Depression and Outcomes in Japanese Outpatients With Cardiovascular Disease

– A Prospective Observational Study –

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Background: The aim of this study was to determine the prevalence of depression assessed by the 9-item test from the Patient Health Questionnaire (PHQ-9) and the effect of depression on adverse cardiovascular outcomes in Japanese outpatients with cardiovascular disease (CVD).

Methods and Results: This prospective observational study enrolled 1,453 outpatients with CVD (mean age 67 ± 13 years; 31.3% female; 32.6% ischemic heart disease). Depression was defined as a PHQ-9 score ≥ 10 . The main composite outcome was the time to death from any cause or a cardiovascular event. 81 patients (5.6%) were diagnosed with depression (PHQ-9 ≥ 10). NYHA class III, living alone, and unemployment were independently associated with depression. During an average follow-up of 584 ± 80 days, the main outcome occurred in 85 patients (5.8%). There was a higher incidence of the main outcome in patients with depression than in those without depression ($P < 0.001$). Depression was an independent predictor of the primary outcome (hazard ratio 4.64, 95% confidence interval 2.24–9.09, $P < 0.001$).

Conclusions: Depression assessed by the PHQ-9 was found in 5.6% of Japanese outpatients with CVD and was an important risk factor for adverse outcomes. (UMIN-CTR No. UMIN 000023514) (*Circ J* 2016; **80**: 2482–2488)

Key Words: Cardiovascular disease; Depression; Japanese; Outcomes; Outpatients

Depression is known to be a possible risk factor for adverse cardiovascular outcomes in patients with coronary artery disease or heart failure.^{1–8} The prevalence of depression is reported to be approximately 20% in outpatients with cardiovascular diseases (CVD); in some reports it reached 30–40% in outpatients with heart failure.^{6,9–13} However, previous studies have used several self-reported methods for measuring depression and the detection of depression likely varies according to these different methods. In Japan, there have been only a few reports about the prevalence of depression (assessed by the Center for Epidemiologic Studies Depression Scale and Beck Depression Inventory)^{14,15} and its effect on outpatients with specific heart disease status such as heart failure or implantable cardioverter-defibrillator (ICD).

Recently, the American Heart Association (AHA) recommended routine depression screening in patients with coronary artery disease using the 9-item test from the Patient Health Questionnaire (PHQ-9).¹⁶ This method is also used for depression screening in patients with heart failure or arrhythmia;

depression assessed by the PHQ-9 is reported to be independently associated with adverse outcomes.^{17–19} To date, there are no data concerning the prevalence of depression assessed by the PHQ-9 in outpatients with CVD in Japan.

Methods

We conducted a prospective observational study of outpatients who visited the outpatient cardiology clinics of Tokyo Women's Medical University Hospital (between March 2013 and May 2013), Tokyo Women's Medical University Medical Center East (between December 2013 and February 2014) and Tokyo Women's Medical University Aoyama Hospital (March 2014). Patients with dementia, delirium, or other conditions (eg, endstage of other life-threatening diseases) that made it difficult for them to complete a self-reported written questionnaire were excluded. A total of 1,453 outpatients with CVD were enrolled in this study. The protocol was approved by the institutional review board of Tokyo Women's Medical University

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(approval no. 2899). All patients gave written informed consent.

Cardiovascular Diseases

Coronary artery disease was defined as positive stress test findings, coronary angiography demonstrating at least 75% stenosis or coronary spastic angina documented by acetylcholine provocation test, a history of prior myocardial infarction, or a history of revascularization procedures. Valvular and congenital heart diseases were diagnosed by angiographic, hemodynamic or echocardiographic testing or a history of valvular or congenital cardiac surgery. Aortic and mitral regurgitation were defined as valvular disease with at least moderate regurgitation on color-flow Doppler echocardiography. Nonischemic cardiomyopathies were defined as ventricular myocardial abnormalities in the absence of coronary artery disease or valvular, pericardial or congenital heart disease. Pulmonary artery hypertension was defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg with a pulmonary wedge pressure ≤ 15 mmHg at rest estimated by right heart catheterization. Aortic disease, peripheral artery disease and other vascular diseases were diagnosed by angiographic or echocardiographic findings or by a history of vascular surgery or intervention. Arrhythmias and conduction disorders without structural heart disease included atrial, supraventricular and ventricular arrhythmias, sick sinus syndrome and atrioventricular block in the absence of structural heart disease. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or a history of treatment for hypertension. Left ventricular ejection fraction (LVEF) was calculated by left ventriculography, echocardiography or radionuclide angiography.

Assessment of Depression

Patient recruitment was conducted by investigators in outpatient cardiology clinics; upon giving consent, participants completed the questionnaires in the waiting area outside the consulting room after their consultation. Subsequently, research coordinators confirmed completion of all items of the questionnaire and then collected them. Depressive symptoms were assessed using the Japanese version of the PHQ-9.²⁰ The PHQ-9 is a self-reported scale containing 9 symptoms that reflect the diagnostic criteria for depression. It has been developed with each of the 9 criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for clinical depression on a scale from 0 (not at all) to 3 (nearly every day).²¹ Overall scores may, therefore, range from 0 to 27. Kroenke et al reported that PHQ-9 scores ≥ 10 had a sensitivity of 88% and a specificity of 88% for major depression;²¹ Muramatsu et al reported that PHQ-9 scores ≥ 10 on the Japanese version had a sensitivity of 84% and a specificity of 95% for major depression in Japanese patients.²⁰ Therefore, in this study depression was defined as a PHQ-9 score ≥ 10 .

Follow-up

Patients were observed as outpatients at the hospital or their general practitioner's clinic at 1- to 3-month intervals up to December 2015. Patients receiving pacing device therapy, including pacemakers, cardiac resynchronization therapy (CRT) and ICD, were also followed every 3–6 months at the pacemaker/ICD clinic. The occurrence of ventricular tachyarrhythmias requiring ICD therapy, including shock and antitachycardia pacing, was obtained by reviewing event details and ECGs stored on the ICD disks. Only episodes of ventricular tachycardia or fibrillation requiring ICD therapy for termination

were included in the analysis. Information about deceased subjects was obtained from medical records, family members, their patient's general practitioner and the admitting hospital. Six (0.4%) patients were lost to follow-up.

Clinical Outcomes

The main clinical outcome was a composite of death from any cause or cardiovascular events from the time of enrollment to the first event. Cardiovascular death was defined as death from myocardial or cerebral infarction, other vascular causes, heart failure or documented sudden cardiac death. Cardiovascular events included non-fatal myocardial infarction, hospitalization for heart failure, unstable angina, revascularization, stroke, refractory arrhythmia, ventricular tachyarrhythmia requiring ICD therapy, and other cardiovascular events. Acute coronary syndrome (ACS) was defined according to the American College of Cardiology/American Heart Association criteria.^{22,23} Revascularization included angioplasty, stenting and coronary artery bypass grafting. Heart failure was defined on the basis of symptoms and signs, such as dyspnea, rales and ankle edema, and the need for treatment with diuretics, vasodilators, positive inotropic drugs or an intra-aortic balloon pump. Stroke was defined as a new focal neurological deficit of vascular origin lasting >24 h. Stroke was further classified by etiology, including intracranial hemorrhage, ischemia diagnosed by computed tomography or magnetic resonance imaging if available, or uncertain cause. Refractory arrhythmia was defined as a supra-ventricular or ventricular tachyarrhythmia requiring external defibrillation or pacing, intravenous antiarrhythmic drugs, catheter ablation, or ICD, and bradyarrhythmia requiring implantation of a pacemaker. Other cardiovascular events included peripheral artery disease, dissecting aortic aneurysm, and rupture of an aortic aneurysm.

Statistical Analysis

Data are presented as mean $\pm$ standard deviation (SD), number, median and range. Baseline clinical data were compared between the groups with and without depression using Student's t-test and the Mann-Whitney U test. Categorical variables were subjected to chi-square analysis. Univariate and multivariate analyses using Cox proportional hazards model were performed to determine the relationship of the following baseline characteristics and depression: age ≥ 65 years, female sex, New York Heart Association (NYHA) functional class III, LVEF $\leq 35\%$, hypertension, hemodialysis, implantation of an ICD/CRT with a defibrillator (CRT-D), living status and work status. The cumulative event-free rates were calculated using the Kaplan-Meier method. Differences in event-free rates were compared using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazards model were performed to assess the relationships between depression and the main outcome, independent of the following confounders: age ≥ 65 years, female sex, nonischemic cardiomyopathy, plasma B-type natriuretic peptide (BNP) concentration using the Shionoria assay ≥ 170 pg/ml,^{24,25} NYHA functional class III, LVEF $\leq 35\%$, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula <60 ml/min/1.73 m², diabetes mellitus, hypertension, hemodialysis, implantation of ICD/CRT-D, living status and work status. The forward stepwise method was used for the multivariate analyses with entry or removal on the basis of P values set at 0.05. A P-value of <0.05 was considered significant. Data analyses were performed with SPSS statistical software (version 11.01, SPSS Inc, Chicago, IL, USA).

Table 1. Characteristics of Study Patients With CVD

	Total (n=1,453)	PHQ-9 ≥10 (n=81)	PHQ-9 <10 (n=1,372)	P value
Age (years)	67±13	65±14	66±13	0.564
Female	455 (31.3)	39 (48.1)	416 (30.3)	0.008
CVD				0.022
Coronary artery disease	473 (32.6)	19 (23.5)	454 (33.1)	
Nonischemic cardiomyopathy	351 (46.9)	33 (40.7)	318 (23.2)	
Valvular heart disease	125 (8.6)	3 (3.7)	122 (8.9)	
Arrhythmia without structural heart disease	325 (22.4)	16 (19.8)	309 (22.5)	
Pulmonary artery hypertension	4 (0.2)	1 (1.2)	3 (0.2)	
Congenital heart disease	53 (3.6)	3 (3.7)	50 (3.5)	
Other	117 (8.1)	6 (7.4)	116 (8.4)	
Plasma BNP (pg/ml)	152 (4–3,358)	216 (4–1,632)	148 (4–3,358)	0.045
NYHA functional class				
I/II/III/IV	710/717/26/0	27/48/6/0	683/669/20/0	0.024
LVEF (%)	51±12	49±12	51±15	0.023
eGFR (ml/min/1.73 m²)	57±20	55±25	57±14	0.355
Medical comorbidities				
Hypertension	729 (50.2)	29 (35.8)	700 (51.0)	0.008
Diabetes	366 (25.2)	16 (19.8)	350 (25.5)	0.246
Dyslipidemia	618 (42.5)	23 (28.4)	118 (8.6)	0.060
Hemodialysis	32 (2.2)	10 (12.3)	22 (1.6)	<0.001
Cerebrovascular disease	14 (1.0)	2 (2.5)	12 (0.9)	0.153
Major depression	2 (0.1)	0	2 (0.1)	0.731
Implanted pacing device				
Pacemaker/CRT-P	72 (5.0)	6 (7.4)	66 (4.8)	0.295
ICD/CRT-D	96 (6.6)	10 (12.3)	86 (6.2)	0.035
Medications				
β-blockers	823 (56.6)	49 (60.5)	774 (56.4)	0.472
ACE inhibitors/ARBs	834 (57.4)	49 (60.5)	785 (57.2)	0.563
Spironolactone/eplerenone	228 (15.7)	17 (21.0)	208 (15.2)	0.152
Calcium-channel blockers	424 (29.2)	17 (21.0)	407 (29.7)	0.094
Aspirin/other antiplatelet drugs	508 (34.8)	29 (35.8)	479 (34.9)	0.870
Warfarin/DOACs	487 (33.5)	28 (34.6)	459 (33.5)	0.832
Amiodarone	144 (9.9)	9 (11.1)	135 (9.8)	0.712
Other antiarrhythmic drugs	93 (6.4)	7 (8.6)	86 (6.2)	0.396
Antidepressants	2 (0.2)	0	2 (0.2)	0.735
Living alone	227 (15.6)	20 (24.7)	207 (15.1)	0.021
Work status				
Employed	678 (46.7)	25 (30.9)	653 (47.6)	0.003
Unemployed/retired	775 (53.3)	56 (69.1)	719 (52.4)	

Data are mean±SD or n (%) or median (range). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CRT-D, CRT with a defibrillator; CRT-P, CRT with a pacemaker; CVD, cardiovascular disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PHQ-9, 9-item Patient Health Questionnaire.

Results

Patients

Of the 1,544 patients who provided consent, 1,453 completed the PHQ-9 and were included in this study; 81 (5.6%) patients met the criteria for depression as assessed by the PHQ-9. **Table 1** shows the characteristics and a comparison of patients with and without depression (PHQ-9 ≥10). There was no significant difference in age between groups; the proportions of females, nonischemic cardiomyopathy, plasma BNP level, NYHA functional class and hemodialysis were higher among the patients with depression than in those without. LVEF and

the proportion of hypertension were lower in patients with depression than in those without. There was a higher rate of ICD/CRT-D implantation in patients with depression. However, there was no significant difference in the rate of medication use, including β-blockers, between patients with and without depression. Two patients (0.2%) who were diagnosed with major depression by a psychiatrist had taken antidepressants, and their PHQ-9 scores were <10. Compared with patients without depression, more patients with depression were living alone and were unemployed/retired. Multivariate analysis showed that female sex (hazard ratio (HR) 1.77, 95% confidence interval (CI) 1.10–2.83, P=0.017), NYHA functional

Figure 1. Kaplan-Meier curves for the main outcome (death from any cause or a cardiovascular event) in cardiovascular outpatients with a score on PHQ-9 of <10 (not depressed) or ≥10 (depressed). PHQ-9, 9-item Patient Health Questionnaire.

	PHQ-9 ≥10 (n=81)	PHQ-9 <10 (n=1,372)	P value
Death from any cause	3	17	0.064
Cardiovascular death	2	7	0.029
Sudden death	1	3	0.090
Heart failure	1	4	0.159
Non-cardiovascular death	1	10	0.610
Infection-related death	0	5	0.586
Colon carcinoma	1	2	0.036
Cerebral event	0	1	0.808
Unknown	0	2	0.731
Hospitalization reason			
Heart failure	6	24	0.001
ACS	2	8	0.046
Revascularization	1	9	0.541
Stroke	2	1	0.006
Refractory arrhythmia	0	3	0.674
Ventricular tachyarrhythmia requiring ICD therapy	1	3	0.090
Other cardiovascular events	1	4	0.159

ACS, acute coronary syndrome. Other abbreviations as in Table 1.

class III (HR 4.59, 95% CI 1.60–11.48, $P=0.006$), living alone (HR 1.98, 95% CI 1.13–3.31, $P=0.016$) and unemployment (HR 1.89, 95% CI 1.16–3.16, $P=0.010$) were significantly associated with depression.

Depression and Clinical Outcomes

During an average follow-up of 584 ± 80 days, the main outcome occurred in 85 patients (5.8%). Kaplan-Meier curves for the main outcome are shown in [Figure 1](#). There was a significantly higher incidence of the main outcome in patients with depression than in those without depression. Causes of death and each cardiovascular event are shown in [Table 2](#). The incidence rates of cardiovascular death, hospitalization for

heart failure, hospitalization for ACS and hospitalization for stroke were higher in patients with depression than in those without depression. Kaplan-Meier curves for death from any cause, death from cardiovascular cause, and cardiovascular events are shown in [Figure 2](#). There were significantly higher rates of all-cause death, cardiovascular death and cardiovascular events in patients with depression than in those without depression.

Multivariate analysis revealed that patients with depression had an increased risk of the main outcome (HR 4.64, 95% CI 2.24–9.09, $P<0.001$), which was independent of plasma BNP ≥ 170 pg/ml, NYHA functional class III, LVEF $\leq 35\%$, eGFR < 60 ml/min/1.73 m² and unemployment ([Table 3](#)).

Figure 2. Kaplan-Meier curves for death from any cause (**A**), death from cardiovascular cause (**B**), and a cardiovascular event (**C**) in cardiovascular outpatients with a score on PHQ-9 of <10 (not depressed) or ≥10 (depressed). PHQ-9, 9-item Patient Health Questionnaire.

Table 3. Univariate and Multivariate Analyses for the Main Outcome in a Study of Patients With CVD

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
PHQ-9 ≥ 10	5.36 (2.82–9.63)	<0.001	4.64 (2.24–9.09)	<0.001
Age ≥ 65 years	1.60 (0.96–2.80)	0.069		
Female sex	1.01 (0.60–1.65)	0.951		
Nonischemic cardiomyopathy	0.84 (0.52–1.38)	0.485		
Plasma BNP ≥ 170 pg/ml	5.42 (3.36–8.77)	<0.001	2.26 (1.22–4.08)	0.009
NYHA class III	20.95 (8.01–50.65)	<0.001	6.84 (3.27–13.86)	<0.001
LVEF $\leq 35\%$	3.86 (2.27–6.39)	<0.001	2.32 (1.25–4.15)	0.008
eGFR < 60 ml/min/1.73 m ²	2.59 (1.61–4.28)	<0.001	2.23 (1.12–4.25)	0.022
Diabetes	1.08 (0.62–1.80)	0.861		
Hypertension	0.87 (0.59–1.39)	0.581		
Hemodialysis	6.36 (2.60–14.00)	<0.001	2.99 (0.93–8.21)	0.060
Implantation of ICD/CRT-D	3.82 (2.01–6.25)	<0.001	1.25 (0.60–2.50)	0.529
Living alone	1.58 (0.87–2.71)	0.121		
Unemployment/retired	2.23 (1.37–3.72)	0.001	1.86 (1.09–3.27)	0.022

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Discussion

Our study revealed that the prevalence of depression assessed by the PHQ-9 was 5.6% in Japanese outpatients with CVD. There was a significantly higher incidence of the main outcome (death from any cause or a cardiovascular event), in patients with depression than in those without depression. Depression defined as a PHQ-9 ≥ 10 was shown to be an independent factor for worse clinical outcomes in Japanese CVD patients.

A previous study from the National Health Interview Survey data of 30,801 US adults reported that the 12-month prevalence of major depression was 9.3% in patients with coronary artery disease, 8.0% in those with hypertension and 7.9% in those with congestive heart failure compared with 4.8% in those with no chronic medical disorder.²⁶ A recent report by Moullec et al, using the Primary Care Evaluation of Mental Disorders, a standardized structured psychiatric interview, showed that 6% of 750 outpatients with and without a history of coronary artery disease who were referred for an exercise stress test (mean age 58 ± 10 years, 31% females) had a current major depressive disorder and the 21-item self-reported questionnaire Beck Depression Inventory II was useful in screening for depression.²⁷

The AHA recommends routine depression screening of patients with coronary artery disease using the PHQ-9.¹⁶ This method is a brief self-reported questionnaire and easy to use in practice. Recent reports showed that a cut-off of PHQ-9 score ≥ 10 is useful for screening for depression in patients with heart failure or other cardiac conditions, including coronary artery disease.^{16–19} This study is the first to assess the prevalence of depression determined by the PHQ-9 in Japanese outpatients with CVD. Although the method of measuring depression and the patient characteristics were different, the prevalence rate ($\approx 6\%$) of depression in stable outpatients with CVD was comparable to that reported previously.²⁷ The PHQ-9 may be an accurate and easy-to-use tool to screen for depression in Japanese patients in the cardiovascular outpatient clinic.

Among our patients, female sex, NYHA functional class III, living alone and being unemployed were associated with depression. Depression is known to be common among patients with heart failure and higher rates of depression are present

among patients with increased NYHA functional class.²⁸ Japanese patients with heart failure have a higher proportion of nonischemic etiology compared with those in Western countries where the majority of heart patients have an ischemic etiology.^{29–31} In our study, the higher proportion of nonischemic cardiomyopathy might be related to higher NYHA functional class in patients with depression than in those without.

Sociodemographic characteristics are also associated with depression. From the World Mental Health surveys, females are on average twice as likely as men to be depressed; marital status (being separated from a partner, divorced or widowed) was a consistently significant correlate of major depression.³² Poor social status, such as living alone and being unemployed, was also associated with depression. This is consistent with a previous study in Japan that reported higher depression scores in single persons on in those with lower incomes.³³

Depression is associated with poor outcomes in patients with CVD,⁶ whether outpatients or inpatients.³⁴ Furthermore, in the present study the rates of cardiovascular death and events, including hospitalization for heart failure, ACS and stroke, were higher in patients with depression than in those without. Although the pathophysiologic mechanisms are not fully understood, depression is an important risk factor for adverse cardiovascular events. Screening for depressive symptoms in outpatients with CVD is important.

Study Limitations

First, this was a cohort study consisting of university hospitals. The prevalence of coronary artery disease was one-third and half of the patients were in heart failure of NYHA functional class II/III. Our results limit generalization to Japanese practice. Second, the studied patients were not consecutively enrolled, although we concentrated on recruiting patients during a short-term enrollment period (1 or 3 months) in each hospital. From these limited data, we could not determine the contribution of depression to the clinical condition of several patients with CVD. Third, 2 patients in the non-depressive group had received antidepressants because of major depression diagnosed before the study. These patients with improved depressive symptoms controlled with antidepressants were not detected by the PHQ-9. Fourth, the overall number of subjects was relatively small; therefore, subgroup analysis was not feasible.

Conclusions

Our results suggested a depression rate of 5.6% in Japanese cardiovascular outpatients, especially those with moderate to severe heart failure, living alone or unemployed. Depression was associated with subsequent cardiovascular outcomes or death and may be an important risk factor for adverse cardiovascular events in outpatients.

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Conflict of Interest Statement

The authors have no conflicts of interest.

Competing Interests

None declared.

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