Frequency of Angina Pectoris and Secondary Events in Patients With Stable Coronary Heart Disease (from the Heart and Soul Study)

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The extent to which angina pectoris (AP) predicts secondary cardiovascular events beyond independent of measures of disease severity is unknown. We evaluated the association between AP frequency and secondary events in patients with stable coronary heart disease (CHD). We administered the Seattle Angina Questionnaire to 1,023 participants with stable CHD enrolled from September 2000 to December 2002 and followed for a median of 8.9 years. We used Cox proportional hazards to evaluate the association of AP frequency with death and subsequent hospitalization for AP, revascularization, myocardial infarction (MI), or heart failure. At enrollment, 633 (62%) participants reported no AP, 279 (27%) reported monthly AP, and 111 (11%) reported daily or weekly AP. During follow-up, 396 participants died, 204 were hospitalized for AP, 194 for revascularization, 140 for MI, and 188 for heart failure. Compared with participants without AP, participants with daily or weekly AP were more likely to be hospitalized for AP (hazard ratio [HR] 3.3; 95% confidence interval [CI] 2.3 to 4.7; p <0.001), revascularization (HR 2.0; 95% CI 1.3 to 2.9; p = 0.001), or heart failure (HR 1.6; 95% CI 1.0 to 2.5; p = 0.03) and more likely to die (HR 1.5; 95% CI 1.1 to 2.0; p = 0.01). AP was not independently associated with MI (HR 1.3; 95% CI 0.8 to 2.3; p = 0.29). After adjusting for demographics, co-morbidities, treadmill exercise capacity, ejection fraction, and inducible ischemia, frequency of AP remained independently associated with hospitalization for AP (HR 2.4; 95% CI 1.6 to 3.6; p <0.001), revascularization (HR 1.7; 95% CI 1.1 to 2.7; p = 0.02), and death (HR 1.4; 95% CI 1.0 to 2.0; p = 0.045). In conclusion, in outpatients with stable CHD, AP frequency predicts higher rates of secondary cardiovascular events and death, independent of objective measures of disease severity. **(Am J Cardiol 2014;114:997−1002)**

We sought to determine whether the frequency of angina pectoris (AP) was associated with long-term risk of cardiovascular events in a prospective cohort study of 1,023 outpatients with stable coronary heart disease (CHD). We also evaluated whether the association between AP frequency and cardiovascular events was explained by other baseline risk factors and objective measures of CHD.

Methods

We evaluated 1,023 participants from the Heart and Soul Study, a prospective cohort study originally designed to investigate the effects of psychosocial factors on health outcomes in patients with stable CHD. Detailed methods of this study have been previously described.[1] In brief, participants were eligible if they had at least one of the following: history of myocardial infarction (MI), angiographic evidence of ≥50% stenosis in ≥1 coronary vessels, evidence of exercise-induced ischemia by treadmill electrocardiogram or stress nuclear perfusion imaging, or a history of coronary revascularization. Participants were excluded if they were unable to walk 1 block, had an acute coronary syndrome within the previous 6 months, or were likely to move out of the area within 3 years.

Between September 11, 2000, and December 20, 2002, 1,024 participants were enrolled from 12 outpatient clinics in the San Francisco Bay Area, including 549 (54%) with a history of MI, 237 (23%) with a history of revascularization but not MI, and 238 (23%) with a diagnosis of coronary disease that was documented by their physician, based on a positive angiogram or treadmill test in >98% of cases. All study participants completed a full-day evaluation including medical history, extensive questionnaires, blood tests, and an exercise treadmill test with echocardiograms at baseline and after stress. The analytic cohort for this investigation included the 1,023 participants who completed the AP frequency domain of the Seattle Angina Questionnaire (SAQ). All participants provided informed consent. This study was approved by the institutional committee on human research.

The primary predictor was AP frequency measured with the SAQ.[2] The SAQ is a 19-item, self-administered questionnaire that has been validated for use in patients with CHD. The questionnaire is divided into several domains, including AP frequency, quality of life, treatment

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Table 1
Baseline characteristics of 1023 participants reporting angina frequency

Characteristic	Angina Frequency			p-Value
	Absent	Monthly	Daily or Weekly	
	N = 633	N = 279	N = 111	
Age (years), mean ± SD	68 ± 11	65 ± 11	66 ± 12	<0.001
Male	534 (84%)	221 (79%)	85 (77%)	0.048
Caucasian	391 (62%)	156 (56%)	67 (60%)	0.28
Smoking	100 (16%)	67 (24%)	34 (31%)	<0.001
Hypertension	421 (67%)	213 (76%)	89 (80%)	0.001
Myocardial infarction	330 (52%)	151 (54%)	66 (59%)	0.28
Heart failure	89 (14%)	63 (23%)	27 (24%)	0.001
Diabetes	155 (24%)	81 (29%)	29 (26%)	0.37
Revascularization	382 (60%)	155 (56%)	65 (59%)	0.42
Depressive symptoms	79 (12%)	75 (27%)	45 (41%)	<0.001
Body mass index (kg/m^2)	28 ± 5	29 ± 6	28 ± 7	0.04
Systolic blood pressure (mm Hg)	133 ± 20	135 ± 23	130 ± 20	0.16
Diastolic blood pressure (mm Hg)	74 ± 11	77 ± 12	72 ± 10	0.001
Total cholesterol (mg/dl)	176 ± 40	182 ± 48	175 ± 41	0.13
HDL cholesterol (mg/dl)	46 ± 14	46 ± 15	45 ± 14	0.71
LV ejection fraction (%)	62 ± 9	62 ± 10	61 ± 10	0.69
LV mass index (g/m^2)	97 ± 25	100 ± 30	101 ± 26	0.11
Medications				
Beta-blockers	352 (56%)	162 (58%)	79 (71%)	0.01
ACE-inhibitors or ARBs	319 (50%)	139 (50%)	66 (59%)	0.19
Statins	421 (67%)	168 (60%)	68 (61%)	0.12
Aspirin	449 (71%)	206 (74%)	86 (77%)	0.34
Calcium channel blockers	146 (23%)	64 (23%)	37 (33%)	0.06
Nitrates	116 (18%)	103 (37%)	78 (70%)	<0.001
Seattle Angina Questionnaire, median (IQR)				
Angina frequency	100	80 (80−90)	50 (40−60)	<0.001
Quality of life	92 (70−100)	67 (50−75)	42 (25−58)	<0.001
Physical limitation	86 (67−100)	67 (50−86)	50 (33−67)	<0.001

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; HDL = high-density lipoprotein; IQR = interquartile range; SD = standard deviation.

Table 2
Angina frequency, physical activity, and treadmill exercise testing in 944 participants

Characteristic	Angina Frequency			p-Value
	Absent	Monthly	Daily or Weekly	
	(N = 593)	(N = 250)	(N = 101)	
Physically inactive	177/592 (30%)	100/249 (40%)	49/101 (49%)	<0.001
Treadmill exercise capacity (METs), mean ± SD	7.6 ± 3.5	7.0 ± 2.8	6.3 ± 3.4	<0.001
Angina reported during exercise testing				<0.001
None	581 (98%)	220 (88%)	80 (79%)	
Non-limiting	8 (1%)	14 (6%)	9 (9%)	
Limiting	4 (1%)	16 (6%)	12 (12%)	
Inducible myocardial ischemia	141/589 (24%)	59/247 (24%)	28/101 (28%)	0.70

METs = metabolic equivalents; SD = standard deviation.

satisfaction, and physical limitation. The AP frequency domain includes 2 questions with Likert scale responses. The questions are "Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or AP?" and "How many times have you had to take nitroglycerin for your chest pain, chest tightness, or AP?" Scores for AP frequency are translated into a score on a 100-point scale, with 100 representing no AP and 0 representing AP occurring ≥4 times/day. Scores for the physical limitation domain of the SAQ were also calculated on a 100-point scale, with 100 representing no limitation and 0 representing severe physical limitations because of AP.

Participants were divided into categories of AP frequency based on SAQ scores, defined as absent (score 100), monthly (score 61 to 99), weekly (score 31 to 60), and daily (score 0 to 30). Because only 10 participants reported daily AP, those with daily or weekly AP were combined into a single category for analysis.

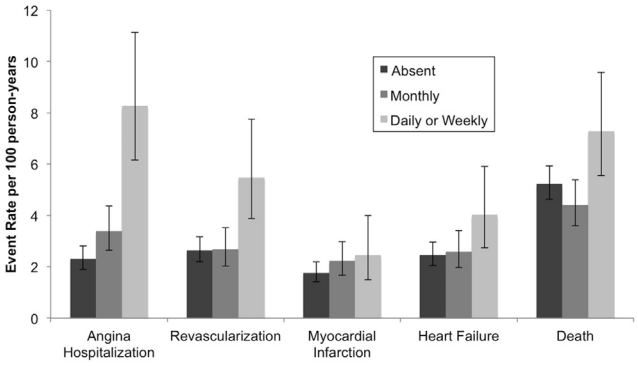

Figure 1. Cardiovascular events by angina pectoris frequency in 1,023 participants.

Annual telephone interviews were conducted with participants or their proxy to inquire about interval hospitalization or death. For any reported event, medical records, electrocardiograms, death certificates, autopsy, and coroner's reports were obtained. Each event was adjudicated by 2 independent and blinded reviewers. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third, blinded adjudicator, if needed.

Hospitalization for AP was strictly defined as hospitalization for definite or probable AP on the basis of symptoms, physician diagnosis, medical treatment, documented CHD, revascularization during admission, stenosis >70% documented during admission, ischemia by electrocardiogram, or ischemia by stress testing. Hospitalization for chest pain was not considered AP without objective evidence of cardiac ischemia. Revascularization was defined as percutaneous coronary intervention or coronary artery bypass graft surgery. MI was defined using standard diagnostic criteria.[3] Heart failure was defined as hospitalization for signs and symptoms of heart failure. Death was verified by death certificates.

Demographic characteristics, medical history, and smoking status were collected by self-report questionnaire. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire, a self-report instrument that measures the frequency of depressive symptoms, with a score of 10 or higher being classified as having depressive symptoms.[4] We measured weight and height to calculate body mass index (kg/m^2). Supine blood pressure at rest was measured with a standard sphygmomanometer. Participants were asked to bring their medications to the study appointment, and research personnel recorded all current medications and categorized using Epocrates Rx (Epocrates, Inc., San Mateo, California). Total and high-density lipoprotein cholesterol were determined from 12-hour fasting serum samples.

Participants underwent symptom-limited treadmill exercise testing according to a standard Bruce protocol (those unable to complete the standard protocol underwent operator-modified grade and speed adjustments) with continuous 12-lead electrocardiogram monitoring. Exercise capacity was estimated as the total METs achieved at peak exercise.[5] Before exercise, participants underwent complete 2-dimensional echocardiograms at rest with all standard views using an Acuson Sequoia Ultrasound System (Siemens Medical Solutions, Mountain View, California) with a 3.5-MHz transducer. Standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views were used to calculate chamber sizes (indexed to body surface area) and left ventricular ejection fraction.[6] At peak exercise, precordial long- and short-axis and apical 2- and 4-chamber views were obtained to ascertain wall motion abnormalities. We defined exercise-induced ischemia as the presence of 1 or more new wall motion abnormalities at peak exercise that were not present at rest. A single experienced cardiologist, who was blinded to the results of questionnaires and clinical histories, interpreted all echocardiograms.

Baseline characteristics were compared across categories of AP frequency using the chi-square test for categorical variables and 1-way analysis of variance for continuous variables. Fisher's exact test was performed for categorical variables with fewer than 5 participants in a cell. Event rates per 100 person-years were calculated by category of AP frequency. Cox proportional hazards models were used to compare event rates between participants without AP with participants with daily or weekly AP. We adjusted models for all investigated baseline characteristics (demographics, co-morbidities, medications, and treadmill exercise capacity) associated with AP frequency with $p < 0.10$ and EF and inducible ischemia. We constructed Cox proportional hazards models representing AP frequency as a continuous variable by numerical SAQ AP frequency score and for the association of SAQ physical limitation scale with outcomes. We tested the proportional hazards assumption by evaluating Schoenfeld residuals and found no violations of the proportional hazards assumption (all $p > 0.05$ for association between residuals and time). Multiple imputation was performed using iterative chained equations for covariates with missing data, including smoking (n = 3), hypertension (n = 3), history of heart failure (n = 6), diastolic blood pressure (n = 10), β-blocker use (n = 13), exercise capacity (n = 80), EF (n = 27), and inducible ischemia (n = 86). All analyses were performed using Stata, version 12 (StataCorp LP, College Station, TX).

Results

In 1,023 participants completing the SAQ, 633 (61.9%) reported no AP, 279 (27.3%) reported monthly AP, 101 (9.9%) reported weekly AP, and 10 (1.0%) reported daily AP. Participants with daily or weekly AP were less likely to be men, more likely to be current smokers, more likely to have a history of hypertension or heart failure, more likely to have depressive symptoms, and more likely to take β blockers, calcium channel blockers, and nitrates (Table 1). Compared with participants who had no AP or weekly AP, those with monthly AP were younger, had higher body mass index, and had higher diastolic blood pressure.

Participants with daily or weekly AP were less likely to be physically active, had lower exercise capacity, and were more likely to experience AP with treadmill testing but not more likely to have inducible ischemia on stress echocardiogram (Table 2). During or immediately after the exercise treadmill test, AP was reported by 21% of participants (21 of 101) who reported daily or weekly AP on the SAQ and by 2% of participants (12 of 589) who did not report AP on the SAQ.

Participants were followed for a median of 8.9 years (interquartile range 5.4 to 9.9 years, longest follow-up

Table 3
Risk of subsequent cardiovascular events among participants with daily or weekly (vs. no) reported angina

	Hospitalization for Angina		Revascularization		Myocardial Infarction		Heart Failure		Death	
	HR (95% CI)*	p-Value	HR (95% CI)*	p-Value	HR (95% CI)*	p-Value	HR (95% CI)*	p-Value	HR (95% CI)*	p-Value
Unadjusted	3.3 (2.3, 4.7)	<0.001	2.0 (1.3, 2.9)	0.001	1.3 (0.8, 2.3)	0.29	1.6 (1.0, 2.5)	0.03	1.5 (1.1, 2.0)	0.01
Model 1†	2.5 (1.7, 3.7)	<0.001	1.8 (1.1, 2.7)	0.01	1.0 (0.5, 1.7)	0.87	1.3 (0.8, 2.1)	0.25	1.5 (1.1, 2.0)	0.02
Model 2‡	2.4 (1.6, 3.6)	<0.001	1.7 (1.1, 2.7)	0.01	1.0 (0.5, 1.7)	0.88	1.2 (0.7, 2.0)	0.47	1.4 (1.0, 1.9)	0.08
Model 3§	2.4 (1.6, 3.6)	<0.001	1.7 (1.1, 2.7)	0.02	0.9 (0.5, 1.7)	0.85	1.3 (0.8, 2.1)	0.32	1.4 (1.0, 2.0)	0.045

* Hazard ratio (HR) and 95% confidence interval (CI) for cardiovascular events in participants with daily or weekly angina compared to participants without angina at baseline.
† Model 1 adjusts for age, sex, smoking, hypertension history, heart failure history, body mass index, diastolic blood pressure, beta-blocker use, calcium-channel blocker use, and nitrate use.
‡ Model 2 adjusts for the factors in Model 1 + depressive symptoms.
§ Model 3 adjusts for the factors in Model 2 + treadmill exercise capacity, left ventricular ejection fraction, and inducible ischemia.

Table 4
Risk of cardiovascular events by physical limitation entered as a continuous variable

	Hospitalization for Angina		Revascularization		Myocardial Infarction		Heart Failure		Death	
	HR (95% CI)*	p-Value	HR (95% CI)*	p-Value	HR (95% CI)*	p-Value	HR (95% CI)*	p-Value	HR (95% CI)*	p-Value
Unadjusted	1.4 (1.2, 1.6)	<0.001	1.2 (1.1, 1.4)	0.001	1.2 (1.1, 1.4)	0.003	1.5 (1.4, 1.7)	<0.001	1.3 (1.2, 1.4)	<0.001
Model 1†	1.3 (1.1, 1.4)	0.001	1.2 (1.0, 1.4)	0.008	1.1 (1.0, 1.3)	0.11	1.4 (1.2, 1.6)	<0.001	1.3 (1.2, 1.4)	<0.001
Model 2‡	1.3 (1.1, 1.4)	0.001	1.2 (1.0, 1.4)	0.02	1.2 (1.0, 1.4)	0.09	1.3 (1.2, 1.6)	<0.001	1.3 (1.2, 1.5)	<0.001
Model 3§	1.2 (1.1, 1.4)	0.004	1.2 (1.0, 1.4)	0.03	1.1 (0.9, 1.3)	0.46	1.2 (1.0, 1.4)	0.04	1.1 (1.0, 1.3)	0.01

* Hazard ratio (HR) and 95% confidence interval (CI) for cardiovascular events per 20 unit decrease (worsening) in Seattle Angina Questionnaire Physical Limitation scale (1−100).
† Model 1 adjusts for age, sex, smoking, hypertension history, heart failure history, body mass index, diastolic blood pressure, beta-blocker use, calcium-channel blocker use, and nitrate use.
‡ Model 2 adjusts for the factors in Model 1 + depressive symptoms.
§ Model 3 adjusts for the factors in Model 2 + treadmill exercise capacity, left ventricular ejection fraction, and inducible ischemia.

11.4 years). Of participants surviving to 5 years, 667 of 780 (86%) completed a follow-up examination at 5 years. During follow-up, 204 (19.9%) participants were hospitalized for AP, 194 (19.0%) underwent coronary revascularization, 140 (13.7%) experienced MI, 188 (18.4%) were hospitalized for heart failure, and 396 (38.7%) died. Compared with participants without AP, participants with daily or weekly AP were more likely to be hospitalized for AP, undergo revascularization, be hospitalized for heart failure, and die (Figure 1 and Table 3). Participants with daily or weekly AP were also more likely to be hospitalized for MI, but this was not statistically significant.

After adjusting for clinical risk factors (age, gender, smoking, hypertension history, heart failure history, body mass index, diastolic blood pressure, β-blocker use, calcium-channel blocker use, and nitrate use), depressive symptoms, treadmill exercise capacity, ejection fraction, and inducible ischemia, participants with daily or weekly angina had more than twice the risk of hospitalization for AP, 70% higher risk of revascularization, and 40% higher risk of death (Table 3). However, AP was not independently associated with MI or heart failure after adjustment for objective measures of CHD and depressive symptoms.

When AP frequency by SAQ was considered as a continuous variable (score from 0 to 100, with 100 representing no AP), higher AP frequency was associated with higher rates of AP hospitalization (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.4 to 1.8, p <0.001), revascularization (HR 1.4, 95% CI 1.2 to 1.6, p <0.001), and heart failure (HR 1.2, 95% CI 1.0 to 1.4, p = 0.02) but not significantly associated with MI (HR 1.2, 95% CI 1.0 to 1.4, p = 0.07) or death (HR 1.1, 95% CI 1.0 to 1.4, p = 0.09). After adjusting for clinical risk factors, depressive symptoms, treadmill exercise capacity, ejection fraction, and inducible ischemia, each 20-unit worsening in AP frequency score predicted a 40% higher risk of AP hospitalization (adjusted HR 1.4, 95% CI 1.2 to 1.7, p <0.001) and a 30% higher risk of revascularization (adjusted HR 1.3, 95% CI 1.1 to 1.5, p = 0.002) but was not significantly independently associated with MI, heart failure, or death.

Greater physical limitation because of AP, measured by the SAQ physical limitation scale (score from 0 to 100, with 100 representing no physical limitation because of AP), was also associated with higher rates of cardiovascular events (Table 4). After adjusting for clinical risk factors, depressive symptoms, treadmill exercise capacity, EF, and inducible ischemia, each 20-unit worsening in physical limitation because of AP predicted a 20% higher risk of AP hospitalization, a 20% higher risk of revascularization, a 20% higher risk of heart failure hospitalization, and a 10% higher risk of death (Table 4).

We conducted a sensitivity analysis for the association of SAQ AP frequency and SAQ physical limitation with outcomes by including physical inactivity in the fully adjusted

model but found that the additional inclusion of physical inactivity did not meaningfully change the point estimates or conclusions.

Discussion

In this study of 1,023 patients with CHD, we found that self-reported AP was predictive of future AP hospitalization, revascularization, and death during 8.9 years of follow-up. This association was independent of clinical risk factors, depressive symptoms, and objective measures of disease severity, including treadmill exercise capacity, ejection fraction, and inducible ischemia. These findings underscore the importance of considering patient-reported symptoms in the care of CHD patients because self-reported AP frequency is not only important to patients but also captures elements of risk not otherwise identified by objective measures.

Our results extend the findings of previous reports in several important ways. First, we showed that daily or weekly AP was predictive of future hospitalization for AP, revascularization, and death, independent of objective measures of disease severity. Previous studies have found that AP is associated with mortality[7–9] but have not been able to quantify the risk of future hospitalization for AP or revascularization independent of objective measures of cardiac disease severity.

Second, we found that exercise treadmill testing did not induce AP or ischemia in most participants who reported frequent AP, and most participants with inducible ischemia did not report frequent AP on the SAQ. Exercise stress testing has imperfect sensitivity and specificity for obstructive coronary artery disease[10] and also appears to have limited correlation with patient-reported symptoms. This demonstrates the importance of assessing both patient-reported and objective measures of cardiac disease severity. We have demonstrated that measurement of patient-reported AP frequency, an inexpensive measure, provides independent prognostic information about AP hospitalization, revascularization, and death. Measurement of patient-reported health status is increasingly recognized as an important tool in the care of patients with CHD,[11,12] and our findings provide additional evidence for the importance of patient-reported symptoms.

Third, we noted that AP frequency was associated with depressive symptoms and that adjusting for clinical risk factors and depressive symptoms reduced the association between AP frequency and cardiovascular events. Self-reported AP frequency is known to be associated with depressive symptoms,[13–15] and depressive symptoms are associated with adverse cardiovascular events, largely because of behavioral factors and physical inactivity.[1] However, few previous studies have been able to account for the effects of depressive symptoms. Our findings suggest that although depressive symptoms explain some of the association between AP frequency and outcomes, AP frequency remains predictive of outcomes beyond the influence of depressive symptoms.

Finally, many patients with AP limit their physical activity in response to symptoms of AP. Physical limitation because of AP is associated with mortality.[16] We demonstrated that in our cohort, physical limitation because of AP is associated with cardiovascular events. In addition, we demonstrated that adjusting for objective measures of cardiac disease severity, including exercise capacity, EF, and inducible ischemia, did not diminish the association between AP frequency and death or hospitalization for AP or revascularization. Together, this suggests that although physical limitation because of AP does affect outcomes, considering the results of formal exercise testing does not diminish the association between patient-reported AP frequency and outcomes.

Our findings have limitations. First, most participants were urban men, which limits generalizability. AP frequency has also been associated with poorer outcomes in women,[8] and women and men with stable AP have similar overall event rates of events.[17] Second, this study was not designed to determine the effects of treatment strategies on outcomes. The effectiveness of specific treatment strategies for improving outcomes by reducing AP frequency merits further study. Third, we analyzed outcomes regarding AP measured at the beginning of the study, which does not account for the influence of subsequent changes in AP symptoms. Finally, as with all observational studies, we cannot exclude the possibility of residual confounding by unmeasured factors. However, we had very detailed data about the patients.

Disclosures

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