detected coronary flow velocity and flow-reserve and Doppler flow-wire analysis, making this technique potentially useful for assessment of the functional significance of atherosclerotic plaques. Substantial improvement in current MRA techniques will be necessary before its application to population risk stratification.

## Summary

The noninvasive assessment of cardiovascular risk is an important aspect of modern medical care. Current risk factor modification can substantially reduce the morbidity and mortality associated with this leading cause of death. As used in the Framingham approach, the traditional risk factors provide reasonable stratification of cardiovascular risk. Among the new

measurements under evaluation for improving risk assessment, hs-CRP, arterial stiffness (measured directly or as pulse pressure), and ankle-brachial index are best suited for population screening. ■

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