Emerging Risk Factors for Coronary Heart Disease: A Summary of Systematic Reviews Conducted for the U.S. Preventive Services Task Force

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Background: Traditional risk factors do not explain all of the risk for incident coronary heart disease (CHD) events. Various new or emerging risk factors have the potential to improve global risk assessment for CHD.

Purpose: To summarize the results of 9 systematic reviews of novel risk factors to help the U.S. Preventive Services Task Force (USPSTF) evaluate the factors' clinical usefulness.

Data Sources: Results from a MEDLINE search for English-language articles published from 1966 to September 2008, using the Medical Subject Heading terms *cohort studies* and *cardiovascular diseases* in combination with terms for each risk factor.

Study Selection: Studies were included if the participants had no baseline cardiovascular disease and the investigators adjusted for at least 6 Framingham risk factors.

Data Extraction: Study quality was evaluated by using USPSTF criteria and overall quality of evidence for each risk factor by using a modified version of the Grading of Recommendations, Assessment, Development, and Evaluation framework. Each factor's potential clinical value was evaluated by using a set of criteria that emphasized the importance of the effect of that factor on the reclassification of intermediate-risk persons.

Data Synthesis: 9 systematic reviews were conducted. C-reactive protein (CRP) was the best candidate for use in screening and the most rigorously studied, but evidence that changes in CRP level lead to primary prevention of CHD events is inconclusive. The other evaluated risk factors were coronary artery calcium score as measured by electron-beam computed tomography, lipoprotein(a) level, homocysteine level, leukocyte count, fasting blood glucose, periodontal disease, ankle–brachial index, and carotid intima–media thickness. The availability and validity of the evidence varied considerably across the risk factors in terms of aggregate quality, consistency of findings, and applicability to intermediate-risk persons in the general population. For most risk factors, no studies assessed their usefulness for reclassifying intermediate-risk persons.

Limitations: Because of lack of access to original data, no firm conclusions could be drawn about differences in risk prediction among racial and ethnic groups. The review did not emphasize within-cohort comparisons of multiple risk factors.

Conclusion: The current evidence does not support the routine use of any of the 9 risk factors for further risk stratification of intermediate-risk persons.

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Clinicians use the Framingham risk score to stratify persons according to their 10-year risk for coronary death or myocardial infarction, also known as *major* or *hard* coronary heart disease (CHD) events (1, 2). The Framingham risk score predicts major CHD events well in different demographic and ethnic groups (3). Guidelines recommend using the Framingham risk score, or a modified version of it, to identify high-risk persons (persons with a 10-year risk >20%), who benefit from aggressive risk-reduction measures (4, 5).

In the United States, 23 million adults with no history of cardiovascular disease are classified as intermediate-risk by the Framingham score, meaning they have a 10-year risk for major CHD events of 10% to 20% (6). New or emerging risk factors, particularly inflammatory markers and markers of atherosclerotic burden, might identify those in this group who are actually at high risk and might benefit from more aggressive risk reduction. More than 100 emerging risk factors have been proposed for their potential to improve global risk assessment (7). However, consensus conferences held in 1998 (8) and 2002 (4, 9) recommended against using these factors in the absence of stronger data to support their ability to independently predict CHD events. These consensus groups also noted that assays for some markers were not sufficiently standardized for clinical use. Among the few tests proven to predict cardiovascular events, none had been demonstrated to reclassify as high-risk a subgroup of persons who were initially classified as intermediate-risk by using the Framingham risk score (9).

Table 1 outlines the criteria a new risk factor must meet to be clinically useful for reclassifying intermediate-risk patients' risk for major CHD events (9–12). Key to these criteria is the concept that the value a new risk factor adds to a risk scoring system (such as the Framingham system) cannot be judged solely by its ability to predict

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Table 1. **Criteria for Evaluating the Clinical Value of a New Risk Factor**

To be useful for reclassifying patients currently considered to be at intermediate risk for major CHD events, a new risk factor must meet the following criteria:*

1. It should be easily and reliably measured. Laboratory, radiographic, or clinical measurement should have accepted population reference values. A relatively high prevalence of abnormal values and a substantial proportion of normal values should be found among intermediate-risk persons.
2. It should be an independent predictor of major CHD events in intermediate-risk persons who have no history of coronary artery disease and no coronary equivalents, such as cerebrovascular or peripheral vascular disease.
3. When assessed in intermediate-risk persons, it should reclassify a substantial proportion of them as high-risk.
4. Reclassified individuals should be managed differently than they would have otherwise been, and new or additional treatment they receive should reduce their risk for CHD events.
5. If 2 or more risk factors provide similar prognostic information, then convenience, availability, cost, and safety may be important in choosing among them.

CHD = coronary heart disease.
* On the basis of references 9 through 12.

major CHD events independent of other risk factors. Most studies use a hazard ratio (or other risk ratio) to measure how well a new risk factor predicts major CHD events, controlling for the Framingham risk factors. From a clinical viewpoint, calculating a risk ratio is a necessary but far from sufficient step because it does not enable judgment of the effect of using the new test in persons classified as intermediate-risk by the Framingham risk score.

Studies may also measure how well a new prognostic risk factor improves discrimination when incorporated into the Framingham risk score. However, a marker that has a small effect on discrimination may have a large effect on the reclassification of persons from 1 risk group to another (13–18). To estimate the effect of a new risk factor on reclassification, investigators must compare the proportion of persons classified as high-risk by each model, then assess whether the agreement between the predicted and actual event rates in subgroups of persons who have different levels of risk (that is, calibration) has improved. Measuring discrimination is insufficient to judge the clinical effect of the new test without also measuring calibration and reclassification (19).

A better approach is to calculate the Framingham risk score, classify all participants, and then see how well the new risk factor reclassifies those who were assigned to the intermediate-risk group. This sequential approach provides a direct measure of the number or proportion of intermediate-risk persons who could be reclassified by the new test. This type of analysis provides the best information about the clinical effect of using the new test to further stratify intermediate-risk patients.

Using these considerations and the criteria in **Table 1** as a guide, we conducted a series of systematic reviews to help the U.S. Preventive Services Task Force (USPSTF) determine which of 9 risk factors should be used to further stratify intermediate-risk persons. Members of the USPSTF determined the risk factors to evaluate: ankle–brachial index (ABI), leukocyte count, fasting blood glucose level, periodontal disease, carotid intima–media thickness (IMT), coronary artery calcium (CAC) score as measured by electron-beam computed tomography, serum homocysteine level, lipoprotein(a) level, and C-reactive protein (CRP) level. The details of several of these reviews are published elsewhere (20–23). We provide a summary overview of the main findings of this series of systematic reviews.

METHODS

We searched MEDLINE for English-language articles (1966 through September 2008) by using the Medical Subject Heading terms *cohort studies* and *cardiovascular diseases* in combination with terms for each of the tests under study. We also searched the reference lists of published reports. We included only studies that recruited participants with no known cardiovascular disease, reported major CHD events, and adjusted for 6 or 7 Framingham risk factors (5 or 6, if participants with diabetes were excluded) in this summary. When we found several reports based on the same cohort, we used the most recent analysis unless an older one used stronger analytic methods. The systematic reviews were originally conducted for literature searches through 2006. Several of those reviews were published or submitted for publication as separate papers. For the current review, we updated the literature searches through September 2008 for ABI, leukocyte count, fasting blood glucose level, carotid IMT, and lipoprotein(a) level. We updated the literature search for electron-beam computed tomography through July 2008.

Critical Appraisal and Quality of Evidence

To assess the quality of each study, we used the USPSTF criteria for cohort studies (10) and applied a modified Grading of Recommendations, Assessment, Development, and Evaluation framework to assess the overall quality of evidence for each risk factor (24). Specifically, we considered the limitations, consistency, precision, applicability to the target population (intermediate-risk adults with no known cardiovascular disease), dose–response relationship, and likelihood of publication bias for the entire set of studies about the risk factor. These ratings for the overall quality of evidence reflect our confidence in the estimate of the risk factor's usefulness for reclassifying intermediate-risk persons as high-risk. The ratings also reflect appropriate control for confounders and applicability to intermediate-risk persons, among other considerations.

Table 2. **Risk Factor Characteristics**

Risk Factor	Description (Reference)	Tests, Assays, or Devices, and Availability	Agreement Among Methods (Reference)	Decision Limits or Categories and Reliability for Use in Risk Assessment (Reference)*
CRP level	A serum protein involved in immune and inflammatory responses.	Conventional, highly sensitive, and cardiac CRP; turbometric highly sensitive CRP assay is the most widely used; widely available	Cardiac CRP assays have a lower detection limit of <1.0 mg/L and an FDA indication for use in cardiac risk stratification (27)	Low (<1 mg/L), intermediate (1–3 mg/L), and high (>3 mg/L). Most epidemiologic studies used a single measurement. With any particular assay, use of 2–3 serial measurements for baseline assessment provides reliability similar to that of an LDL cholesterol assay. Interassay agreement has not been evaluated in the setting of cardiac risk assessment.
CAC score	Calcium content of the coronary arteries estimated from a radiographic image by using 1 of several scoring systems (28–30).	EBT or EBCT, MDCT; available at specialized centers; examination takes 10–15 min	Cardiac risk studies used EBCT; MDCT, the newer technology, provides better visualization of the coronary arteries but is used to calculate a CAC score for cardiac risk assessment	None, 1–100, 101–300, and >300. Categories vary among studies, but usually elevated values are compared with zero. No established norms for the general population. Some epidemiologic studies used 2 scans. The reliability of repeated scans has been evaluated in the research setting (31, 32) but not in everyday practice.
Lipoprotein(a) level	A particle found in serum that contains apolipoprotein B and the glycoprotein apolipoprotein(a). It has structural similarities to LDL and plasminogen.	Turbometric, nephelometric, electroimmunodiffusion, ELISA, and immune fluorescence assays; widely available	Poor agreement among different methods (33)	<300 mg/L and >300 mg/L. Categories vary among studies. No established norms for the general population. Most epidemiologic studies used 1 measurement. Variation among study methods is thought to explain discrepant results among cohort studies.
Homocysteine level	An amino acid found in serum, produced in the liver from methionine.	ELISA, enzymatic, and other assays; widely available	Good agreement among different methods	No accepted categories for cardiac risk assessment. Most studies compare quantiles or estimate a risk ratio per 5-μmol/L difference in serum levels. Could be used as a continuous variable in risk assessment. Most epidemiologic studies used 1 measurement.
Leukocyte count	The number of leukocytes in a given volume of blood.	Automated cell counters; universally available	Reliable	No accepted categories for cardiac risk assessment. Most studies compare quantiles. Could be used as a continuous variable in risk assessment. Most epidemiologic studies used 1 measurement.
Fasting glucose concentration	The quantity of glucose in a given volume of blood.	Various assay methods; universally available	Reliable	No accepted categories for cardiac risk assessment. Most studies compare quantiles. Could be used as a continuous variable in risk assessment. Most epidemiologic studies used 1 measurement.
Periodontal disease	Pocket formation, recession of the gingiva, and tooth loss.	Physical examination and plain radiography; widely available	Interobserver agreement in primary care unknown	Descriptors (such as mild, aggressive, or chronic) are used widely in everyday practice, but categories for use in cardiac risk assessment are not well defined. Most epidemiologic studies used 1 examiner.
Ankle–brachial index	The ratio of the systolic blood pressure at each ankle to the systolic blood pressure in the right arm.	Doppler ultrasonography devices and blood pressure cuffs; universally available	Reliable	Normal (>90% or >85%) and low (<90% or <85%). Several other cutoff values have been used. A recent meta-analysis used deciles (34). Epidemiologic studies used the lower of 2 measurements.

Table 2—**Continued**

Risk Factor	Description (Reference)	Tests, Assays, or Devices, and Availability	Agreement Among Methods (Reference)	Decision Limits or Categories and Reliability for Use in Risk Assessment (Reference)*
Carotid IMT	Thickness of the intima and media, part of the carotid artery wall. In practice, the combined thickness of the intima and medial layers is measured at ≥1 site (common carotid, carotid bifurcation, and internal carotid arteries).	High-resolution B-mode ultrasonography; the equipment is widely available, but estimation of carotid IMT is performed in specialized centers	Reliability in large epidemiologic studies is good, but reliability in practice unknown	No accepted categories for cardiac risk assessment. Use of age-adjusted and sex- and race-specific values from the major epidemiologic studies is recommended (35), but it is not clear how widely they are used. Epidemiologic studies used various measurements. No established consensus for which measurement approach is best for cardiovascular risk assessment (36).

CAC = coronary artery calcium score; CRP = C-reactive protein; EBCT = electron-beam computed tomography; EBT = electron-beam tomography; ELISA = enzyme-linked immunosorbent assay; FDA = U.S. Food and Drug Administration; IMT = intima–media thickness; LDL = low-density lipoprotein; MDCT = multidetector computed tomography.
* Information reflects the usual practice in epidemiologic studies.

Appropriate Control for Confounding With the Framingham Risk Factors

Most novel risk factors are correlated with Framingham risk factors, so investigators who do not adjust or adjust inappropriately for 1 or more Framingham factors may overestimate the novel factor's predictive ability (25, 26). Inappropriate adjustment occurs when a variable (for example, a self-reported history of taking medication for cholesterol) is used as a proxy for a better predictor (such as measured total cholesterol or high-density lipoprotein cholesterol levels). We can have confidence in a study's results only when all Framingham risk factors have been correctly measured and adjusted for.

Applicability to Intermediate-Risk Persons

Cohorts that included intermediate-risk persons provide more pertinent information about risk factors. Estimates of the predictive ability of a particular marker vary depending on the pattern and prevalence of other risk factors in the population (19). A few studies used the Framingham risk score to classify participants, which provided direct information about the proportion who were at intermediate risk and the effect of using the new test. In most studies, however, we used average annual event rates and the prevalence of the Framingham risk factors to infer that the study population included intermediate-risk persons.

Other Considerations

We also considered the other criteria listed in **Table 1**. For some of these criteria (such as test reliability, convenience, cost, or safety), we used information not otherwise included in the literature search.

Role of the Funding Source

This study was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the USPSTF. Agency staff and USPSTF members participated in development of the initial scope of this work and reviewed interim analyses and the final report. A draft version was distributed to content experts for review. Agency approval was required before this manuscript could be submitted for publication, but the authors are solely responsible for the content and the decision to submit it for publication.

RESULTS

The **Appendix Table** (available at www.annals.org) shows how often a particular risk factor was evaluated among the 75 cohorts that have studied at least 1 novel risk factor. Serum tests that can be done on stored samples, such as for CRP, homocysteine, or lipoprotein(a), have been evaluated in the largest, highest-quality, and most diverse population-based studies. The strongest evaluations came from studies in which the cohorts had been followed for 10 years or more and all Framingham risk factors were measured before treatment for hyperlipidemia or hypertension was initiated. Conversely, data about electron-beam computed tomography, carotid IMT, and periodontal disease are relatively sparse. Because radiologic tests (electron-beam computed tomography and carotid IMT) and physical examination (ABI and periodontal examinations) cannot be done retrospectively, few studies of the large, widely studied cohorts used in cardiovascular epidemiology research evaluated these risk factors. Most evaluations of these tests were weaker, in that persons were followed for less time or had incomplete evaluations that did not measure all relevant Framingham risk factors at the time of inception. Many of the cohorts listed in the **Appendix Table** (available at www.annals.org) had no publications that met the inclusion criteria for our reviews. Many adjusted for too few traditional risk factors or reported composite outcomes that included stroke, angina, or revascularization rather than nonfatal myocardial infarction and coronary deaths. Results for this broader group of studies are re-

Table 3. **Summary: Strength of Evidence and Magnitude of Effect**

Factor	Strength of Evidence					
	Cohorts, *n*	Limitations	Applicability to Intermediate-Risk Persons	Other Considerations*	Prediction of Cardiovascular Events, Effectiveness of Treatment, and Harms (Reference)	Overall Strength of Evidence
CRP level	10	Some	Good	Dose–response relationship	Weight loss, exercise, smoking cessation, statins, and fibrates reduce serum CRP levels (37–39), but none of these effects have yet been linked to a reduced risk for major CHD events.‡	Good
Electron-beam computed tomography	8	Some§	Some uncertainty‖	Sparse or imprecise data and inconsistent results	Effects of treatment unclear. Radiation exposure.	Fair
Lipoprotein(a) level	6	Some	Significant uncertainty‖	None	Effect of treatment independent of LDL-c is unclear.	Fair
Homocysteine level	9	Some	Significant uncertainty‖	None	Treatment with folate decreases serum levels but is ineffective for secondary prevention of major CHD events.‡ The effect of folate on major CHD events† for primary prevention is unknown.	Fair
Leukocyte count	11	Some	Some uncertainty‖	Weak or absent association and inconsistent results	No specific treatment available.	Fair
Fasting glucose concentration	10	Serious**	Significant uncertainty‖	Weak or absent association and inconsistent results	Effects of treatment on major CHD events† unclear.	Fair
Periodontal disease	1	Some	Significant uncertainty‖	Sparse or imprecise data	Predictive of CVD events††. Effects of treatment on major CHD events† unclear.	Fair
Ankle–brachial index	3	Serious**	Significant uncertainty‖	Sparse or imprecise data	Predictive of some CVD events††. Effects of treatment on major CHD events† unclear.	Poor
Carotid intima–media thickness	3	Serious**	Significant uncertainty‖	Sparse or imprecise data	Predictive of some CVD events††. Effects of treatment independent of LDL-c unclear.	Poor

CAC = coronary artery calcium; CHD = coronary heart disease; CRP = C-reactive protein; CVD = cardiovascular disease; LDL-c = low-density lipoprotein cholesterol; NHANES = National Health and Nutrition Examination Survey.
* Negative factors include imprecise or sparse data, high risk for reporting bias, effect of plausible residual confounding, or a weak or absent association. Positive factors include a strong or very strong association, evidence of a dose–response gradient, or all plausible unmeasured confounders that would increase the magnitude of the observed rate ratio.
† From meta-analyses of cohort studies unless otherwise noted.
‡ Nonfatal myocardial infarction and coronary death.
§ Most studies had self-selected patients. Not evaluated in the major population-based cohorts. Use of self-report for Framingham risk factors could inflate estimates of the contribution of CAC score. Results given are for 2 population-based, good-quality cohort studies.
‖ Studies did not establish applicability of results to intermediate-risk persons.
¶ Estimates are from the general population rather than from an intermediate-risk group.
** The major limitations were including patients with known coronary artery disease or symptomatic peripheral vascular disease or not reporting CHD events as an end point.
†† Includes major CHD events, stroke, and death due to cerebrovascular disease, and "soft" cardiac outcomes, such as revascularization or onset of angina.

ported elsewhere (20–23). **Table 2** (27–36) includes a description of each test and information about its reliability, availability, reference values, and population norms (criterion 1 in **Table 1**). **Table 3** (37–45) summarizes the information the USPSTF considered in assessing the potential benefit of using each risk factor to predict major CHD events in intermediate-risk persons.

The available evidence varied considerably for each of the risk factors. For periodontal disease, ABI, and carotid IMT, good-quality studies relevant to predicting major CHD events were sparse, which provided insufficient data for estimating pooled risk ratios for major CHD events. For leukocyte count and fasting blood glucose level, good-quality cohort studies did not consistently predict major CHD events. Although we found CRP level, CAC score on electron-beam computed tomography, lipoprotein(a) level, and homocysteine level to be independent predictors of major CHD events when added to Framingham risk factors, the quality of the evidence for these 4 risk factors varied considerably. For most of the 9 risk factors, no stud-

Table 3—**Continued**

Magnitude of Effect		
Adjusted Risk Ratio (95% CI) for Major CHD Events† and Comparison†	**Range Reclassified as High-Risk, % (Studies, *n*)**	**Prevalence of Abnormal Values in Intermediate-Risk or General Population (Reference)**
1.58 (1.37–1.83) for >3.0 vs. <1.0 mg/L; 1.22 (1.11–1.33) for 1.0–3.0 vs. <1.0 mg/L	5 to 15 (3)	23% of men and 37% of women in NHANES had CRP levels >3.0 mg/L (40)
–	5 to 15 (1)	Probably common; 26% of adults in the Rotterdam cohort aged 62–85 y had CAC scores >400 (41)¶
1.45 (1.11–1.89) for ≥300 vs. <300 mg/L	–	14% of women and 11.4% of men in the Framingham cohort had lipoprotein(a) levels >300 mg/L (42, 43)¶
1.09 (1.02–1.17) per 5-μmol/L increase	–	25.8% of men and women in the Hoom cohort age 50–75 y had homocysteine levels >14 μmol/L (44)¶
Inconsistent results (range, 1.01–2.10)	–	–
–	–	–
Insufficient data	–	Probably common; 23% of U.S. adults had periodontitis and 35% had no teeth (45)¶
–	–	Men, 3.3%; women, 10%
–	–	Poor evidence

ies assessed their usefulness for reclassifying intermediate-risk persons, information critical to a complete assessment of a factor's potential clinical utility. Although the evidence that CRP level may be used to correctly reclassify intermediate-risk persons is promising, it is insufficient to conclude that changes in CRP level lead to primary prevention of CHD events. The current evidence, therefore, does not support the routine use of any of the 9 risk factors for further risk stratification of intermediate-risk persons.

CRP Level

Of the 9 markers we evaluated, CRP was the best candidate for use in screening. Our findings support the use of CRP level to stratify those with a Framingham risk score of 15% to 20%, but some gaps in the evidence remain. First, although we found more evidence about reclassification for CRP level than for any other novel risk factor, the evidence is still sparse. A CRP level greater than 3.0 mg/L reclassified 5% of intermediate-risk women in the Women's Health Study (19, 46) and none in the Cardiovascular Health Study (47)—an inconsistent and possibly small effect. In the 2 studies of men (47, 48), high CRP level clearly identified a high-risk subset of persons with a Framingham risk score between 15% and 20%, but we do not know how many—a consistent but imprecise effect.

Second, it is unclear whether performing a CRP test to guide treatment goals is more beneficial than intensifying treatment goals in all intermediate-risk persons. Interventions that reduce CRP (weight loss, exercise, smoking cessation, statins, and fibrates) are already known to reduce the risk for coronary events. A primary prevention trial of rosuvastatin, 20 mg, versus placebo in 17 802 patients with a CRP level greater than 2 mg/L and a low-density lipoprotein cholesterol level less than 3.36 mmol/L (<130 mg/dL) was terminated early because of "overwhelming benefit" (49). The investigators did not provide the number of participants who could be classified as low- or intermediate-risk on the basis of their Framingham risk score, so the applicability of this trial to intermediate-risk persons is not clear.

CAC Score on Electron-Beam Computed Tomography

Electron-beam computed tomography can be used to quantify calcification of the coronary arteries into a CAC score (28). A newer device, the multidetector computed tomography scanner, provides better visualization of the coronary arteries and is also being evaluated as a screening test, particularly for ruling out coronary disease noninvasively among low-risk persons (50, 51).

Relatively sparse data from a small number of studies and inconsistent results among these cohorts weakened confidence in our estimates of the risk ratio. We focused on 5 studies that we judged most likely to be accurate because of their valid study designs (41, 52–55). These studies provided measures of the incremental predictive value of CAC scoring for coronary events. As in a previous systematic review (25), we found wide variation in estimates of the risk ratio for higher calcium scores. Studies with notable limitations, including self-referral of participants, unblinded outcome adjudication, and ascertainment of Framingham risk factors by self-report rather than biochemical measurement, found higher relative risk estimates. For example, the hazard ratio for a CAC score of 1 to 100 compared with 0 was 1.39 (CI, 0.65 to 2.69) in the best-quality study (55), versus 2.25 (CI, 1.63 to 3.02) for men and 2.27 (CI, 1.64 to 2.91) for women (53), and 3.98 (CI, 1.72 to 8.79) (54), 4.04 (CI, 1.64 to 9.93) (41), and 8.91 (CI, 2.21 to 35.87) (52) in the other, lower-quality studies. The estimates had substantial heterogeneity ($Q = 6.90$, $I^2 = 42.0\%$, $P = 0.140$) for scores of 101 to 300 versus 0, but removal of 1 study reduced heterogeneity to 0 ($Q = 3.28$, $I^2 = 0.0\%$, $P = 0.51$). The study in question was the best-quality one (55), which suggests that flaws in the other studies, particularly incorrect or incomplete adjustment for other risk factors, inflated their estimates of the risk ratio. Because of the inconsistent and widely variable risk estimates, the variation in cutoff points used by different studies, and the lack of population-based refer-

ence standards, we have not reported a summary risk ratio estimate for electron-beam computed tomography in **Table 3**.

The effect on reclassification is even less certain. Our review disagrees with one published in 2007 by the American College of Cardiology and American Heart Association guideline committee (56), which said that 4 studies provided information about reclassification and estimated that, among intermediate-risk persons, a CAC score in the highest tertile (>400) conferred an annual rate of major CHD events of 2.4%. Their report did not describe how they derived this estimate or how many intermediate-risk patients in the 4 studies had a CAC score greater than 400. In our review of these studies (plus 6 others), we found that only 1 evaluated reclassification in an intermediate-risk group. In that study, participants with CAC scores of 300 or greater had the event rate of a high-risk group (>2% per year), made up 18% of intermediate-risk patients, and potentially could have been reclassified as high-risk (55). The main weakness of the study was that the sample was self-selected rather than population-based. More population-based cohort studies relevant to intermediate-risk persons would facilitate the development of definitive guidelines regarding screening with CAC scoring.

Lipoprotein(a) Level

Although lipoprotein(a) is of epidemiologic interest as a potential risk factor, most studies had little relevance to cardiac risk stratification in the clinical setting. Our summary risk ratio estimate supports a relationship between lipoprotein(a) level and CHD events; however, we are uncertain about the applicability of the evidence to intermediate-risk patients. Studies combined low- and high-risk samples and included a broader range of cardiovascular events. Some cohorts undoubtedly included intermediate-risk persons, but no analyses were done to determine how well the risk ratio calculated for the entire sample applied to this subset, and no study directly examined the effect on reclassification of intermediate-risk persons. Other information in **Tables 2** and **3** suggest that lipoprotein(a) level is unlikely to be useful for stratifying intermediate-risk persons; commercial assays are poorly standardized, and the prevalence of high serum levels (>1.07 μmol/L) in intermediate-risk persons is uncertain.

Homocysteine Level

Homocysteine is of epidemiologic interest as a potential risk factor, but the applicability of the body of evidence to intermediate-risk patients is uncertain, with most studies having little relevance to cardiac risk stratification in the clinical setting. No studies conducted analyses to determine the relative risk for CHD events specifically in intermediate-risk persons, and many studies included a broader range of cardiovascular events. Although consistent findings from a large number of cohort studies strongly support a relationship between homocysteine level and the risk for cardiovascular events (23), its value as a risk factor for major coronary events is less certain. In a meta-analysis of the subset of studies that adjusted for 6 or 7 Framingham risk factors and reported major CHD events, each 5-μmol/L increase in homocysteine level confers an approximately 9% increase in the risk for CHD events that is independent of traditional CHD risk factors (RR, 1.09 [CI, 1.02 to 1.17]). (For U.S. adults between 50 and 75 years of age, a 5-μmol/L increase is approximately the mean difference between the 75th and 95th percentile [57].) Inclusion of studies that did not adjust for all Framingham risk factors or that included other cardiovascular outcomes increased the estimated risk to approximately 20% (23). No studies have directly examined the effect of homocysteine level on the reclassification of intermediate-risk persons.

Leukocyte Count

In 14 studies (of 13 cohorts) (58–71), the total leukocyte count did not predict major CHD events consistently. In addition, analyses were not limited to intermediate-risk persons, and the quality of adjustment for Framingham risk factors was a serious problem in several studies (60–64, 67–69). The relationship between leukocyte count and CHD events also varied with the timing of the assessment of end points (58, 59, 66).

Fasting Blood Glucose Level

No study consistently found that elevated fasting blood glucose level could predict CHD events. Only 1 (72) of the 10 cohort studies eligible for our review (73–79) found an association—a weak association—between fasting glucose level and CHD events after 4 years of follow-up.

Periodontal Disease

Periodontal disease is common among adults in the United States and is a potential source of chronic inflammation. We investigated whether different manifestations of periodontal disease (periodontitis, tooth loss, gingivitis, and bone loss) are independent risk factors for cardiovascular disease (22) or major CHD events. Our review and meta-analyses suggest that periodontal disease is an independent, though relatively weak, risk factor for CHD. Several studies, which were based on either dental examinations or self-report, found periodontal disease to be independently associated with increased risk for CHD (45, 80, 81), whereas other studies found no association (82–84). For cardiovascular diseases in general, relative risk estimates for different categories of periodontal disease ranged from 1.24 (CI, 1.01 to 1.51) for periodontitis to 1.34 (CI, 1.10 to 1.63) for persons with 0 to 10 teeth. We found significant statistical heterogeneity across studies that was not explained in subgroup analyses by differences in sex, definition of cardiovascular events, or method of periodontal disease assessment. However, the sensitivity of these subgroup analyses was poor, and we could not rule out differences in measurement of the risk factor or outcomes as causes of heterogeneity. We did not find any direct evidence that periodontal examination would be use-

ful for reclassifying persons classified as intermediate-risk by the Framingham risk score.

ABI

The ABI is an indicator of peripheral arterial disease—atherosclerotic disease that involves the large arteries of the lower extremity. The ABI is determined by measuring systolic blood pressure at the ankle, based on palpation or ultrasonographic measurement of the dorsalis pedis pulse, and dividing this by the systolic blood pressure measured in the arm. An ABI less than 0.9 is the cutoff point commonly used to indicate possible significant compromise of lower-extremity arterial blood flow. In the Framingham cohort, the principal risk factors for CHD events (hyperlipidemia, hypertension, and smoking) were found to be equally good as predictors of incident peripheral artery disease. The Adult Treatment Panel III recommends managing patients with peripheral arterial disease, which is classified as a coronary equivalent, as if they were at high risk according to the Framingham system (4, 5).

In our original systematic review, we found no evidence that ABI independently predicts the risk for incident CHD events in persons without symptomatic peripheral arterial disease. We reviewed 514 abstracts, evaluated 18 potentially relevant articles in detail, and excluded all of them—most commonly because they did not report results separately for participants with no history of CHD or peripheral artery disease or did not adequately adjust for Framingham risk factors.

The Ankle–Brachial Index Collaboration published an individual-data meta-analysis of 16 of these studies in July 2008 (34). The meta-analysis only included participants with no history of CHD, and investigators calculated a Framingham risk score for each participant. Rates of major CHD events were reported in 11 cohorts of men and 10 cohorts of women. Overall, 7.4% had an ABI of 0.9 or less. When added to the Framingham risk score, an ABI less than 0.9 improved discrimination from 0.646 (CI, 0.643 to 0.657) to 0.655 (CI, 0.643 to 0.666) in men and from 0.605 (CI, 0.590 to 0.619) to 0.658 (CI, 0.644 to 0.672) in women.

The results from the 2008 meta-analysis for reclassification of intermediate-risk persons are imprecise. Of 7392 men with a baseline Framingham risk score of 10% to 19% (mean, 13%), only 3.3% had an ABI less than 0.9, and the 10-year risk among these men was 16%, still within the intermediate-risk range. Among men with a Framingham risk score from 15% to 19% and an ABI less than 0.9, the pooled 10-year risk for major CHD events was 20.2 (CI, 8.0 to 32.3), but the proportion with a posttest Framingham risk score greater than 20% was not reported. The results for women were much more promising; 10% of those classified as intermediate-risk at baseline had an ABI less than 0.9, and these had a 10-year risk of 25%.

The Ankle–Brachial Index Collaboration publication presented no information about how well the Framingham risk score and the ABI predicted major CHD events in the individual studies, making it impossible to judge the consistency or heterogeneity of results or the validity of the pooled results. For the purpose of judging the value of ABI in reclassifying asymptomatic intermediate-risk persons according to their risk for major CHD events, the meta-analysis had important flaws. Most important, the article does not say whether participants with a known history of stroke, transient ischemic attacks, or symptomatic peripheral artery disease were excluded from the analysis. Inclusion of such patients could increase the apparent predictive ability of ABI but reduce its relevance to asymptomatic persons. In addition, we cannot judge the adequacy of Framingham risk factor measurement, which may have been inconsistent among the studies, from the pooled discrimination statistics reported in the article. Of concern, the adjusted 10-year risk for major CHD events among men with a Framingham risk score in the high-risk range (20% to 29%) was 15.3% (CI, 11.5 to 19.1), which suggests underadjustment. For these reasons, this recent publication did not change our original assessment that the evidence is insufficient to assess the value of ABI for cardiac risk assessment in asymptomatic intermediate-risk persons.

Carotid IMT

Carotid IMT, as measured by carotid ultrasonography, has been used widely in the context of randomized trials as a measure of the progression of atherosclerotic disease (85–87). Evaluations of carotid IMT as a risk factor have focused primarily on stroke or a broad range of cardiovascular events (88–105). Among this broad group of studies, differences in measurement of carotid IMT, extensive overlap with other risk factors for coronary events, inadequate measurement and adjustment of these risk factors, and different definitions of end points contributed to the wide variation in risk ratios (36).

Only 3 studies of carotid IMT estimated an adjusted risk ratio for major coronary events, rather than a broader measure that included stroke or other cardiovascular events, in persons without prevalent cardiovascular disease. In the ARIC (Atherosclerosis Risk in Communities) Study, adding carotid IMT scores to a risk prediction equation based on Framingham risk factors slightly improved the prediction of subsequent CHD among healthy adults, particularly men (93, 94). Carotid IMT persisted as an independent risk factor in the other cohorts after full or partial adjustment for Framingham risk factors (103, 105).

A major roadblock has been the lack of consensus on examination techniques and population-based standards for interpreting quantitative IMT measures. Studies used different methods to measure carotid IMT, which makes comparisons or quantitative synthesis of the results across studies unreliable. Recently, a consensus panel of experts (35) proposed standards for conducting examinations and reference values for U.S. adults based on 2 large cohort studies (106, 107), one of which (ARIC) has also pub-

lished data about coronary risk prediction (94). Even if these standards are widely adopted, their usefulness in cardiac risk assessment needs to be validated in prospective, population-based cohort studies that use appropriate methods to measure other risk factors and examine the added predictive ability of carotid IMT in persons classified as intermediate-risk by the Framingham risk score.

Summary

To be clinically useful, a novel CHD risk factor must meet the various criteria we discuss. The current evidence does not satisfy all of these criteria for any of the 9 new risk factors that we evaluated. The available evidence varies among the risk factors and is lacking in different ways for different criteria. For some factors, good-quality studies relevant to predicting major CHD events were sparse and data were therefore insufficient, even for estimating pooled risk ratios. For others, an adequate body of studies did not consistently find that the factor in question independently predicted major CHD events, a necessary but not sufficient criterion. A new risk factor should, when added to traditional Framingham risk factors, reclassify a substantial proportion of originally intermediate-risk persons as high-risk. In addition, such reclassification should result in clinical management that is different than it would otherwise have been, and that is effective in reducing the risk for incident CHD. Although several novel risk factors are independent predictors of major CHD events, only the effect of CRP level on risk reclassification has been evaluated by good-quality studies. Although promising evidence indicates that CRP level can be used to correctly reclassify intermediate-risk persons, evidence that changes in CRP level reduce the risk for incident CHD events is insufficient.

Discussion

As Lloyd-Jones and colleagues recently pointed out (108), "assessments of new prognostic tests should not rely solely on associations measured by relative risks." Our results illustrate the importance of considering multiple criteria to evaluate whether a new risk factor should be incorporated into guidelines for coronary risk assessment in primary care. In addition to the limitations of individual studies, the consistency, precision, and applicability of the body of evidence to the target population are critical components of this evaluation. Future research should also rigorously evaluate the effect of a new risk factor on the reclassification of intermediate-risk persons, as well as the effectiveness of more aggressive risk-reduction measures that are undertaken as a consequence of that reclassification.

Our review has limitations. First, in the absence of access to original data, we could not draw firm conclusions about differences in risk prediction among racial and ethnic groups for most risk factors. Recent studies (54, 109) have found no major differences in CAC scores among racial groups. Cohort studies, such as the Multi-Ethnic Study of Atherosclerosis (110) and the ARIC Study (111), recruited diverse groups of participants, but ethnic and racial minority populations were poorly represented in many cohorts. Future studies particularly need to validate proposed additions in different groups, in the manner that has been done for the Framingham risk score (3).

In addition, our review did not emphasize within-cohort comparisons among novel risk factors. Several articles (112–116) have made head-to-head comparisons of multiple risk factors. Comparison of multiple prognostic factors in the same cohort can add significantly to our confidence in estimates of effect (114). The **Appendix Table** (available at www.annals.org) (117–212), which indirectly compares within-cohort findings, illustrates this principle. For example, separate articles from the ARIC Study found that CRP level and carotid IMT, but not fasting glucose, homocysteine, or leukocyte count, independently predicted cardiac events. If formally analyzed, results like these may deserve more weight than results from cohorts in which all risk factors tested have impressive results. Direct within-cohort comparisons can provide important insights. For example, in the Multi-Ethnic Study of Atherosclerosis, CAC scores were clearly superior to carotid IMT for predicting cardiovascular events (95). A recent report from the Cardiovascular Health Study (90) compared carotid IMT with CRP level. Both predicted cardiovascular events, after adjusting for other risk factors, but an elevated CRP level was associated with increased cardiovascular disease risk and all-cause mortality risk only in patients with detectable atherosclerosis. Future systematic reviews should take findings from such comparisons as these into account.

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