Journal of the American College of Cardiology Vol. 48, No. 11, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.07.063

Course of Depressive Symptoms and Medication Adherence After Acute Coronary Syndromes

An Electronic Medication Monitoring Study

Nina Rieckmann, PHD,* William Gerin, PHD,† Ian M. Kronish, MD,‡ Matthew M. Burg, PHD,† William F. Chaplin, PHD,‖ Grace Kong, MA,‖ François Lespérance, MD,§ Karina W. Davidson, PHD†¶

New York, New York; and Montreal, Quebec, Canada

OBJECTIVES We tested whether improvements in depressive symptoms precede improved adherence to aspirin in patients with acute coronary syndromes (ACS).

BACKGROUND Depression is associated with medication nonadherence in patients with ACS, but it is unclear whether changes in depression impact on adherence.

METHODS Electronic medication monitoring was used to measure adherence to aspirin during a 3-month period in a consecutive cohort of 172 patients (25 to 85 years) recruited within 1 week of hospitalization for ACS. Depressive symptom severity was assessed using the Beck Depression Inventory (BDI) during hospitalization and at 1 and 3 months after hospitalization. Adherence was defined as the percentage of days aspirin was taken as prescribed.

RESULTS Depression severity in hospital was associated with nonadherence in a gradient fashion: 15% of non-depressed patients (BDI score 0 to 4), 29% of mildly depressed patients (BDI score 10 to 16), and 37% of patients with moderately-to-severely depressive symptoms (BDI score >16) took aspirin less than 80% of the time ($p = 0.03$). A cross-lagged path analytic model revealed that improvements in depressive symptoms in the first month after the ACS were associated with improvements in adherence rates in the subsequent 2 months (standardized direct effect −0.32, $p = 0.016$).

CONCLUSIONS Diagnosis and treatment of depressive symptoms may improve medication adherence in patients after ACS. (J Am Coll Cardiol 2006;48:2218–22) © 2006 by the American College of Cardiology Foundation

Patient nonadherence complicates physicians' attempts to optimize care. In patients with heart disease, poor adherence to prescribed medications is common (1–3) and is associated with increased mortality and rehospitalization (1,4–6). Eight to 20% of post-acute coronary syndrome (ACS) patients discontinue cardiac protective medications within 6 months of hospital discharge (2).

See page 2223

Depression (with an estimated lifetime prevalence of 15% to 20%) has been shown to be associated with poor adherence across many patient samples, including those with coronary artery disease (7–9). Depression is common in patients who experience an ACS; approximately 1 in 3 patients experiences depressive symptoms during hospitalization (10). Moreover, depressive symptoms during hospitalization are independently associated with an adverse medical prognosis (11). Poor medication adherence has been proposed as a mechanism to explain why depressed patients as compared with non-depressed patients are at increased risk for mortality and other adverse outcomes after ACS (12,13). Previous data linking depression and adherence, however, is derived from cross-sectional or prospective studies that cannot address questions of temporal sequence and do not take into account that in many patients, depressive symptoms improve over the course of time (whether treated or untreated), whereas in others, symptoms worsen (8,9). Although it is a plausible assumption, no study has yet demonstrated that improvements in depressive symptoms lead to improvements in treatment adherence.

We used a cross-lagged panel design that included correlations of 3 consecutive assessments of depressive symptoms and medication adherence to address this question. This design can answer which of 2 variables temporally precedes the other. We tested whether changes in depressive symptoms from time 1 to time 2 precede changes in adherence from time 2 to time 3, or whether changes in adherence precede changes in depressive symptoms.

METHODS

Participants. Patients with unstable angina or acute myocardial infarction were recruited within 1 week of their hospitalization for ACS. Institutional review boards of 3 university hospitals (Mount Sinai Hospital, New York, New York, and Yale–New Haven Hospital and Hospital of St. Raphael, New Haven, Connecticut) approved this study,

From the *Department of Psychiatry, Mount Sinai School of Medicine, New York, New York; †Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York; ‡Division of General Internal Medicine, Mount Sinai School of Medicine, New York, New York; §Department of Psychiatry, Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada; ‖Department of Psychology, St. Johns University, Queens, New York; and the ¶Cardiovascular Institute, Mount Sinai School of Medicine, New York, New York. Supported by grants HC-25197, HL-076857, and HL-04458 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

Manuscript received May 9, 2006; revised manuscript received July 17, 2006, accepted July 23, 2006.

Abbreviations and Acronyms
ACS = acute coronary syndromes
BDI = Beck Depression Inventory

and all patients provided informed consent. Patients had to be prescribed a daily dose of either 81 mg or 325 mg of aspirin. Patients were ineligible if they indicated the use of weekly pill boxes and were unwilling to use an electronic capped pill bottle instead or if they lived in nursing homes. Additional exclusion criteria were current alcohol and/or substance abuse and cognitive impairment.

Depression assessment. Patients were eligible for the study if they had a baseline score on the Beck Depression Inventory (BDI) (14) that was consistent with at least mild-to-moderate depression (BDI score ≥10), which has been associated with increased mortality risk after an ACS event (15,16). Patients were also eligible if they reported no depression (BDI score 0 to 4). The BDI was readministered at 1 and 3 months after the baseline score.

Three BDI groups were used to examine difference between non-depressed (BDI 0 to 4), mildly depressed (BDI 10 to 16), and moderately-to-severely depressed (BDI >16) patients at baseline. The BDI was used as a continuous variable in the cross-lagged panel model.

Adherence assessment. Upon hospital discharge, patients were provided with a 90-day supply of aspirin in a Medication Event Monitoring System (APREX Corp, Fremont, California) bottle. This device records the date and time on each occasion the bottle cap is opened. The data from this system were collected continuously during the 3-month follow-up period. Adherence was defined as the percentage of days the bottle was opened the correct number of times (once a day). In addition to the continuous adherence score used in the cross-lagged panel model, a categorical adherence variable was computed. Nonadherence was defined as <80% days the correct number of pills was taken. Patients were informed that aspirin adherence was being monitored but did not receive any additional counseling about adherence.

Statistical analyses. Differences in characteristics between non-depressed, mildly, and moderately depressed patient groups were compared using analysis of variance for continuous variables and a chi-square test for dichotomous variables. Logistic regression was used to examine the association between depressive symptom groups at baseline and medication adherence across the 3 months, controlling for sociodemographic characteristics and the Charlson comorbidity index (17).

Cross-sectional and prospective relationships between depression and adherence were tested in a cross-lagged panel design using structural equation modeling (conducted using AMOS for windows 4.0 (18). Cross-lagged panel models examine the predictive association of 2 variables over time, each controlling for the effects at earlier time points. For example, depression at time 2 is residualized by depres-

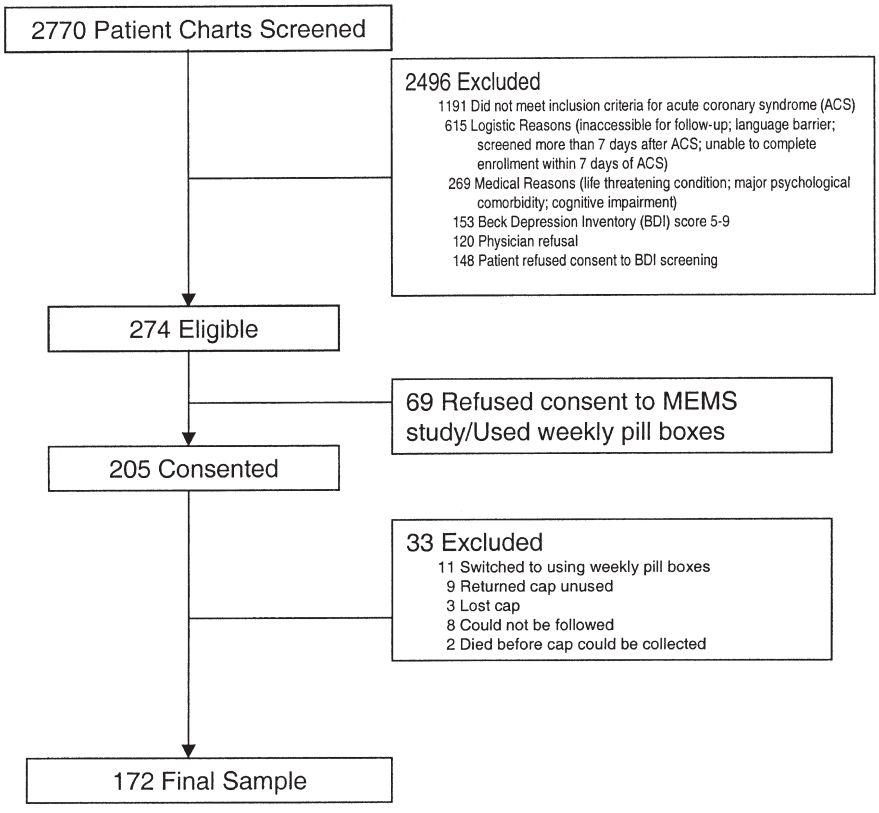

Figure 1. Flowchart of participants. MEMS = medication event monitoring system.

JACC Vol. 48, No. 11, 2006
December 5, 2006:2218–22

Table 1. Baseline Sample Characteristics*

Variable	Non-Depressed (n = 93)	Mildly Depressed (n = 49)	Moderately to Severely Depressed (n = 30)	p Value†
Age, yrs	59.7 ± 11.6	60.8 ± 14.2	55.8 ± 9.2	0.18
Female, n (%)	35 (37.6)	26 (53.1)	16 (53.3)	0.12
White, n (%)	79 (84.9)	46 (93.9)	24 (80.0)	0.17
Hispanic, n (%)	1 (1.1)	3 (6.1)	4 (13.3)	0.02
Schooling, yrs	13.9 ± 2.6	13.6 ± 3.1	13.0 ± 3.5	0.32
Charlson Comorbidity Index	1.2 ± 1.5	1.2 ± 1.2	1.7 ± 1.6	0.19

*Plus-minus values are mean ± SD. †Continuous variables were compared using analysis of variance. Categorical variables were compared with chi-square statistics.

sion at time 1 and thus represents change in depression from time 1 to time 2.

A model was tested that included: 1) correlations among the 3 continuous depression measures and the 3 adherence measures over time (stability of each variable); 2) cross-sectional correlations between depression and adherence; and 3) cross-(time-) lagged correlations between depression and adherence (and changes in these variables). Maximum likelihood estimation was used to estimate overall model fit using the chi-square goodness-of-fit statistic.

RESULTS

Of 274 eligible patients, 205 (74.8%) consented to the study. Refusers (those not consenting and those not willing to switch from a pill box) had significantly higher mean (±SD) levels of depressive symptoms on the BDI compared with consenting patients (11.0 ± 9.8 vs. 8.2 ± 8.7; $p < 0.05$). A total of 33 patients (16.1%) did not complete the study (Fig. 1). Patients who did not complete the study did not significantly differ from patients who did on age, gender, and depressive symptom severity (all $p > 0.35$). Sociodemographic characteristics of patients who participated are displayed in Table 1.

In-hospital depression and adherence after discharge. The mean (±SD) number of days aspirin was monitored was 83.0 ± 13.6 and did not differ between the 3 depression groups. Depression severity was associated with nonadherence in a gradient fashion (Fig. 2): 15% (14 of 93) of non-depressed patients, 29% (14 of 49) of mildly depressed patients, and 37% (11 of 30) of patients with moderate-to-severe depressive symptoms were nonadherent (chi-square = 7.4, $p = 0.03$). Compared with non-depressed patients, those with severe depressive symptoms had a 3-fold odds of not taking medications as prescribed (odds ratio 3.3; 95% confidence interval 1.3 to 8.3). This association was stronger after adjustment for potential confounders (odds ratio 3.7; 95% confidence interval 1.3 to 10.6).

Changes in depression and changes in adherence over time. Figure 3 displays the cross-lagged panel model relating changes in depressive symptoms to changes in adherence over time (overall model fit: chi-square = 9.74, $p = 0.021$). As expected, higher depressive symptom scores at baseline were associated with lower adherence within the first 2 weeks after discharge.

Changes in depressive symptoms from baseline (T1) to 1 month (T2) were inversely related to changes in adherence rates from 1 month (T2) to 3 months (T3; standardized direct effect −0.32, $p = 0.016$), indicating that medication adherence increased in patients after depression had improved, and it decreased in patients whose depressive symptoms had worsened. To describe the size of this effect, a 1 standard deviation decrease on the BDI (5.9 points) resulted in a one-third standard deviation increase in adherence (6.7%). In contrast, changes in adherence from the first week after discharge (T1) to 1 month (T2) were unrelated to changes in depressive symptoms from 1 month (T2) to 3 months (T3) (standardized direct effect 0.02; $p = 0.70$).

DISCUSSION

Depression is a burdensome psychosocial problem and a risk marker for mortality with a high prevalence among patients with ACS (10,11,15,16). It has been associated with poor medication adherence in patients with coronary artery disease (8,9), but no study has assessed whether improvements in depressive symptoms result in improved medication adherence.

We found a gradient relation between the severity of in-hospital depressive symptoms and rates of nonadherence, similar to findings from the Heart and Soul Study (9). However, in our sample rates of nonadherence were approx-

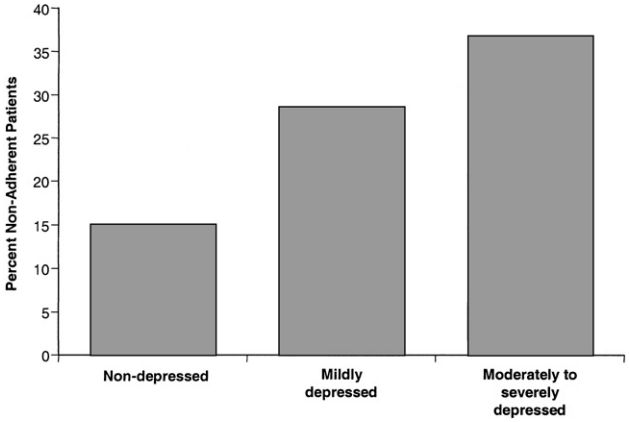

Figure 2. Proportion of nonadherent (aspirin taken <80% of days) patients in 3 groups: non-depressed (Beck Depression Inventory [BDI] score 0 to 4), mildly depressed (BDI 10 to 16), and moderately to severely depressed (BDI >16).

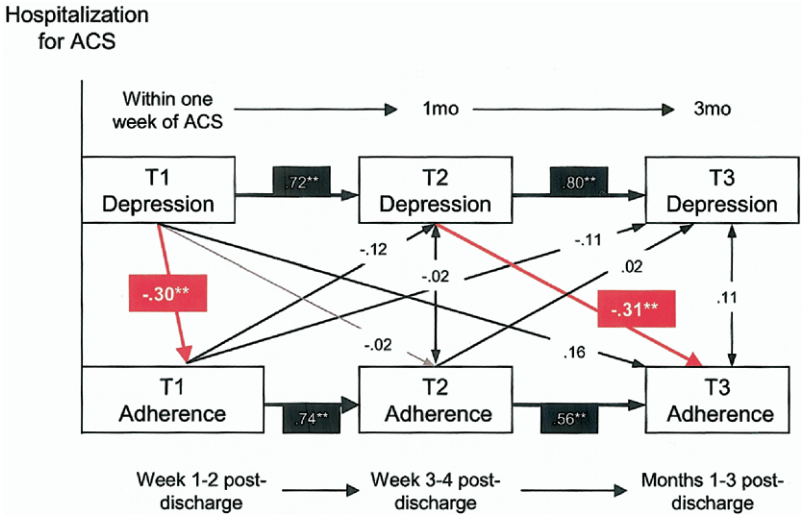

Figure 3. Cross-lagged panel model testing the relationship between depression and adherence over time. **p < 0.01. ACS = acute coronary syndromes.

imately 3 times greater. One major difference between the 2 studies is that we used an electronic assessment of medication adherence, whereas the Heart and Soul Study assessed nonadherence by self-report, suggesting that patients may overestimate their level of adherence.

We monitored adherence to only 1 medication—aspirin—whereas the self-report questions in the Heart and Soul Study asked about all medications. We have no information regarding adherence to medication other than aspirin, nor did we take into account the total number of medications patients were prescribed. However, this is unlikely to explain higher nonadherence rates in our study. Patients had a simple regimen (1 tablet per day), and the monitored drug (aspirin) has few side effects, both of which should predict better, not worse, adherence.

Our study might underestimate nonadherence rates in post-ACS patients because patients who refused participation were significantly more depressed. Patients with BDI scores of 5 to 9 at baseline were excluded from the study, which might have yielded inflated coefficients in our analysis. Adherence rates in our sample might not generalize to patients who use weekly pill boxes because we excluded those patients.

In this observational study, we showed that improvements in depressive symptoms were associated with subsequent improvements in adherence rates in a relatively short period of time. This has potential implications for future adherence interventions. Although medication adherence has been the target of a large number of interventions, these have, for the most part, not been very effective or were very complex (19,20). It is not known why these interventions tend to have small effects on improving adherence and clinical outcomes; perhaps treating depression first will show promise in future interventions designed to increase medication adherence.

Reprint requests and correspondence: Dr. Karina W. Davidson, Department of Medicine, Columbia University College of Physicians and Surgeons, 622 West 168th Street, PH9 Center, Room 948, New York, New York 10032. E-mail: kd2124@columbia.edu.

REFERENCES

1. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. Med Care 2002;40:794–811.
2. Eagle KA, Kline-Rogers E, Goodman SG, et al. Adherence to evidence-based therapies after discharge for acute coronary syndromes: an ongoing prospective, observational study. Am J Med 2004;117:73–81.
3. Sud A, Kline-Rogers EM, Eagle KA, et al. Adherence to medications by patients after acute coronary syndromes. Ann Pharmacother 2005; 39:1792–7.
4. Dartnell JG, Anderson RP, Chohan V, et al. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. Med J Aust 1996;164:659–62.
5. Horwitz RI, Viscoli CM, Donaldson RM, et al. Treatment adherence and risk of death after a myocardial infarction. Lancet 1990;336: 542–5.
6. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 1990;263:1653–7.
7. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101–7.
8. Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. Health Psychol 1995;14:88–90.
9. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the heart and soul study. Arch Intern Med 2005;165:2508–13.
10. Thombs BD, Bass EB, Ford DE, et al. Prevalence of depression in survivors of acute myocardial infarction. J Gen Intern Med 2006;21: 30–8.
11. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004;66:802–13.
12. Zellweger MJ, Osterwalder RH, Langewitz W, Pfisterer ME. Coronary artery disease and depression. Eur Heart J 2004;25:3–9.
13. Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, Bush DE. Patients with depression are less likely to follow recom-

mendations to reduce cardiac risk during recovery from a myocardial infarction. Arch Intern Med 2000;160:1818–23.
14. Beck AT, Steer RA. Manual for the Beck Depression Inventory. San Antonio, TX: Psychological Corp., 1993.
15. Lespérance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation 2002;105: 1049–53.
16. Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation 1995;91: 999–1005.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
18. Arbuckle JA, Wothke W. AMOS 4.0 User's Guide. Chicago, IL: SPSS Inc., 1999.
19. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. JAMA 2002;288:2868–79.
20. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions to enhance medication adherence. Cochrane Database Syst Rev 2005:CD000011.