Self-reported Medication Adherence and Cardiovascular Events in Patients With Stable Coronary Heart Disease

The Heart and Soul Study

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Background: Nonadherence to physician treatment recommendations is an increasingly recognized cause of adverse outcomes and increased health care costs, particularly among patients with cardiovascular disease. Whether patient self-report can provide an accurate assessment of medication adherence in outpatients with stable coronary heart disease is unknown.

Methods: We prospectively evaluated the risk of cardiovascular events associated with self-reported medication nonadherence in 1015 outpatients with established coronary heart disease from the Heart and Soul Study. We asked participants a single question: "In the past month, how often did you take your medications as the doctor prescribed?" Nonadherence was defined as taking medications as prescribed 75% of the time or less. Cardiovascular events (coronary heart disease death, myocardial infarction, or stroke) were identified by review of medical records during 3.9 years of follow-up. We used Cox proportional hazards analysis to determine the risk of adverse cardiovascular events associated with self-reported medication nonadherence.

Results: Of the 1015 participants, 83 (8.2%) reported nonadherence to their medications, and 146 (14.4%) developed cardiovascular events. Nonadherent participants were more likely than adherent participants to develop cardiovascular events during 3.9 years of follow-up (22.9% vs 13.8%, $P=.03$). Self-reported nonadherence remained independently predictive of adverse cardiovascular events after adjusting for baseline cardiac disease severity, traditional risk factors, and depressive symptoms (hazards ratio, 2.3; 95% confidence interval, 1.3-4.3; $P=.006$).

Conclusions: In outpatients with stable coronary heart disease, self-reported medication nonadherence is associated with a greater than 2-fold increased rate of subsequent cardiovascular events. A single question about medication adherence may be a simple and effective method to identify patients at higher risk for adverse cardiovascular events.

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Nonadherence to physician treatment recommendations is an increasingly recognized cause of adverse outcomes and increased health care costs, particularly among patients with cardiovascular disease.[1] Nonadherence to medication recommendations is remarkably common with average estimated adherence rates of 51% to 79%, depending on the number of daily doses.[2] Nonadherence to medications, including placebo, has been associated with an increase in mortality in patients with hyperlipidemia, diabetes mellitus, congestive heart failure, and those who have had a myocardial infarction (MI).[3-10]

Prior studies demonstrating an increase in adverse cardiovascular outcomes associated with nonadherence have measured adherence by pill count or pharmacy refills.[7,8,10] Whether asking patients a single question about medication adherence can identify those at increased risk for cardiovascular events is unknown. In addition, no large study has examined the association between medication nonadherence and adverse cardiovascular outcomes in a cohort of patients with stable coronary heart disease (CHD), after adjustment for other factors associated with nonadherence. For example, given the association between depression and adverse cardiovascular outcomes,[11] it is important to correct for such potential confounding factors.

We sought to assess the predictive validity of self-reported nonadherence and to evaluate how the magnitude of risk associated with self-reported nonadherence compares with that associated with hypertension, smoking, and diabetes. In a cohort of 1015 outpatients with stable CHD, we administered a single-item mea-

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sure of self-reported adherence and examined the association of self-reported nonadherence with cardiovascular events during 3.9 years of follow-up.

METHODS

PARTICIPANTS

The Heart and Soul Study is a prospective cohort study of psychosocial factors and cardiovascular outcomes in patients with CHD. Details regarding our recruitment procedures were published earlier.[12-14] Briefly, we recruited outpatients with documented CHD from 2 Veterans Affairs Medical Centers (San Francisco and Palo Alto, California), 1 university medical center (University of California, San Francisco), and 9 community health clinics in Northern California. Documented CHD was defined by the presence of at least 1 of the following: a history of MI, angiographic evidence of at least 50% stenosis in 1 or more major coronary vessels, prior evidence of exercise-induced ischemia by treadmill or nuclear perfusion testing, a history of percutaneous or surgical coronary artery revascularization, or a diagnosis of CHD by an internist or a cardiologist. Patients were excluded if they reported an MI in the prior 6 months, were unable to walk 1 block, or were planning to move from the local area within 3 years.

A total of 1024 participants were recruited and enrolled in the study between September 1, 2000, and December 31, 2002. Of these, 9 participants were excluded because they did not complete our measure of adherence, leaving a total of 1015 participants for this analysis. At baseline, all participants completed a daylong study examination, including a comprehensive health interview, a blood draw, and an exercise treadmill test with stress echocardiography. This protocol was approved by the appropriate institutional review boards, and all participants provided written informed consent.

PREDICTOR VARIABLE

Our primary predictor variable was a single question about overall medication adherence[12]: "In the past month, how often did you take your medications as the doctor prescribed?" Possible responses were: "All of the time" (100%), "Nearly all of the time" (90%), "Most of the time" (75%), "About half the time" (50%), or "Less than half the time" (<50%). Because of the small number of participants in the latter categories, we defined nonadherence as 75% of the time or less.

OUTCOME VARIABLES

To identify cardiovascular events (CHD death, MI, or stroke), we conducted annual telephone follow-up interviews with participants (or their proxy) to ask about death or hospitalizations. For any reported event, 2 independent and blinded adjudicators retrieved and reviewed medical records, electrocardiograms, death certificates, and coroner's reports. If both adjudicators agreed on the outcome classification, it was binding. If there was disagreement, they conferred, reconsidered their classification, and requested consultation from a third, blinded adjudicator as necessary.

Death was considered to be CHD death if the participant died during the same hospitalization in which an acute MI was documented or the participant experienced sudden CHD death defined as an unexpected, otherwise unexplained fatality within 1 hour of the onset of terminal symptoms. Myocardial infarction was defined by the presence of biomarkers in a setting in which signs, symptoms, and/or electrocardiographic findings were consistent with acute ischemia as outlined by standard diagnostic criteria.[15] Stroke was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or other nonischemic cause.

OTHER VARIABLES

Age, sex, ethnicity, educational level, marital status, income, living situation, smoking status, alcohol use, medical history, and depressive symptoms were determined by questionnaire. We measured weight and height and calculated body mass index (calculated as weight in kilograms divided by height in meters squared). Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Medication categories were categorized using an electronic portable drug resource (Epocrates Rx; San Mateo, California). To evaluate the presence and severity of depressive symptoms, we administered the well-validated 9-item Patient Health Questionnaire.[16,17] Higher scores indicate more severe depressive symptoms. Serum creatinine, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels were tested on venous blood samples drawn after an overnight fast.

To assess baseline severity of cardiovascular disease, we performed resting echocardiography for assessment of left ventricular ejection fraction. Participants also completed a symptom-limited, graded exercise treadmill test according to a standard Bruce protocol. Exercise capacity was defined as metabolic equivalent tasks achieved at peak exercise. We determined angina frequency by asking participants, "Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness, or angina?"[18]

STATISTICAL ANALYSIS

Differences in characteristics between adherent and nonadherent participants were compared using the standard 2-tailed *t* tests for continuous variables and χ^2 tests for dichotomous variables. For our primary analysis, we used Cox proportional hazards models to calculate the rate of adverse cardiovascular events in those reporting medication nonadherence compared with those reporting medication adherence. To determine the relative hazard of cardiovascular events independently associated with nonadherence, we adjusted for the following variables selected because of their clinical importance or association with nonadherence: age, sex, race, educational level, smoking, hypertension, diabetes, depressive symptoms, angina symptoms, number of cardiovascular medications, use of β-blocker, use of statin, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, and left ventricular ejection fraction. We verified the proportional hazards assumption for all models. Hypertension, diabetes, and smoking are well-established risk factors for cardiovascular events, so we also report the relative rate of events associated with these disorders as a benchmark against which to evaluate the magnitude of risk associated with medication nonadherence. For the aforementioned analyses, we report unadjusted and adjusted hazards ratios (HRs) with 95% confidence intervals (CIs). All analyses were performed using SAS version 8 (SAS Institute, Cary, North Carolina).

RESULTS

Of the 1015 participants with stable CHD, 83 (8.2%) reported nonadherence to their medications (taking medications as the physician prescribed 75% of the time or

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Table 1. Characteristics of 1015 Participants by Adherence Status

Variable	Nonadherent (Not as Prescribed) (n=83)	Adherent (as Prescribed) (n=932)	*P* Value
Demographics[a]			
Age, y	64±11	67±11	.006
Female	24 (28.9)	156 (16.7)	.005
White race	32 (38.6)	576 (61.9)	<.001
Married	30 (36.1)	404 (43.5)	.20
High school graduate	63 (75.9)	819 (88.1)	.002
Annual income, <$20 000	44 (53.0)	450 (48.6)	.44
Psychosocial and behavioral factors			
Live alone	26 (31.3)	328 (35.3)	.47
Current smoking	24 (28.9)	176 (19.0)	.03
Regular alcohol use	25 (30.9)	268 (28.9)	.71
Body mass index, mean[b]	29.1±6.0	28.3±5.2	.19
Depressive symptoms (PHQ score)	7.6±6.4	4.9±5.3	<.001
Comorbidities			
Hypertension	58 (70.7)	663 (71.3)	.91
Diabetes mellitus	19 (22.9)	244 (26.2)	.50
Myocardial infarction	39 (47.0)	506 (54.3)	.18
Stroke	12 (14.6)	135 (14.5)	.98
Serum creatinine	1.2±1.2	1.2±0.6	.96
Weekly angina	22 (26.5)	164 (17.6)	.05
Medication use			
No. of cardiovascular medications	2.0±1.3	2.6±1.2	<.001
β-Blocker	34 (41.0)	558 (59.9)	<.001
Renin-angiotensin system blocker	34 (41.0)	488 (52.4)	.05
Diuretic	22 (26.5)	278 (29.8)	.53
Statin	39 (47.0)	617 (66.2)	<.001
Aspirin	58 (69.9)	732 (78.5)	.07
Cardiac function			
LDL cholesterol	128.1±44.9	102.0±31.4	<.001
HDL cholesterol	49.9±14.0	45.5±14.0	.006
LV ejection fraction	0.64±0.08	0.61±0.10	.05
Poor exercise capacity (METS <5)	16 (21.6)	211 (24.5)	.58

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; METS, metabolic equivalent tasks; PHQ, Patient Health Questionnaire.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4. To convert HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259.

[a] Data are given as mean±SD and number (percentage).

[b] Calculated as weight in kilograms divided by height in meters squared.

less). Compared with adherent participants, nonadherent participants were younger, more likely to be female, and less likely to be white or high school educated (**Table 1**). Nonadherent participants were more likely than adherent participants to be current smokers and have higher depressive symptom (Patient Health Questionnaire) scores. Nonadherent participants were also more likely to have weekly angina, were less likely to be taking a β-blocker or statin, and had higher cholesterol levels and left ventricular ejection fraction.

A total of 146 (14.4%) participants developed cardiovascular events during a mean follow-up of 3.9 years

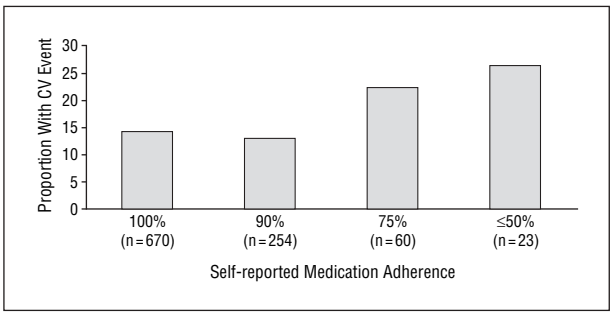

Figure 1. Proportion with subsequent cardiovascular (CV) event (myocardial infarction, stroke, or coronary heart disease death) by the percentage of time in the past month when participants reported taking medications as prescribed (*P* = .20 for proportion with events across all 4 adherence categories; *P* = .03 for proportion with events in patients with adherence ≤75% vs >75% of the time).

(range, 0.09-5.7 years), and 8 of 1015 (0.8%) were lost to follow-up. Among the 1007 participants with complete follow-up data, 41 died of CHD, 97 had MIs, and 31 had strokes. Cardiovascular events occurred in 13.9% (93 of 670) of participants who reported taking medications as prescribed all of the time, 13.4% (34 of 254) of participants who reported taking medications as prescribed nearly all of the time, 21.7% (13 of 60) of participants who reported taking medications as prescribed most of the time, and 26.1% (6 of 23) of participants who reported taking medications as prescribed half of the time or less (**Figure 1**). Overall, 22.9% (19 of 83) of nonadherent participants developed cardiovascular events compared with 13.7% (127 of 924) of adherent participants (*P* = .03). After multivariate adjustment, nonadherence remained independently predictive of cardiovascular events (**Table 2** and **Figure 2**).

Of the 1015 participants, 721 (71.0%) had a history of hypertension, 263 (25.9%) had diabetes mellitus, and 200 (19.7%) were current smokers. In a multivariate adjusted model, the relative rate of cardiovascular events associated with nonadherence (HR, 2.3; 95% CI, 1.3-4.3; *P* = .006) was similar to those associated with diabetes (HR, 2.1; 95% CI, 1.4-3.2; *P* < .001) and current smoking (HR, 1.9; 95% CI, 1.2-3.2; *P* = .009) but appeared greater than that associated with hypertension (HR, 1.4; 0.9-2.3; *P* = .20).

COMMENT

We found that a single-item measure of self-reported medication nonadherence was associated with a greater than 2-fold increased risk of CHD death, MI, or stroke in 1007 outpatients with stable CHD. During 3.9 years of follow-up, self-reported medication nonadherence was at least as powerful a predictor of adverse cardiovascular events as diabetes and current smoking. This association between medication nonadherence and adverse events was independent of important potential confounding variables, including age, educational level, income, cardiovascular risk factors, cardiac disease severity, and depression. Our findings demonstrate that self-reported medication nonadherence identifies patients at increased risk for secondary cardiovascular events.

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Table 2. Association of Medication Nonadherence With CHD Death, Myocardial Infarction, and Stroke in 1007 Participants With Stable CHD

Variable	Unadjusted HR (95% Confidence Interval)	*P* Value	Adjusted HR[a] (95% Confidence Interval)	*P* Value
CHD death	2.0 (0.8-4.8)	.12	3.8 (1.3-10.7)	.01
Myocardial infarction	1.4 (0.7-2.6)	.34	1.5 (0.7-3.6)	.33
Stroke	2.8 (1.2-6.9)	.02	4.4 (1.4-13.9)	.01
Any of the above	1.8 (1.1-3.0)	.03	2.3 (1.3-4.3)	.006

Abbreviations: CHD, coronary heart disease; HR, hazards ratio.
[a]Adjusted for age, sex, race, educational level, smoking, depressive symptoms, diabetes mellitus, hypertension, number of cardiovascular medications, use of β-blocker, use of statin, left ventricular ejection fraction, weekly angina, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level.

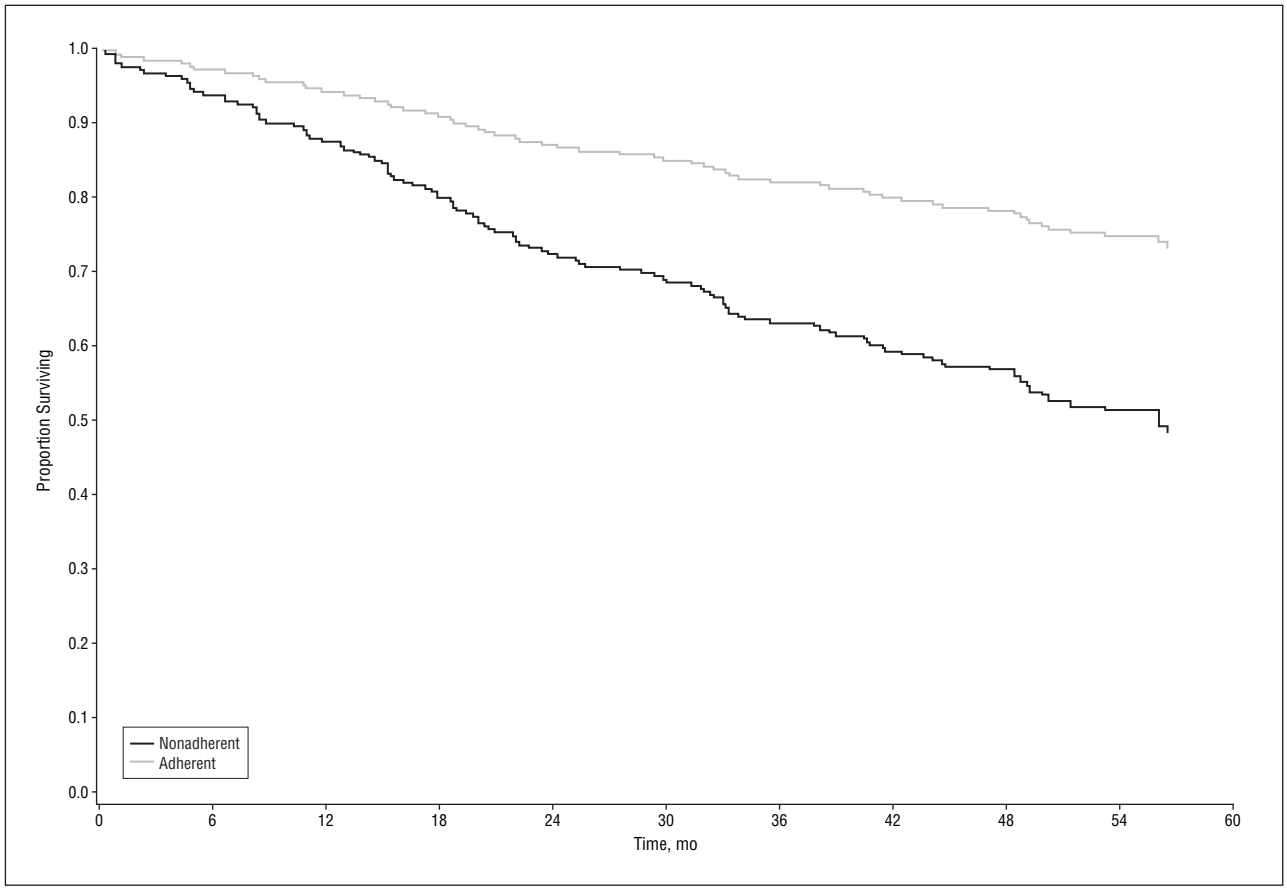

Figure 2. Proportion surviving without a cardiovascular event (myocardial infarction, stroke or coronary heart disease death) by self-reported medication adherence at baseline, adjusted for age, sex, race, educational level, smoking, diabetes mellitus, hypertension, depressive symptoms, number of cardiovascular medications, use of β-blocker, use of statin, left ventricular ejection fraction, weekly angina, high-density lipoprotein cholesterol level and low-density lipoprotein cholesterol level (*P*=.006).

Prior studies of patients with cardiac disease have demonstrated medication nonadherence to be associated with adverse outcomes. The Coronary Drug Project studied the effect of clofibrate in the treatment of hyperlipidemia in patients with CHD.[4] Although there was no benefit of clofibrate compared with placebo at 5 years' follow-up, those patients who were more than 80% adherent to the protocol prescription had a substantially lower mortality than those who were nonadherent. Similar findings were noted in the placebo group. In the Beta Blocker Heart Attack Trial, patients who were not adherent to propranolol hydrochloride had an increased risk of death 1 year after an MI.[3] Again, nonadherence (<75%) was predictive of mortality even in the placebo group. This risk was independent of the severity of MI and sociodemographic features such as educational level, life-stress, or social isolation. In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial of patients who have had an MI, poor adherence to treatment with amiodarone or placebo (<80%) was associated with an increased risk of sudden cardiac death and all-cause mortality.[5] In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity trial, poor adherence to the study drug (<80%) as measured by pill count was asso-

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ciated with increased mortality, and this association was independent of whether the study drug was candesartan or placebo.[6] Recently, Ho et al[8] showed in a prospective cohort of patients that medication discontinuation 1 month after MI hospitalization was associated with a lower 1-year survival. Rasmussen et al[10] showed that poor adherence to statins and β-blockers after an MI was associated with an increase in mortality rate.

The consistent association between nonadherence to placebo and adverse outcomes in these trials may be the result of a "healthy adherer" effect. Patients who report adherence to their medications are probably less likely to engage in risky behaviors and more likely to be adherent to other treatment recommendations than those who report nonadherence to medications. Therefore, the association we observed between medication nonadherence and subsequent cardiovascular events may be the result of a less healthy overall lifestyle rather than medication nonadherence alone; however, this was recently called into question.[10] Our study extends the observations of prior studies to patients with stable CHD. To our knowledge, only the Coronary Drug Project has studied the outcome of medication nonadherence in patients with stable CHD. Furthermore, few prior studies have adjusted for potential confounders and none have adjusted for depression. Because depression has been established as a risk factor for morbidity and mortality in patients with CHD[11] and depression has been associated with medication nonadherence,[12] this is an important confounder that must be measured.

Although a number of methods are available for measuring medication adherence, each has its advantages and disadvantages and no particular method (other than direct serum levels) is considered the gold standard.[1] Self-reported medication adherence has been shown to correlate well with pill count[19] and electronic monitoring of bottles.[20] In addition, several prior studies have used self-report for the assessment of medication adherence.[21,22] Although prior studies have shown self-reported adherence to be reliable, estimates of adherence rates are often inflated compared with pill counts and may be affected by comorbidities such as depression and cognitive function.[19,21,23,24] Our study further demonstrates the predictive validity of self-reported medication adherence as a simple and effective method to identify patients with an increased risk of adverse cardiovascular events. A straightforward method to distinguish patients at risk for nonadherence helps to target the use of reminders or other more comprehensive interventions that can effectively improve adherence and clinical outcomes.[25]

It should be noted that the prevalence of nonadherence in our study population was remarkably low (only 8%) and likely underestimates the prevalence of nonadherence in outpatients with cardiovascular disease. Patients who volunteer for research studies tend to be more health-conscious than the general population. Moreover, our participants were enrolled in a clinical study with frequent contact with the medical system. It has been demonstrated that patients tend to adhere more closely to treatment recommendations in the few days before and after a clinic appointment, a phenomenon known as "white coat" adherence.[26] Also, when assessing self-reports, adherence may be overestimated in an effort to "please the physician." Despite its low prevalence in our study population, however, nonadherence was still an independent risk factor for cardiovascular events.

Several limitations must be considered in interpreting the results of this study. First, we measured overall adherence rather than adherence to specific medications. However, as described before, adherence to any medication recommendation, including placebo, has been associated with adverse events in prior studies. Second, as discussed before, the overall rate of nonadherence was low so that the absolute effect on outcomes may be underestimated. Finally, most of the participants in our study were men, so the results may not generalize to women.

In conclusion, we found that in a prospective study of 1007 outpatients with stable CHD, medication nonadherence was predictive of a greater than 2-fold increased rate of CHD death, MI, or stroke, independent of several potential confounders, including depression. The increased rate of cardiovascular events associated with nonadherence was similar in magnitude to the rate associated with diabetes or smoking. Our findings suggest that self-reported adherence may be a simple and straightforward method to identify patients at risk for adverse cardiovascular outcomes in patients with CHD.

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