Prevention Conference V
Beyond Secondary Prevention: Identifying the High-Risk Patient for Primary Prevention
Tests for Silent and Inducible Ischemia

Writing Group II

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Writing Group II addressed the question of whether tests that assess silent ischemia or inducible ischemia add to prognostic information gained from standard risk factors in asymptomatic patients without known coronary disease. The tests reviewed included the exercise electrocardiogram (ECG), exercise and pharmacological (stress) echocardiogram (echo), exercise and pharmacological myocardial perfusion imaging, ambulatory ECG monitoring, and positron emission tomography.

These noninvasive tests detect myocardial ischemia associated with obstructive coronary artery disease (CAD). To date, their greatest application has been diagnostic, in the evaluation of patients with symptoms of angina or a previous clinical manifestation of coronary heart disease (CHD). One limitation of the methods used to detect stress-induced (exercise or pharmacological stress) myocardial ischemia is the dependence of these methods on the presence of flow-limiting coronary stenosis. As with all diagnostic studies, their predictive value is dependent on the prevalence of disease in the population tested. When used in a population with a low prevalence of CHD, such as an asymptomatic population undergoing cardiovascular screening, these tests are expected to have low positive predictive value, and the majority of positive test results represent false-positive responses (Figure). Also central to the discussions of Writing Group II was the recognition that the majority of future events among patients with CHD are related to severity of obstruction, plaque instability, and total atherosclerotic burden.1

Writing Group II was specifically concerned with delineating the prognostic information available from these tests that could contribute toward identifying patients at higher risk for major CHD-related events.

Exercise ECG Testing

The use of the exercise ECG to screen subjects who are asymptomatic for CAD is historically a complex issue. There may be poor predictive value in the nonselective use of the test, and invalid abnormal responses (false-positive) may lead to psychological and work disability as well as unnecessary medical expense. Among asymptomatic individuals, there is evidence that development of an ischemic ECG response at low workloads of exercise testing is associated with a higher incidence of future events such as angina pectoris, myocardial infarction, and sudden death. More specifically, ST depression ≥1 mm occurring within 6 minutes on the Bruce protocol (6 to 7 METs*) has been associated with an increased relative risk of cardiovascular events in men; however, the absolute risk of cardiac events in these populations without associated cardiovascular risk factors remains low.2 A study in which the Ellestad protocol was used in asymptomatic men and women with known CHD3 found that ECG changes and exercise duration ≤5 minutes correlated with subsequent CHD in men >40 years old, but investigators concluded that the exercise ECG was of limited value in women and in men ≤40 years of age.

With regard to subjects who are asymptomatic but who also have risk factors for CHD, the results of exercise ECG testing are prognostically useful. In the Seattle Heart Watch Study,2 men with ≥1 risk factor (positive family history, smoking, hypertension, blood pressure >140/90 mm Hg, hypercholesterolemia [total cholesterol >240 mg/dL]) and 2 abnormalities on exercise testing (chest pain, exercise duration <6 minutes, ST depression >1 mm, or <90% predicted heart rate) had a 30-fold increase in 5-year cardiac risk. Exercise testing had no predictive value in the group with no risk factors. In the Lipid Research Clinics Coronary Primary Prevention Trial, of 3775 asymptomatic hypercholesterolemic men, half of whom were taking cholestyramine and half of whom were taking placebo, there was a 5.7 times greater

*MET indicates metabolic equivalent, ie, 3.5 mL·kg⁻¹·min⁻¹ of ventilatory oxygen consumption.
risk of death due to coronary heart disease in the placebo group among those with a positive exercise test result (≥1-mm ST-segment depression or elevation on exercise testing) than among those with a negative test result. Overall, during a mean follow-up period of 7.4 years, there was a 6.7% mortality rate in the group with a positive test result versus 1.3% in the group with a negative test result. Interestingly, a positive test result was not significantly associated with nonfatal myocardial infarction. The Multiple Risk Factor Intervention Trial (MRFIT) reported a nearly 4-fold increase in the 7-year coronary mortality rate among asymptomatic middle-aged men with elevated levels of CHD risk factors and an abnormal exercise ECG and suggested that the exercise ECG might serve to identify high-risk men who could benefit from risk factor reduction.

There is a paucity of similar data regarding the use of the exercise ECG in women and the elderly (age >75 years). In this regard, the limitations of exercise ECG in these populations is reflected by the lower sensitivity and specificity of ST-segment alteration in women and the elderly. It is of interest that treadmill exercise capacity was recently shown to be the most accurate predictor of prognosis in both men and women in a study that also assessed the value of ST-segment changes.

In 12 studies, investigators used the exercise test to screen asymptomatic individuals for cardiovascular risk and to predict subsequent events. Subjects were screened for silent heart disease and have been monitored for cardiac events for 5 to 10 years. Considerably different results have been obtained in these studies according to the end points considered. When angina is included as an end point, non-specific symptoms in a subject with an abnormal test result are more likely to be diagnosed as coronary disease during the follow-up period. Hard end points, such as death or myocardial infarction, eliminated this misclassification and are more appropriate for classifying cardiovascular risk. The earliest exercise test studies in asymptomatic people included angina as an end point, whereas the 4 most recent studies used only hard end points such as nonfatal myocardial infarction and coronary death. As shown in the Table, the first studies tested 5526 subjects and ranged in size from 113 to 1390 individuals. Sensitivity was 50%; specificity, 90%; risk ratio, 9 times; and predictive value of a positive response, 25%. This means that 1 of 4 subjects with abnormal test results eventually had a cardiac event such as angina. The 4 most recent studies included >12,000 subjects and monitored them only for hard end points. The sensitivity of the exercise test was ~25%; specificity, ~90%; risk ratio, 4 times; and predictive value of a positive response, only 5%. In other words, in these studies, 1 of 20 people with an abnormal test result eventually had a cardiac event such as death, and risk was 4-fold higher in those with positive test results than in those with negative test results.

Thus, routine use of the exercise ECG in completely unselected asymptomatic populations before office screening for risk cannot be recommended. In asymptomatic men >40 years old with ≥1 risk factor, exercise testing may provide useful information as a guide to aggressive risk factor intervention or the need to further evaluate the cause of myocardial ischemia. The role of exercise testing in women and the elderly (>75 years of age) as a guide to identifying the high-risk patient for primary prevention requires further study.

### Exercise and Pharmacological Stress Echocardiography

Stress echocardiography (SE) is based on the premise that myocardial ischemia leads to left ventricular dyssynergy that can be detected by 2-dimensional echo. Either exercise (treadmill or bicycle) or medication (usually dobutamine) is used as the stress modality. Although SE has been reported to increase the sensitivity and specificity of stress testing to detect CHD, most studies have focused on patients with known or suspected CHD who have a high pretest probability of disease. Few truly asymptomatic individuals have been evaluated for long-term prognosis.

Recent studies demonstrate that wall motion abnormalities at peak stress are among the most important predictors of an adverse outcome. These findings have been extended to
include elderly patients\textsuperscript{19} and those with an intermediate pretest likelihood of disease.\textsuperscript{20} It is possible to ascertain low risk status through the use of SE. Several studies have examined the prognosis of patients after a normal exercise or pharmacological SE.\textsuperscript{21–23} Absence of an inducible wall motion abnormality is associated with an excellent prognosis. In a recent study of 1325 patients (28\% of whom were asymptomatic), cardiac event–free survival after a normal exercise echocardiogram was 99\%, 98\%, and 97\% at 1, 2, and 3 years, respectively.\textsuperscript{22} This favorable prognosis was observed even in subgroups with an intermediate or high pretest likelihood of disease. Predictors of subsequent cardiac events were age, workload achieved, angina, and left ventricular hypertrophy.

In conclusion, only limited data exist to support the use of SE as a screening tool or in combination with noninvasive risk factors to evaluate asymptomatic populations. Also, the addition of echocardiographic imaging to routine stress testing increases the cost and complexity of the examination. Although SE may be of value in assessing women and the elderly with increased risk factors, further studies are needed to define its role in identifying the high-risk patient for primary prevention.

Exercise and Pharmacological Myocardial Perfusion Imaging

Myocardial perfusion imaging has evolved as an important clinical tool in the evaluation of patients with known or suspected CHD, and numerous studies involving thousands of patients attest to its diagnostic and prognostic capabilities in such patients. Inducible ischemia by perfusion imaging identifies a high-risk subset when used in patients with known or suspected CHD, and the magnitude of risk is related to the magnitude of ischemic myocardium.\textsuperscript{24} Conversely, patients with normal myocardial perfusion images have a \(<1\% \text{ risk per year of death or myocardial infarction.}\textsuperscript{24,25}

The development of perfusion defects with exercise or pharmacological stress is dependent on abnormal coronary vasodilator reserve; thus, myocardial perfusion imaging is potentially useful for detecting only those patients who have flow-limiting coronary artery stenosis. Therefore, perfusion imaging would be expected to have little or no practical value in the detection of patients with early coronary atherosclerotic disease who may be candidates for aggressive primary prevention strategies.

In high-risk asymptomatic populations such as those with a positive family history of CHD (a sibling with CHD before age 60), exercise thallium testing has been reported to identify an increased relative risk of death or myocardial infarction if the stress ECG was abnormal (relative risk [RR] 6.8), stress thallium was abnormal (RR 3.8), or both tests were abnormal (RR 61.3).\textsuperscript{26} Among 2104 patients without angina and without known CHD, 78\% had normal myocardial perfusion imaging, and the likelihood of death or myocardial infarction was 0.3\% per year, whereas the small subset (9\% of patients) with moderate to severe perfusion defects had an annual risk of death of 5.6\% and of myocardial infarction of 2.2\%.\textsuperscript{24} These patients underwent perfusion imaging for clinical indications; thus, these latter data may not be representative of the results of screening an unselected asymptomatic population. It is postulated that stress thallium scintigraphy might be particularly useful in the risk assessment of men \(\geq 45\) years old with a family history of premature coronary disease. The available data suggest that myocardial perfusion imaging should not be used broadly in screening unselected asymptomatic populations\textsuperscript{27} but may be valuable in selected populations considered at particularly high risk for CHD.

Ambulatory ECG Monitoring

Because the majority of information about ambulatory ECG (Holter) monitoring for detection of ischemia was gained from studies in patients with known disease, its role as a tool to screen cardiovascular disease in healthy individuals, even those at increased risk, must be extrapolated from research that was not designed to answer that question. The sensitivity and specificity of ST-segment depression for angiographically proven CAD in patients with chest pain has been reported as 62\% and 61\%, respectively, which is less than the 67\% and 75\% specificity reported in the same population with treadmill ECG testing.\textsuperscript{28} Because of the low sensitivity and specificity of ambulatory ECG monitoring, published recommendations suggest that it is an inaccurate modality to exclude the presence of coronary disease. In the guidelines for use of ambulatory ECG published by the ACC/AHA Task Force,\textsuperscript{29} its use for detecting myocardial ischemia in asymptomatic individuals is considered a class III indication, ie, a condition for which there is general agreement that it is not a useful test.

Positron Emission Tomography

The basis for detecting CHD with positron emission tomography (PET), like conventional radionuclide methods, is detection of flow heterogeneity during maximal coronary hyperemia. In addition, PET may be used to quantify reduced regional myocardial blood flow reserve in regions subtended by diseased coronary arteries. With both of these methods, CHD is only detectable if coronary stenosis is hemodynamically significant. Because PET is insensitive for the detection of coronary stenoses of \(<50\%\), its use as a screening test for CHD and risk stratification of asymptomatic patients is not cost-effective.\textsuperscript{30}

In patients with familial and secondary hypercholesterolemia, PET has revealed decreased myocardial blood flow reserve that correlated inversely with total plasma and LDL cholesterol.\textsuperscript{31} PET has also been used to quantify changes in the size and severity of myocardial perfusion abnormalities in patients with CHD after risk factor modifications.\textsuperscript{32} Thus, although significant issues surround the cost-effectiveness of PET in the evaluation of asymptomatic patients at risk for CHD, preliminary research suggests that there may be future applications of this technique in the detection of coronary endothelial dysfunction and the noninvasive monitoring of aggressive medical therapy and risk factor modification.

Conclusions

Data are quite limited regarding the prognostic utility of noninvasive measures of inducing myocardial ischemia in apparently asymptomatic persons. Very few prognostic studies have included adequate numbers of asymptomatic sub-
jects. Therefore, conclusions about the role of such testing for the purpose of risk assessment are limited. With the exception of exercise ECG testing in asymptomatic men with increased cardiovascular risk profiles, few data exist to support the use of the noninvasive testing modalities discussed by Writing Group II to screen asymptomatic populations for high-risk subclinical CHD. Future research should investigate the role of these techniques in association with global risk assessment (summarized by Writing Group I) to further define prognosis, guide intensity of therapy, and monitor the effectiveness of risk-intervention strategies.

References


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