In contrast to the relative ease of recognition and clarity of treatment and prevention strategies in patients with symptomatic coronary heart disease (CHD), a major problem of detection, treatment, and prevention of CHD exists in the large population who have no symptoms of heart disease yet are at increased risk to develop CHD. Prevention of CHD events in such asymptomatic individuals has traditionally been called “primary prevention,” as it aims to prevent first CHD events. Awaiting the clinical diagnosis of CHD before beginning risk factor reduction will miss the opportunity to prevent a substantial number of CHD events, and the American public will continue to suffer from a heavy burden of CHD. This is particularly critical for people whose first presentation is sudden cardiac death or disability. Thus, the opportunity to prevent CHD events, rather than be forced to treat the acute events and their future consequences, has substantial appeal.

Risk reduction tailored to a patient’s specific risk has evolved significantly over the past several decades and has been shown to be effective when appropriately applied. Similarly, guidelines based on risk assessment have advanced considerably. Clinicians have also become increasingly familiar with the rationale for considering absolute risk rather than relative risk, for calculating the number needed to treat, and for understanding the importance of predicting a wide range of different future clinical outcomes (beyond mortality). Risk assessment was the central principle delineated at the 27th Bethesda Conference, entitled “Matching the Intensity of Risk Factor Management With the Hazard for Coronary Disease Events” (1). Despite this, our ability to accurately determine risk remains limited, especially for those asymptomatic people found to be in intermediate risk ranges based on standard risk assessment (Fig. 1). The latter group includes many individuals with asymptomatic or “subclinical” atherosclerosis. This task force report addresses the conceptual framework and background information necessary for understanding answers to the overriding question for this 34th Bethesda Conference: Can Atherosclerosis Imaging Techniques Improve the Detection of Patients at Risk for Ischemic Heart Disease?

Atherosclerosis imaging, including many different emerging technologies, may enhance the detection and treatment of patients at risk for CHD. However, it is essential first to address aspects of the problem, including its scope and history, and to understand theoretical issues involving risk prediction and contemporary nonimaging approaches.

Confusion exists over the common terminologies that describe both clinical and laboratory diagnoses of conditions related to coronary atherosclerosis. For the purpose of this Bethesda Conference, we will use the term “coronary heart disease” (CHD), defined as cardiac events or symptoms related to myocardial ischemia and/or injury due, in the vast majority of cases, to atherosclerosis. Such events include unstable angina, myocardial infarction (MI), and sudden death due to ischemic heart disease. Some studies cited also include angina, or “new-onset” angina, as an “event.” It is important to recognize that coronary atherosclerosis, ischemia, and events exist as a continuum. The former need not necessarily lead to the latter, whereas the latter is virtually always preceded by the presence of the former. The challenge, then, is not only to “detect” coronary atherosclerosis, but also to “predict” which individuals, in whom coronary atherosclerosis is detected, will progress to develop CHD events.

Confusion also exists regarding the definition of “risk.” Although a full discussion of risk is beyond the scope of this report, it is important for the reader to understand that absolute risk refers to that percentage chance that an event will occur over a specific time period. Relative risk refers to the ratio or odds of an individual’s risk compared either to low risk or average risk (varies by study). Finally, when considering risk or reviewing studies, one must remember to ask: “Risk of what?” The risk of developing a single event (such as cardiac death) will be quite different from the risk of developing any one of a number of events (e.g., the typical combined cardiac end point used in many studies), or the risk of having atherosclerosis identified by an imaging technique. Importantly, for consideration of issues raised in subsequent task forces, it is critical to remember that the risk of having atherosclerosis is very different from the risk of actual events. In understanding risk, one must carefully distinguish between diagnosis (e.g., presence of coronary calcium or carotid intima-media thickening) and prognosis (e.g., chance of developing an acute coronary syndrome).

SCOPE OF THE PROBLEM

Age-adjusted (CHD) mortality rates have declined by approximately 50% since peaking in the U.S. between 1960
and 1970. Nonetheless, by all measures, the burden of CHD in the U.S. continues to be high. The decline in cardiovascular disease is less in the subpopulations of lower socioeconomic and certain ethnic groups and in geographic areas of the country with poor socioeconomic profiles, in which the burden of subclinical disease is substantial. Although age-adjusted death rates have declined over the past two decades, the absolute mortality rate from cardiovascular disease has not. Coronary heart disease accounts for over one-half million deaths (1 out of every 5) in the U.S. yearly (2). The lifetime risk of CHD after age 40 years has been estimated at 49% for men and 32% for women (3). Even for those who survive to age 70 years, lifetime risk for CHD has been estimated at 35% for men and 24% for women (3).

Risk factors for CHD account for a large proportion of the burden of heart disease in the U.S. today, suggesting that risk-factor identification and risk-lowering treatment could postpone or prevent the majority of CHD events. This is best demonstrated by studying CHD risk in persons lacking any of the major CHD risk factors (as the reference group). In a report from several U.S. cohorts, age-adjusted CHD mortality rates per 100,000 person-years among men with the lowest risk factor values at baseline ranged from rates of 2 to 6 in men 18 to 39 years of age and from 44 to 88 in men ages 40 to 59. Lowest risk status was defined as having all of the following favorable risk factor traits at baseline: serum cholesterol less than 200 mg/dl, systolic blood pressure (SBP) less than or equal to 120 mm Hg, diastolic blood pressure (DBP) less than or equal to 80 mm Hg, noncurrent smoker, no history of diagnosed diabetes, no previously diagnosed MI or hypertension, and no baseline electrocardiogram (ECG) abnormality. Estimated CHD mortality rates for those with at least one major risk factor is substantially increased in both women (approximately four-fold) and men (approximately five- to eight-fold) (4).

Healthy life habits can also define members of the population who are at low risk for CHD. In a report from the Nurses’ Health Study (5), relative risk for CHD events (fatal and nonfatal) was 82% lower among nonsmoking, non-obese (body mass index less than 25) women who engaged in more than 30 min of moderate-to-vigorous exercise/day, consumed at least half a drink of an alcoholic beverage daily, and scored in the highest 40% of the cohort for consumption of a diet high in cereal fiber, marine n-3 fatty acids, and folate, with a high ratio of polyunsaturated

Figure 1. Data from the Framingham Heart Study experience. Much of the middle-aged population has a low to intermediate risk for hard CHD (myocardial infarction or CHD death). Even up to age 80 years, more than three-quarters of women experience a 10-year risk of CHD that falls below 10%. The risks are higher for men, and by age 60 the majority of men are at intermediate (10% to 20% per 10 years) or high risk (greater than 20% per 10 years) for CHD. Figure courtesy Peter W. F. Wilson, MD, Framingham Heart Study (unpublished data).
to saturated fat and low in transfat and glycemic load (5). Thus, optimal risk-factor status confers a very low risk of CHD, an important concept as newer detection modalities are considered. Unfortunately, the prevalence of optimal risk-factor status in developed countries is low (about 10% or less of adults). Thus, among the many individuals with coronary risk factors who are at increased risk of developing incident CHD, the challenge is to identify accurately those who ultimately will develop CHD. Compounding the high prevalence of risk factors and unhealthy life habits is the fact that risk factors are inadequately assessed and treated (6).

**PRESENTATION OF CHD IN THE POPULATION**

Understanding the demographics of CHD is critical for the evaluation of issues involving the early detection of the disease. Many factors influence how patients present with CHD. A large majority of sudden cardiac deaths occurring outside the hospital are in individuals without preceding signs or symptoms of disease. The presentation of CHD is also affected by nonbiologic factors such as socioeconomic status and the attributes of the care system itself. Approximately 12.6 million Americans have CHD manifested as MI, angina pectoris, or both (2). For 1999, the overall CHD death rate in the U.S. was 195.6 per 100,000 population. Of the estimated 1.1 million Americans who experience MI annually, 650,000 are first-time events, and 450,000 are recurrences (2). More than 45% of these events are fatal, most from cardiac arrest associated with ventricular fibrillation. Approximately 250,000 people a year die of CHD without being hospitalized. Approximately 400,000 new cases of stable angina and about 150,000 new cases of unstable angina occur annually. The National Center for Health Statistics reported in 1996 that nearly 60% of those patients who were admitted with a diagnosis of unstable angina were over 65 years of age, and 46% of patients of all ages were women (7). Time trends suggest that the incidence of CHD and stroke, which declined through the 1970s and 1980s, has peaked and the actual prevalence rates have begun to increase as our population ages. Paradoxically, improvements in care, by leading to improvements in survival, appear to be resulting in greater numbers of CHD events overall. As this occurs, the imperative to predict these events with more accuracy grows proportionally.

**DETECTION**

Despite many available risk assessment approaches, a substantial gap remains in the detection of asymptomatic individuals who ultimately develop CHD. The Framingham and European risk scores, and more recently the Framingham-based National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) risk score (8), all emphasize the classic CHD risk factors incorporated into useful predictive models. However, this standard CHD, “evidence based,” multiple risk factor assessment approach is only moderately accurate for the prediction of short- and long-term risk of manifesting a major coronary artery event, particularly an event such as sudden death, in healthy populations (9,10). It is uncertain whether the addition of newly emphasized risk markers will sufficiently assist in the quantitative assessment of CHD risk to allow adequate precision for optimal matching of the intensity of management to the level of risk.

A potentially important discrepancy has arisen in our understanding of the role of conventional risk factors and atherosclerosis compared to the development of CHD events. Although considerable data suggest that there is a very low event rate in people with extremely low risk profiles, the presence of risk factors in studies of subclinical atherosclerosis detected by imaging techniques appears to explain the presence and extent of disease less completely. For example, in a study of over 600 army personnel without known CHD, of the traditional risk factors evaluated only low-density lipoprotein (LDL) cholesterol was independently associated with coronary artery calcification by electron-beam computed tomography (EBCT) (11). In that study the relationship between coronary calcium and the Framingham risk score was positive but weak. Data from the Cardiovascular Health Study did demonstrate that traditional risk factors were determinants of subclinical disease, but appeared to have a smaller association with clinical disease once subclinical disease developed (12).

Finally, in recent work from the Framingham Heart Study, the global risk score did correlate with the presence of subclinical aortic atherosclerosis, but only weakly (r ~ 0.20) (13). If confirmed, this apparent difference in the relationship between risk factors and clinical versus subclinical disease might have important implications in the role of subclinical detection and risk prediction. As will become evident throughout this Bethesda Conference, the relationship between the demonstration of atherosclerosis has a variable, and often uncertain, relationship to the development of future CHD events.

An understanding of certain principles of screening needs to precede any evaluation of screening techniques. Accordingly, we review Bayes’ theorem and use exercise stress testing to illuminate issues of predictive accuracy and pretest probability.

**Bayes’ theorem.** The predictive value of any test depends on the sensitivity and specificity of the test, and on the prevalence of the condition in the population being tested. This notion, based on Bayes’ theorem, has been extensively explored and discussed in the field of exercise stress testing. In simple terms, the greater the likelihood that the condition being screened for is present in an individual or in the population (pretest probability), the greater the validity of a positive test and likelihood that this is a true positive. Thus, the problem with using a test in any population where there is a low likelihood of the condition being present is that a positive result has limited value (i.e., it is more likely to be a false positive). Figure 2 demonstrates how even a test with high sensitivity and specificity will yield a low predictive...
Despite that, the absolute risk of a cardiac event is quite low with risk factors, in whom disease prevalence is lower. For young adults and middle-aged or older women, even coronary events. The same predictive power does not hold for middle-aged men with elevated levels of traditional risk factors carries independent predictive power for major coronary events. The same predictive power does not hold for young adults and middle-aged or older women, even with risk factors, in whom disease prevalence is lower. Despite that, the absolute risk of a cardiac event is quite low in those patients with positive stress tests who have no risk factors, while the presence of at least one risk factor associated with abnormalities on stress testing is associated with substantial (30-fold) higher five-year risk compared to those with no risk factors present (14,15). Thus, despite the markedly higher relative risk, the absolute likelihood of event remains low, and because of the low baseline risk, the chance of a false positive test is high.

The impact of this problem of low pretest probability is considerable. Large studies suggest that the positive predictive value of exercise ECG testing in asymptomatic people is less than 10% for predicting “hard” CHD events (cardiac death and MI) (16,17). The addition of myocardial imaging does not greatly improve predictive accuracy unless patients are selected because of the presence of one or more risk factors (18). Hence, the expense of the test and its low yield of positive outcomes make it unsuitable for routine risk assessment in asymptomatic individuals, except, perhaps, among those at high baseline risk (high pretest probability), a lesson that must be remembered when considering other noninvasive tests for the detection of cardiovascular risk.

The challenge facing any screening test that has less than perfect performance when applied to a low prevalence population is illustrated in Figure 3. In this example, an analogy is made using data from Hachamovitch et al. (19), which quantified the incremental value of single-photon emission computed tomography (SPECT) perfusion imaging over Duke treadmill score for predicting cardiac events in a symptomatic population. Figure 3 demonstrates that the more sensitive test, the SPECT, predicted a greater number of events (Fig. 3A), compared to the less sensitive Duke treadmill score. However, when examined according to the absolute number of events, subjects with low/normal and intermediate/mild test results actually accounted for the majority of events (Fig. 3B). This problem is amplified in a low prevalence population. Although this concept does not undermine the importance of screening a population, it does illustrate the reality that, with any less than perfect test, a majority of subjects at true risk may still go undetected. Other tests for CHD risk must be evaluated in low risk populations, and predictive accuracy must be measured in these low risk populations, before such tests can be recommended for risk assessment.

**ATHEROSCLEROSIS DETECTION FROM OTHER TESTS**

Other approaches to cardiovascular risk prediction have been considered because exercise stress testing cannot be regarded as an appropriate means of identifying a large pool of asymptomatic high-risk people. As discussed in later Task Force documents, several noninvasive tests are now available that directly detect atherosclerosis in different vascular beds. Because atherosclerosis is a generalized macrovascular disease, lesions in one vascular territory predict disease in other arterial regions. Similar risk factors are present among patients with coronary, peripheral, and...
carotid atherosclerosis. Of particular importance is evidence that disease in noncoronary arteries is a powerful predictor of CHD mortality. In fact, ATP III has termed aortic, peripheral, and carotid artery disease as "Coronary Heart Disease Equivalents" because the level of CHD risk and CHD event rates associated with these conditions is approximately equivalent to the level of risk seen in stable CHD (8). The rate of CHD events in persons with atherosclerotic vascular disease in other territories is similar to event rates in patients with known CHD. Thus, screening for atherosclerosis in other vascular regions has been considered for CHD risk evaluation.

**Nonimaging detection of CHD risk.** Our understanding of the clinical manifestations of atherosclerosis derives from the study of pathophysiology, epidemiology, and from clinical trials, and has added substantially to our ability to identify and modify risks for CHD. Nonetheless, important limitations exist in our ability to precisely identify individuals who should be targeted for aggressive risk modifying interventions. It is thus appropriate to review current clinically available approaches to stratify risk of CHD.

**History and physical examination.** Although often underemphasized in today's world of advanced technology, the history and physical examination continue to play an important role in assessing the risk for CHD in both asymptomatic and symptomatic subjects. The history identifies important components, including the presence or absence of cardiac symptoms, known major risk factors for CHD, and comorbid conditions. The physical examination is complementary to the history and may enhance the assessment of the presence of vascular disease and CHD risk factors. Although history is very sensitive for the detection of CHD, the physical examination is not. In a two-year study of 630 patients, the history correctly detected the diagnosis in
two-thirds of the patients and physical examination in just one-fourth (20).

**Traditional risk factors (Table 1).** Ever since the initiation of the Framingham Heart Study more than 50 years ago, our knowledge of CHD risk and the benefit of risk modification has grown considerably. In fact, the term “risk factor” was coined by an early Framingham investigator (21). We now identify both “traditional” risk factors and newer “novel” risk factors (Table 2). Although the identification of traditional risk factors does not identify all CHD risk, the absence of all major risk factors does identify those individuals at very low risk. For high-risk patients, the major traditional risk factors account for between 50% and 80% of subsequent cardiovascular events (15,22).

### IDENTIFYING THE HIGH-RISK ASYMPTOMATIC PATIENT: GLOBAL RISK ASSESSMENT

Mathematical models incorporating assessment of major CHD risk factors have been used to predict general levels of risk (e.g., low, intermediate, or high) and to estimate the yearly percentage risk (absolute risk) of future events (9,10,23). Estimates or scores derived from these models (Table 2) are now commonly known as "global" risk scores. Formal endorsement of global risk scoring to identify higher risk individuals has come from the American Heart Association (AHA), the American College of Cardiology (ACC), the European Society of Cardiology, and most recently ATP III (8,23). As national guidelines have advanced, clinicians have been presented with increasingly more sophisticated ways to assess risk (23,24). Both ATP II and Joint National Committee (JNC) VI published in 1993 and 1997, respectively, used “risk factor counting.” The most recent European and U.S. lipid guidelines (ATP III) use a score derived from the Framingham Heart Study to estimate 10-year risk of having a cardiac event to help divide patients into low, intermediate, and high risk subgroups, and specifies different intensities of treatment for each subgroup.

A modification to this subgrouping has recently been suggested to improve CHD risk assessment in asymptomatic people (10). This approach considers a less than 0.6% per year (less than 6% over 10 years) risk for coronary events as “low-risk.” Such individuals generally are free of any major CHD risk factors. A 0.6% to 2.0% per year (6% to 20% over 10 years) risk is termed “intermediate risk,” and includes most individuals with at least one major positive CHD risk factor. Those with greater than or equal to 2.0% per year (greater than or equal to 20% over 10 years) risk are “high-risk” as they have a level of risk equivalent to patients with stable established CHD. We have adopted these definitions of levels of risk for this Bethesda Conference. Huge numbers of people in the U.S. would appear to be candidates for risk factor reduction efforts and for public health initiatives (Fig. 1).

The most recent "global risk score" version (8) includes the following variables: age, gender, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking status, SBP, and hypertension treatment (yes/no). The individual’s average CHD health information is entered either into a score sheet, computer, Web page, or palm pilot, and an absolute yearly risk (percent chance of a major coronary event) or 10-year risk is calculated. The current version estimates the likelihood of MI or cardiac death (“hard events”), as these end points are well validated. Diabetes is not part of the ATP III risk algorithm, as the diagnosis of adult onset diabetes mellitus is itself considered a CHD risk equivalent (high risk even without other risk factors or clinically evident CHD), thus having a 10-year risk of approximately 20%.

Can global risk assessment sufficiently identify individuals at risk for cardiovascular events and focus preventive treatment appropriately? Is the test sufficiently sensitive to detect the majority of people at risk and specific enough to exclude those at lower risk? Is a staged testing strategy more

**Table 1. Risk Force #1—Coronary Heart Disease Risk**

<table>
<thead>
<tr>
<th>Major independent risk factors</th>
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<tbody>
<tr>
<td>Cigarette smoking</td>
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<tr>
<td>Elevated blood pressure</td>
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<tr>
<td>Elevated serum total and LDL cholesterol</td>
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<tr>
<td>Low serum HDL cholesterol</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Advancing age</td>
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<tr>
<td>Other (predisposing) risk factors</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Abdominal obesity</td>
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<tr>
<td>Physical inactivity</td>
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<tr>
<td>Family history of premature CHD</td>
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<tr>
<td>Ethnic characteristics</td>
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<tr>
<td>Psychosocial factors</td>
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<tr>
<td>Conditional risk factors</td>
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<tr>
<td>Elevated serum triglycerides</td>
</tr>
<tr>
<td>Small LDL particles</td>
</tr>
<tr>
<td>Elevated serum homocysteine</td>
</tr>
<tr>
<td>Elevated serum lipoprotein(a)</td>
</tr>
<tr>
<td>Prothrombotic factors (e.g., fibrinogen)</td>
</tr>
<tr>
<td>Inflammatory markers (e.g., C-reactive protein)</td>
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</tbody>
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CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein. Adapted from Grundy (25).

**Table 2. Examples of Approaches to Risk Assessment With Multiple Coronary Heart Disease Risk Factors**

<table>
<thead>
<tr>
<th>NCEP: ATP I and II—Risk-factor counting</th>
<th>ATP III—Global Risk</th>
<th>European Societies of Cardiology, Atherosclerosis, and Hypertension</th>
<th>Framingham Risk Score</th>
<th>British Regional Heart Study (BRHS) Risk Score</th>
<th>Sheffield Coronary Risk Tables</th>
<th>GREAT (General Rule to Enable Atheroma Treatment)</th>
<th>Munster Heart Study (PROCAM) Risk Score</th>
<th>Dundee Coronary Risk Disc</th>
<th>National Heart Foundation of New Zealand Guidelines</th>
<th>West of Scotland Cardiovascular Event Reduction Tool (CERT)</th>
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</thead>
<tbody>
<tr>
<td>Adapted from Greenland P, et al. (10).</td>
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appropriate than using a single testing strategy for all patients, regardless of risk-factor levels, global risk assessment, or other means of sorting patients prior to further testing? Unfortunately, these questions remain largely unanswered, and they should be the focus of future investigations.

Greenland et al. (10) have recently suggested an approach to the office-based assessment of asymptomatic patients centered on global risk assessment. This approach begins by utilizing the Framingham risk scoring method to estimate absolute coronary risk. Subsequently, individuals are stratified into low risk (less than 6% 10-year absolute risk), an intermediate risk group (risk 6% to 20% per 10 years), and high-risk group (risk greater than 20% over 10 years). They estimate that of the U.S. adult population, 35% fall into the low-risk group, 40% into the intermediate group, and 25% into the highest-risk group. This compares favorably with proportional risk estimates for men developed by Wilson for this Bethesda Conference, but overestimates the proportion of women in intermediate and high-risk groups (Figs. 1a and 1b). Patients at low risk are easily categorized, and they require primarily reassurance and advice regarding healthy lifestyles, whereas the high-risk group (risk greater than 20% for 10 years) will benefit from aggressive risk factor reduction. As so often is true in medicine, the intermediate group represents the greatest challenge for treatment decisions. However, even in the high-risk category, several issues can be raised:

- Are there high-risk group individuals who should be submitted to further risk testing to assess interventional options beyond risk factor modification? How can these subjects be identified?
- If further CHD risk assessment identifies significant abnormalities, can the further testing refine the indications for an intervention such as angiography or coronary artery revascularization?

Substantial questions remain for the large group of people at intermediate risk.

- Which patients in this group should or should not be recommended for drug treatment or other interventional therapies?
- How should patients within the intermediate group be best stratified with additional testing?

NOVEL, PREDISPENDING, AND CONDITIONAL RISK FACTORS

“Novel” risk factors (Table 1) have received considerable attention in the published reports, both for their role in advancing our understanding of atherosclerotic pathophysiology and for their possible ability to improve identification of high-risk individuals. Because of the apparent ability of certain of these factors to influence the effects of the known major risk factors, Grundy (25) has termed some of these as “conditional” risk factors. They can be divided into infection/inflammatory markers and serum markers.

Infection/inflammatory markers. Markers of inflammation such as high sensitivity C-reactive protein (CRP) elevated white blood cell count (WBC), and positive serology for bacterial and/or viral infections have all been reported to be associated with an increased incidence of CHD events (26,27). Prospective studies of CRP have shown elevated levels to be associated with two- to four-fold higher risk of different cardiovascular end points (26–30). In the Nurses’ Health Study (29), CRP was shown to improve cardiovascular risk prediction significantly when added to total and HDL cholesterol evaluation. Ridker (30) has proposed that increasing CRP levels can add to the predictive value of lipid assessment. Data from the Women’s Health Study show an incremental prognostic value to CRP when added to the Framingham risk score (31). Nevertheless, there remains considerable debate regarding the use of CRP as a risk marker because of difficulty identifying a “cut point” for prognostic significance of this marker and concerns about reliability and accuracy (32,33). The utility of CRP testing across different ethnic groups is also unknown. Thus, routine measurement of CRP is not currently recommended by the American Heart Association (34).

Serum markers. An elevated homocysteine level has been shown in many but not all studies to be associated with an increased risk of CHD (35). The data do not yet suggest that routine measurement of homocysteine would be beneficial in risk assessment. Many additional serum lipid markers, including small dense LDL, apolipoproteins A1 and B, and lipoprotein (a), have been related to increases in CHD risk. Owing to insufficient prospective data, variability of and access to testing, and questions of cost-effectiveness, these markers have not yet been found to add value to CHD risk assessment beyond those identified under traditional risk factor assessments (22,34).

An illustrative comparison of the relative risk of future events among women for the most commonly used novel markers and standard lipids is shown in Figure 4 (32). Considerable overlap exists in confidence intervals, which are quite large. Thus, although likely useful for comparing populations or groups, one can see that the precision of a risk estimate for any of the novel markers in an individual patient is likely to be poor. Furthermore, the estimates shown in Figure 4 compare only the highest risk quartile with the bottom quartile—again useful for understanding a population but virtually useless for an individual, whose individual risk lies somewhere along a continuous spectrum.

Figure 5 demonstrates how a mathematical model based on factors similar to those employed in the Framingham risk-scoring system can improve upon risk prediction when compared to simple risk-factor counting, as assessed by receiver operating characteristic (ROC) curves. Estimation of risk by the Framingham risk score, or any similarly derived regression equations, can be seen to represent a “low
bar” on the risk-prediction ladder. This tool is widely accessible, easily used, and almost cost-free. The evidence-base for using this approach is robust. Many of the potential tools available to help further risk stratify those within this group, such as CRP measurements, coronary calcium scoring, or carotid ultrasound for intima-medial thickness (IMT) measurement, have been the subject of considerable additional attention, as discussed in this Bethesda Conference document. Improvements in risk estimation should be viewed in the context of their relative benefit when added to the Framingham risk score (or a similar algorithm).

CURRENT BARRIERS TO RISK ASSESSMENT

Because CHD is the leading cause of morbidity and mortality in the U.S., and because as much as half of the mortality from this disease occurs in previously asymptomatic individuals, the principal barrier to identifying at-risk asymptomatic individuals is the sheer magnitude of the problem. The first challenge that should be addressed, well beyond the scope of this Bethesda Conference, involves the need for a greater understanding and awareness of the potential risk for CHD by both our adult population and by medical professionals. Awareness is a population issue that no screening approach can address, no matter how optimal. Inadequate adherence to medical and lifestyle interventions has been increasingly recognized as an important medical problem. Principles embodied in approaches to improve adherence with therapies may also be applied to understanding the adherence barriers in risk screening and prediction.

Such barriers can be divided into three categories: those that exist: 1) for patients in the population, 2) for physicians and other caregivers, and 3) for the medical system itself. Although a detailed discussion of these issues is beyond the scope of this report, several principles can be noted:

- **Awareness**—individuals and professionals must be aware of the important concept that the level of risk intervention (and subsequent benefit) depends upon identifying those at highest risk.
- The public and professionals must have access to understandable risk assessing strategies and technologies. A recent study (36) suggests that routine calculation of CHD risk in primary care settings is hindered by poor availability of risk factor data and by inappropriate and consequently inaccurate use of risk-calculation tools.
- Risk assessment modalities need to be valid and reproducible. The validity across different populations, ages, genders, and ethnic backgrounds must be understood.

Another important barrier is the absence of prospective data demonstrating added benefit when additional risk assessment is added to global risk scoring. Unfortunately, to date, most studies evaluate emerging laboratory tests and technologies compared to baseline population estimates, or compared to other risk assessment strategies. Further barriers in risk assessment include aspects of understanding risk itself, specifically “risk of what?” An ideal hierarchy might be proposed, such as 1) identify those at risk for sudden cardiac death, then 2) those at risk for MI or stroke,

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**Figure 4.** Comparison of the magnitude of relative risk of future cardiovascular events associated with abnormal values of different risk factors or combination of risk factors. The data are derived from initially healthy women in the Nurses’ Health Study. In each case, relative risk is shown (black box) for individuals in the top versus the bottom quartile for each factor, 95% confidence intervals are shown by the horizontal lines. (Ridker [30]).
followed by 3) individuals at risk for angina or claudication. However, in assessing risk, it is clear that individual tools and technologies will not be equally accurate with respect to predicting different end points. For example, identification of extensive carotid atherosclerosis by carotid ultrasound is presumably more likely to be predictive of future stroke than would be true by the identification of coronary calcium by EBCT. Both techniques have been shown to be helpful in predicting of future coronary events. When comparing risk assessment strategies, comparisons will need to be made for equivalent end points.

Measurement of risk itself is also problematic. Changes in absolute risk (the probability of developing an event over a finite period of time) must be the critical starting point for risk assessment and evaluation of risk reduction strategies. However, absolute risk increases are often quite small, as is absolute risk reduction, even for established risk lowering therapies. Thus, relative risk and relative risk reduction are often considered (relative risk is the ratio of absolute risk in a patient undergoing the risk assessment compared to risk level for a person at average or at low levels of risk). Relative risk is useful for comparing different techniques or interventions. Finally, the duration of risk prediction is important. Some approaches for risk assessment are likely to be more useful for near-term prediction of events (e.g., stress testing), whereas others are more likely to be useful in assessing risk over the long term or life of an individual (e.g., LDL cholesterol level).

The size of the population studied in evaluation of risk prediction is also of critical importance. Many studies have employed statistically inadequate sample sizes. Because CHD events are relatively unusual in low-risk and even in intermediate-risk populations, large populations are required to accurately assess the usefulness of any risk prediction strategy. Finally, as this field moves forward, the clinician and investigator must keep in mind several factors in the evaluation of any diagnostic or screening test, beyond the reported accuracy and predictive value of the test:

- Is there a referral bias?
- Is the reference population valid?
- How are uninterpretable tests handled in the analysis?
- Is the test population excessively homogeneous?
- Is the test practical to put into practice?
- Is it practical to put the results of the test into practice?
- What are the down-stream costs and the cost-effectiveness of the test?

**THE DETECTION GAP**

Magnitude of the detection gap. There is no debate that a detection gap exists. The size of this gap can only be estimated by orders of magnitude, in part because we cannot count those individuals who remain undetected. For exam-
example, ATP III estimates (8) that approximately 36 million individuals require drug treatment for elevated LDL cholesterol levels, others suggest the number could be more (37). Yet, only 10 million to 15 million Americans are currently receiving lipid-lowering drugs. The last national blood pressure guideline report (38) estimated that about one-third of hypertensives in the U.S. population were undetected. With the estimated number of people with hypertension in this country at 50 million, that leaves very large numbers at risk yet undetected. Nearly half a million sudden deaths (most with CHD) and over a million MI occur yearly in the U.S. Thus, the size of the at-risk population could also be estimated as follows: high-risk individuals have an approximate risk per year of 2% or greater; if there are 650,000 sudden primary deaths and MIs annually, the total at risk population would equal 30 million to 37 million or more. The number receiving comprehensive risk-lowering therapies is clearly vastly lower than that sum.

**Effective application.** Despite opportunities to refine risk assessment in order to focus on and reduce risk more effectively, there exists the larger problem of effectively applying recommendations to patients. Various guidelines have been published by the ACC/AHA for both primary and secondary prevention and have been recently updated. Guidelines have also been published clarifying the focus of risk assessment and guiding clinical intervention.

Unfortunately, however, it has been shown that, although clinicians may be aware of guidelines, such guidelines are not effectively or routinely applied to practice. Pearson et al. (39) demonstrated in a group of medical practices that provider awareness of NCEP guidelines was quite high (95%). However, the number of patients within those practices treated to goal levels was unacceptably low (18%). Fonarow et al. (40), using National Registry of Myocardial Infarction (NRMI)-3 data, reported that only 31.7% of patients (138,000) with acute MI were discharged on lipid-lowering therapy. They also demonstrated that a large numbers at risk yet undetected. Nearly half a million sudden deaths (most with CHD) and over a million MI occur yearly in the U.S. Thus, the size of the at-risk population could also be estimated as follows: high-risk individuals have an approximate risk per year of 2% or greater; if there are 650,000 sudden primary deaths and MIs annually, the total at risk population would equal 30 million to 37 million or more. The number receiving comprehensive risk-lowering therapies is clearly vastly lower than that sum.

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**Potential for incremental information to improve prediction of CHD events.** As already reviewed, numerous possible approaches are now available to improve risk assessment, thereby potentially useful to decrease the detection gap. Many of these are widely available, relatively valid, and safe. Our understanding of their cost effectiveness is evolving and will be discussed later in this Bethesda Conference. Previous guidelines and scientific advisories have encouraged use of newer approaches, but advice generally has been relatively nonspecific. For example, the AHA Prevention V Conference suggested “more routine use of office-based risk assessment” (15). Further specific refinement of this advice is clearly needed. The perspective offered by Greenland, Smith, and Grundy (10) advances this general approach. Figure 6 (taken from their report) is illustrative. It demonstrates how additional test results can either substantially increase or decrease the probability estimate of a future CHD event by increasing the chance that a positive result is a true positive, or that a negative result is a true negative. (Adapted from Greenland et al. [10]).
and beneficial (32,42). Investigators and clinicians should adopt new diagnostic or prognostic testing based on the same firmly established, evidence-based standards used for adoption of new therapies on procedures. Furthermore, it remains clear that even optimally applied global risk assessment would continue to lead to a gap in our ability to predict those individuals at greatest risk for developing CHD events. The magnitude of this gap, although not precisely quantifiable, is likely very large.

FUTURE DIRECTIONS

1. A detection gap in CHD prognosis exists. The precise size of this gap is unknown, but is likely substantial. Prospective study is needed to identify its magnitude and implications.
2. Current CHD risk screening tools are imperfect and imperfectly applied. Because these are not optimally accurate, opportunities exist (e.g., with newer biologic markers and/or atherosclerosis imaging) for their refinement. Current CHD risk-screening tools should be the subject of effectiveness testing. Greater commitment is needed toward funding such research initiatives.
3. Based upon the Bayes’ theorem, the application of atherosclerosis imaging is theoretically best suited to intermediate risk populations. Before this application becomes practice there is need for a greater body of supporting evidence in which the incremental benefit of obtaining such information is demonstrated.
4. Concomitant with efforts to utilize atherosclerosis imaging for more accurate detection of CHD risk, the community of cardiologists must champion CHD prevention, beginning by fully translating existing data on effective risk-screening and interventions into practice.

TASK FORCE 1 REFERENCE LIST

Atherosclerosis is composed of cellular and acellular elements that combine to form a variety of plaque types (Table 1, Fig. 1). With respect to atherosclerosis imaging, four plaque histologic characteristics are considered in this Task Force report: necrotic core, fibrous cap, calcium, and inflammatory activity. The relative prevalence of these components depends on the degree of stenosis, the clinical coronary heart disease syndrome, and nonlocal factors including the patient’s gender and traditional and nontraditional risk factors.

**Components of Atherosclerosis That Form Targets for Atherosclerosis Imaging**

Several studies (1–4) have reported the relationship between the following types of plaque components and degree of stenosis.

**Necrotic core.** A necrotic core is present in approximately 25% of plaques with less than 50% cross-sectional stenosis, and this increases in prevalence with increasing stenosis severity. Above 70% cross-sectional luminal narrowing, about 75% of plaques will demonstrate a necrotic core.

**Fibrous cap.** Fibrous cap atheromas are defined as plaques with a well-defined lipid core covered by a fibrous cap, which may be relatively acellular (made of dense collagen) or may be rich in smooth cells. No data in autopsy studies are available regarding the prevalence of fibrous caps of various thickness. Stenosis severity is directly related to the proportion of dense fibrous tissue (type I collagen) in the fibrous cap, and inversely related to smooth-muscle-cell–rich areas (2–4).

**Calcium.** The presence of calcium is strongly correlated with stenosis severity (3–6) (Fig. 2) and is modulated by age. As age advances, the mean percent calcified area increases both for plaques with moderate (greater than or equal to 50% to less than 75% cross-sectional area) luminal narrowing and severe (75% to 90% cross-sectional luminal area) narrowing (5). Importantly, a thrombotic, recanalized total occlusion may be devoid of calcification. The incidence of calcification in total occlusions may be partly a function of lesion age (7).

**Inflammatory activity.** Inflammation, both of the intima and adventitia, increases in prevalence with increasing percent stenosis (1).