

with hemodynamically similar coronary lesions may have stable or stabilized coronary lesions with a low risk for future coronary events. The present report suggests that additional diagnostic techniques to identify vulnerable plaque should be reserved for patients with an abnormal CRP level, such as in patients with intermediate lesions in whom PTCA was deferred. Furthermore, additional studies are necessary to answer the question of whether a high dose of statins, either alone or in combination with PTCA, are beneficial for these patients.

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Relation of Self-Reported Angina Pectoris to Inducible Myocardial Ischemia in Patients With Known Coronary Artery Disease: The Heart and Soul Study

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To determine whether self-reported angina pectoris is associated with objective evidence of myocardial ischemia, we assessed angina symptoms, using the Seattle Angina Questionnaire, and measured ischemia using stress echocardiography in 933 patients with known coronary artery disease. We observed no association between self-reported angina pectoris and objective evidence of inducible ischemia. ©2003 by Excerpta Medica, Inc.

(*Am J Cardiol* 2003;92:705–707)

The American College of Cardiology and the American Heart Association guidelines have recommended evaluation and treatment of coronary artery disease (CAD) based on symptoms alone.¹ These guidelines stem from studies that demonstrate a strong association between angina pectoris and myocardial ischemia in patients without known CAD.^{2–7} It is unclear whether symptoms of angina are associated with objective evidence of ischemia in patients with known CAD. If angina pectoris is not associated with

myocardial ischemia in patients with known CAD, then aggressive anti-ischemic medical therapy and consideration of coronary intervention should probably not be based on patient-reported symptoms alone. To determine whether angina pectoris is associated with inducible ischemia, we assessed self-reported angina, using the Seattle Angina Questionnaire,⁸ and measured inducible ischemia using stress echocardiography in 933 patients with known CAD.

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Between September 2000 and May 2002, we recruited 966 participants from 2 Department of Veterans Affairs Medical Centers, 1 University medical center, and 9 public health clinics in the Community Health Network in San Francisco, California. Patients were eligible to participate if they had any of the following: a history of myocardial infarction, angiographic evidence of $\geq 50\%$ stenosis in ≥ 1 coronary vessel, exercise-induced ischemia by treadmill or nuclear testing, a history of coronary revascularization, or a diagnosis of coronary disease that was documented by an internist or cardiologist. Patients were excluded if they were unable to walk 1 block or were planning to move from the local area within 3 years.

Of the 966 participants recruited, 33 were unable to complete exercise treadmill stress echocardiography for orthopedic or other reasons, leaving 933 participants for this cross-sectional analysis. All participants completed a day-long baseline study examination that included a comprehensive health status and medical history questionnaire followed by exercise treadmill stress echocardiography. This protocol was approved by the appropriate institutional review boards, and all participants provided written informed consent.

The primary predictor variable was frequency of angina as assessed by the Seattle Angina Questionnaire.⁸ The Seattle Angina Questionnaire is a 19-item, self-administered questionnaire that has been shown

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TABLE 1 Characteristics of 933 Study Participants With Known Coronary Heart Disease, Stratified by Frequency of Self-reported Angina Pectoris

Variable	Angina Pectoris			p Value
	≥1/wk (n = 171)	<1/wk (n = 161)	Absent (n = 601)	
Age (yrs)	64 ± 11	66 ± 11	68 ± 11	<0.001
Men	78%	81%	85%	0.04
White	59%	58%	62%	0.49
Systemic				
Hypertension	75%	79%	66%	0.002
Myocardial infarction	58%	52%	52%	0.37
Congestive heart failure	22%	19%	14%	0.04
Stroke	15%	16%	12%	0.33
Diabetes mellitus	31%	21%	24%	0.07
Coronary revascularization	59%	56%	61%	0.43
Current smoker	30%	20%	17%	<0.001
Regular alcohol use	27%	26%	31%	0.43
Physically active	51%	64%	70%	<0.001
Body mass index (kg/m ²)	28 ± 6	29 ± 6	28 ± 5	0.03
New York Heart Association class III or IV	49%	25%	12%	<0.001
Medications				
β blocker	65%	60%	56%	0.10
Statin	64%	60%	67%	0.21
Renin-angiotensin inhibitor	51%	52%	52%	1.0
Aspirin	81%	82%	77%	0.28
Total cholesterol (mg/dl)	178 ± 45	180 ± 46	176 ± 40	0.41
High-density lipoprotein (mg/dl)	46 ± 13	46 ± 16	46 ± 14	0.89
Low-density lipoprotein (mg/dl)	102 ± 32	108 ± 40	103 ± 32	0.22
Glycosylated hemoglobin	6.2 ± 1.5	5.8 ± 0.9	5.9 ± 1.1	0.01
Creatinine clearance (ml/min)	86 ± 29	80 ± 27	81 ± 28	0.11
Ejection fraction ≤55%	20%	14%	17%	0.26
Systolic blood pressure ≥140 (mm Hg)	33%	34%	35%	0.85
Diastolic blood pressure ≥90 (mm Hg)	97%	93%	97%	0.10
Pulse pressure (mm Hg)	57 ± 17	56 ± 13	58 ± 15	0.32

Values are reported as percentages or mean ± SD.

TABLE 2 Association Between Angina Frequency and Inducible Ischemia in 933 Participants With Known Coronary Artery Disease

	Proportion With ischemia	Unadjusted OR (95% CI) (n = 933)	p Value	Adjusted OR* (95% CI) (n = 875)	p Value
Angina frequency					
None (n = 601)	24%	1.0		1.0	
<1/wk (n = 161)	27%	1.2 (0.8–1.8)	0.35	1.4 (0.9–2.2)	0.12
≥1/wk (n = 171)	23%	1.0 (0.7–1.5)	0.91	1.0 (0.6–1.6)	0.99
Nitroglycerin use					
None (n = 778)	23%	1.0		1.0	
<1/wk (n = 69)	28%	1.3 (0.7–2.2)	0.42	1.4 (0.8–2.5)	0.30
≥1/wk (n = 85)	32%	1.5 (0.9–2.5)	0.08	1.3 (0.7–2.2)	0.42

*All variables from Table 1 were entered into forward stepwise ordinal logistic regression models; the above measurements were forced into the models. In both models, the variables associated with ischemia (at p < 0.10) were age, white race, history of myocardial infarction, creatinine clearance, glycosylated hemoglobin, and left ventricular ejection fraction ≤55%.
CI = confidence interval; OR = odd ratio.

to be a valid and reproducible measure of the health status of patients with CAD.⁹ A primary domain of the questionnaire is the angina frequency scale, which includes 2 questions with Likert-scale responses (categorized as none, less than once per week, or once or more per week). Our primary predictor variable was: “Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or angina?” Our secondary predictor variable was: “How many

times have you had to take nitroglycerin for your chest pain, chest tightness, or angina?”⁸

The outcome variable was cardiac ischemia as measured by exercise treadmill testing with stress echocardiography.⁹ We performed resting and stress echocardiograms using an Acuson Sequoia Ultrasound System (Mountain View, California) with a 3.5-MHz transducer. Before exercise, standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views obtained during breath-hold were planimetered using a computerized digitization system to determine end-systolic and end-diastolic left-ventricular volume and left ventricular ejection fraction. At peak exercise, apical 2-chamber, 4-chamber, and precordial long- and short-axis views were obtained to detect the development of right or left ventricular dilation or wall motion abnormalities during exercise. Results from the stress echocardiogram were graded as having none, 1, 2, or >2 exercise-induced wall motion abnormalities by an expert cardiologist (NBS) who was blinded to patient-reported angina.

Age, gender, ethnicity, medical history, smoking status, alcohol use, and New York Heart Association functional classification were determined by questionnaire. We measured weight and height and calculated body mass index (kilograms per square meter). We measured systolic and diastolic blood pressure and calculated pulse pressure. Physical activity was determined using the multiple-choice question: “Which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?” Participants who answered fairly, quite, very, or extremely active (vs not at all or a little active) were considered physically active.

Participants were instructed to bring their medications to the examination, and study personnel recorded all current medications. Fasting serum samples were obtained for measurements of creatinine, glycosylated hemoglobin, total cholesterol, high-density lipoprotein, and low-density lipoprotein after a 12-hour fast. We estimated creatinine clearance using 24-hour urine collections.

Differences in characteristics between participants with and without angina were compared using analysis

of variance for continuous variables and chi-square tests for dichotomous variables. We then used logistic regression to examine the association between angina frequency and the presence of ischemia (defined as any exercise-induced wall motion abnormality by stress echocardiography). To obtain adjusted risk estimates, we entered all variables from Table 1 into forward stepwise logistic regression models with ischemia as the dependent variable. Because angina frequency was our primary predictor variable, we forced the angina frequency and nitroglycerin use categories (none, less than once per week, or at least once per week) into these multivariable models. Any Table 1 variables that were independently associated with ischemia (at $p < 0.1$) were also retained in the models.

We also performed analyses stratified by 3 a priori subgroups: history of myocardial infarction, diabetes, and revascularization. Finally, to determine whether angina was predictive of severe ischemia, we examined the association between angina frequency and severe ischemia (defined as ≥ 2 wall motion abnormalities by stress echocardiography).

Comparing participants with and without angina, we had $>80\%$ power (2-tailed $\alpha = 0.05$) to detect a 10% difference (25% vs 35%) in the proportion of patients who had any ischemia, and $>80\%$ power to detect a 6% difference (5% vs 11%) in the proportion of patients who had severe ischemia. All analyses were performed using Statistical Analysis Software (version 8, SAS Institute, Inc., Cary, North Carolina).

Of the 933 participants, 171 (18%) reported angina at least once per week, 161 (17%) reported angina less than once per week, and 601 (64%) reported no angina (Table 1). Compared with participants who did not have angina, those who reported angina were younger, less likely to be male, more likely to have hypertension, congestive heart failure or diabetes, more likely to smoke, and less physically active. Participants with angina had a greater body mass index, greater glycosylated hemoglobin, and worse functional status than those without angina.

Of the 933 participants, 226 (24%) had inducible ischemia (defined as any exercise-induced wall motion abnormality by stress echocardiography). We observed no association between self-reported angina or inducible ischemia, or between frequency of nitroglycerin use and inducible ischemia, in univariate and multivariate analyses (Table 2). In subgroup analyses stratified by history of myocardial infarction, history of revascularization, and history of diabetes, we also found no association between self-reported angina and inducible ischemia (all p values >0.2).

Finally, we observed no association between self-reported angina and severe ischemia. Of the 933 participants, 71 (8%) had severe ischemia (defined as >2 wall motion abnormalities by stress echocardiography). Severe ischemia was present in 9% of participants (16 of 171) with angina once or more per week, 9% of those (14 of 161) with angina less than once per week, and 7% of those (41 of 601) without angina ($p = 0.46$).

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We found that self-reported angina is not associated with the presence of inducible myocardial ischemia in patients with known CAD. Overall, about 25% of participants had inducible ischemia, but those reporting angina pectoris were no more likely than those without angina pectoris to have objective evidence of ischemia. This lack of association between angina and ischemia was persistent in the subgroups stratified by history of myocardial infarction, history of revascularization, and history of diabetes.

These results suggest that it may be time to reevaluate our current approach of using symptoms alone to guide management decisions in patients with established CAD as recommended by the American College of Cardiology/American Heart Association guidelines.¹ Because about 75% of patients with angina pectoris do not have ischemia, our data suggest that objective evidence of ischemia should be obtained to verify angina symptoms before more aggressive anti-ischemic medical therapy or coronary evaluation is undertaken. Even in the absence of angina pectoris, 25% of participants had evidence of inducible ischemia by stress echocardiography, suggesting that routine stress testing may be necessary to identify ischemia in patients with known CAD. These findings are supported by follow-up from the Asymptomatic Cardiac Ischemia Pilot study,¹⁰ which found that ischemia-guided drug therapy compared with angina-guided drug therapy decreased total mortality, the rate of myocardial infarction, and the rate of recurrent cardiac hospitalization in patients with CAD.

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