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Biochemical Markers of Cardiovascular Disease Risk

Prepared under the direction of the
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Description of Treatment/Procedure

Atherosclerosis is now recognized as an inflammatory disease. Endothelial dysfunction, potentially caused by one or a combination of factors, is the first step. A lipid profile is the accepted method of assessing an individual's risk for coronary heart disease (CHD). However, traditional risk factors (tobacco use, age, gender, family history, hypertension, diabetes, and lipid levels) do not identify all patients who will experience a cardiovascular event. Biochemical markers of the steps leading to the development of atherosclerotic lesions may complement the traditional risk factor profile. These would include markers of lipoprotein metabolism (lipoprotein (a)), endothelial dysfunction (homocysteine), fibrinolysis (plasminogen activation inhibitor 1), and inflammation (C-reactive protein).

Potential Uses

The routine use of emerging risk factors assessment in the context of primary prevention is not recommended. Testing for emerging risk factors may be appropriate for assessment of atherosclerosis not explained by traditional risk factors or when the atherosclerosis is more severe than would be expected based on the traditional risk factor profile. Testing would not be of value for a patient with no atherosclerosis but this is typically unknown.

Contraindications

There are no known contraindications.

Efficacy of Treatment/Procedure

Much of the evidence, to date, has focused on C-reactive protein (CRP) and total homocysteine (tHcy). Prospective studies of the relationship between CRP and cardiovascular risk have found greater risk of disease in patients with elevated CRP levels. A high-sensitivity CRP assay is needed. CRP levels are reduced with statin therapy but it is unknown whether decreased CRP levels result in a decreased risk of CHD. Prospective studies of the relationship between tHcy and cardiovascular disease have typically found little association between tHcy levels and vascular risk. Although the addition of folic acid to enriched grain products has resulted in reduced levels of tHcy, it is unclear whether reducing tHcy levels improves cardiovascular morbidity and mortality.

Committee Summary

With regard to biochemical markers of cardiovascular disease risk, the ICSI Technology Assessment Committee finds:

1. The basic lipid profile (high-density lipoprotein, low-density lipoprotein, and triglycerides) provides a useful indication of cardiovascular disease risk and serves as a guide for statin therapy in a primary prevention context.
2. CRP, if measured by high-sensitivity assay (hs-CRP), may have independent value as a predictor of cardiovascular disease risk and independent value in identifying patients with normal lipids who could benefit from treatment (Conclusion Grade II). hs-CRP elevations can be caused by inflammatory conditions and, therefore, are not specific for cardiovascular assessment in individual patients. Further study is needed to determine if decreasing CRP levels would decrease cardiovascular disease risk.
3. The relevance of studies of tHcy as a risk factor for cardiovascular disease is unclear given the decreasing tHcy levels as a result of mandatory folic acid supplementation. It remains unproven whether lowered tHcy levels will result in reduced morbidity and mortality from cardiovascular disease.
4. Other biochemical markers do not add to the prediction of risk above that achieved using lipid measures and hs-CRP.
5. Assessment of the markers is safe, requiring only a blood sample for analysis.

Technology Assessment Report

Biochemical Markers of Cardiovascular Disease Risk

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TA#66

Approved: January, 2003

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ICSI Technology Assessment Report Process

- A topic is selected by the Technology Assessment Committee based on expression of interest in that topic from the ICSI medical groups or ICSI sponsoring health plans.
- A work group of 4 to 6 physicians and other health care professionals who are experts in the topic area is assembled (with a formally designated leader).
- The literature search is completed using MEDLINE and PREMEDLINE; in addition, bibliographies of articles obtained from the literature search are examined to identify articles that may have been missed and work group members are asked to provide key references. The evidence is graded according to the system described in the reference section of the report.
- The ICSI staff person prepares a draft report.
- The work group meets to review the draft report and directs the ICSI staff person in revising the report.
- The work group leader presents the report to the ICSI Technology Assessment Committee. Committee members review the report to determine whether the conclusions are supported by the evidence cited. The Committee often requests revisions prior to approving the report for review and comment.
- The report is distributed to the ICSI Medical Groups for review and comment. Comments received are shared with the work group members and revisions to the report are made, if necessary.
- The Technology Assessment Committee reviews the comments and the work group response and makes the final decision regarding approval of the report for distribution.
- Reports are reviewed bi-annually and revised, if warranted.

Description of Technology/Procedure

Atherosclerosis is now recognized as an inflammatory disease, not merely an accumulation of lipids within the artery wall. Endothelial dysfunction is viewed as the first step in atherosclerosis. The dysfunction may be caused by elevated and modified low-density lipoproteins (LDLs); free radicals resulting from cigarette smoking, hypertension or diabetes mellitus; elevated plasma homocysteine levels; infectious microorganisms; or combinations of these and other factors. In response to injury, compensatory actions alter the normal homeostatic properties of the endothelium resulting in increased adhesiveness of the endothelium (with respect to leukocytes or platelets); changes in permeability; a change from anticoagulant to procoagulant properties; and formation of vaso-active molecules, cytokines, and growth factors. If the injury is not effectively neutralized, the inflammatory response leads to migration and proliferation of smooth-muscle cells that become intermixed with the area of inflammation forming an intermediate lesion. As the artery wall thickens, there is also gradual dilation to maintain the lumen. The numbers of macrophages and lymphocytes multiply within the lesion and result in the release of hydrolytic enzymes, cytokines, chemokines, and growth factors. The cycle continues leading to further enlargement and restructuring of the lesion. Eventually there is a fibrous cap covering a core of lipid and necrotic tissue (an advanced, complicated lesion). When the artery can no longer compensate for the lesion by dilation, the lesion intrudes into the lumen and changes the blood flow. These lesions may rupture or erode exposing pro-coagulant material which is thought to be the proximate cause of acute events including unstable angina or myocardial infarction. The mechanism is similar to other chronic inflammatory-fibroproliferative diseases (including cirrhosis, rheumatoid arthritis, and pancreatitis) (Ross, 1999; Albert, 2000).

A lipid profile, including LDL, high density lipoprotein (HDL), and triglyceride levels is the accepted method of assessing an individual's risk for coronary heart disease (CHD). LDL is considered the major atherogenic lipoprotein while increased levels of HDL may protect against the development of atherosclerosis. Elevated serum triglycerides can be considered as a marker for atherogenic remnant lipoproteins. The National Cholesterol Education Program (NCEP) reported that evidence from a variety of study types (from basic laboratory studies to controlled clinical trials) indicates a strong causal relationship between elevated LDL cholesterol and CHD (NCEP, 2001). Similarly, it was reported that elevated serum triglycerides are directly associated with increased risk for CHD and low HDL levels were inversely associated with risk for CHD (NCEP, 2001).

Nonlipid risk factors, including hypertension, cigarette smoking, diabetes mellitus, age, male gender, and a family history of coronary artery disease, are considered major, independent risk factors for CHD (NCEP, 2001). Obesity, physical inactivity, and an atherogenic diet are major risk factors but do not appear to contribute to risk independently of other risk factors (NCEP, 2001). The presence of multiple risk factors is associated with an increased risk of CHD. However, neither hyperlipidemia nor the nonlipid risk factors are capable of identifying all patients who will experience a myocardial infarction (MI) nor do all patients with a significant risk factor profile develop symptomatic disease (Albert & Ridker, 1999; Nass, Wiviott, Allen, Post, Blumenthal, 2000; Rader, 2000). Other factors or combinations of factors may modulate the risk.

Biochemical markers of the steps leading to the development of atherosclerotic lesions have been proposed as emerging risk factors for assessing an individual's cardiovascular disease risk. Examples of emerging risk factors would be markers of lipoprotein metabolism (lipoprotein (a) [Lp(a)], cholesteryl ester transfer protein [CETP], lipoprotein lipase [LPL]), endothelial dysfunction (homocysteine), fibrinolysis (fibrinogen, plasminogen activator inhibitor 1 [PAI-1], tissue-type plasminogen activator [tPA]), and inflammation (C-reactive protein [CRP], interleukin-6 [IL-6], soluble CD40 ligand [sCD40L], lipoprotein-associated phospholipase A₂ [Lp-PLA₂]). Markers of endothelial function and cell adhesion (P-selectin, E-selectin, adhesion

molecules), antioxidants (vitamin E, vitamin C), and oxidative stress (serum 7 beta-hydroxycholesterol) are also being studied. At present, most of the markers are not approved for screening and there are no uniform reference data for normal values in the population (Pahor, Elam, Garrison, Kritchevsky, & Applegate, 1999; Nass et al., 2000; Packard et al., 2000; Schönbeck, Varo, Libby, Buring, & Ridker, 2001). In addition, for most of the markers, there is a lack of measurement standardization, a lack of consistency of findings, and a lack of evidence that the marker adds to risk prediction above that possible with traditional risk factors (Greenland et al., 2000).

The American Heart Association's Prevention Conference V (Smith, Greenland, Grundy, 2000), recommended that asymptomatic patients at intermediate risk for future coronary events undergo additional testing to better stratify risk. Of the recommended tests, CRP, Lp(a), homocysteine, fibrinogen, and PAI-1 (along with triglycerides and small LDL particles) were classified as conditional risk factors (correlation to CAD events has been established but quantitative relation to major coronary events remains to be defined adequately in large prospective studies). Cigarette smoking, elevated blood pressure, elevated serum cholesterol (LDL or apolipoprotein B [Apo B]), low HDL cholesterol, and diabetes mellitus were classified as causative risk factors (research has identified a direct relationship to CAD events). Overweight and obesity, physical inactivity, male sex, family history of premature coronary heart disease, socioeconomic factors, behavioral factors, and insulin resistance were classified as predisposing risk factors (contributing to the development of the causal and conditional risk factors). Left ventricular hypertrophy was classified as a susceptibility risk factor (Grundy et al., 2000; Nass et al., 2000; Smith, Greenland, & Grundy, 2000).

The NCEP report review of emerging risk factors concluded the following (NCEP, 2001):

- 1) Lp(a): the quantitative contribution of elevated Lp(a) to CHD risk beyond major risk factors is uncertain; standardized methods for measuring Lp(a) available only in a few reference laboratories; no clinical trial evidence supports a benefit from lowering Lp(a) levels
- 2) Apolipoprotein B: proposed as an alternative to LDL cholesterol as a risk factor; standardized apolipoprotein B measures are not widely available; the body of evidence in favor of apolipoprotein B has not been developed sufficiently to justify replacing LDL cholesterol
- 3) Apolipoprotein AI: carried in HDL; standardized methodology for estimating apolipoprotein AI is not widely available; predictive power beyond HDL cholesterol is uncertain; measurement is not recommended for routine risk assessment
- 4) Homocysteine: elevated serum levels are positively correlated with risk for CHD but strength of association is not as great as that for the major risk factors; homocysteine is not considered a major risk factor to modify LDL-cholesterol goals; routine measurement is not recommended as part of a risk assessment to modify LDL-cholesterol goals for primary prevention
- 5) Fibrinogen: along with other thrombogenic/hemostatic factors (such as activated factor VII, PAI-1, tPA, von Willebrand factor, factor V Leiden, protein C, and antithrombin III) indicates an increased risk for CHD independent of cholesterol levels; laboratory measurements for prothrombotic factors are not widely available and have not been standardized; measurement of prothrombotic factors is not recommended as part of routine assessment of CHD risk
- 6) CRP: high-sensitivity CRP (hs-CRP) appears to be the most reliable inflammatory marker available, to date; the extent to which hs-CRP (or any other marker of inflammation) provides extra prediction beyond all the major risk factors combined is uncertain; routine measurement of inflammatory markers for the purpose of modifying LDL-cholesterol goals in primary prevention is not recommended

Much of the research, to date, has addressed the relationships between CHD and two markers: CRP and homocysteine. These markers are the focus of this report.

Potential Uses

The routine use of emerging risk factor assessment in the context of primary prevention is not recommended (NCEP, 2001; Kushner & Sehgal, 2002; Mosca, 2002; Wilson, 2002). Testing would not be of value for a patient with no atherosclerosis but this is typically unknown.

Testing for emerging risk factors may be appropriate for assessment of atherosclerosis not explained by traditional risk factors or when the atherosclerosis is more severe than would be expected based on the traditional risk factor profile. Testing may also assist in identifying patients for whom more aggressive intervention is warranted or for whom lifestyle modification, alone, is adequate (Nass et al., 2000; Wilson, 2002).

Contraindications

There are no known contraindications.

Efficacy of Treatment or Procedure

C-Reactive Protein

The rise in CRP during unstable angina or acute MI has been found to be associated with outcomes (including recurrence). Recent studies have focused on the relationship between baseline CRP and subsequent risk of cardiovascular or cerebrovascular events in apparently healthy individuals. There is also evidence of an association between elevated CRP levels and the development of type 2 diabetes mellitus in healthy middle-aged women (Pradhan, Manson, Rifai, Buring, & Ridker, 2001).

An algorithm for prediction of cardiovascular disease risk using both the ratio of total cholesterol to HDL cholesterol and hs-CRP level was proposed by Rifai and Ridker (2001b). Both markers were expressed as quintiles and relative risks for the 25 possible combinations of quintile levels were determined. The addition of hs-CRP to the lipid measure was found to improve the ability to predict cardiovascular disease risk. It was noted that hs-CRP should not be evaluated if a patient has experienced recent (within the past 2 weeks) infection or trauma and that 2 measurements should be made (no more than 1 month apart) with the lowest value used to determine the quintile score. The addition of hs-CRP to a standard lipid screening protocol may improve risk prediction among those with high as well as low cholesterol levels and may help to target proven therapies.

At present, there are several factors that limit the suitability of CRP as an effective screening test for cardiovascular risk (Kushner & Sehgal, 2002; Mosca, 2002). One issue is reliability. Although Ridker (2001) reported that the assays for hs-CRP have a degree of variability and classification accuracy comparable to that for cholesterol screening, Kushner and Sehgal (2002) questioned that finding. Within-subject variabilities of 42% to 61% were reported and the authors noted that CRP levels can fluctuate substantially from day to day.

Another issue is the effectiveness of early detection. Direct evidence from prospective trials is needed to establish if there are effective therapies to decrease levels of CRP and, then, whether a decrease in CRP would decrease cardiovascular disease risk (Vorchheimer & Fuster, 2001; Rifai & Ridker, 2001a; Kushner & Sehgal, 2002; Mosca, 2002). Rifai and Ridker (2001a) noted that before hs-CRP would be suitable for use in a routine clinical setting, population-based cutpoints (for interpretation and risk assessment) need to be developed, potential therapeutic strategies need to be identified, and the reliability of systems used to measure CRP needs to be established. Kushner and Sehgal (2002) commented on the variety of factors that are associated with minor CRP elevation including noninflammatory states, genetic factors, and biological aging.

A third issue is the accuracy of the prediction. Relative risks have been reported but positive predictive values and absolute risks have not. Therefore, it is not possible to state the actual risk for coronary disease in a given individual with moderate CRP elevation (Kushner & Sehgal, 2002). Mosca (2002) noted that the association of CRP with increased risk of cardiovascular disease is reduced when adjustment is made for other risk factors. It remains unclear whether CRP is a marker, a causative agent, or a consequence of coronary heart disease.

Both case-control (Doggen, Berckmans, Sturk, Manger Cats, & Rosendaall, 2000; Sakkinen, Abbott, Curb, Rodriguez, Yano, & Tracy, 2002) and prospective nested case-control designs (Kuller et al., 1996; Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997; Tracy et al., 1997; Ridker, Buring, Shih, Matias, & Hennekens, 1998; Ridker, Glynn & Hennekens, 1998; Ridker, Cushman, Stampfer, Tracy & Hennekens, 1998; Koenig et al., 1999; Danesh et al., 2000; Ridker, Hennekens, Buring & Rifai, 2000; Ridker, Stampfer, & Rifai, 2001; Ridker, Rifai, Clearfield et al., 2001; Albert, Danielson, Rifai, Ridker et al., 2001; Pradhan et al., 2002) have been used to evaluate the association between CRP levels and subsequent CHD events. Only the prospective studies that used a high-sensitivity assay for CRP are summarized below.

Prospective Studies

Ridker, Buring, Shih, Matias, and Hennekens (1998) presented results from the Women's Health Study, a primary prevention trial that enrolled postmenopausal female health professionals with no history of MI, stroke, or transient ischemic attack. Cases were defined as those who experienced (in the three years after enrollment) MI, stroke, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, or cardiovascular death. Two controls were matched (age and smoking pattern) to each case. There were 122 cases and 244 controls. An experimental hs-CRP assay was used. The cases had higher median hs-CRP levels at baseline ($p=0.0001$). The risk of future vascular events increased as quartile of hs-CRP increased. For women in the fourth quartile (compared to the first quartile), the adjusted RR of any event was 4.1 (95%CI 1.7-9.9). The adjusted RR of MI or stroke was 5.5 (95%CI 1.8-16.6). The addition of hs-CRP to a model that included hyperlipidemia, hypertension, diabetes, family history of coronary disease, and body mass index improved the prediction of future vascular events ($p=0.005$ compared to models without hs-CRP). Elevated hs-CRP was found to predict future cardiovascular events in women in low-risk subgroups (e.g., no hypertension or no family history).

A subsequent analysis of the data utilized a commercially available hs-CRP assay (Ridker, Hennekens, Buring, & Rifai, 2000). Several other markers of inflammation were also analyzed. At baseline, the women who developed cardiovascular events had a significantly higher body mass index, and a greater percentage had histories of diabetes, hypertension, or parental MI before age 60 years (all $p<0.05$). They also had significantly higher levels of hs-CRP; serum amyloid A; soluble intercellular adhesion molecule type 1; interleukin-6; total, LDL, and HDL cholesterol; apolipoprotein B-100; ratio of total cholesterol to HDL cholesterol; and homocysteine (all $p<0.03$). Compared with the lowest quartile, women in the highest quartile of hs-CRP (RR=4.4; 95%CI 2.2-8.9), serum amyloid A (RR=3.0; 95%CI 1.5-6.0), soluble intercellular adhesion molecule type 1 (RR=2.6; 95%CI 1.3-5.1), interleukin-6 (RR=2.2; 95%CI 1.1-4.3), total cholesterol (RR=2.4; 95%CI 1.3-4.7), LDL cholesterol (RR=2.4; 95%CI 1.3-4.6), apolipoprotein B-100 (RR=3.4; 95%CI 1.8-6.8), ratio of total to HDL cholesterol (RR=3.4; 95%CI 1.8-5.9), and homocysteine (RR=2.0; 95%CI 1.1-3.8) were at increased risk for future cardiovascular events (univariate analysis). After adjustment of other plasma markers and traditional risk factors, only hs-CRP (RR=1.5; 95%CI 1.1-2.1) and ratio of total to HDL cholesterol (RR=1.4; 95%CI 1.1-1.9) were independent predictors of risk.

Using a subset of men enrolled in the MONICA (Monitoring Trends and Determinant in Cardiovascular Disease) Augsburg Cohort Study, Koenig et al. (1999) examined the relationship between CRP ("sensitive" assay) and first major CHD event (fatal or nonfatal MI including sudden cardiac death). The 936 men were 45 to 64 years old at enrollment. Follow-up was 8 years. There were 53 first major events (26 fatal and 27 nonfatal). For a one standard

deviation increase in log-CRP level, the hazard rate ratio of CHD events was 1.67 (95%CI 1.29-2.17). The value remained significant after adjusting for age and smoking status.

Danesh et al. (2000) presented data from a study of 5,661 men ages 40 to 59 at enrollment in 1978-1980. The loss to follow-up was less than 1%. Major coronary heart disease has been recorded for 507 men (223 deaths, 284 nonfatal MI). The 1,026 controls were frequency matched to cases on the basis of town of residence and age in 5 year intervals. At baseline, there were a higher percentage of smokers and persons with evidence of coronary disease (ischemia on ECG or reported history of angina or MI) among the cases. The cases also had a higher body mass index, higher blood pressure, lower forced expiratory volume, and higher total cholesterol, lower HDL cholesterol and higher triglyceride levels. A "sensitive" CRP assay was used. Men in the upper third of baseline CRP concentration had higher risk of incident CHD than those in the bottom third (adjusted OR=2.13; 95%CI 1.38-3.28). Similar findings were reported for serum amyloid A protein (OR=1.65; 95%CI 1.07-2.55). The analysis was repeated for those subjects with no evidence of CHD at entry with similar results. A meta-analysis of population-based studies representing 1,953 cases indicated a risk ratio for CHD of 2.0 (95%CI 1.5-2.5) for persons in the top third of CRP levels (vs. the bottom third).

Data on risk factors for the development of PAD in the Physician's Health Study participants were presented by Ridker, Stampfer, and Rifai (2001). The average follow-up period was 9 years. The present analysis included 140 cases (apparently healthy men who subsequently developed either intermittent claudication or hospitalizations for peripheral arterial revascularization) and 140 controls (matched on age, smoking status, and length of follow-up). Eleven lipid and non-lipid markers (including total, high-density lipoprotein, and low-density lipoprotein cholesterol; Total/HDL cholesterol ratio; triglycerides; tHcy; hs-CRP; Lp(a); fibrinogen, apolipoprotein A-I [apo A-I], and apolipoprotein B-100 [apo B-100]) were studied. At baseline, traditional risk factors (i.e., diabetes, hypertension, family history of cardiovascular disease) were more prevalent among the cases but only the prevalence of diabetes was significantly higher (6.4% vs. 1.4%; $p=0.03$). There were significant differences at baseline for total, LDL, HDL, and Total/HDL cholesterol values (all $p<0.01$ with all but HDL higher among the cases). Levels of apo A-I, apo B-100, fibrinogen, and hs-CRP were also significantly higher in the cases (all $p\leq 0.02$). Lp(a) and tHcy did not differ significantly. All of the cholesterol measures plus apo B-100, fibrinogen, and hs-CRP were significant (all $p<0.05$) predictors of risk. The strongest predictor was the TC/HDL ratio (RR=3.4, 95%CI 1.7-7.0 for highest quartile vs. lowest). Among the non-lipid measures, hs-CRP had the highest relative risk (RR=2.5, 95%CI 1.3-5.0). Adjusting for hypertension, body mass index, family history of premature atherosclerosis, exercise frequency, and diabetes did not alter the results appreciably. Of the non-lipid markers, only the addition of hs-CRP and fibrinogen (inflammatory markers) increased the predictive value of models based on total cholesterol or the TC/HDL ratio.

The relationship between statin therapy and hs-CRP levels was studied by Ridker, Rifai, Clearfield, et al. (2001). The participants were 6,605 men and women enrolled in a randomized, placebo controlled, primary prevention trial of lovastatin. All had average levels of total and LDL cholesterol but below-average levels of HDL. The study excluded those with uncontrolled hypertension, secondary hyperlipidemia, diabetes requiring insulin, or body mass 50% greater than desirable. The follow-up period averaged 5.2 years during which time patients were monitored for the occurrence of first acute coronary events (MI, unstable angina, or sudden death from cardiac causes). The lovastatin group had a lower rate of reaching this endpoint (RR=0.63; 95%CI 0.5-0.79). At baseline and at one year, levels of hs-CRP and lipids were analyzed. The rates of coronary events increased as baseline levels of hs-CRP increased. The unadjusted risk of acute coronary events increased by 21% (19% in adjusted analysis) with each increasing quartile of baseline hs-CRP levels. These values were similar to those observed for an increase of 1.0 in the total/HDL cholesterol ratio. With lovastatin therapy, there was a 14.8% reduction ($p<0.001$) in the median level of hs-CRP after 1 year of treatment. There was no significant effect of placebo. The effect of lovastatin on hs-CRP was not explained by

changes in lipid parameters. Lovastatin was found to be effective in patients with LDL levels above the median regardless of hs-CRP levels but also for those with LDL levels below the median who had elevated hs-CRP levels. A similar trend was observed when the total/HDL cholesterol ratio was used instead of the LDL levels.

Albert, Danielson, Rifai, Ridker et al. (2001) studied the relationship between pravastatin and hs-CRP. The study included primary and secondary prevention cohorts. In the primary prevention cohort, 2,013 men and women with no prior history of cardiovascular disease but with baseline LDL levels of ≥ 130 mg/dL were randomized to receive pravastatin or placebo. hs-CRP and lipid levels were assessed at baseline, 12, and 24 weeks. Of 999 patients assigned to the placebo group and 1,014 patients assigned to the pravastatin group, 12 week blood samples were available for 837 and 865, respectively, and 24 week blood samples were available for 666 and 673, respectively. In the event of missing hs-CRP levels, the analysis called for carrying forward the most recent value. At baseline, the two groups were similar in age, gender, smoking status, ethnicity, body mass index, percent with diabetes, estrogen use, aspirin use, cholesterol levels, and hs-CRP. Baseline hs-CRP levels were poorly correlated (all $r \leq 0.1$) with baseline lipid levels. At 24 weeks, there were significant reductions in total cholesterol (16%), LDL cholesterol (24%), and triglycerides (18%) as well as significant increases in HDL cholesterol (6.6%) (all $p < 0.001$) for patients in the pravastatin group. There were no significant changes in the placebo group. hs-CRP levels decreased by 14.7% at 12 weeks and 14.2% at 24 weeks ($p < 0.001$) in the pravastatin group with no significant change in the placebo group. The effect of pravastatin was consistent across subgroups identified on the basis of age, sex, smoking status, diabetes status, medication (aspirin, HRT) use, and lipid levels. There did not appear to be an association between the change in hs-CRP concentration at 24 weeks and the change in cholesterol levels.

Pirro et al. (2001) used a prospective design to study the association between elevated hs-CRP levels and risk for future ischemic heart disease (IHD). The subjects were 2,037 men, ages 47 to 76 years at baseline (1985), without IHD when enrolled in the study 12 years earlier (1973). Follow-up data were collected at 5 years after baseline. IHD was defined as angina of effort, coronary insufficiency, nonfatal MI, and coronary death. There was a significant difference ($p = 0.004$) in survival curves for men with CRP levels above vs. below the median for the group (1.77 mg/L). Of the 1,016 men with CRP levels below 1.77 mg/L, 39 (3.8%) had a first IHD event. Of the 1,021 with CRP levels of 1.77 mg/L or higher, 66 (6.4%) developed IHD. The relative risk for IHD among those with high CRP concentrations (≥ 1.77 mg/L) was 1.8 (95%CI 1.2-2.7). The addition of lipid risk factors attenuated the relative risk associated with elevated CRP levels but did not eliminate it. Adjustment for non-lipid risk factors (such as age, smoking status, history of diabetes, etc.) did cause the association to become nonsignificant. Duration of follow-up and age were also factors with higher relative risk values for patients with less than 2 years of follow-up and for patients 55 years old or younger at baseline.

In the study presented by Pradhan et al. (2002), postmenopausal women (ages 50-79 at enrollment) with no history of cardiovascular disease or cancer were followed for a median of 2.9 years. In addition to the typical baseline measures (medical history, family history of premature coronary artery disease, medication and vitamin use, blood pressure, diabetes, smoking status, alcohol consumption, physical activity level, ethnicity) hormone replacement therapy (HRT) status (never, past, or current use of unopposed estrogen or estrogen with progestin) was recorded. The study cases were 304 women who developed a first MI during the follow-up. The study controls were 304 women, matched by age, smoking status, ethnicity, and follow-up time, who did not experience an MI. hs-CRP, IL-6, and lipid levels were measured using the baseline plasma samples. At baseline, the cases had a higher prevalence of traditional cardiovascular risk factors (higher BMI; greater percent with history of hypertension, diabetes, and family history; and greater frequency of no physical activity; all $p \leq 0.01$). There were fewer current HRT users and more never users in among the cases ($p = 0.01$). Baseline levels of CRP and IL-6 were higher for the cases (both $p < 0.001$). When grouped according to HRT status, CRP and IL-6 levels remained higher in cases than controls regardless

of HRT status (all $p \leq 0.01$) and current users (both cases and controls) had higher levels of CRP ($p \leq 0.001$) but not IL-6. LDL-cholesterol, total cholesterol, triglycerides, and the ratio of total cholesterol to HDL-cholesterol were also higher in the cases (all $p < 0.05$). HDL-cholesterol was lower among the cases ($p < 0.001$). After adjustment for all risk factors considered in the study (including use of HRT), the odds ratio for the risk of coronary heart disease for an individual in the 4th quartile of CRP vs. the 1st quartile was 2.1 (95%CI 1.1-4.1). The corresponding value for IL-6 was similar (OR=2.1; 95%CI 1.1-4.0).

The relationship between CRP levels and sudden cardiac death (SCD) was the focus of the study by Albert, Ma, Rifai, Stampfer, and Ridker (2002). The subjects were participants in the Physician's Health Study – male physicians, ages 40-84 years at enrollment, with no history of MI, stroke, transient ischemic attack, or cancer. Although the study was a randomized trial of aspirin, β -carotene, both drugs, or placebo, at the time of the baseline blood sample all participants were taking active oral aspirin as part of the run-in period. There were 97 SCD cases during the 17 year follow-up period. The mean time to SCD was 9.2 years (range 0.7 to 16.8 years). The 197 controls were randomly chosen from the participants without SCD (and free of cardiovascular disease) who matched cases based on age, length of follow-up, and smoking status. Lipid levels, hs-CRP, and tHcy were measured. The cases were more likely to have a history of diabetes or hypertension and a parent who experienced a MI before age 60 years (all $p < 0.01$). The cases were less likely to drink moderate amounts of alcohol ($p < 0.01$) and were less likely to have been assigned to the aspirin group ($p < 0.05$). The baseline median CRP level was higher in the cases than the controls ($p = 0.01$). Of the other plasma levels measured, only the total cholesterol to HDL-cholesterol ratio was significantly higher in the cases ($p = 0.04$). Compared to men in the lowest quartile of CRP, the relative risk for SCD for men in the highest quartile was 2.78 (95%CI 1.35-5.72). The increase in risk for men in the second or third quartiles was not significant. Neither tHCY nor any of the lipid measures was associated with an increased risk for SCD.

Ridker, Rifai, Rose, Buring, and Cook (2002) measured hs-CRP and LDL cholesterol in 27,939 participants from the Women's Health Study (an ongoing evaluation of aspirin and vitamin E for the primary prevention of cardiovascular events in women 45 years of age and older). The cut-off points for quintiles of CRP and LDL cholesterol were established using data from 15,745 women who were not using hormone-replacement therapy (HRT) at the time of the blood sample. The adjusted (for age, smoking status, diabetes, blood pressure, HRT use) relative risk of a first cardiovascular event for patients in increasing quintiles of CRP were 1.0 (the first quintile or reference level), 1.4 (95%CI 0.9-2.2), 1.6 (95%CI 1.1-2.4), 2.0 (95%CI 1.3-3.0), and 2.3 (95%CI 1.6-3.4). For LDL cholesterol, the corresponding values were 1.0, 0.9 (95%CI 0.7-1.2), 1.1 (95%CI 0.8-1.4), 1.3 (95%CI 1.0-1.7), 1.5 (95%CI 1.1-2.0). Higher relative risks associated with higher CRP levels than with higher LDL levels were also observed for the different categories of cardiovascular events (coronary heart disease, ischemic stroke, or cardiovascular death). Relative risks according to CRP quintile were higher for women who were not using HRT at baseline while relative risks according to LDL quintile were more similar for non-users and users of HRT. CRP and LDL levels were minimally correlated ($r = 0.08$) which would suggest that the two markers were identifying different high-risk groups. Adjusted relative risks were determined for various combinations of CRP and LDL. With low-CRP and low-LDL as the reference group, the relative risk for women with low-CRP and high-LDL was 1.5 (95%CI 1.0-2.1). For women with high-CRP and low-LDL, the relative risk was 1.5 (95%CI 1.1-2.1). For women with high-CRP and high-LDL, the relative risk was 2.1 (95%CI 1.5-2.8). Similar results were found when only those women who were not using HRT at baseline were considered. In another analysis, adjustment for all components of the Framingham risk score was done. Relative risks for increasing quintiles of CRP were 1.0, 1.3, 1.4, 1.7, and 1.9. For non-users of HRT the corresponding values were 1.0, 1.6, 1.5, 1.8, and 2.2. At all levels of estimated 10-year risk based on the Framingham risk score, CRP was a strong predictor of cardiovascular risk.

Homocysteine

The relationship between tHcy levels and cardiovascular disease has been investigated using both retrospective, case-control studies (Aronow & Ahn, 1997 and 2000; Schwartz et al., 1997; Dierkes et al., 1998; Kawashiri et al., 1999; Verhoef et al., 1999; Rothenbacher et al., 2002) and prospective cohort or nested case-control studies (Folsom et al., 1998; Bostrom et al., 1999; Ridker, Manson, Buring, Shih, Matias, & Hennekens, 1999; Hoogeveen et al., 2000; Voutilainen, Lakka, Hämelehti, Lehtimäki, Poulsen, & Salonen, 2000; Knekt et al., 2001; Vollset et al., 2001). In general, the prospective studies have found a weaker association between tHcy and cardiovascular disease than the case-control studies (Christen, Ajani, Glynn, & Hennekens, 2000). In addition, tHcy levels are more strongly associated with the recurrence of an event than a first-ever event. There is likely an interaction between tHcy and other cardiovascular disease risk factors (such as smoking, hypertension, and elevated cholesterol) as well as an individual's genetic predisposition to thrombosis. Clinical trials using tHcy-reducing therapy (including folic acid and vitamins B₆ and B₁₂) are underway (Kuller & Evans, 1998; Refsum & Ueland, 1998; Eikelboom, et al., 1999; Ueland, et al., 2000). There is a need to establish whether normalization of tHcy levels improves cardiovascular morbidity and mortality (Welch & Loscalzo, 1998). The addition of folic acid to enriched grain products (mandatory as of January 1998), has been found to decrease the incidence of hyperhomocysteine due to folate deficiency (Malinow et al., 1998; Jacques, Selhub, Bostom, Wilson & Rosenberg, 1999). There is, however, a genetic component that cannot be overcome by folic acid supplementation.

Plasma homocysteine levels are typically measured during the fasting state. Methionine loading (with plasma homocysteine measured before and 4 to 6 hours after an oral dose of methionine) is a way of stressing the homocysteine metabolic pathway and may be more sensitive than measurement of fasting levels. Normal fasting plasma homocysteine values range from 5 to 15 $\mu\text{mol/L}$. There is no standard definition of an elevated homocysteine level (Eikelboom et al., 1999).

Retrospective Cohort Study

Data from Framingham Study participants were reported by Bostom et al. (1999). The subjects were 1138 men and 795 women from the original cohort. The baseline examinations for the tHcy analysis were done between May, 1979 and May, 1982 with follow-up to May, 1992. At baseline, the mean age was 70 years (range 59-91). The primary outcome variables were all-cause and cardiovascular disease mortality. Most of the cardiovascular disease deaths were due to coronary heart disease or stroke. At baseline, mean tHcy levels were higher in men than women ($p < 0.001$). There were no differences in tHcy levels due to presence or absence of diabetes or in current smokers versus non-smokers. There were 653 deaths; 244 of the deaths were attributed to cardiovascular disease. The adjusted relative risk for all-cause mortality associated with an elevated tHcy level ($\geq 14.26 \mu\text{mol/L}$ representing the 75th percentile) was 1.54 (95%CI 1.31-1.82); the adjusted relative risk for cardiovascular mortality was 1.52 (95%CI 1.16-1.98). Significant relative risk values for both all-cause mortality and cardiovascular mortality were also observed for age (per year increase), diabetes (defined by use of insulin or oral hypoglycemic agents or by any recorded blood glucose level $\geq 11 \text{mmol/L}$), smoking (defined as current cigarette smoking), and systolic blood pressure (per 20mmHg increase).

Prospective Studies

Based on selected subjects from a prospective cohort study, Folsom et al. (1998) compared tHcy levels in those who developed CHD and those who did not. At recruitment to the cohort study, subjects were 45 to 64 years of age. For the tHcy sub-study, those with prevalent CHD (defined as history of MI, prior cardiovascular surgery, or prior coronary angioplasty), stroke, or transient ischemic attack at baseline were excluded. The median follow-up time, during which incident CHD cases (defined as definite or probable MI, silent MI between ECG examination, definite CHD death, or coronary revascularization) were identified, was 3.3 years. Information on tHcy, B vitamins, and related genotypes was determined for the incident CHD

cases and a stratified random sample from the rest of the cohort. There were 232 incident CHD cases and 537 in the reference sample (10 of whom were also CHD cases). Quintile cutpoint were determined for tHcy levels. In the cohort sample, plasma folate, vitamin B₁₂, and vitamin B₆ were inversely associated across tHcy quintiles (p for trend all <0.01). As tHcy level increased, dietary folate decreased (p=0.01), waist/hip ratio increased (p=0.03), alcohol consumption increased (p=0.05), percent with hypertension increased (p=0.02), percent taking vitamin supplements decreased (p<0.01), and prevalence of MTHFR homozygosity increased (p=0.01). Compared to the cohort sample, the incident CHD cases had higher baseline levels of vitamin B₆ (p<0.01); no other variable was significantly different. Adjusting for age, sex, race, study center, total and HDL cholesterol, hypertension, diabetes, and smoking status, the relative risk of CHD ranged from 0.79 to 1.28 across quintiles of tHcy concentration (all p>0.05); from 0.66 to 0.82 across quintiles of plasma folate concentration (all p>0.05); from 0.28 for the highest quintile (95%CI 0.1-0.7) to 0.81 (p>0.05) across quintiles of plasma vitamin B₆ concentrations; and from 0.53 to 0.95 across quintiles of plasma vitamin B₁₂. This analysis included both men and women. A preliminary analysis indicated that interactions by sex were not significant after other risk factors were considered. In addition, the number of women with CHD incidents was low.

Eligible participants in the Women's Health Study (WHS) were evaluated to determine whether elevated tHcy in healthy post-menopausal women could predict the risk of developing cardiovascular disease (Ridker et al., 1999). Cases were defined as those with adequate baseline blood samples who experienced a cardiovascular event (death due to coronary heart disease, nonfatal MI or stroke, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting) during the 3-year follow-up period. Controls were chosen from those with adequate baseline blood samples and who were free from cardiovascular disease during the follow-up. They were matched for age and smoking status. There were 122 cases (85 MI or stroke, 37 coronary revascularizations) and 244 controls. The mean age at baseline was 59.3 years. Cases and controls differed (p=0.001 except as indicated) at baseline in percent with hyperlipidemia, hypertension, family history of premature MI (p=0.04), and diabetes. Baseline tHcy was higher in the cases than controls (p=0.02). The relative risk for future cardiovascular event was significant only for those in the highest quartile of tHcy (>13.26 μmol/L) (RR=2.0; 95%CI 1.1-3.8). The corresponding value for MI or stroke was 2.2 (95%CI 1.1-4.6). The trends for increased risk of cardiovascular event or MI/stroke with increased level of tHcy were significant (both p≤0.02). Adjusting for baseline differences in other coronary risk factors, an increase in tHcy of 5 μmol/L was associated with a 24% increase in risk of any cardiovascular event (p=0.05). Although baseline multivitamin supplementation was associated with significantly reduced tHcy levels, adjusting for multivitamin intake did not alter the association between tHcy and cardiovascular risk.

Hoogeveen et al. (2000) prospectively studied the effect of elevated tHcy and type 2 diabetes on mortality. Baseline data were collected from 2,484 men and women ages 50 to 75 years of age. Some of the individuals had cardiovascular disease at baseline. A "subcohort" of 715 persons was identified that included 334 with normal glucose tolerance, 197 with impaired glucose tolerance, and 184 with type 2 diabetes mellitus. All persons who died during the 5 year follow-up (n=171 including 75 from the subcohort) formed the case group. The control group consisted of the 640 persons from the subcohort who survived the 5 year follow-up. A cause of death was identified for 160 of the 171 cases (93.6%); 76 died of cardiovascular disease. Based on data from the entire cohort, the 5-year risk of death was 5.7% in those with normal glucose tolerance, 7.1% in those with impaired glucose tolerance, and 18.5% in those with type 2 diabetes. For those with hyperhomocysteinemia (tHcy>14 μmol/L), the 5-year risk of death was 10.8%; those with tHcy values of 14 μmol/L or less had a 5 year risk of death of 5.5%. The adjusted odds ratio for 5-year overall mortality with tHcy>14 μmol/L was 1.56 (95%CI 1.07-2.30). In patients with diabetes, the 5 year mortality associated with tHcy>14 μmol/L was 2.51 (95%CI 1.07-5.91); for non-diabetics, the value was 1.34 (95%CI 0.87-2.06). There was no

difference in mean tHcy concentration between those who died of cardiovascular death and those who died of non-cardiovascular death.

The association between tHcy and risk of acute coronary events in middle-aged men was the subject of the study by Voutilainen et al. (2000). The study enrolled 2,682 men age 42, 48, 54, or 60 years at baseline. For the tHcy analysis, men with prevalent CHD (a history of acute coronary event or angina pectoris, angina pectoris on effort, or use of nitroglycerin at least once per week) were excluded. Of 2,005 remaining in the analysis, 163 had a coronary event during the follow-up period (an average of approximately 9 years). One control subject per case was identified (matched for age, examination year, and residence). There was no difference in mean tHcy level between cases and controls. Cases did have significantly higher blood pressure, lower HDL cholesterol, and higher urinary secretion of nicotine metabolites (all $p \leq 0.003$). An elevated plasma tHcy level ($>12.6 \mu\text{mol/L}$ which was the 75th percentile) was not associated with an increased risk of a coronary event. MTHFR genotype (C677T mutation) information was available for 168 of the subjects. The mean tHcy concentration did not differ significantly between homozygotes, heterozygotes, or non-carriers.

Knekt et al. (2001) enrolled 3,479 women, ages 45 to 64 years, in a prospective, nested case-control study to explore the predictive value of Hcy. A history of heart disease was reported by 757 women. Cases were defined as women who experienced a major coronary event (MI or coronary death) during 9 to 12 years of follow-up. There were 75 cases among women free of heart disease at baseline and 74 among women with known heart disease. Controls (149 without heart disease, 147 with) were matched on age, municipality, and presence of heart disease at baseline. Development of a major coronary heart disease event (in women with or without known heart disease at baseline) was associated with higher levels of smoking, diabetes, hypertension, serum cholesterol, and serum triglycerides. There was no association between serum Hcy and the incidence of major coronary events in women who were free of heart disease at baseline (adjusted RR=0.77, 95%CI 0.24-2.45 for highest quintile of Hcy vs. lowest; p for trend=0.72). There was, however, a significant association for women with a history of heart disease (adjusted RR=3.32, 95%CI 1.05-10.5).

The data presented by Vollset et al. (2001) were from 4,766 men and women ages 65-67 years at the time of enrollment. Based on self-reported medical history, the total group was divided into low-risk ($n=3,318$) and high-risk ($n=1,448$) groups. The high risk group included those with any history of MI, stroke, angina pectoris, or diabetes mellitus plus anyone being treated for hypertension. During the follow-up period (a median of 4.1 years), 259 deaths occurred. Death certificates, available for 257 individuals, indicated 121 deaths due to cardiovascular disease. For the low-risk group, the mortality ratio for cardiovascular mortality was not significant when those with high tHcy concentrations were compared to those with low tHcy concentrations (adjusted MR=1.85, 95%CI 0.30-11.33). The association was significant for those in the high-risk group (adjusted MR=3.96, 95%CI 1.29-12.16) and the total study group (adjusted MR=3.48; 95%CI 1.38-8.79). The mortality ratios are adjusted for total cholesterol, blood pressure, smoking, BMI, physical activity, age, and sex with the mortality ratios for the total group also adjusted for baseline risk status.

Reviews of the Evidence

A systematic review by Christen et al. (2000) focused on whether the strength of the evidence of an association between homocysteine and cardiovascular disease varied according to study design. The review included studies of CHD and cerebrovascular disease. All studies were classified as either cross-sectional, case-control, or prospective (including nested case-control studies). Four cross-sectional studies that investigated the association between elevated homocysteine and CHD generally reported an increased odds of CHD in persons with high homocysteine levels. However, the confidence intervals were wide and only one study found a significant association. Of 15 case-control studies that reported relative risks, 11 found that elevated homocysteine levels were significantly associated with an increased risk of CHD. Among the 7 prospective studies reviewed, 2 reported a significant association between

elevated homocysteine levels and CHD. For the association between homocysteine and cerebrovascular disease, 6 of 9 case-control studies, 1 of 2 prospective studies, and the only reported cross-sectional study found significant associations.

A meta-analysis of 30 prospective and retrospective studies was reported by the Homocysteine Studies Collaboration (2002). All of the patients included in the analysis were free of preexisting cardiovascular disease, at least 40 years old at baseline, and with measured homocysteine levels between 3 and 40 $\mu\text{mol/L}$. From the 30 studies, 5,073 ischemic heart disease events and 1,113 stroke events were identified. In 12 prospective studies, an odds ratio (for the risk of ischemic heart disease associated with a 25% lower homocysteine level) of 0.83 (95%CI 0.77-0.89) was observed (adjusted for sex and age at enrollment and corrected for regression dilution bias). In 12 retrospective studies with population controls, the odds ratio was 0.67 (95%CI 0.62-0.71) while in 3 retrospective studies with other controls, the odds ratio was 0.73 (95%CI 0.64-0.83). However, the tests for heterogeneity were significant ($p=0.02$ for prospective studies, $p=0.001$ for population controlled retrospective studies and other retrospective studies). With further adjustment for smoking, systolic blood pressure, and total cholesterol level, the odds ratio for ischemic heart disease associated with a 25% lower homocysteine level (prospective studies only) was 0.89 (95%CI 0.83-0.96). The heterogeneity statistic was reduced. For stroke, the adjusted OR was 0.81 (95% CI 0.69-0.95). Elevated homocysteine was regarded as, at most, a modest independent predictor of IDH and stroke risk in healthy populations.

Klerk et al. (2002) completed a meta-analysis of case-control studies of CHD risk that provided data on the MTHFR 677C \rightarrow T polymorphism. Individuals with the polymorphism have reduced activity of the MTHFR enzyme and, as a result, higher homocysteine levels and lower folate levels. The analysis included 34 published studies and 6 unpublished studies with a total of 11,162 cases and 12,758 controls. The overall risk for CHD was higher among individuals with the TT genotype than the CC genotype (OR=1.16; 95%CI 1.05-1.28). However, there was significant ($p<0.01$) heterogeneity among the individual studies. One factor was the origin of the study. The increased risk of CHD with the TT genotype was significant for the studies that originated in Europe (OR=1.14; 95%CI 1.01-1.28) but not for the studies that originated in North America (OR=0.87; 95%CI 0.73-1.05). The test for heterogeneity was not significant within the European studies or within the North American studies. When folate status was considered (among 3,262 cases and 4,472 controls), the presence of the TT genotype was associated with an increased risk of CHD relative to CC genotype only among patients with low folate status (OR=1.44; 95%CI 1.12-1.83). Low folate status was associated with an increased risk of CHD for patients with CC and CT genotypes, as well. The authors concluded that in the presence of adequate folate status, screening for MTHFR 677C \rightarrow T would be of little clinical value. Impaired folate metabolism with accompanying high homocysteine levels is associated with an increased risk of CHD.

Safety of Treatment or Procedure

The evidence (or lack thereof), as cited in the literature, pertaining to:

- a. morbidity rate (side effects) - *there is minimal risk of minor side effects (bleeding, infection) associated with collecting the blood sample for the analysis; there were no reported side effects in the literature*
- b. mortality rate - *there is minimal risk of mortality associated with collecting the blood sample for the analysis; there were no reported fatalities associated with the testing*
- c. training and experience required to perform the procedure safely - *although the procedure may be performed safely, the physician ordering and interpreting the test should understand the various factors (such as age, HRT status, other medical conditions) that influence the level of a given marker*

- d. where the procedure should be performed (e.g., volume of procedures, skilled support team, location/need for follow-up visits, etc.) - *testing for CRP should be done by a laboratory capable of high-sensitivity analysis*
- e. co-morbidities that increase the risk associated with the procedure - *none reported*
- f. potential for inappropriate use of the technology - *most markers are not of value in general assessment of CHD risk; further research is needed to determine if selected markers may be useful for selected subgroups of patients*

Alternative Forms of Testing

Alternatives to using biochemical markers to assess an individual's risk for cardiovascular disease include the traditional risk factor profile (tobacco use, age, gender, hypertension, family history of coronary artery disease, diabetes mellitus, and hyperlipidemia) or more extensive and, in some cases, invasive procedures (stress testing, electron-beam computed tomography scan, and coronary angiography).

Other non-invasive tests that are effective in identifying endothelial dysfunction and early disease include assessment of large and small artery elasticity or compliance, measurement of blood pressure rise during a standardized exercise test, photographic examination of the retinal vasculature, ultrasound assessment of intimal-medial thickness of the carotid artery and a urine sample for microalbuminuria. These tests require further validation for specificity and sensitivity, but they are likely to become in the future standard screening tests to identify the subgroup of the population in need of assessment of biochemical markers and aggressive treatment to slow disease progression.

Epidemiology and Costs

The approximate laboratory cost for a CRP assay is \$50.00. The approximate cost for a total homocysteine assay is \$120.00.

A cost-effectiveness analysis of hs-CRP testing in Germany and Italy was reported by Ess and Szucs (2001). The primary prevention model was based on 300,000 apparently healthy males in three age groups (35-44, 45-54, and 55-64 years). Each age group was further subdivided by total cholesterol and LDL levels (high, borderline, or desirable). Those with borderline lipid levels were further subdivided based on the presence of 2 or more risk factors. The consequences of testing or not testing for CRP were evaluated. Three strategies were analyzed: A) no testing for CRP, decision to treat based on lipid levels and other risk factors, B) test for CRP every 2 years; if CRP > 3 mg/l, borderline lipid levels, and < 2 risk factors treat with statins; otherwise treat with aspirin, C) all patients with CRP > 3 mg/l treated with aspirin. For strategies B and C, patients who qualified for lipid-lowering treatment, regardless of CRP levels, were considered to receive statins. The follow-up period was five-years. Compared with the no testing model, a 6% to 22% reduction in the number of cardiovascular events over 5 years was estimated for the 2 intervention strategies with greater reductions in the older age groups. Greater use of statins (strategy B) was associated with a greater reduction in the number of cardiovascular events but was higher in cost. Strategy C resulted in cost savings for the 45 to 54 and 55-64 year old groups. The cost-effectiveness profiles (cost per life-years saved) were favorable for both strategies in the two older age groups. Testing for hs-CRP was found to assist in better targeting individuals at higher risk thus improving outcomes in a cost-effective manner.

Nallamothe, Fendrick, Rubenfire, Saint, Bandekar, and Omenn (2000) studied the potential benefits of lowering homocysteine levels. Three strategies were considered: a) no intervention b) "treat all" - daily supplementation with 400µg folic acid and 400µg vitamin B₁₂ or c) "screen and treat" - daily supplementation only for those with elevated homocysteine levels (>11

$\mu\text{mol/L}$). The analysis was based on the assumption that lowering elevated homocysteine levels would reduce excess CHD risk by 40%. In the base-case analysis, it was assumed that 50% of the individuals would take the supplements regularly enough to derive benefit from treatment. Two hypothetical populations were evaluated: 40-year-old men and 50-year-old women. The clinical benefits (life-years saved) were somewhat higher for the treat all strategy than the screen and treat strategy (8.7 vs. 8.5 life-years per 1000 men and 3.9-3.7 life-years per 1000 women as compared with the no intervention strategy). However, the cost per life-year saved of the screen and treat strategy was less than that of the treat all strategy (\$13,600 vs. \$31,800, respectively, for men; \$27,500 vs. \$77,200 for women).

The study by Tice et al. (2001) looked at the effect of grain fortification (with folic acid) on CHD prevention. The authors noted that the efficacy of reducing homocysteine levels to prevent CHD events has not been established by clinical trial data. The baseline assumptions were a) 100% compliance with the vitamin therapy, b) vitamin therapy reduced homocysteine levels by 33%, c) the relative risk reduction per 5 $\mu\text{mol/L}$ decrease in homocysteine level was 29%, d) the annual cost of vitamin therapy was \$20.29 (1997 data), and e) the cost of a homocysteine assay was \$26.32 (1996 data). Two primary prevention strategies were modeled: a) treat everyone with no known CHD with a daily supplement of 1 mg of folic acid and 0.5 mg vitamin B₁₂ and b) measure homocysteine levels and treat only those with levels $>10\mu\text{mol/L}$. Men and women were modeled separately. Five age groups were considered (10 year increments from 35 to 84 years). With the baseline assumptions, the model, overall, predicted reductions of 13% (men) and 8% (women) in myocardial infarctions and decreases of 13% (men) and 9% (women) in CHD deaths over a 10 year period. In the primary prevention setting, the model predicted that, for men in any of the 5 age groups and using either of the prevention strategies, there would be a savings of lives and money relative to men who consumed fortified grains alone. The maximum cost savings would be expected if men ages 45 years and older were screened and treated if they had elevated homocysteine levels. Treating all men 45 years and older was estimated to cost \$9,000 per quality-adjusted life-year (QALY) saved compared to a screen and treat strategy for this age group. All other strategies were predicted to have cost-effective ratios above the threshold (\$40,000/QALY) that is generally considered cost-effective. Treating women 75 years and older was predicted to have a cost-effectiveness ratio of \$1,200/QALY compared to grain fortification alone. If women 65 to 74 years were screened and treated if indicated, the cost-effectiveness ratio was estimated to be \$5,500/QALY above that if women 75 years and older were treated. Treating all women 65 years and older was projected to have an incremental cost-effectiveness ratio of \$8,800/QALY compared to the screen and treat approach. Treating all women 55 years and older was associated with an incremental cost-effectiveness ratio of \$39,000/QALY. All other strategies would not be considered cost-effective.

Summary

With regard to biochemical markers of cardiovascular disease risk, the ICSI Technology Assessment Committee finds the following:

1. The basic lipid profile (high-density lipoprotein, low-density lipoprotein, and triglycerides) provides a useful indication of cardiovascular disease risk and serves as a guide for statin therapy in a primary prevention context.
2. CRP, if measured by high-sensitivity assay (hs-CRP), may have independent value as a predictor of cardiovascular disease risk and independent value in identifying patients with normal lipids who could benefit from treatment (Conclusion Grade II based on Class B and C evidence, See Appendix). hs-CRP elevations can be caused by inflammatory conditions and, therefore, are not specific for cardiovascular assessment in individual patients. Further study is needed to determine if decreasing CRP levels would decrease cardiovascular disease risk.

3. The relevance of studies of tHcy as a risk factor for cardiovascular disease is unclear given the decreasing tHcy levels as a result of mandatory folic acid supplementation. It remains unproven whether lowered tHcy levels will result in reduced morbidity and mortality from cardiovascular disease.
4. Other biochemical markers do not add to the prediction of risk above that achieved using lipid measures and hs-CRP.
5. Assessment of the markers is safe, requiring only a blood sample for analysis.

References

Evidence is classed and graded as described below.

I. CLASSES OF RESEARCH REPORTS

A. Primary Reports of New Data Collection:

- Class A: Randomized, controlled trial
- Class B: Cohort study
- Class C: Non-randomized trial with concurrent or historical controls
Case-control study
Study of sensitivity and specificity of a diagnostic test
Population-based descriptive study
- Class D: Cross-sectional study
Case series
Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

- Class M: Meta-analysis
Systematic review
Decision analysis
Cost-effectiveness analysis
- Class R: Consensus statement
Consensus report
Narrative review
- Class X: Medical opinion

II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in Section I, above, and are assigned a designator of +, -, or \emptyset to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

The symbols +, -, \emptyset , and N/A found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:
+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;
- indicates that these issues have not been adequately addressed;
 \emptyset indicates that the report or review is neither exceptionally strong or exceptionally weak;
N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* 2002;105:2595-2599. (Class C)

Albert MA, Danielson E, Rifai N, Ridker PM, for the PRINCE investigators. Effect of statin therapy on C-reactive protein levels. The Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and a cohort study. *JAMA* 2001;286:64-70. (Class A)

Albert MA, Ridker PM. The role of C-reactive protein in cardiovascular disease risk. *Curr Cardiol Rep* 1999;1:99-104. (Class R)

Albert MA. The role of C-reactive protein in cardiovascular disease risk. *Curr Cardiol Rep* 2000;2:274-279. (Class R)

Aronow WS, Ahn C. Association between plasma homocysteine and coronary artery disease in older persons. *Am J Cardiol* 1997;80:1216-1218. (Class D)

Aronow WS, Ahn C. Increased plasma homocysteine is an independent predictor of new coronary events in older persons. *Am J Cardiol* 2000;86:346-347. (Class C)

Bostom AG, Silbershatz H, Rosenberg IH, et al. Nonfasting plasma total homocysteine levels and all-cause and cardiovascular disease mortality in elderly Framingham men and women. *Arch Intern Med* 1999;159:1077-1080. (Class B)

Christen WG, Ajani UA, GlynnRJ, Hennekens CH. Blood levels of homocysteine and increased risks of cardiovascular disease. *Arch Intern Med* 2000;160:422-434. (Class M)

Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000;321:199-204. (Class C)

Dierkes J, Bisse E, Nauck M, et al. The diagnostic value of serum homocysteine concentration as a risk factor for coronary artery disease. *Clin Chem Lab Med* 1998;36:453-457. (Class C)

Doggen CJ, Berckmans RJ, Sturk A, Manger Cats V, Rosendaal FR. C-reactive protein, cardiovascular risk factors and the association with myocardial infarction in men. *J Intern Med* 2000;248:406-414. (Class C)

Eikelboom JQ, Lonn E, Genest J, Hankey G, Yusuf S. Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. *Ann Intern Med* 1999;131:363-375. (Class R)

- Ess SM, Szucs TD. Medical-economical aspects of high sensitivity C-reactive protein assay for the prediction of coronary heart disease. An analysis in Germany and Italy. *Ital Heart J* 2001;2:1-8. (Class M)
- Folsom AR, Nieto FJ, McGovern PG, et al. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 1998;98:204-210. (Class C)
- Greenland P, et al. (Writing Group III). AHA Conference Proceedings. Prevention conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention: non-invasive tests of atherosclerotic burden. *Circulation* 2000;101:e16-e22. (Class R)
- Grundy SM, et al. (Writing Group I). AHA Conference Proceedings. Prevention conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention: medical office assessment. *Circulation* 2000;101:e3-e11. (Class R)
- Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke. *JAMA* 2002;288:2015-2022. (Class M)
- Hoogeveen EK, Kostense PJ, Jakobs C, et al. Hyperhomocysteinemia increases risk of death, especially in type 2 diabetes : 5-year follow-up of the Hoorn Study. *Circulation* 2000;101:1506-1511. (Class C)
- Jacques PF, Selhub J, Bostom AG, Wilson PWF, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *N Engl J Med* 1999;340:1449-1454. (Class C)
- Kawashiri M, Kajinami K, Nohara A, et al. Plasma homocysteine level and development of coronary artery disease. *Coronary Artery Dis* 1999;10:443-447. (Class C)
- Klerk M, Verhoef P, Clarke R, Blom HJ, Kok FJ, Schouten EG, for the MTHFR Studies Collaboration Group. *JAMA* 2002;288:2023-2031. (Class M)
- Knekt P, Alftan G, Aromaa A, et al. Homocysteine and major coronary events: a prospective population study amongst women. *J Intern Med* 2001;249:461-465. (Class C)
- Koenig W, Sund M, Frohlich M, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999;99:237-242. (Class B)
- Kuller LH, Evans RW. Homocysteine, vitamins, and cardiovascular disease. *Circulation* 1998;98:196-199. (Class R)
- Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relationship of C-reactive protein and coronary heart disease in the MRFIT nested case-control study: Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1996;144:537-544. (Class C)
- Kushner I, Sehgal AR. Is high-sensitivity C-reactive protein an effective screening test for cardiovascular risk? *Arch Intern Med* 2002;162:867-869. (Class R)
- Malinow MR, Duell PB, Hess DL, et al. Reduction of plasma homocyst(e)ine levels by breakfast cereal fortified with folic acid in patients with coronary heart disease. *N Engl J Med* 1998;338:1009-1015. (Class A)
- Mosca L. C-reactive protein – to screen or not to screen? *N Engl J Med* 2002;347:1615-1617. (Class R)
- Nallamotheu BK, Fendrick AM, Rubenfire M, Saint S, Bandekar RR, Omenn GS. Potential clinical and economic effects of homocyst(e)ine lowering. *Arch Intern Med* 2000;160:3406-3412. (Class M)
- Nass CM, Wiviott SD, Allen JK, Post WS, Blumenthal a R. Global risk assessment for lipid therapy to prevent coronary heart disease. *Curr Cardiol Rep* 2000;2:424-432. (Class R)

- National Cholesterol Education Program. Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Bethesda, MD: National Heart, Lung, and Blood Institute, 2001. (Class R)
- Packard CJ, O'Reilly DSJ, Caslake MJ, et al. for the West of Scotland Coronary Prevention Study Group. Lipoprotein-associated phospholipase A₂ as an independent predictor of coronary heart disease. *N Engl J Med* 2000;343:1148-1155. (Class C)
- Pahor M, Elam MB, Garrison RJ, Kritchevsky SB, Applegate WB. Emerging noninvasive biochemical measures to predict cardiovascular risk. *Arch Intern Med* 1999;159:237-245 (Class R)
- Pirro M, Bergeron J, Dagenais GR, et al. Age and duration of follow-up as modulators of the risk for ischemic heart disease associated with high plasma C-reactive protein levels in men. *Arch Intern Med* 2001;161:2474-2480. (Class B)
- Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001;286:327-334. (Class C)
- Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incidence coronary heart disease: prospective analysis from the Women's Health Initiative Observational Study. *JAMA* 2002;288:980-987. (Class C)
- Rader DJ. Inflammatory markers of coronary risk. *N Engl J Med* 2000;343:1179-1182. (Class R)
- Refsum H, Ueland PM. Recent data are not in conflict with homocysteine as a cardiovascular risk factor. *Curr Opin Lipidol* 1998;9:533-539. (Class R)
- Ridker PM. High-sensitivity C-reactive protein. Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001;103:1813-1818. (Class R)
- Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;98:731-733. (Class C)
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973-979. (Class C)
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 1998;97:425-428. (Class C)
- Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998;97:2007-2011. (Class C)
- Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836-843. (Class C)
- Ridker PM, Manson JE, Buring JE, Shih J, Matias M, Hennekens CH. Homocysteine and risk of cardiovascular disease among postmenopausal women. *JAMA* 1999;281:1817-1821. (Class C)
- Ridker PM, Rifai N, Clearfield M, et al. for the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. *N Engl J Med* 2001;344:1959-1965. (Class A)
- Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557-1565. (Class B)

- Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis. A comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 2001;285:2481-2485. (Class C)
- Rifai N, Ridker PM. High-sensitivity C-reactive protein: a novel and promising marker of coronary heart disease. *Clin Chem* 2001a;47:403-411. (Class R)
- Rifai N, Ridker PM. Proposed cardiovascular risk assessment algorithm using high-sensitivity C-reactive protein and lipid screening. *Clin Chem* 2001b;47:28-30. (Class X)
- Ross R. Atherosclerosis - an inflammatory disease. *N Engl J Med* 1999;340:115-126. (Class R)
- Rothembacher D, Fischer HG, Hoffmeister A, et al. Homocysteine and methylenetetrahydrofolate reductase genotype: association with risk of coronary heart disease and relation to inflammatory, hemostatic, and lipid parameters. *Atherosclerosis* 2002;162:193-200. (Class C)
- Sakkinen P, Abbott RD, Curb JD, Rodriguez BL, Yano K, Tracy RP. C-reactive protein and myocardial infarction. *J Clin Epidemiol* 2002;55:445-451. (Class C)
- Schönbeck U, Varo N, Libby P, Buring J, Ridker P. Soluble CD40L and cardiovascular risk in women. *Circulation* 2001;104:2266-2268. (Class C)
- Schwartz SM, Siscovick DS, Malinow MR, et al. Myocardial infarction in young women in relation to plasma total homocysteine, folate, and a common variant in the methylenetetrahydrofolate reductase gene. *Circulation* 1997;96:412-417. (Class C)
- Smith SC, Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V. Beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. *Circulation* 2000;101:111-116. (Class not assignable).
- Stehbens WE. Epidemiological risk factors of coronary heart disease are not causal in atherosclerosis. *Clin Exp Hypertens* 2000;22:445-453.
- Strandberg TE, Tilvis RS. C-reactive protein, cardiovascular risk factors, and mortality in a prospective study in the elderly. *Arterioscler Thromb Vasc Biol* 2000;20:1057-1060.
- Tice JA, Ross E, Coxson PG, et al. Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease: effect of grain fortification and beyond. *JAMA* 2001;286:936-943. (Class M)
- Tracy RP, Lemaitre RN, Psaty BM, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* 1997;17:1121-1127. (Class C)
- Ueland PM, Refsum H, Beresford SA, Vollset SE. The controversy over homocysteine and cardiovascular risk. *Am J Clin Nutr* 2000;72:324-332. (Class R)
- Verhoef P, Meleady R, Daly LE, Graham IM, Robinson K, Boers GH. Homocysteine, vitamin status and risk of vascular disease; effects of gender and menopausal status. European COMAC Group. *Eur Heart J* 1999;20:1234-1244. (Class C)
- Volsett SE, Refsum H, Tverdal A, et al. Plasma total homocysteine and cardiovascular and noncardiovascular mortality: the Hordaland Homocysteine Study. *Am J Clin Nutr* 2001;74:130-136. (Class B)
- Vorchheimer DA, Fuster V. Inflammatory markers in coronary artery disease. Let prevention douse the flames. *JAMA* 2001;286:2154-2156. (Class R)
- Voutilainen S, Lakka TA, Hamelahti P, Lehtimäki T, Poulsen HE, Salonen JT. Plasma total homocysteine concentration and the risk of acute coronary events: the Kuopio Ischaemic Heart Disease Risk Factor Study. *J Intern Med* 2000;248:217-222. (Class C)

Welch GN, Loscalzo J. Homocysteine and atherosclerosis. *N Engl J Med* 1998;338:1042-1050. (Class R)

Wilson PWF. Homocysteine and coronary heart disease: how great is the hazard? *JAMA* 2002;288:16-17. (Class R)

Appendix

See next pages

Conclusion Grading Worksheet

Work Group's Conclusion: CRP, if measured by high-sensitivity assay (hs-CRP), may have independent value as a predictor of cardiovascular disease risk and independent value in identifying patients with normal lipids who could benefit from treatment.

Conclusion Grade: II

Author/Year	Design Type	Class	Quality +, -, 0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Ridker, Hennekens, Buring, & Rifai, 2000	Nested Case-control	C	0	-Women's Health Study participants (post-menopausal; health professionals; no history of MI, stroke, TIA) -Cases: experienced CV event in 3 yrs after enrollment -Controls: matched for age, smoking; 2 per case	-122 cases, 244 controls -Cases had higher BMI, greater percentage with history of diabetes, hypertension, or parental MI before age 60 (all p<0.05) -For cardiovascular event (highest quartile of CRP vs. lowest): unadjusted RR=4.4 (95%CI 2.2-8.9); adjusted RR=1.4 (95%CI 1.1-2.1)	-The addition of the measurement of C-reactive protein to screening based on lipid levels may provide an improved method of identifying women at risk for cardiovascular events.
Pirro et al., 2001	Cohort	B	0	-2,037 Quebec Cardiovascular Study participants (men, 47-76 yrs old at baseline, no ischemic heart disease when enrolled)	-CRP cutoff was 1.77 mg/L (median of group); 3.8% of men with CRP below cutoff had first IHD event; 6.4% of men with CRP above cutoff had first IHD event -RR for ischemic heart disease (high CRP vs low CRP): 1.8 (95%CI 1.2-2.7) -Addition of lipid risk factors attenuated RR but did not eliminate; with addition of non-lipid risk factors RR was no longer significant	-Plasma CRP levels may provide independent information on IHD risk only in younger middle-aged men and in the case of IHD events that may occur relatively soon after the baseline evaluation.

Conclusion Grading Worksheet (cont)

Author/Year	Design Type	Class	Quality +, -, 0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Pradhan et al., 2002	Nested Case-control	C	0	<p>Women's Health Initiative participants (postmenopausal, ages 50-79 at enrollment, no cardiovascular disease or cancer)</p> <p>Followed median of 2.9 years</p> <p>Cases: first MI during follow-up</p> <p>Controls: matched on age, smoking, ethnicity, & follow-up time (1 per case)</p>	<p>-304 cases, 304 controls</p> <p>-Cases had higher prevalence of traditional risk factors at baseline; more never-users of HRT, higher CRP (all $p \leq 0.01$)</p> <p>-Adjusted OR (risk of coronary heart disease in 4th quartile vs. first): 2.1 (95%CI 1.1-4.1)</p>	<p>-CRP (and IL-6) independently predict vascular events among apparently healthy postmenopausal women. HRT increases CRP levels. However, use or non-use of HRT had less importance as a predictor of cardiovascular risk than did baseline levels of CRP.</p>
Albert, Ma, Rifai, Stampfer, Ridker, 2002	Nested Case-control	C	0	<p>Physician's Health Study participants (males; 40-84 yrs at enrollment; no history of MI, stroke, TIA, or cancer)</p> <p>-19 year follow-up</p> <p>-Cases: sudden cardiac death</p> <p>-Controls: no sudden cardiac death or other cardiovascular disease, matched on age, length of follow-up, smoking (2 per case)</p>	<p>-97 cases, 197 controls</p> <p>-Cases more likely to have history of diabetes, hypertension, parent with MI before age 60 (all $p < 0.01$); higher median CRP ($p = 0.01$)</p> <p>-Adjusted RR for highest quartile CRP vs lowest: 2.8 (95%CI 1.35-5.72)</p>	<p>-These prospective data suggest that CRP levels may be useful in identifying apparently healthy men who are an increased long-term risk of sudden cardiac death.</p>
Ridker, Rifai, Rose, Buring, & Cook, 2002	Cohort	B	0	<p>-27,939 Women's Health Study participants (45 years and older)</p>	<p>-Adjusted RR for first cardiovascular event (highest quintile vs. lowest quintile CRP): 2.3 (95%CI 1.6-3.4)</p> <p>-Adjusted RR for first cardiovascular event (highest quintile vs. lowest quintile LDL): 1.5 (95%CI 1.1-2.0)</p> <p>-Adjusted (for Framingham risk score components) RR (highest quintile vs. lowest quintile CRP): 1.9</p>	<p>-These data suggest that the C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score.</p>