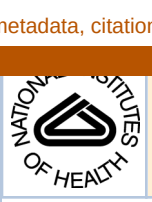

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Medication Adherence, Depressive Symptoms, and Cardiac Event-Free Survival in Patients with Heart Failure

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Abstract

Background—Medication nonadherence and depressive symptoms predict hospitalization and death in patients with heart failure (HF). Depressed patients have lower medication adherence than non-depressed patients. However, the predictive power of the combination of medication adherence and depressive symptoms for hospitalization and death has not been investigated in patients with HF.

Objective—To explore the combined influence of medication adherence and depressive symptoms for prediction of cardiac event-free survival in patients with HF.

Method—We monitored medication adherence in 216 HF patients who completed the Patient Health Questionnaire-9 (PHQ-9) at baseline. Medication adherence was measured objectively using Medication Event Monitoring System (MEMS). Patients were followed for up to 3 1/2 years to collect data on cardiac event(s). Survival analyses were used to compare cardiac event-free survival between/among groups.

Results—The risk of experiencing a cardiac event for patients with medication nonadherence and depressive symptoms was 5 times higher compared to those who were medication adherent without depressive symptoms. The risk of experiencing a cardiac event for patients with only one risk factor was 1.2–1.3 times that of those with neither risk factor.

Conclusion—Medication nonadherence and depressive symptoms had a negative synergistic effect on cardiac event-free survival in patients with HF.

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Disclosures
The authors have nothing to disclose.

Keywords

medication adherence; depressive symptoms; heart failure; outcomes

Introduction

Heart failure (HF) is a chronic syndrome with high incidence and prevalence, and high rates of morbidity and mortality.[1] In a meta-analysis, Rutledge and associates reported that more than one fifth (21.5%) of patients with HF suffer from clinically significant depression [2] that adversely affects health-related outcomes (e.g., more hospitalizations and death).[2, 3] Emergency department (ED) visits, hospitalizations and death are higher in HF patients with depressive symptoms compared to those without depressive symptoms.[2, 3, 4] Specifically, patients with HF and depressive symptoms have twice the risk of ED visits and a 29% increase in health care costs compared to those without depressive symptoms.[2] Faris and colleagues[3] examined a cohort of 396 patients with HF and also found that clinically depressed patients were three times more likely to die compared to non-depressed patients.

Medication nonadherence [4–10, 16] also has been shown to independently predict worse event-free survival and higher rates of ED visits, hospitalizations, and death in patients with HF. However, medication adherence rates in this population are low, between 40–60%.[11, 12] Patients with depressive symptoms are more likely to be nonadherent to their prescribed medication than those without depressive symptoms.[13] The power of the combination of medication adherence and depressive symptoms for prediction of cardiac event-free survival has not been previously investigated in patients with HF. Accordingly, the purpose of this study was to explore the predictive power of the combination of medication adherence and depressive symptoms for cardiac event-free survival in patients with HF.

Methods

Study Design

This was a secondary data analysis of two prospective studies in which patients with HF were enrolled to measure medication adherence (measured objectively using the Medication Event Monitoring System [MEMS]) and cardiac event-free survival.[10, 14] Both studies used identical inclusion and exclusion criteria. The first study tested the mediating effects of nonadherence on the association between depression and HF patient outcomes. The second study was a randomized controlled trial to determine the effect of an intervention on morbidity and mortality outcomes. In this data analysis, we examined the relationships among medication adherence, depressive symptoms, and cardiac event-free survival in patients with HF.

Samples and Setting

Detailed eligibility criteria and recruitment methods have been published previously.[11, 14, 15, 21] Briefly, patients were recruited from both outpatient cardiology clinics and inpatient cardiology units. Patients with and without systolic dysfunction were included if they had a confirmed diagnosis of chronic HF and were prescribed the same dose of HF medications for at least 3 months. Patients who had obvious cognitive impairment or a co-existing terminal illness were excluded.

Measurement of Variables

Medication adherence—Medication adherence was assessed daily for 1–3 months (3 months for the first study and 1 month for the second study) using the MEMS (AARDEX®-

USA, Union City, CA). The MEMS registered the date and time of cap openings. From the MEMS data, medication adherence was calculated from number of days the correct number of doses were taken during the monitoring period /total days during the monitoring period * 100%.[16] Patients who took the correct number of doses on at least 88% of days were defined as medication adherent, while all others were as nonadherent. This cutpoint was chosen based on a study demonstrating that adherence at or above 88% predicted better event-free survival.[11]

Depressive symptoms—Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9).[17, 18] The PHQ-9 consists of nine items on a scale rated from 0 (not at all) to 3 (nearly every day). The instrument is scored by adding the item ratings. Total scores of the PHQ-9 can range from 0 to 27; higher scores indicate worse depressive symptoms. Patients who score 10 or greater are considered to have clinically significant depressive symptoms (positive for mild to severe depression).[17] The PHQ-9 is a reliable [17] and valid [17, 18] scale that has been used to measure depressive symptoms in patients with HF.[18] Internal consistency of the PHQ-9 in this study had a Cronbach's alpha of .83.

Cardiac event-free survival—The outcome variable was the composite end-point of time to the first cardiac event, whether it was a cardiac-related emergency department visit, hospitalization, or death. Data on cardiac events were collected monthly by patient phone calls, hospital record review, and review of death certificates.

Variables of interest—The following sociodemographic, clinical, and psychological data were collected to completely describe the sample, compare differences in characteristics by groups, and obtain data on potential confounding variables.

Sociodemographics: Age, gender, marital status, ethnicity, and education level were collected from patient interview.

Clinical variables: New York Heart Association (NYHA) functional class was assessed by patient interview.[19] Left ventricular ejection fraction (LVEF), etiology of HF, and prescribed medications were collected from the medical record and patient interview.

Psychological variable: Anxiety was assessed using the Brief Symptom Inventory (BSI) anxiety subscale.[20] The anxiety subscale of the BSI consists of six items. Patients were asked to rate their level of distress on a scale from 0 (not at all) to 4 (extremely). The scores of the 6 items are summed and averaged for a total score that can range from 0 to 4; higher scores indicate a greater level of anxiety. The anxiety subscale of the BSI is a reliable (Cronbach's $\alpha = .87$)[20] and valid scale that has been used to measure anxiety in patients with HF[21] and myocardial infarction.[20] For this sample, the Cronbach's α was .84.

Procedure

This study was approved by the appropriate Institutional Review Board. All patients provided informed, signed consent. Patients' sociodemographic and clinical characteristics, anxiety, and depressive symptoms were collected by interview and medical record review at baseline. After completion of the baseline assessment, patients were given instructions on use of the MEMS bottle. Patients started to use the MEMS bottle from baseline. They returned the MEMS bottle after one or three months of continuous use of the MEMS device. Patients or family members were contacted monthly by phone to collect outcome data.

Data Management and Analysis

All data analyses were performed using SPSS (Chicago, IL), version 17.0; a significance level of .05 was chosen to indicate statistical significance. An evidence-based cutpoint of 88% medication adherence rate by the MEMS[11] was used to categorize patients into adherent and nonadherent groups. Patients were divided into presence or absence depressive symptoms groups based on the cutpoint score of 10 on the PHQ-9. We examined differences between medication adherent and nonadherent and between presence or absence depressive symptoms groups using independent t-tests and chi-square tests. Patients were further divided into 4 groups: (1) medication adherent without depressive symptoms; (2) medication adherent with depressive symptoms; (3) medication nonadherent without depressive symptoms; and (4) medication nonadherent with depressive symptoms. We used one way analysis of variance (ANOVA) with the Least Significant Difference (LSD) post hoc tests and Pearson chi-square tests to evaluate differences among the 4 groups.

The Kaplan-Meier and log-rank test was used to compare the time to cardiac event-free survival: (1) between patients in the adherent and nonadherent groups; (2) in the presence or absence of depressive symptoms; and (3) among adherent without depressive symptoms, adherent with depressive symptoms, nonadherent without depressive symptoms, and nonadherent with depressive symptoms groups. Cox proportional hazards regression modeling was used to assess the time to cardiac event-free survival between adherent and nonadherent groups, between presence or absence depressive symptoms groups, and among these four groups with and without adjusting for the following potential confounding variables: age, NYHA functional class, angiotensin converting enzyme inhibitor (ACEI) use, and anxiety (these variables were different among groups, please see Table 2). To account for differences between the two studies, we also controlled for study group (i.e., study 1 or study 2) and group assignment (i.e., usual care or intervention) in the final Cox regression models.

Results

Patient Characteristics

A total of 216 patients with HF who had complete PHQ-9 and MEMS data were included in the analysis. The mean age of patients in the sample was 60 ± 12 years, about one third of patients were female. The majority of the patients were Caucasian (85%) and married (62%). Full sample characteristics and comparison of medication adherent vs. nonadherent groups and presence or absence depressive symptoms are presented in Table 1.

Medication adherence

Of the total sample, 88 out of the 216 patients were classified as nonadherent to prescribed HF medication. As shown in the Table 1, patients in the medication nonadherent group had more depressive symptoms ($p = .018$) and higher anxiety scores ($p = .009$) than those in the adherent group.

Depressive symptoms

The mean of the PHQ-9 was 6.3 (standard deviation = 5.5). More than one quarter (26%) of the patients in this study had depressive symptoms. Patients with depressive symptoms were younger ($p = .003$), had higher percentage of patients with NYHA III/IV ($p < .001$), higher anxiety scores ($p < .001$), and were more commonly medication nonadherent ($p = .018$), and fewer were taking ACEI ($p = .016$) (Table 1) than patients without depressive symptoms.

Medication adherence and depressive symptoms

When we compared the characteristics of the 4 patient groups stratified by medication adherence and depressive symptoms, there were differences in NYHA class, ACEI use, and anxiety among groups (Table 2). Patients who were medication adherent without depressive symptoms were older compared with those who were medication nonadherent with depressive symptoms ($p = .022$). More patients who were medication nonadherent with depressive symptoms were prescribed an ACEI compared with the other groups. Regardless of medication adherence, more patients with depressive symptoms were in NYHA Class III or IV and had higher levels of anxiety than patients with no depressive symptoms.

Association of medication adherence with cardiac event-free survival

The time to the first cardiac event was significantly shorter in nonadherent patients than in adherent patients ($p = .005$, Figure 1). In simple Cox regression modeling (Table 3), medication adherence predicted cardiac event-free survival (hazard ration [HR] =2.1). After controlling for study group, group assignment, age, NYHA functional class, ACEI use, and anxiety, patients who were medication nonadherent still had 1.8 times the risk of experiencing a cardiac event compared to patients who were adherent (Table 3).

Association of depressive symptoms with cardiac event-free survival

The composite endpoint of cardiac event-free survival was significantly shorter in patients with depressive symptoms than those without depressive symptoms ($p < .001$, Figure 2). Depressive symptoms predicted cardiac event-free survival before and after controlling for covariates. Patients with depressive symptoms had more than twice the risk of experiencing a cardiac event compared to patients without depressive symptoms (Table 3).

Combined Effect of Medication Adherence and Depressive Symptoms on Cardiac Event-free Survival

Of the total sample, 103 (47%) patients were classified as medication adherent without depressive symptoms, 25 (12%) were medication adherent with depressive symptoms, 58 (27%) were medication nonadherent without depressive symptoms, and 30 (14%) were medication nonadherent with depressive symptoms. In the Kaplan-Meier and log-rank test, the composite endpoint of cardiac event-free survival was significantly worse in patients who were nonadherent with depressive symptoms than in other groups (chi-square = 29.7, $p < .001$). In the Cox regression, patients who were nonadherent with depressive symptoms experienced the shortest cardiac event-free survival of all the other groups ($p < .001$). Patients who were nonadherent with depressive symptoms had a 5 times higher risk of a cardiac event than those who were adherent without depressive symptoms ($p < .001$). In the Kaplan-Meier and log-rank test, the composite endpoint of cardiac event-free survival was significantly worse in NYHA III/IV patients than those with NYHA I/II (chi-square = 4.238, $p = 0.04$). When adding study group, group assignment, age, NYHA functional class, ACEI use, and anxiety to the model, patients who were nonadherent with depressive symptoms had a 5.2 times higher risk of cardiac events than patients who were adherent without depressive symptoms (Table 4). NYHA class was no longer a significant predictor of cardiac event-free survival in the multiple Cox regression. Patients who were nonadherent without depressive symptoms or those who were adherent with depressive symptoms had a 1.2–1.3 times higher risk of a cardiac event than those who were adherent without depressive symptoms before and after controlling for covariates (Table 4).

Discussion

This is the first study to explore the prediction of cardiac event-free survival from the combination of medication adherence and depressive symptoms in patients with HF. We found that medication adherence and depressive symptoms independently predicted cardiac event-free survival in patients with HF. Consistent with prior investigators' findings, HF patients who were adherent to prescribed medications had a lower risk of cardiac events than those who were nonadherent.[10, 11] Likewise, HF patients who had depressive symptoms had a higher risk of ED visits, hospitalizations, or death than those who had no depressive symptoms.[2, 3]

The most striking finding from this study was that medication adherence and depressive symptoms in combination predicted cardiac event-free survival in patients with HF in a synergistic fashion. In the Cox regression model, when HF patients were divided into 4 groups stratified by medication adherence and depressive symptoms, the risk of experiencing a cardiac event for patients with both risk factors (medication nonadherence and depressive symptoms) was 5 times compared to those who were medication adherent without depressive symptoms before and after adjusting for covariates; while the risk of experiencing a cardiac event for patients with only one risk factor was 1.3 times that of those with neither risk factor.

We identified three studies in which both medication adherence and depressive symptoms predicted health outcomes.[22–24] Morgan and colleagues [22, 50] found that difficulty taking medications, an aspect of medication nonadherence, and depressive symptoms in patients with HF were independent predictors of worse health status scores on the Kansas City Cardiomyopathy Questionnaire. In a recent prospective study in 107 heart transplantation recipients, Favaro and associates [24] investigated the role of major depression and medication adherence in the prediction of outcomes from cardiac transplantation and found that presence of an episode of major depression prior to cardiac transplantation indirectly predicted mortality through post-transplant malignancies, while poor medication adherence was a significant predictor of mortality. In a sample of 111 patients with HF, Moser and colleagues[23] examined whether nonadherence mediated the relationship between depression and outcomes and found that medication adherence but not dietary sodium adherence mediated the link between depression and rehospitalization/mortality. Our findings were consistent with these prior investigators' findings that both medication nonadherence and depressive symptoms predicted poor outcomes. However, the combined effect of medication adherence and depressive symptoms was not examined in these studies. Our study advances our understanding of this relationship by demonstrating that medication nonadherence and depressive symptoms in combination, predicted worse cardiac event-free survival in patients with HF before and after controlling for some important covariates. Therefore, clinicians should take both medication adherence and depressive symptoms seriously, screen/assess regularly, and should strive to provide appropriate intervention/treatment when needed.

It is well-documented that depressive symptoms predict shorter cardiac event-free survival.[2, 3, 25–29, 4, 23, 24, 25, 26] Patients with depressive symptoms were more likely to have ED visits,[25] hospital readmissions,[25, 26, 28] and death[26, 27] compared with those without depressive symptoms.[24, 25] There are several mechanisms that could be related to the association between depressive symptoms and increased risk for ED visits, hospitalization, or death. Patients with depressive symptoms have lower heart rate variability,[30, 31] a higher inflammatory response,[32] hyperactivity of sympathetic nervous system, greater severity of HF,[29] higher platelet activity, and more frequent myocardial ischemia which may explain, in part, worse outcomes.[33] In the current HF literature, NYHA classification has been found to be related to depressive symptoms[34–36] and survival[37, 38] in patients with HF, and also been

used to assess HF severity.[39, 40] In our study, patients with depressive symptoms were more likely to have advanced HF as reflected by NYHA functional class compared with those without depressive symptoms. In the Kaplan-Meier and log-rank test, patients with NYHA III/IV had shorter cardiac event-free survival than those with NYHA I/II. This result is consistent with prior studies showing the impact of NYHA on rehospitalization or mortality in HF.[37, 38] However, when we adjusted NYHA class in the Cox regression, NYHA class was not a predictor of cardiac event-free survival, suggesting that the observed relationship among medication adherence, depressive symptoms, and outcomes was not a result of confounding. However, we cannot rule out the possibility of unmeasured confounders (e.g., inflammatory markers) in this observational study.

In addition to these physiologic factors, medication adherence is one of the most common explanations linking depression and worse outcomes.[3, 25, 27] Investigators have suggested that worse outcomes of patients with depressive symptoms might be associated with reduced adherence to medical therapy.[3, 25, 27] In our study, more patients with depressive symptoms were medication nonadherent than without depressive symptoms. Our result was consistent with most prior studies that depression was associated with medication nonadherence.[41–48]

Many studies have focused on why depressed patients are more likely to be nonadherent than non-depressed patients. Investigators have suggested the reasons for patients with depressive symptoms are more likely to be nonadherent to their treatment regimen might due to greater feelings of hopelessness, being socially isolated, withdrawal from social network, possible reductions in the cognitive functioning that may affect memory, and no energy to carry out medical regimen.[27, 49] In a sample of 280 patients with HF, excessive daytime sleepiness and mild cognitive decline were 2.5 times more likely to be medication nonadherent than those without excessive daytime sleepiness or cognitive decline.[50] However, we did not examine these variables in our study. Therefore, more research is needed to explore the linkages between depressive symptoms and medication adherence.

When we compared sociodemographic, clinical, and psychological variables among 4 groups (stratified by medication adherence and depressive symptoms), age, NYHA functional class, ACEI use, functional status, and anxiety were different among groups. Patients with medication nonadherent and depressive symptoms group were younger, were more likely to be NYHA III/IV class, were less likely to use ACEI, had worse functional status, and had a higher level of anxiety than those in other groups. However, when we adjusted for age, NYHA class, ACEI use, and anxiety in the Cox regression model, patients with medication nonadherence and depressive symptoms still had the highest risk of experiencing a cardiac event, suggesting that the predictive power of the combination of depressive symptoms and medication adherence for cardiac event-free survival was robust.

Limitations

Participants were recruited from one Southern tertiary hospital. Our sample included 85% Caucasian, 65% male, and 62% married patients. Therefore, our findings warrant further study to confirm these results in a more diverse sample of patients with HF.

Second, we have small sample size within some of the 4 adherence/depression groups. Future studies of this phenomenon should include a larger number of each group, especially for medication adherent/nonadherent patients with depressive symptoms so that the complex dynamics surrounding depressive symptoms, medication adherence and outcomes can be better illuminated. Thus our findings should be considered exploratory and the need for replication emphasized.

Third, we assessed HF severity using NYHA class instead of a more objective marker such as natriuretic peptides. However, investigators have shown plasma brain natriuretic peptide (BNP) levels were significantly increased in accordance with the NYHA class.[51] And even the measure of natriuretic peptide has limitations with regard to its ability to accurately reflect severity of heart failure. For example, extreme values of plasma BNP do not correlate with the presence of HF or cardiomyopathy, thus limiting the usefulness of BNP as a marker of HF severity.[52]

Finally, medication adherence might be inflated by using the MEMS because patients knew their medication-taking behaviors were monitored (i.e., Hawthorne effect). However, the MEMS is considered a "gold standard" measure to assess medication adherence in the current adherence literature and is the closest way to get to actual behavior.[53] From prior validation studies of the MEMS, serum blood levels were correlated with MEMS data indicating that patients take their medication when they open the MEMS caps and further studies have demonstrated that there was no Hawthorne effect with the use of the MEMS.[54]

Conclusion

The major finding of this study was that medication adherence and depressive symptoms combined to produce a synergistic effect in the prediction of cardiac event-free survival. The study highlights the importance of medication adherence and patient's depressive symptoms. Interventions to improve clinical outcomes should address both medication adherence and depressive symptoms.

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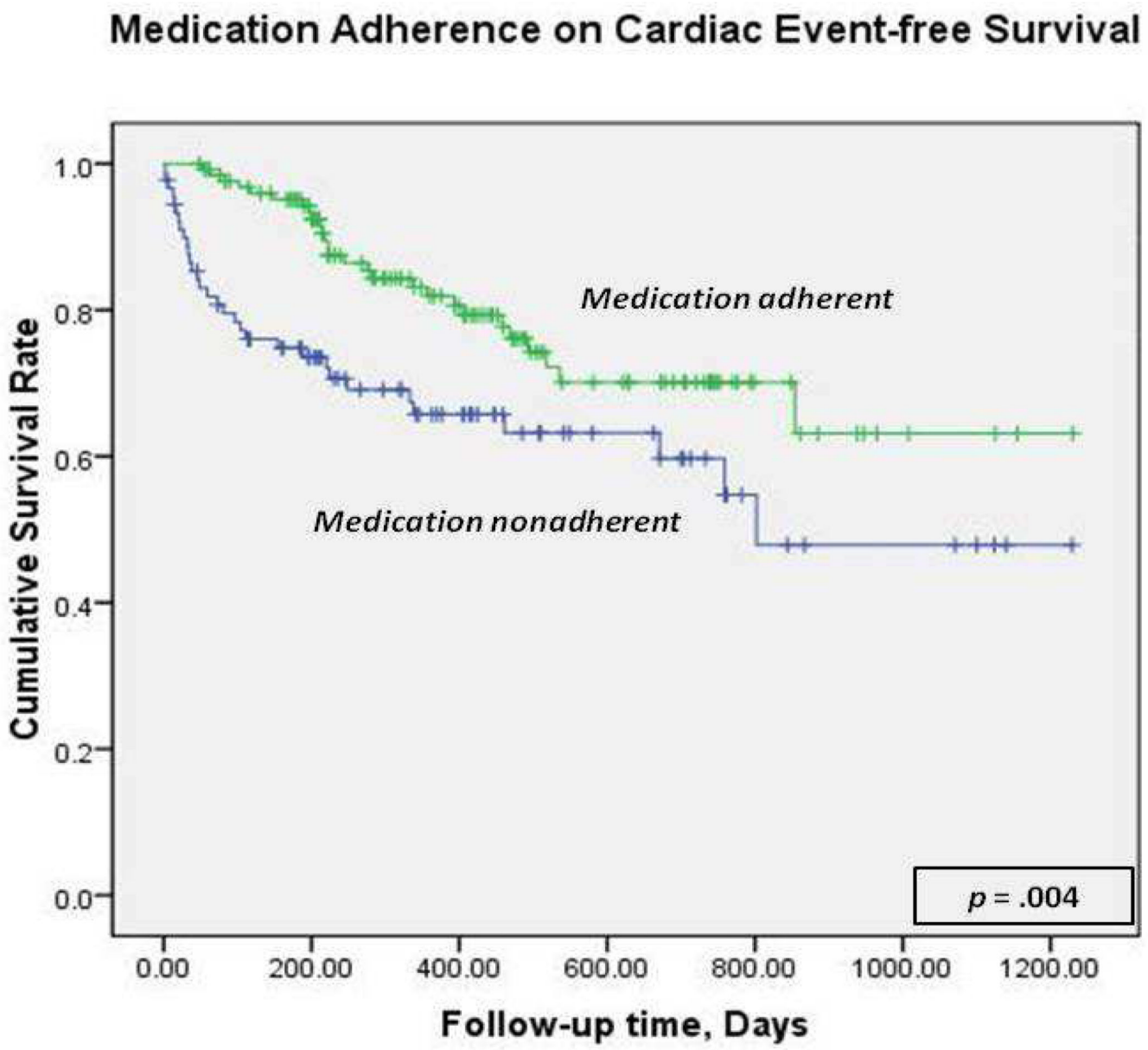

Figure 1.
Medication adherence and cardiac event-free survival

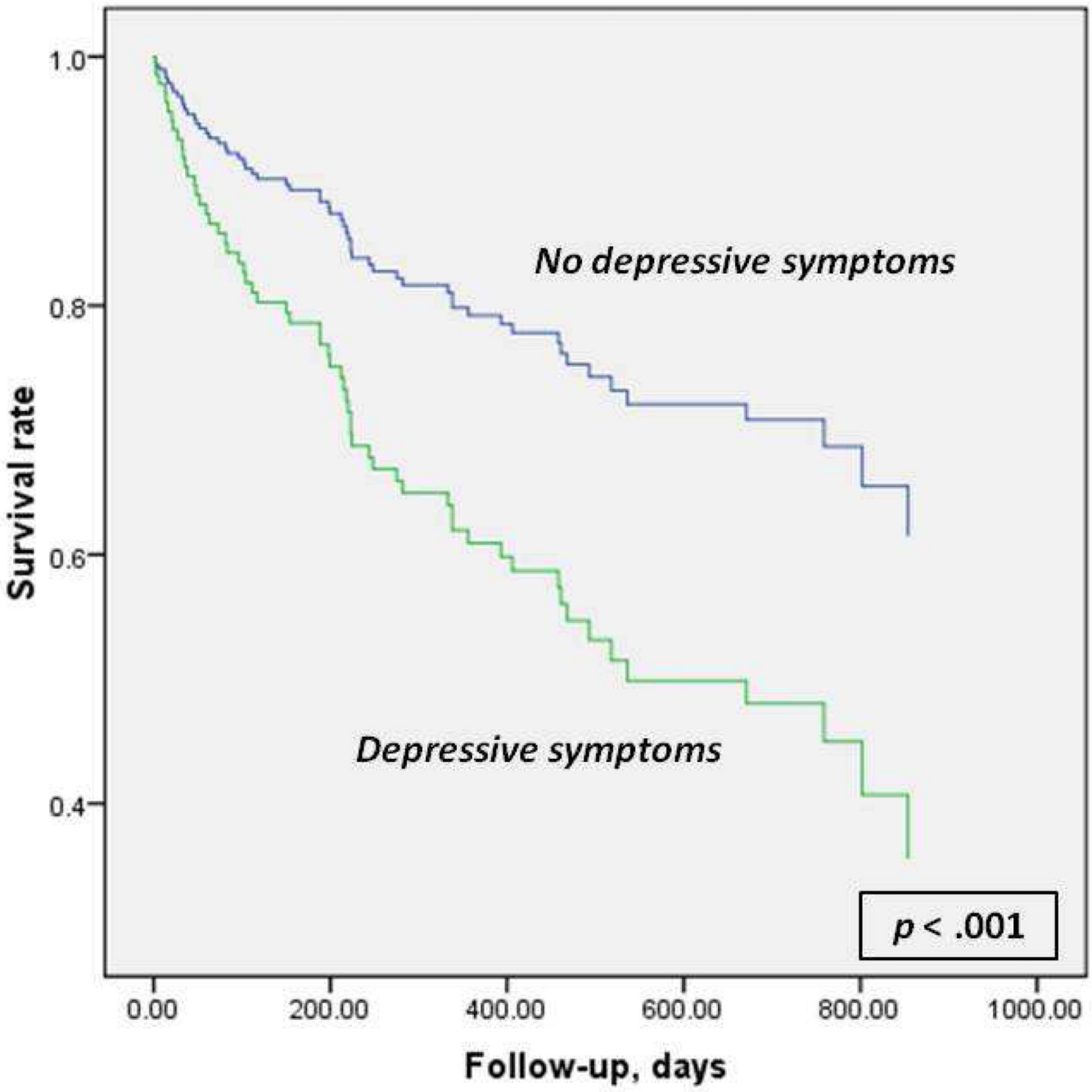

Figure 2.
Depressive symptoms and cardiac event-free survival

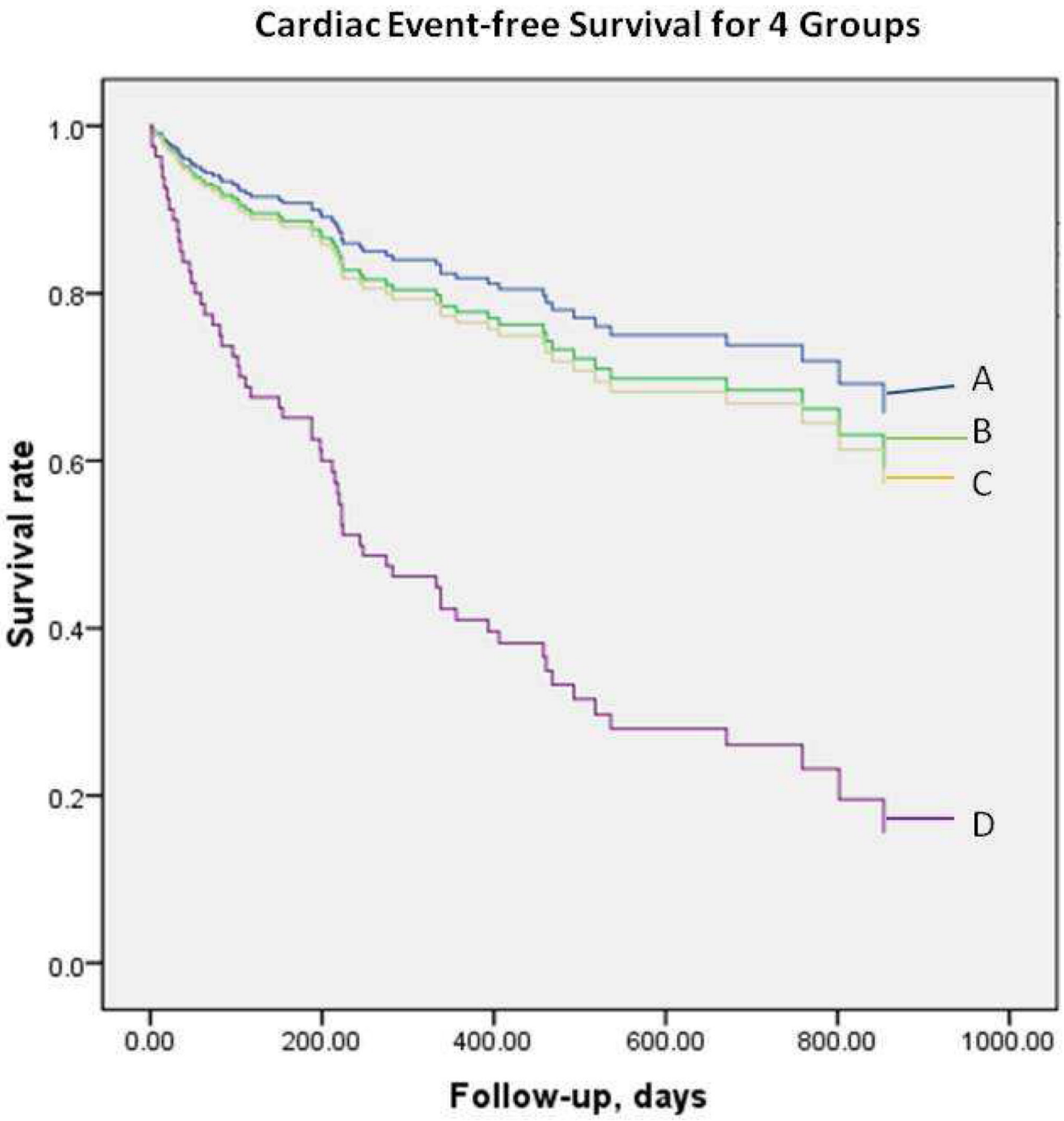

Figure 3.
Cardiac event-free survival for patients stratified by medication adherence and depressive symptoms.
A: Medication adherent without depressive symptoms
B: Medication adherent with depressive symptoms
C: Medication nonadherent without depressive symptoms
D: Medication nonadherent with depressive symptoms

Table 1

Sample characteristics and comparison of clinical and demographic characteristics by medication adherence and depressive symptoms classification

Characteristics	Overall (N = 216)	Medication Adherent (n = 128)	Medication Nonadherent (n = 88)	*p*	Depressive symptoms (n = 55)	No depressive symptoms (n = 161)	*p*
Age, years	60 ± 12	61 ± 11	60 ± 12	.41	57 ± 9	62 ± 12	.003
Male	141 (65)	86 (67)	55 (63)	.56	33 (60)	108 (67)	.41
Married	133 (62)	83 (64)	50 (56)	.26	32 (58)	101 (63)	.63
Caucasian	184 (85)	112 (88)	72 (82)	.33	47 (86)	137 (85)	1.00
Education, years	13 ± 3	13 ± 4	13 ± 3	.32	12 ± 3	13 ± 3	.06
Etiology: Ischemia	108 (51)	61 (48)	47 (55)	.33	24(44)	84 (53)	.35
NYHA III/IV	122 (57)	66 (52)	56 (64)	.17	42 (76)	80 (50)	< .001
LVEF, %	35.8 ± 14.3	35.6 ± 14.6	36.1 ± 13.7	.80	35.8 ± 15.3	35.9 ± 14.0	.97
ACEI use	152 (71)	96 (76)	56 (64)	.07	31 (57)	121 (75)	.02
ARB use	26 (12)	13 (10)	13 (15)	.40	5 (9)	21 (13)	.63
Beta-blocker use	198 (91)	118 (92)	80 (90)	.63	50 (91)	148 (91)	1.0
Diuretics use	148 (68)	85 (66)	63 (71)	.59	45 (82)	103 (64)	.04
Aldosterone antagonist use	44(20)	26 (20)	18 (20)	1.00	12 (22)	32 (20)	.85
Anti-depressant use	44 (20)	26 (20)	18 (21)	1.00	21 (38)	23 (14)	< .001
Anxiety score	.65 ± .70	.54 ± .57	.80 ± .82	.009	1.24 ± .77	.45 ± .54	< .001
Medication nonadherent	88 (41)	-	-	-	30 (55)	58 (36)	.018
Depressive symptoms	55 (26)	25 (20)	30 (34)	.018	-	-	-

Data are presented as means ± SD, or N (%), interval level data compared by independent t-test, categorical by Chi-square; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; ACEI =angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker.

Table 2

Comparison of characteristics among four groups stratified by medication adherence and depressive symptoms

	Medication adherent		Medication nonadherent		*p* value	Post hoc by LSD test
	Without depressive symptoms (n = 103)	With depressive symptoms (n = 25)	Without depressive symptoms (n = 58)	With Depressive symptoms (n = 30)		
Group	A	B	C	D		
Age	62 ± 12	58 ± 8	61 ± 12	56 ± 10	.07	A > D
NYHA III/IV	46 (45)	20 (80)	34 (59)	22 (73)	.001	-
ACEI use	79 (77)	17 (71)	42 (72)	14 (47)	.017	-
Anxiety	.41 ± .47	1.07 ± .64	.51 ± .64	1.39 ± .85	< .001	A, C > B, D
Diuretics use	64 (62)	21 (84)	39 (66)	24 (80)	.279	-

Data are presented as means ± SD, or N (%), interval level data compared by Analysis of Variance (ANOVA with the Least Significant Difference [LSD] post hoc tests), categorical by Chi-square; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; ACEI =angiotensin-converting-enzyme inhibitor.

Table 3

Cox regression modeling: medication adherence alone and depressive symptoms alone on Cardiac Event-free Survival (N = 216)

Variables	Hazard Ratio	95% CI	*p*
Simple Cox Regression: without adjusting			
Medication adherence *			
Medication adherent	1.0	-	-
Medication nonadherent	2.07	1.242–3.462	.005
Depressive symptoms **			
No depressive symptoms	1.0	-	-
Depressive symptoms	2.65	1.568–4.489	< .001
Cox Regression: adjusting for covariates †			
Medication adherence ‡			
Medication adherent	1.0	-	-
Medication nonadherent	1.80	1.065–3.042	.028
Depressive symptoms §			
No depressive symptoms	1.0	-	-
Depressive symptoms	2.404	1.255–4.606	.008

CI: confidence interval

* chi-square = 8.117; $p = .004$;

** chi-square = 14.278; $p < .001$

† Controlling for study group, group assignment, age, New York Heart Association functional class, and angiotensin-converting-enzyme inhibitor use.

‡ chi-square = 19.187; $p = .008$

§ chi-square = 22.02; $p = .003$

Table 4

Cox regression modeling: combined effects of medication adherence and depressive symptoms on Cardiac Event-free Survival (N = 216)

Variables	Hazard Ratio	95% CI	*p*
Simple Cox Regression: without adjusting *			
Medication adherent without depressive symptoms	1.0	-	-
Medication adherent with depressive symptoms	1.41	.568–3.5	.46
Medication nonadherent without depressive symptoms	1.366	.704–2.652	.14
Medication nonadherent with depressive symptoms	4.949	2.6–9.423	< .001
Cox Regression: adjusting for covariates **			
Step 1			
Study group	1.447	.752–2.786	.27
Group assignment	2.577	1.085–6.119	.03
Step 2			
Age	1.003	.980–1.026	.82
NYHA	1.291	.863–1.932	.21
ACEI use	.757	.429–1.334	.34
Anxiety	1.412	1.003–1.988	.048
Step 3			
Medication adherent and no depressive symptoms	1.0	-	-
Medication adherent and depressive symptoms	1.302	.492–3.445	.60
Medication nonadherent and no depressive symptoms	1.227	.625–2.407	.55
Medication nonadherent and depressive symptoms	5.175	2.318–11.551	< .001

CI: confidence interval

* chi-square = 30.537, $p < .001$

** chi-square = 37.818, $p < .001$

NYHA=New York Heart Association functional class, ACEI=angiotensin-converting-enzyme inhibitor.