without. Our results suggest that ICD shocks may contribute to the persistence of depression in ICD patients.

Bilge et al. reported that depression score according to the Hospital Anxiety and Depression scale was significantly higher in patients with recent shocks (within last 6 months) than in those without (any shocks occurring more than 6 months previously).[13] Our results showed no significant difference in the presence of recent shock (within 6 months) between patients with and without depression at the 2-year time point. The proportion of patients who received ICD for secondary prevention was quite different between our study and Bilge's study (22% vs 71%), and the rate of patients with recent shock in Bilge's study was twice as high as that in our study. This inconsistency may be partially due to differences in the backgrounds of the patients. It remains unclear whether the length of time elapsed between ICD shocks is associated with depression.

The relationship between the time since implantation and QOL has been investigated in several studies, but most research was unable to assess the effect of ICD therapy status on QOL because of an insufficient number of shocks during rather short follow-up periods.[4] In this study, we found no relationship between time since implantation and the occurrence of depression.

Limitations

There were several limitations inherent to this study. First, all subjects enrolled in this study were hospitalized patients and were heterogeneous. More than half had newly implanted ICDs, and their clinical status varied. Consecutive inpatients admitted over 8 months were entered into the study to minimize selection bias. Data concerning clinical conditions at the time of ICD therapy were not available. In addition, there was treatment bias, including pharmacotherapy. Furthermore, the number of subjects was relatively small, and therefore subgroup analysis was not feasible.

Conclusion

Depression is not uncommon among patients who meet criteria for ICD implantation and persists over time particularly when functional status is impaired. Depression is associated with a higher incidence shock therapy.

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ORIGINAL ARTICLE
Preventive Medicine

Depression and Outcomes in Hospitalized Japanese Patients With Cardiovascular Disease

– Prospective Single-Center Observational Study –

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Background: Several studies have suggested that depression poses a risk in cardiovascular patients. The aim of the present study was to evaluate the prevalence of depression and its effect on cardiovascular events and mortality in Japanese inpatients with cardiovascular disease.

Methods and Results: A total of 505 patients hospitalized with cardiovascular disease (28% female; mean age, 61±14 years; 31% ischemic heart disease; 47% New York Heart Association [NYHA] class II–IV; 25% implantation of pacing devices) were enrolled in the present prospective observational study. The Zung Self-Rating Depression Scale (SDS) was used to screen for depression. The primary outcome was the time to death or cardiovascular event, and the secondary outcome was death. In total, 109 patients (22%) were diagnosed with depression (Zung SDS index score ≥60). NYHA class III/IV, defibrillator implantation, and being unmarried were independently associated with depression. During an average follow-up period of 38±15 months, 92 patients (18%) reached the primary outcome. There was a higher incidence of the primary outcome in patients with depression than in those who were not depressed (P<0.01). Depressed patients had a significantly higher rate of mortality than non-depressed patients (P<0.01). Depression was an independent predictor of the primary outcome (hazard ratio, 2.25; 95% confidence interval: 1.30–3.92, P<0.01).

Conclusions: Depression was not uncommon in Japanese inpatients with cardiovascular disease and was associated with cardiovascular outcomes. (*Circ J* 2011; **75:** 2465–2473)

Key Words: Cardiovascular disease; Depression; Inpatient; Mortality; Outcome

Several studies have suggested that depression is a possible risk factor for adverse outcomes in patients with coronary artery disease or heart failure.[1–7] While cardiac events may cause and prolong depression in patients with cardiac disease,[8–10] the prevalence of depression is reported to be approximately 20% in outpatients with coronary artery disease and 30–40% in outpatients with heart failure.[6,11–14] In patients hospitalized for acute myocardial infarction, 16–45% are depressed,[6,8,11] and the presence of depressive symptoms is a significant risk factor for subsequent cardiac events in elderly myocardial infarction patients.[15] In hospitalized heart failure patients, depression is also common and is independently associated with poor outcomes.[2,3,16,17] Understanding these issues could help cardiologists identify inpatients with depression and deliver the most appropriate care.

Cultural and ethnic differences influence depressive symptoms and the interpretation of depression as an illness.[18–20] In Japan, there have been few reports about the prevalence of depression and its effect on patients with cardiovascular disease.[14,15,21] To date, there have been no reports concerning the prevalence of depression in hospitalized patients with cardiovascular disease in Japan.

The aim of the present study was to evaluate the prevalence of depression and the effect of depression on subsequent cardiovascular events and mortality in Japanese patients hospitalized with cardiovascular disease.

Methods

We conducted a prospective observational study in patients who were admitted to the cardiology department of Tokyo Women's Medical University Hospital between June 2006 and April 2008. Patients with dementia, delirium, or other conditions that make it difficult to complete a self-reported written questionnaire (eg, unconsciousness, in intensive care, end-stage of another life-threatening disease) were excluded. The protocol was approved by the institutional review board of Tokyo Women's Medical University. All patients gave written informed consent.

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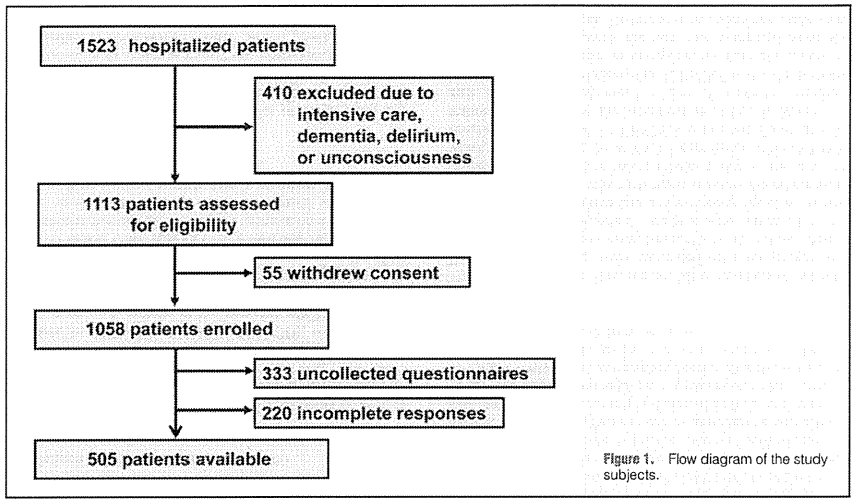

Figure 1. Flow diagram of the study subjects.

Cardiovascular Disease

In the present study, structural heat disease consisted of the following disorders: left ventricular (LV) systolic dysfunction and/or marked LV dilatation (unless secondary to severe valve regurgitation), LV diastolic dysfunction associated with congestive heart failure, coronary heart disease, right heart disease with at least moderate right ventricular dilation, moderate or severe tricuspid regurgitation, pulmonary hypertension, LV hypertrophy, left-sided valvular disease, and congenital heart disease. Coronary artery disease was defined as positive stress test findings, coronary angiography demonstrating at least 75% of stenosis or coronary spastic angina as documented on an acetylcholine provocation test, a history of prior myocardial infarction, or a history of revascularization procedures. Valvular and congenital heart diseases were diagnosed on angiographic, hemodynamic or echocardiographic findings 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. Non-ischemic 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 of ≥25 mmHg with a pulmonary wedge pressure of ≤15 mmHg at rest, as estimated on right heart catheterization. Aortic disease, peripheral artery disease and other vascular diseases were diagnosed on angiographic or echocardiographic findings, or 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. LV ejection fraction (LVEF) was calculated using left ventriculography, echocardiography or radionuclide angiography.

Assessment of Depression

Most patients received psychological questionnaires within a few days after hospital admission. For patients who initially required intensive treatment, these questionnaires were given after their transfer to the general cardiology wards. The Zung Self-Rating Depression Scale (SDS) has been used to screen for depression and to measure the severity of depression in numerous settings.[22–26] The Zung SDS is a self-reporting, 20-question instrument that assesses the psychological and somatic symptoms of depression. It has good internal consistency and validity, encompassing most DSM-IV criteria for major depression.[26–32] The Zung SDS has been found to be the primary discriminating variable for distinguishing depressed from non-depressed people.[33] It has shown a positive likelihood ratio for major depression of 3.3 (95% confidence interval [CI]: 1.3–8.1), and negative likelihood ratio of 0.35 (95%CI: 0.2–0.8).[24] The Zung SDS has also been used in clinical studies to assess depression in cardiovascular disease.[15,34–37] Ten questions are positively worded, and 10 are negatively worded. Each question is scored on the following 4-point scale: 1, a little of the time; 2, some of the time; 3, good part of the time; and 4, most of the time. To obtain a total score, the positive items are reversed, and then the items are summed. This raw score is converted to a 100-point scale (SDS index). Zung SDS index scores range from 25 to 100 and are interpreted as follows: within the nor-

Table 1. Patient Characteristics

	Total (n=505)	Depression (n=109)	No depression (n=396)	P value
Age (years)	61±14	61±13	59±15	0.45
Female	143 (28)	36 (33)	107 (27)	0.26
Cardiovascular disease				0.24
Coronary artery disease	159 (31)	24 (22)	135 (34)	
Non-ischemic cardiomyopathy	114 (23)	30 (28)	84 (21)	
Valvular heart disease	65 (13)	15 (14)	50 (13)	
Arrhythmia without structural heart disease	143 (28)	32 (29)	111 (28)	
Pulmonary artery hypertension	3 (1)	1 (1)	2 (1)	
Congenital heart disease	6 (1)	2 (1)	4 (1)	
Others	15 (3)	5 (5)	10 (3)	
Plasma BNP on admission (pg/ml)	251 (4–4,335)	378 (5–4,335)	215 (4–3,400)	<0.01
NYHA functional class on admission (I/II/III/IV)	269/191/30/15	41/45/16/7	228/146/14/8	<0.01
NYHA functional class at discharge (I/II/III/IV)	275/206/23/1	41/46/21/1	234/160/2/0	<0.01
LVEF (%)	48±15	49±15	46±16	0.11
eGFR (ml·min^{-1}·1.73 m^{-2})	61±14	61±14	61±14	0.73
Current smoker	70 (14)	14 (12)	56 (14)	0.72
History of atrial fibrillation	85 (17)	16 (15)	69 (17)	0.49
Medical comorbidities				
Hypertension	166 (32)	29 (27)	137 (35)	0.11
Diabetes	86 (17)	16 (15)	70 (18)	0.46
Dyslipidemia	141 (28)	23 (21)	118 (30)	0.06
Hemodialysis	32 (6)	10 (9)	22 (6)	0.18
Cerebrovascular disease	8 (1.5)	2 (2)	6 (2)	0.81
Major depression	8 (1.5)	5 (5)	3 (1)	0.01
Implanted pacing devices before admission				
Pacemaker/CRT-P	54 (11)	13 (12)	41 (10)	0.64
ICD/CRT-D	73 (14)	26 (24)	47 (12)	0.02
Implanted pacing devices at discharge				
Pacemaker/CRT-P	64 (13)	13 (12)	51 (13)	0.79
ICD/CRT-D	95 (19)	29 (27)	66 (17)	0.01
Medications at the time of questionnaire				
β-blockers	248 (49)	52 (48)	196 (49)	0.74
ACE inhibitors/ARBs	278 (55)	60 (55)	218 (55)	0.99
Spironolactone/eplerenone	120 (24)	37 (34)	83 (21)	0.68
Calcium channel blockers	284 (56)	54 (50)	230 (58)	0.11
Aspirin	172 (34)	29 (27)	143 (36)	0.06
Warfarin/heparin	142 (28)	34 (32)	108 (27)	0.64
Amiodarone/nifekalant	60 (12)	22 (20)	40 (10)	<0.01
Intravenous inotropics	3 (1)	2 (2)	1 (0.3)	<0.01
Intravenous vasodilator	5 (1)	4 (4)	1 (0.3)	<0.01
Antidepressants	8 (2)	5 (5)	3 (1)	0.01
Medications at discharge				
β-blockers	259 (51)	57 (52)	202 (51)	0.81
ACE inhibitors/ARBs	308 (61)	72 (66)	236 (59)	0.21
Spironolactone/eplerenone	136 (27)	40 (37)	96 (24)	0.01
Calcium channel blockers	289 (57)	55 (50)	234 (59)	0.10
Aspirin	186 (37)	33 (30)	153 (39)	0.10
Warfarin	160 (32)	44 (40)	116 (29)	0.03
Amiodarone	68 (13)	25 (23)	43 (11)	0.05
Antidepressants	8 (2)	5 (5)	3 (1)	0.01
Education				0.33
High school	314 (62)	74 (68)	240 (61)	
College	124 (25)	24 (22)	100 (25)	
Others	67 (13)	11 (10)	56 (14)	
Marital status				<0.01
Unmarried	35 (7)	13 (12)	22 (6)	
Married	448 (89)	83 (76)	365 (92)	
Widowed	22 (4)	13 (12)	9 (2)	
Work status				0.02
Employed	205 (41)	32 (29)	173 (44)	
Housewife	89 (18)	26 (24)	63 (16)	
Unemployed/retired	211 (42)	51 (47)	160 (40)	

Data given as n (%) or mean±SD or median (range).
BNP, B-type natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; CRT, cardiac resynchronization therapy; CRT-P, CRT with a pacemaker; ICD, implantable cardioverter defibrillator; CRT-D, CRT with a defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

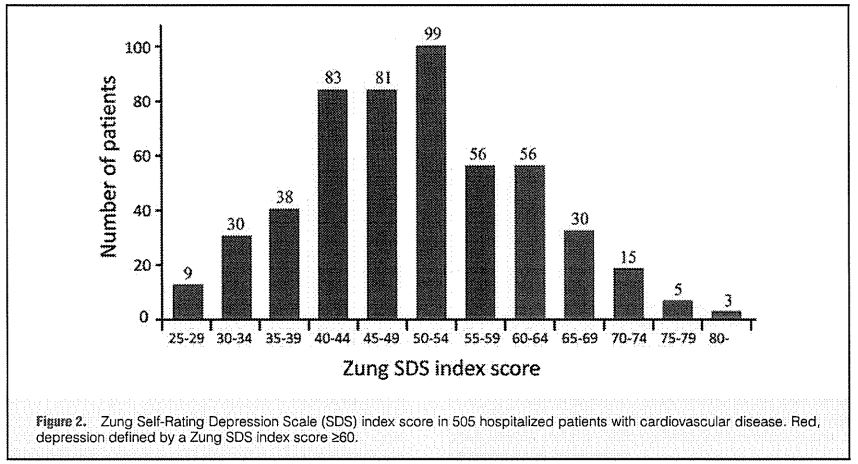

Figure 2. Zung Self-Rating Depression Scale (SDS) index score in 505 hospitalized patients with cardiovascular disease. Red, depression defined by a Zung SDS index score ≥60.

mal range, <50; mildly depressed, 50–59; moderately depressed, 60–69; and severely depressed, ≥70. Because the psychological and physical symptoms of depression may overlap with those of cardiovascular disease, there is a possibility that cardiovascular symptoms may be attributed to depression. Previous studies with cardiovascular disease have often used a cut-off index score of 50 (raw score 40) as a definition of depression.[15,34–37] Higher depression scores (eg, SDS score index ≥60) are associated with increased morbidity and mortality in patients with coronary artery disease.[37,38] A cut-off index score of 60 has been shown to detect clinical depression while avoiding an abundance of false-positive results in patients with cardiovascular or other disease.[10,39–41] In the present study, depression was defined as a Zung SDS index score ≥60.

Follow-up

After discharge, patients were seen as outpatients or at their general practitioner's clinic at 1–3-month intervals up to October 2010. Patients receiving pacing device therapy, including pacemakers, cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD), were also followed every 3–6 months at the pacemaker/ICD clinic. The occurrence of ventricular tachyarrhythmias requiring ICD therapy, including shock and anti-tachycardia pacing, was obtained by reviewing event details and electrograms 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 general practitioners and the admitting hospital.

Clinical Outcomes

The primary 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 due to 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, and ventricular tachyarrhythmia requiring ICD therapy. Unstable angina was defined according to the Braunwald criteria.[42] 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 on computed tomography or magnetic resonance imaging if available) or uncertain cause. Refractory arrhythmia was defined as supraventricular or ventricular tachyarrhythmia requiring external defibrillation or pacing, i.v. anti-arrhythmics such as amiodarone and nifekalant, catheter ablation, or implantation of an ICD, and bradyarrhythmia requiring implantation of a pacemaker. Other cardiovascular events included peripheral artery disease, dissecting aortic aneurysm, and rupture of an aortic aneurysm. The second outcome was death from any cause.

Statistical Analysis

The data are given as either mean±SD or numbers of patients. Baseline clinical data were compared between groups with and without depression using Student's t-test and the Mann–Whitney U-test. Categorical variables were subjected to chi-squares analysis. Multivariate analysis using the Cox proportional hazards model was performed to assess the relationship of the following baseline characteristics to depression: age ≥65 years, female gender, New York Heart Association (NYHA) functional class III/IV, LVEF≤35%, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula <60 ml·min^{-1}·1.73 m^{-2},[43] diabetes mellitus, hemodialysis, implantation of an ICD/CRT with a defibrillator (CRT-D), β-blocker use on admission, marital status and work status. Cumulative event-free rate was calculated using the Kaplan–Meier method. Differences in event-free rates were

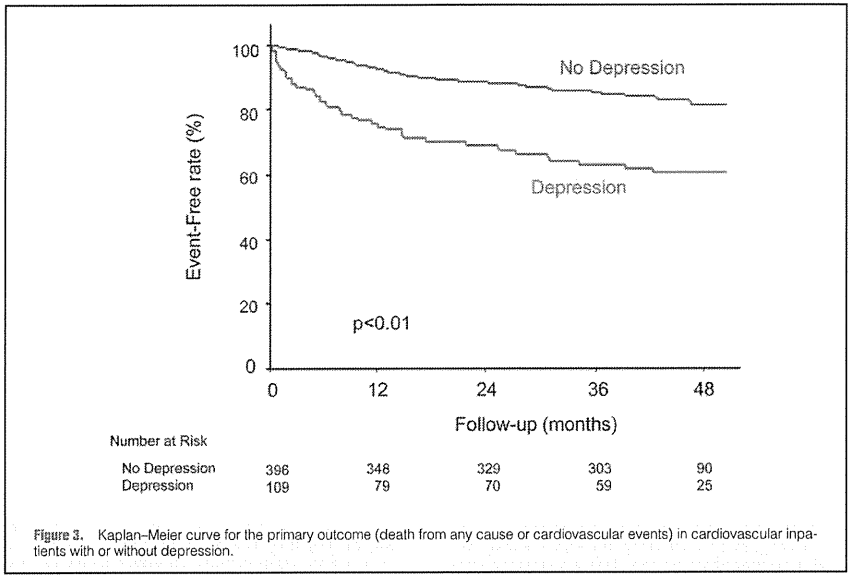

Figure 3. Kaplan–Meier curve for the primary outcome (death from any cause or cardiovascular events) in cardiovascular inpatients with or without depression.

compared using the log-rank test. Multivariate analysis using the Cox proportional hazards model was performed to assess the relationships between depression and the primary outcome, independent of the following confounders at discharge: age ≥65 years, female gender, NYHA functional class III/IV, LVEF≤35%, eGFR <60 ml·min^{-1}·1.73 m^{-2}, diabetes mellitus, hypertension and implantation of an ICD/CRT-D. P<0.05 was considered significant. SPSS version 11.01 (SPSS, Chicago, IL, USA) was used for analysis.

Results

Patients

Of the 1,523 consecutively hospitalized patients, 1,058 patients were enrolled in the present study. Seven hundred and twenty-five questionnaires were collected (collection rate of 68%). Of these, 505 questionnaires had valid responses (response rate of 48%), and these patients were available to participate in the study (Figure 1). The patient characteristics are shown in Table 1. The mean age on admission was 61±14 years, and 28% of the patients were female. A total of 159 patients (31%) had coronary artery disease, 236 (47%) were rated as being in NYHA functional class II–IV on admission, and 127 (25%) had implanted pacing devices on admission. Eight patients (2%) had been treated for major depressive disorder prior to admission. All 505 patients were discharged from hospital, and 230 (46%) were in NYHA functional class II–IV at discharge. At discharge, 159 (31%) had implanted pacing devices. Regarding concomitant medications at discharge, 259 patients (51%) were taking β-blockers, and 68 patients (13%) were taking amiodarone. Eight patients (2%) who were diagnosed with major depression by a psychiatrist were taking antidepressants. No patients were receiving non-pharmacological therapy such as cognitive behavior therapy.

Depression Prevalence

The Zung SDS index scores of all studied patients at baseline are shown in Figure 2. In total, 109 patients (22%) had depression. A comparison of patients' clinical characteristics according to the presence or absence of depression is shown in Table 1. There was no significant difference in age, gender, underlying cardiovascular disease, coexisting conditions or implanted devices between groups. The plasma B-type natriuretic peptide (BNP) level on admission and NYHA functional class on admission and at discharge were higher in patients with depression than in those who were not depressed. There was a higher rate of ICD/CRT-D implantation on admission in patients with depression. There were higher rates of amiodarone/nifekalant use, i.v. inotropic use, i.v. vasodilator use and antidepressant use at the time of the questionnaire in patients with depression. There was no significant difference, however, in the rate of β-blocker use between patients with (48%) and without depression (49%). There were higher rates of spironolactone/eplerenone use, warfarin use and antidepressant use at discharge in patients with depression. Compared with patients without depression, fewer depressed patients were married or employed. Multivariate analysis showed that ICD implantation (hazard ratio [HR], 1.92; 95%CI: 1.00–3.80, P=0.04), NYHA functional class III/IV (HR, 3.03; 95%CI: 1.38–6.67, P<0.01), and unmarried status (HR, 4.32; 95%CI: 2.31–8.09, P<0.01) were significantly associated with depression.

Depression and Clinical Outcomes

During an average follow-up period of 38±15 months, 92 patients (18%) reached the primary outcome. Kaplan–Meier curves for the primary outcome are shown in Figure 3. There was a significantly higher incidence of the primary outcome in patients with depression than in those without depression. Causes of death and each cardiovascular event are listed in Table 2. Kaplan–Meier curves for death from any cause are shown in Figure 4. There was a significantly higher mortality in patients with depression than in those who were not depressed.

Multivariate analysis showed that patients with depression had an increased risk of the primary outcome: death from any

Table 2. Cause of Death and Rate of Cardiovascular Events

	Depression (n=109)	No depression (n=396)	P value
Death from any cause	21	20	<0.01
Cardiovascular death	18	17	<0.01
Sudden death	1	8	0.42
Heart failure	17	5	<0.01
Myocardial infarction	0	2	0.45
Cerebral infarction	0	1	0.59
Peripheral artery disease	0	1	0.59
Non-cardiovascular death	3	3	0.08
Infection-related death	1	1	0.32
Surgery-related death	1	0	0.06
Hepatocellular carcinoma	0	1	0.59
Hepatic failure	1	0	0.06
Pulmonary hemorrhage	0	1	0.59
Hospitalization for heart failure	22	30	<0.01
Hospitalization for unstable angina	2	3	0.31
Hospitalization for revascularization	5	5	0.02
Hospitalization for stroke	0	1	0.59
Hospitalization for refractory arrhythmia	1	3	0.86
Ventricular tachyarrhythmia requiring ICD therapy	3	9	0.77
Hospitalization for other cardiovascular events	1	2	0.61

Abbreviation see in Table 1.

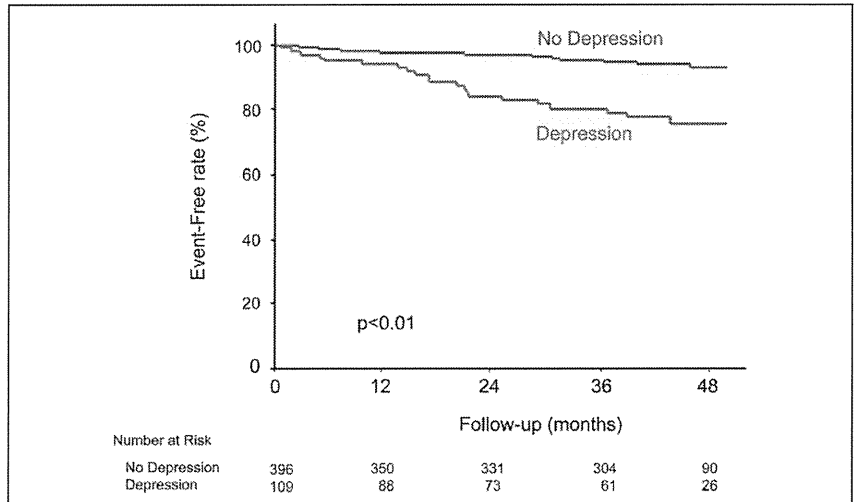

Figure 4. Kaplan–Meier curve for the secondary outcome (death from any cause) in cardiovascular inpatients with or without depression.

cause and cardiovascular events (HR, 1.98; 95%CI: 1.32–2.98, P<0.001; Table 3). This risk was independent of whether patients met the criteria of NYHA functional class III/IV, LVEF≤35% and eGFR <60 ml·min^{-1}·1.73 m^{-2}.

Discussion

The present study has shown that the prevalence of depression was 22% in hospitalized patients with cardiovascular disease. ICD/CRT-D implantation, NYHA functional class III/IV at baseline, unmarried status, and unemployment were associated with depression. Furthermore, higher mortality and death from any cause and cardiovascular events were more prevalent in patients with depression than in those who were not depressed. Finally, depression was shown to be an independent factor for worsening clinical outcome.

Depression is often comorbid with chronic physical disease. The World Health Organization World Health Survey reported that an average of 9.3–23.0% of subjects with one or more physical diseases, such as angina, arthritis, asthma and diabetes, also suffer from depression.[44] A large study based on National Health Interview Survey data of 30,801 US adults reported that the 12-month prevalence of major depression was 9.3% in subjects with coronary artery disease, 9.3% in subjects with diabetes, 8.0% in subjects with hypertension and 7.9% in subjects with congestive heart failure, compared with 4.8% in those with no chronic medical disorder.[45] Recently, the American Heart Association recommended routine depression screening in patients with coronary artery disease using the 2- and 9-item tests from the Patient Health Questionnaires (PHQ-2 and PHQ-9).[46] Sowden et al reported that approximately 9% of 3,504 screened inpatients in cardiac care units had positive PHQ-2 scores (≥3). Of these patients, 74.1% had a PHQ-9 score ≥10, but the details of the patients' clinical backgrounds are unknown.[47] Previous studies have used several methods to measure depression, including the Beck Depression Inventory, SDS, the Hospital Anxiety and Depression Scale, and the Centre for Epidemiologic Studies Depression Scale (CES-D).[5,8] The Sowden et al PHQ-2 cut-off score was higher than that in general use (≥2)[48] to avoid false-negative results. The prevalence of patients with a PHQ-2 ≥2 was at least 15% in the Sowden et al study.[47] In the present study, 22% of all cardiovascular disease inpatients met the criteria for depression (Zung SDS index score ≥60).

The prevalence of depression in the present inpatients was comparable to the prevalence reported previously in Western countries, but the methods for measuring depression varied. In the present patients, ICD/CRT-D implantation and NYHA functional class III/IV as baseline were associated with depression. Previous studies have indicated that ICD implantation improves quality of life (QOL) in most ICD patients,[49,50] but an underlying disease or comorbidity, poor social support, or ICD-specific problems, such as frequent shocks and poor understanding of ICD therapy, increase depressive symptoms and reduce the QOL for ICD patients.[10,50–52] This is an important problem in clinical practice because the number of ICD implantations being carried out to prevent sudden cardiac death is increasing. A meta-analysis showed that depression is common among patients with heart failure, and substantially higher rates of clinically significant depression are present among patients with more severe heart failure.[53] In the present study, concomitant use of amiodarone/nifekalant, i.v. inotropics and i.v. vasodilators at the time of the questionnaire was higher in patients with depression. These findings might be due to a higher proportion of moderate to severe heart failure patients among patients with depression. More than half of the heart failure patients in Japan have non-ischemic etiologies, unlike in Western countries, where the majority of heart failure patient have ischemic etiologies.[54–56] From the present results, regardless of the etiology, severe heart failure, higher plasma BNP and higher NYHA functional class were associated with depression and are risk factors for cardiovascular events and mortality. The prevalence of heart failure increases with age, and depression will be expected to rise in coming years because of the growing elderly population.

Table 3. Multivariate Analysis for the Primary Outcome

	HR (95%CI)	P value
NYHA class III/IV	2.07 (1.14–3.72)	0.01
Implantation of ICD/CRT-D	4.04 (2.15–7.06)	<0.01
eGFR <60 ml·min^{-1}·1.73 m^{-2}	3.26 (1.84–5.76)	<0.01
LVEF≤35%	2.06 (1.03–4.13)	0.04
Depression	2.25 (1.30–3.92)	<0.01
Female gender	1.02 (0.55–1.87)	0.94
Age≥65 years	0.83 (0.48–1.44)	0.83
Diabetes	1.47 (0.74–2.94)	0.26
Hypertension	0.97 (0.53–1.74)	0.91

HR, heart rate; CI, confidence interval. Other abbreviations see in Table 1.

Single or widow status was associated with depression. Regarding socioeconomic status, the employment rate was lower in patients with depression, although work status was not a statistically independent factor for depression. Education also was not related to depression. Using national survey data, Inaba et al reported that the depression score according to CES-D is higher in women, single people, and people with lower incomes in both Japan and the USA, but there is no association between education and depression in Japan; however, depression is inversely related to education in the USA.[57] The present findings that higher prevalences of single people and people with low employment status, but not level of education, were seen in patients with depression might be due to certain common features of Japanese patients with depression.

There are several mechanisms to consider concerning the relationships between depression and poor outcomes in patients with cardiovascular disease.[6] First, behavioral problems decrease patient compliance. Depressive symptoms have been associated with poor adherence to medications, diet, fluid restriction, and exercise as well as poor social support.[2,6,58,59] In the present subjects, poor social status, such as being unmarried or unemployed, was associated with depression. Poor social support also has been reported to be independently associated with worse cardiovascular outcome.[60] Second, biological mechanisms are involved in poor cardiovascular outcomes. Several events have been associated with these poor outcomes, including changes in cardiac autonomic tone, activation of the sympathetic nervous system, enhanced activity of the hypothalamic–pituitary–adrenal axis, and elevated inflammatory and pro-inflammatory processes.[1,2,6,61] Although depression is associated with poorer outcome in patients with cardiovascular disease, its pathophysiologic mechanisms are not completely understood. In the present study, death due to heart failure and hospitalization for heart failure were major adverse cardiovascular events, and the rates of these events were significantly different between patients with and without depression. There was significantly higher use of spironolactone/eplerenone and warfarin at discharge in patients with depression than in those who were not depressed. This difference might be related to a

higher rate of coexisting heart failure in patients with depression. Recently Zuluaga et al suggested that the association between depression and higher long-term mortality in patients hospitalized for heart failure is explained largely by the presence of comorbidities, physical inactivity, and disability.[62] Moreover, several reports concluded that therapy for depression improved depressive symptoms but not cardiovascular outcomes in patients.[6,63,64] In the present study, antidepressant use was higher in patients with depression, but the small rate of usage of these drugs did not contribute to patient outcomes. Depression may be merely a surrogate marker of poor prognosis but it may be an important marker, especially in patients with heart failure. The management of depression and cardiovascular disease, including proactive follow-up by nurses or care managers,[65] intervention with cognitive behavioral therapy, or social support,[66] is important for improving compliance and therapeutic outcomes in patients with cardiovascular disease and depression.

Study Limitations

There were some limitations in the present study. First, this was a single-center cohort study. The clinical characteristics of the present patients might not reflect those of general cardiovascular patients in Japan because the present institution is a university hospital. The prevalence of coronary heart disease was only 31%, and half of the patients were in NYHA functional class II–IV. In addition, there was a treatment bias. Therefore, the present results have limited generalizability in overall cardiac care. Second, the present patients were not consecutively enrolled, and many patients who received emergent or intensive care were not enrolled because it was not possible for them to complete the questionnaire. Moreover, there was an approximately 50% response rate for the Zung SDS questionnaire in the enrolled patients. This self-report 20-item written questionnaire was used as a convenient screening method but was limited by the document return rate from all subjects and the validity of the responses. From these limited data, we could not determine the contribution of depression to clinical condition in several patients with cardiovascular disease. Third, the questionnaire was not completed before discharge. The primary aim of the present study was to evaluate the prevalence and distribution of depression in hospitalized patients. Moreover, the length of hospital stay ranged from a few days to several months because cardiovascular diseases are heterogeneous. For long-term prognosis, an assessment immediately before discharge might be more appropriate. Previous research has demonstrated, however, that depression at the time of hospitalization, not only before discharge, is associated with poor prognosis in patients with cardiovascular disease.[66–69] Although this problem exists, the present results demonstrate the importance of assessment at an early stage of management of cardiovascular patients. Four, because the number of subjects in the present study was relatively small, subgroup analysis was not feasible. To clarify these issues, large multicenter clinical investigations that include several regions in Japan are needed.

Conclusion

The present results suggest that depression is not uncommon in Japanese cardiovascular inpatients, especially in those with heart failure or who are on ICD therapy. Depression is associated with subsequent cardiovascular outcomes or mortality and may be an important marker of poor prognosis.

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Disclosures

Competing interests: none declared.

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REVIEW

Cardiovascular clinical trials in Japan and controversies regarding prospective randomized open-label blinded end-point design

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Recently, results of several cardiovascular clinical trials conducted in Japan were published. Most of them were designed as prospective randomized open-label blinded end-point (PROBE)-type trials, in which patients were randomly allocated to different regimens and both the patients and doctors are aware of the regimen being administered. Although the PROBE design enables performing trials resembling real-world practices, entails low costs and renders patient recruitment easier, it presents several conditions that have to be satisfied to acquire accurate results, due to its open-label nature. Principally, the so-called hard end points, which are judged by objective criteria, should be used as primary end points in order to prevent biases. In this article, a general description of various designs of clinical studies is provided, followed by a description of the PROBE design, and the precautions to be taken while conducting PROBE-designed trials by comparing trials conducted in Japan and the West.
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Keywords: clinical trials; PROBE design; hard end point; soft end point

INTRODUCTION

Evidence-based medicine is thought to be extremely important in contemporary medicine.[1] However, until recently, actual evidence with Japanese subjects has not been sufficiently produced. It is known that despite the westernized lifestyle of the Japanese population, the incidence rate of myocardial infarction remains relatively low.[2] Thus, generation of scientific evidence based on data from Japanese patients is warranted. However, owing the fact that the Japanese healthcare system covers the entire population in principle, and that people have free access to almost any kind of medical institution,[3] it has been rather difficult to recruit patients into clinical trials, especially into randomized, double-blind studies, in which the patients and doctors are required to be unaware of what medicines are being administered. This is the reason why many recent clinical trials conducted in Japan adopted the prospective randomized open-label blinded end-point evaluation (PROBE) design,[4] in which both the patient and the doctor are aware of what medicines are being administered. However, if not designed carefully, the accuracy of the PROBE-style study results can be compromised. In this review, we would first like to discuss the designs used in various studies and then describe the design of PROBE; thereafter, we would like to provide referral to the merits and demerits of the PROBE design trials, accompanied by recent examples.

STUDY DESIGNS USED IN EPIDEMIOLOGICAL STUDIES

Epidemiology is the study of factors affecting the health and illness of a certain population. It does not usually encompass the assessment of the efficacy of drugs or medical devices. However, the principal concepts and methodology used in clinical trials have been generated in epidemiology, and understanding them is important.

Retrospective cohort studies

In retrospective cohort studies, a population set (cohort) is defined and the risks and outcomes are investigated retrospectively. This design of epidemiological studies can be adopted when there is already a database of risks and outcomes of sufficient size. With the recent evolution of information technology, patients' demographic data, laboratory data, prescription data, and morbidity and mortality data are sometimes available over the course of several years. For example, to elucidate the relationship between chronic kidney disease and mortality, a study was conducted by referring to a registry database of coronary revascularization and valve procedures, which revealed that patients having moderate to severe acute kidney injury after CABG surgery showed worse 5-year survival compared with those who having normal or near-normal renal function.[5] However, not all confounding factors might be stored in the database, which limits the use of the results of such a study. If a promising result is obtained, it should be confirmed by performing a prospective randomized control study.

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Retrospective case–control studies

In the case of rare diseases, standard cohort studies will entail long time periods and high costs for identifying the cause, because of the low incidence rates of the diseases. To overcome this challenge, a case–control study might be useful, in which individuals with the disease (case) are compared with those without the disease (control) and are matched with several demographic factors such as age, sex and place of dwelling. The study will retrospectively investigate the exposure to risks in both groups to identify the cause of the disease.

Prospective cohort studies

In this study design, patient background information is collected at the start of the study or when a subject is newly recruited into the cohort and followed up by collecting information on risk exposures and incidence of morbidity and mortality; thereby, the relationships between the presumptive risk factors and disease are investigated. This type of study (for example, the Framingham study[6,7]) has established cardiovascular risk factors such as hypertension, hyperlipidemia resulting from smoking, age and diabetes mellitus. Although it is the most scientifically accurate design, it is laborious and usually involves extremely high costs.

STUDY DESIGNS USED IN CLINICAL TRIALS

In the past, single-blind prospective trials were conducted. However, due to its limited advantage over open prospective trials, currently this type of trial is conducted rarely.

Double-blind, prospective, placebo-controlled trials

Double-blind, prospective, placebo-controlled trials were the standard type of clinical trials that were considered to provide the most reliable results. Numerous trials have been conducted based on this design; such studies showed the value of antihypertensive therapy[8,9] or the efficacy of statins in the primary or secondary prevention of coronary heart diseases.[10,11] One of the major flaws of this design is that, once the efficacy of a treatment is established, it becomes unethical to conduct a placebo-controlled study; another flaw is that it is relatively difficult to recruit patients into this type of trial. Further, it is also difficult to use this type of trials in the assessment of interventional therapies such as comparison of coronary stents or pacemakers.

Double-blind, prospective trials without placebo control

This design allows the evaluation of a new mode of treatment against an established one. Numerous studies have established the efficacy of treating hypertension[8,9] and hypercholesterolemia[10,11] in the management of cardiovascular diseases, the benefits of employing β-blockers[12–15] or angiotensin-converting enzyme inhibitors[16,17] in the management of congestive heart failure, and so on. Thus, as stated above, it is unethical to avoid using these agents under conditions in which they are proven to be effective; in such cases, this trial design is used. The disadvantage of this design is that, because an already proven treatment is used, the difference between the new one and the established one might be marginal; this usually leads to the requirement of a larger number of patients and longer duration of studies.

PROBE DESIGN

The PROBE study was designated by Dr Hansson in 1992 as an alternative to the double-blind, prospective study design.[4] In this type of study, patients are allocated to different treatment regimens in a strictly random fashion. Unlike double-blind studies, the regimens are made obvious to both physicians and patients. An important aspect is that strictly defined end points are adjudicated by an independent committee that is unaware of the treatment allocation, which guarantees the unbiased comparison of therapies and evaluation of study results.

Table 1 Advantages and disadvantages of the PROBE design compared with double-blinded design

	Double-blinded studies	*PROBE studies*
Randomization	+	+
Cost	–	+
Investigator bias	+	–
Patient compliance	–	+
Reliability of end point evaluation	+	+
Similarity to clinical practice	–	+

The + sign denotes that the design has the property, the minus sign denotes that the design lacks the property.
Modified from Blood Press, 1992; 1: 113–119.

Other conditions that require a PROBE design study include cases in which the drug warfarin is administered.[18–20] Warfarin requires strict titration, and thus cannot be used in a double-blind study. Studies that involve the use of interventional devices are also usually designed in an open-label fashion.

As shown in Table 1, the merits of the PROBE design include better patient acceptance, lower cost, and the existence of similarities between PROBE studies and regular clinical practice.

PRECAUTIONS TO BE TAKEN WITH THE PROBE DESIGN

As described in the Introduction, in Japan, it is generally difficult to conduct a randomized, controlled, double-blind study in which both the doctors and patients are unaware of the medicines being administered. Therefore, realistically, large clinical trials have to be conducted in a PROBE fashion in Japan. If PROBE studies are designed and conducted properly, the results will not be biased. One of the ways to ensure accuracy is to use only 'hard end points' in primary end-point assays. Hard end points are end points that can be defined solely by objective criteria; sudden death of any cause, non-fatal myocardial infarction and non-fatal stroke are examples of hard end points. Soft end points, on the other hand, are end points that may be affected by subjective judgements, such as hospitalization due to unstable angina, congestive heart failure or coronary revascularization procedures. These end points might be defined by objective criteria, but if the attending physician deems the patient requires hospitalization or can be medically controlled in an outpatient setting is, for example, at the discretion of the physician. As shown in Table 2, most cardiovascular clinical trials with PROBE designs conducted in the West[18,19,21–33] use only hard end points. In contrast, four major Japanese PROBE-designed trials with clinical outcomes specified as primary end points used soft end points such as unstable angina, exacerbation of heart failure or coronary revascularization procedures.[34–37] One of the reasons might be that the Japanese tend to have lower incidence rates of cardiovascular diseases compared with the westerners[2] and thus, soft end points are required to produce statistically significant differences with a reasonable cohort size. If these end points are reported and adjudicated in an unbiased fashion, the reliability of the results will be the same as those acquired from double-blind studies. In this context, the results of the JIKEI-Heart Study[35] interested the Japanese Medical Society. One reason was that it was one of the few large clinical studies successfully conducted in Japan. This study was conducted to investigate whether addition of an angiotensin receptor

Table 2 Cardiovascular clinical trials conducted in PROBE fashion and their primary end points

Trial name	*Publication year*	*Comparison*	*Primary end point description*	*Hard end points*						*Soft endpoints*					*Significant difference in the primary endpoint*
				Non-fatal MI	*Non-fatal stroke*	*Fatal MI*	*Fatal stroke*	*Sudden death/ resuscitated cardiac arrest*	*Other cardio-vascular deaths*	*All-cause deaths*	*Worsening angina/ unstable angina*	*Exacer-bation of heart failure*	*Any-cause hospital-ization*	*PCI*	
Western trials															
HOT[n]	1998	Three levels of therapeutic BP targets	Major cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death)	○	○	○	○		○						No
STOP-hypertension-2[b]	1999	BP lowering new vs. old drugs	Fatal stroke, fatal myocardial infarction, sudden death and other cardiovascular deaths			○	○	○	○						No
CAPPP[c]	1999	Captopril vs. conventional drugs	Combination of fatal and nonfatal myocardial infarction and stroke, and other cardiovascular deaths	○	○	○	○		○						No
NORDIL[d]	2000	Diltiazem vs. β-blockers and/or diuretics	Fatal and nonfatal stroke, fatal and non-fatal myocardial infarction and other cardiovascular death	○	○	○	○		○						No
ANBP2[e]	2003	ACE-I vs. diuretics	All fatal events+non-fatal cardiovascular events	○	○	○	○	○	○	○	○	○			Yes
SPORTIF III[f]	2003	Ximelagatran vs. warfarin	All strokes (ischemic and hemorrhagic) and systemic embolic events		○		○								No
INVEST[g]	2003	Ca blocker vs. non-Ca blocker	All cause mortality, nonfatal MI or nonfatal stroke	○	○					○					No
LoWASA[h]	2004	Fixed low dose warfarin+aspirin vs aspirin	Cardiovascular event (cardiovascular death or reinfarction or stroke) and cardiovascular death	○	○				○						No
IDEAL[i]	2005	Statin therapy usual vs. intensive	MACE (nonfatal AMI, coronary death or resuscitated cardiac arrest)	○		○		○							No
CIBIS III[j]	2005	Enalapril → bisoprolol vs bisoprolol → enalapril	Combined end point of mortality (death from any cause) and first all-cause hospitalization							○			○		No
ASCOT-BPLA[k]	2005	CCB/ACE-I vs. β-blocker/ diuretics	Non-fatal MI fatal CHD	○		○									No
MOSES[l]	2005	Eprosartan vs. nitrendipine	Composite of all-cause mortality and the number of cardiovascular and cerebrovascular events including all recurrent events	○	○	○	○			○					No
ACTIVE W[m]	2006	Aspirin+clopidogrel vs. warfarin	First occurrence of stroke, non-CNS systemic embolism, myocardial infarction or vascular death	○	○	○	○		○						Yes*
ESPRIT[n]	2006	Aspirin+dypiridamole vs. aspirin	Combined event of 'death from all vascular causes', non-fatal stroke, non-fatal myocardial infarction or major bleeding complication	○	○	○	○		○						Yes
BAFTA[o]	2007	Adjusted dose warfarin vs. aspirin	Incidence of fatal or non-fatal disabling stroke (ischemic or hemorrhagic), intra-cranial hemorrhage or significant arterial embolism		○		○								Yes
Japanese trials															
MEGA[p]	2006	diet vs. diet+pravastatin		○		○		○						○	Yes

Table 2 Continued

Trial name	Publication year	Comparison	Primary end point description	Hard end points: Non-fatal MI	Non-fatal stroke	Fatal MI	Fatal stroke	Sudden death/ resuscitated cardiac arrest	Other cardio-vascular deaths	All-cause deaths	Soft endpoints: Worsening angina/ unstable angina	Exacer-bation of heart failure	Any-cause hospital-ization	PCI	Significant difference in the primary endpoint
			Fatal or nonfatal myocardial infarction, sudden cardiac death, development of unstable angina and coronary revascularization procedures, either coronary artery bypass grafting or percutaneous coronary intervention	○	○	○	○								
JIKEI-HEART[a]	2007	Valsartan vs. non-ARB	Stroke, new or recurrent transient ischemic attack, new or recurrent acute myocardial infarction, new occurrence or exacerbation of heart failure, new occurrence or exacerbation of angina pectoris, dissecting aneurysm of the aorta, lower limb arterial obstruction, transition to dialysis, doubling of plasma Cr levels	○	○	○	○				○	○			Yes
JELIS[r]	2007	EPA+statin vs. statin	Sudden cardiac death, fatal and nonfatal MI, unstable angina pectoris including hospitalization for documented ischemic episodes, and events of angioplasty/stenting or CABG	○		○		○			○			○	Yes
CASE-J[s]	2008	Candesartan vs. amlodipine	Sudden death, new occurrence or recurrence of stroke or TIA, new occurrence, aggravation or recurrence of heart failure, angina pectoris or acute myocardial infarction, renal dysfunction, new occurrence or aggravation of dissecting aneurysm of aorta, arteriosclerotic occlusion of peripheral artery	○	○	○	○	○				○	○		No

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium blocker; CNS, central nervous system; EPA, eicosapentaenoic acid; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous intervention; PROBE, prospective randomized open-label blinded end-point.
[a]Hypertension Optimal Treatment Study.[21]
[b]Study in Total Hip Patients with Hypertension-2 Study.[22]
[c]Captopril Prevention Project.[23]
[d]Nordic Diltiazem Study.[24]
[e]Australian National Blood Pressure Study 2.[25]
[f]Stroke Prevention using an ORal Thrombin Inhibitor in patients with atrial Fibrillation III Study.[18]
[g]International Verapamil-Trandolapril Study.[26]
[h]Low-dose Warfarin and Aspirin Study.[27]
[i]Impact of Cholesterol Reduction Through Aggressive Lipid Lowering Study.[28]
[j]Cardiac Insufficiency Bisoprolol Study III.[29]
[k]Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm.[30]
[l]Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention Study.[31]
[m]Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events.
[n]European/Australian Stroke Prevention in Reversible Ischaemia Trial.[32]
[o]Birmingham Atrial Fibrillation Treatment of the Aged Study.[33]
[p]Management of Elevated Cholesterol in the Primary Prevention Group of the Adult Japanese Study.[33]
[q]ibid.
[r]Japan EPA Lipid Intervention Study.[36]
[s]Candesartan Antihypertensive Survival Evaluation in Japan.[37]
[a]The result was significantly in favor of warfarin.

Table 3 The number of end points in JIKEI HEART Study

	Number of events valsartan group (%)	Number of events non-ARB treatment group (%)	P-value
Primary end point			
Composite end point of stroke, new or recurrent transient ischemic attack, new or recurrent acute myocardial infarction, new occurrence or exacerbation of heart failure, new occurrence or exacerbation of angina pectoris, dissecting aneurysm of the aorta, lower limb arterial obstruction, transition to dialysis, doubling of plasma Cr levels	92 (6.0)	149 (9.7)	0.0002
Secondary end points			
Stroke or transient ischemic attack	29 (1.9)	48 (3.1)	0.0280
New or recurrent acute myocardial infarction	17 (1.1)	19 (1.2)	0.7545
New occurrence or exacerbation of angina pectoris needing hospitalization[a]	19 (1.2)	53 (3.4)	0.0001
New occurrence or exacerbation of heart failure needing hospitalization[a]	19 (1.2)	36 (2.3)	0.0293
Dissecting aneurysm of the aorta	2 (0.1)	10 (0.6)	0.0340
Transition to dialysis, doubling of serum creatinine levels	7 (0.5)	8 (0.5)	0.8966
All-cause mortality	28 (1.8)	27 (1.8)	0.7537
Cardiovascular mortality	9 (0.6)	9 (0.6)	0.9545

[a]End points that are considered to be 'soft end points'.
Modified from *Lancet*. 2007 April 28; **369** (9571):1431–1439.

blocker (valsartan) to conventional treatment was effective in reducing cardiovascular events in Japanese patients with cardiovascular disease. Although the successful lowering of blood pressure was similar in both the valsartan and non-valsartan groups, it was shown that the addition of valsartan to conventional treatment prevented more cardiovascular events than conventional treatment. This superiority of valsartan to other blood pressure-lowering agents, which goes beyond its blood pressure-lowering effect, has not been shown in other clinical trials conducted in a double-blind fashion;[38,39] this is one of the other reasons that the results of this trial interested many individuals. When examined in greater detail, it is obvious that the differences in the number of soft end points are the factors that mainly contributed to the favorable results for valsartan in this study (Table 3). The primary end point of this study is a composite of several pre-specified events, and its components are not clearly shown. However, the number of each component is shown as secondary end points, which is a good indication of the composition of the primary end point. In fact, hard end points such as myocardial infarction or cardiovascular mortality did not differ significantly between the two groups. As is questioned in the editorial that accompanied the article,[40] it cannot be totally ruled out that there might have been underreporting of events in the valsartan group. It is also of great interest that although most studies conducted in the West produced no significant difference as regards the primary end point, results of three of the four studies conducted in Japan were significantly in favor of the study drug, the manufacturer of which was the sponsor (Table 2). These could be considered as examples showing that the results of PROBE-designed trials should be evaluated carefully, especially in cases wherein the results with soft end points are widely discrepant from those with hard end points.

CONCLUSION

Epidemiological studies conducted in prospective cohort design have established cardiovascular risk factors such as hypertension, hyperlipidemia, smoking and age. By applying the ideas and methodologies developed in epidemiological studies, many clinical trials have been conducted to prove the benefits of various medicines.

Randomized, controlled, double-blind clinical trials report the most scientifically accurate results. However, they usually entail high costs, render the recruitment of patients more difficult and are rather discrepant from usual clinical care. The PROBE study design is a feasible alternative to double-blind studies. However, if not designed and conducted properly, it will be more susceptible to biases. Thus, studies conducted with a PROBE design using soft end points included in the primary end point require the participating physicians to adhere to the guidelines for PROBE studies more strictly.

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EDITORIAL

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Eicosapentaenoic Acid (EPA) in Reducing Secondary Cardiovascular Events in Hypercholesterolemic Japanese Patients

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Epidemiological studies have shown that the disease pattern of the population of Inuit is quite different from that of the population of Denmark[1,2] The most evident difference is found in the incidence of coronary heart disease: compared with the Western population, Greenland Eskimos are less than one-tenth as likely to experience acute myocardial infarction[1] One study showed that the 2 populations exhibit different fatty acid composition of the plasma lipids[3] the most notable difference being the significantly higher levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid observed in Greenland Eskimos compared with both Eskimos living in Denmark and the Danes. These 2 fatty acids are mainly of fish oil origin. Similarly, Japanese are also known to have a lower rate of mortality from cardiovascular disease than Westerners in industrialized countries[4] and the Japanese, like Eskimos, are known to consume large amounts of fish. This has led to the hypothesis that a higher rate of fish oil consumption results in a higher concentration of n-3 polyunsaturated fatty acids (PUFA) in the plasma lipids, which in turn results in a lower rate of cardiovascular disease.

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This hypothesis has led to several studies investigating whether an increase in fatty fish consumption or the administration of n-3 PUFA can actually decrease the rate of cardiovascular disease;[5,6] these studies have shown that both methods of intake decrease the mortality rate of patients who have suffered myocardial infarction.

These studies, however, were conducted in Western countries, where fish consumption levels are not as high as in Japan. To determine whether their results were also applicable to the Japanese population, a study, which was named JELIS, was conducted to investigate whether EPA, 1 of the n-3 PUFAs found in fish oil, was effective in reducing the incidence of cardiovascular events in hyperlipidemic Japanese patients? JELIS showed that EPA provides an additional benefit beyond that provided by statin treatment in reducing major coronary events.

A subsequent paper published in this Journal by Matsuzaki et al analyzes in detail a subpopulation of JELIS, all of whom had established coronary heart disease[8] This study shows that the administration of EPA to Japanese with hyperlipidemia and established coronary heart disease decreases the incidence of secondary major cardiovascular events, even though Japanese already consume large amounts of fish, a tendency which might have been expected to diminish the effect of the additional administration of EPA. It also shows that EPA confers its benefits to patients with various backgrounds, including those with prior myocardial infarction or prior coronary intervention, without significantly changing low-density lipoprotein-cholesterol (LDL-C) levels, as indicated by the similarity in LDL-C levels of the control group and the EPA group. The authors conclude that, even in a population that already consumes a large amount of fish, EPA is effective in reducing the incidence of secondary cardiovascular events, and it should be considered as an addition to conventional treatment.

However, there are several points to be made concerning this study. For one thing, when this study was conducted, cholesterol management was not as vigorous as it is today. The LDL-C level achieved in this study was 130 mg/dl, in both the control group and the EPA group, and while this may have been acceptable at the time, the Japan Atherosclerosis Society guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese published in 2007 states that persons with established coronary heart disease should lower their serum LDL-C level to less than 100 mg/dl[9] Further investigation may be necessary to determine whether EPA confers additional benefit in preventing secondary cardiovascular events in the context of modern dyslipidemia management. In addition, the insufficient use of antiplatelet/anticoagulant agents might have affected the results of this study. It is possible that the investigators used these agents less often than is typical for fear of inducing a high rate of adverse bleeding events, because EPA itself has been shown to have antiplatelet properties[10] It has been reported, however, that of 148 n-3 PUFA studies that reported on adverse events, only 1, in which an unusually high dose of 6 g/day of n-3 PUFA was administered, reported an increased incidence of bleeding![11] Moreover, the AHA/ACC guidelines for secondary prevention for patients with coronary and other forms of atherosclerotic vascular disease state that all patients with established coronary heart disease should be administered aspirin unless contraindicated![12] The Japanese Circulation Society guidelines for

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management of anticoagulant and antiplatelet therapy in cardiovascular disease also state that all patients in the chronic phase of ischemic heart disease should be administered low doses of aspirin unless contraindicated. A large-scale observational study, which reported on Japanese patients with coronary artery disease diagnosed with coronary angiography, showed that approximately 87% were given antithrombotics[13] indicating that most physicians are conforming to the published guidelines. Thus another study may be necessary to demonstrate that EPA confers additional benefit in reducing secondary cardiovascular events beyond that conferred by the application of the strategies recommended in today's guidelines.

Another point to consider is the fact that, while this study was conducted in a PROBE (prospective randomized open-label blinded-endpoint) fashion, softer endpoints, such as unstable angina pectoris, angioplasty and stenting, were included in the primary endpoint. As we have observed previously[14] all major recently-published Japanese cardiovascular clinical trials have adopted the PROBE design and yet have included soft endpoints in their primary endpoints. Although adopting the PROBE design makes it easier to recruit more patients into a trial, the inclusion of soft endpoints may hamper the scientific rigor of the study. It would have been better to conduct the study either in a blinded fashion with soft endpoints or in an open-labeled fashion without soft endpoints, although, considering the low incidence of cardiovascular events among the Japanese, even among established coronary heart disease patients, as demonstrated by the study under discussion[8] it may not be realistic to conduct such a study either way.

The study conducted by Matsuzaki et al[8] provides us with the important information that EPA may be effective in reducing cardiovascular events in Japanese patients with established coronary heart disease. However, considering the rapid rate of change in clinical practice not all of its results may be directly applicable to the contemporary practice of cardiology in Japan. Further studies incorporating recent clinical changes, such as stricter LDL-C management and aggressive use of antiplatelet agents, may be necessary to corroborate its results.

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原 著

小児がん患者が退院後に抱える心理社会的問題に関する研究の現状と課題

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要 旨

本研究では，退院後の小児がん患者が抱える心理社会的問題の特徴を明らかにするために，系統的な文献研究を行った．Pub Med，PsychINFO，Web of Science で検索し，21本の文献を分析の対象とした．その結果，社会的機能，情動，行動，身体的健康，個人内に関する問題が検討されており，小児がん患者と健常児との比較では一貫した結果が得られていないことが示された．今後は，患児の特徴や適応に至るまでのプロセスを考慮して検討していく必要がある．

Key Words: 小児がん；心理社会的問題；系統的レビュー

I 背 景

小児がんは，治療成績が向上する一方で，がんの罹患やその治療の影響が長期的に患者の生活面や心理面に及ぶことが指摘されている[1)]．小児がん患者が経験しうる心理社会的問題に関して，これまでに複数のレビュー論文[2-8)]が出されているが，概ね日常生活に問題はないという指摘と，何らかの問題を抱えているという指摘とがあり，一貫した結果が得られていない．これらの背景として，先行研究における次のような問題点を指摘することができる．第1に，患者の属性（年齢や性別，がん種など患者の特徴）の問題である．これまでの研究では，対象となる患児のがん種，診断時の年齢や治療経過年数などが研究によって様々であり，これらの違いが患者に与える影響が十分に検討されていない．第2に，調査方法の問題である．尺度を用いた調査，コホート調査，質的調査など様々な測定方法が用いられており，結果を厳密に比較することが難しい．第3に，健常者との比較である．小児がん患者の状態像を把握するための健常者との比較を行っていない研究も少なくない．この他に，評価者の違いも考慮する必要がある．患者の状態について，患者本人による評価ではなく，教師や両親，医療者など他者評価によって検討している研究が複数みられる．小児がん患者は，退院後に学校や家庭，病院など様々な環境におかれるため，多角的な視点から患者の状態像を把握することは重要である．しかし，親や教師，医療者から見た子どもの問題と，子ども自身が感じている問題には差異があることから[9)]，評価者によって結果が異なってしまうと考えられる．

そこで上述した問題点を踏まえた系統的なレビューを行い，①小児がん患者の属性によって，直面する心理社会的問題にどのような違いが見られるのか，②退院後の小児がん患者が日常生活を送る上で直面する心理社会的問題としてどのような

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ことが取り上げられ，どのように調査されているのか，③健常な人と比較してどのような違いが見られるのかを整理し，退院後の小児がん患者が日常生活を送る上で直面する心理社会的問題を明らかにすることを目的とした．本研究を計画した．なお，患者が感じている問題を把握するために，本研究では患者本人を対象とした論文のみを分析対象とした．

Ⅱ 方 法

1．対象文献の選定

今回，系統的レビューを行う対象となる文献を次のように選定した．文献検索エンジンとしてPub Med, PsychINFO, Web of Scienceを使用し，cancer, children, adolescents, worry, concern, problem, difficulties, adjustment, outpatient, survivorのキーワードのいずれかに該当し，学術誌上で発表された過去10年の論文を検索した．その結果，130本の文献が検索された．これらの論文のアブストラクトを2人の研究者がレビューし，各論文が本研究の趣旨に合致するか否かを検討した．まず，介入研究や論説，医学的数値のみに言及した文献など，小児がん患者の心理社会的問題の調査と明らかに目的の異なる63本の文献が除外された．次に小児がん以外の疾患を含む，あるいはがん種や経過年数など小児がんに関する対象者の詳細な情報が記載されていないなど，対象症例が不適切な23本の文献が除外された．さらに，小児がん患者本人を対象としていない15本の文献，小児がん患者を健常対象者と比較していない8本の文献が除外された．最終的に本研究の対象として21本の文献が選定された（Table 1）．

2．対象文献の分類

対象となった21本の文献で検討されている心理社会的問題を，内容の類似性に基づいて2人の研究者がカテゴリーに分類し，カテゴリー毎に結果を検討した．

Ⅲ 結 果

1．対象文献の概要

抽出された21本の文献で検討された心理社会的問題は，5つのカテゴリーに分類された（Table 2）．具体的には，①社会生活への適応，既婚率や出産率，教育水準，就職率，他者との関係など“社会的機能の問題”，②抑うつ，不安，気分など“情動の問題”，③身体の不調，メンタルヘルス（心身の健康）やPTSR（外傷後ストレス反応）など“身体的健康の問題”，④自尊感情や自己認識など“個人内の認識の問題”，⑤問題行動やコーピングレパートリー（問題解決の方法）など“行動の問題”である．

2．患者の属性による差異

大半の研究においてがん種や治療内容は限定されておらず，調査時の年齢や診断時の年齢も幅広いことが明らかになった．

患者の属性に関してRitchie[23]は，12歳から17歳までの患者を対象に質問紙調査を行い，診断時の年齢が患者の適応と関連する可能性を指摘している．Calaminusら[10]は複数のがん種の患者を対象に質問紙調査を行い，晩期障害が深刻なほど適応が悪いことを指摘している．その他治療内容[20]や副作用[19,30]と心理的適応状態との関連も示唆されている．また脳腫瘍9,11,21），急性リンパ性白血病やウイルムス腫瘍[14,17]の患者が限定的に検討され，これらのがん種の患者は適応が悪い傾向にあることが示された．

3．調査方法の特徴

研究方法に関しては，QOLや気分状態を測定する尺度を用いた量的研究や，学業や結婚の程度・有無を尋ねて集計，比較した量的記述研究が多く見られた．例えばMeeskeら[19]は，Pediatric Quality of Life Inventory[30]を用いて複数のがん種の患者を対象にQOLを測定し，健常者のQOLと比較した．その結果，両者の間に有意な差は見られなかったが，倦怠感や深刻な晩期障害のある患者はそうでない患者よりもQOLが低いことが示された．Dolginら[12]は複数のがん種の患者と健常者に対して半構造化面接（対象者が自由に語る形式をとりながら，同時にこちらの設定した諸項目について聞き取る緩やかな枠組みを持った面接形態）を実施し，教育水準や雇用状態，健康状態などを聴取した．その結果，両者の

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表1 退院後の小児がん患者が抱える心理社会的問題に関する文献一覧

	文献	対象者（N）		平均年齢（歳）		がん種	治療方法	調査方法
		患者群	健常群	調査時	診断時			
10)	Calaminus et al（2007）	36	319	8-18	記載なし	複数	記載なし	質問紙調査（Peds-QL）
11)	Carpentieri et al（2003）	32	Norms	14.6	8.8	脳腫瘍	放射線療法 外科手術 化学療法	質問紙調査（BASC）
12)	Dolgin et al（1999）	64	51	23.5±4.1	11.5±4.7	複数	記載なし	半構造化面接調査（教育水準，雇用状態，軍事サービス，社会的地位，健康状態），質問紙調査（MHI）
13)	Gerhardt et al（2007）	56	60	18.7±0.8	診断時からの年数：7.3±2.2年	複数	記載なし	質問紙調査（SPPA, Status questionnaire）
14)	Hill et al（2003）	102	102	25.9±3.3	4.9±3.5	急性リンパ性白血病 ウイルムス腫瘍	記載なし	面接調査（対人関係，社会的役割，両親との関係）
15)	Koch et al（2006）	1597	43905	1965-1980年生まれの人対象	0-19	複数	記載なし	量的記述調査（社会経済状態）
16)	Langeveld et al（2003）	500	1092	24±5.1	8±4.7	複数	化学療法 放射線療法 外科手術	量的記述調査（教育水準，雇用状態，生活状況，結婚・子どもの有無）
17)	Mackie et al（2000）	102	102	25.6	5.9	急性リンパ性白血病 ウイルムス腫瘍	化学療法 放射線療法	構造化面接調査（SADS-L, DSM-Ⅲ-R, APFA, Raven's standard progressive matricesを用い精神疾患の既往，対人関係，社会的役割に対する貢献度，社会的機能，認知機能を測定）
18)	Meeske et al（2007）	86	105	13.3±2.9	4.0±2.6	複数	化学療法 外科手術 放射線療法	質問紙調査（Peds-QL）
19)	Mulrooney et al（2008）	272	3899	28	7	急性骨髄性白血病	化学療法 放射線療法	量的記述調査（婚姻状況，教育水準，雇用状況，健康保険の加入状況）
20)	Pedreira et al（2006）	18	18	21.2±6.7	8.1±3.7	頭蓋咽頭腫	放射線療法 外科手術	質問紙調査（AGHDA, PGWB）
21)	Reiter-Purtill et al（2003）	69	77	13.48±2.53	診断時からの年数：3.32±0.98年	複数	化学療法 外科手術 放射線療法	質問紙調査（RCP）
22)	Ritchie（2001）	45	Norms	記載なし	14.2±1.5	複数	記載なし	質問紙調査（SEI, HSA）
23)	Robinson et al（2009）	55	60	18.6±0.8	診断時からの年数：7.4±2.4年	複数	記載なし	質問紙調査（CDI, BDI, POMS）
24)	Schwartz & Drotar（2006）	57	83	21.70±2.65	11.35±3.91	複数	化学療法 外科手術 放射線療法	質問紙調査（PCL-C, SF-36, The brief mood rating scale, CES-D, SWLS）
25)	Seitzman et al（2004）	578	396	18歳以上	診断時からの年数：2年以上	急性リンパ性白血病	化学療法	量的記述調査（学業，結婚，出産，就職，健康などの状態を尋ねる） 質問紙調査（Harter ASPP, POMS）
26)	Servitzoglou et al（2008）	103	135	19.8	8.8	複数	記載なし	質問紙調査（SF-36, STAI, BCSEI, the Lazarus and Folkman Ways of Coping, QoLQ）
27)	Shaw et al（2004）	2152	2462	18.9±6.8	7.3±6.0	複数	化学療法 外科手術 放射線療法	量的記述調査（婚姻状況，教育水準，雇用状況，収入）
28)	Stam et al（2006）	353	507	24.3±4.0	7.3±4.7	複数	化学療法 外科手術 放射線療法	質問紙調査（RAND-36, CCSS）
9)	van Dijk et al（2009）	148	Norms	20.8±8.1	1.7±1.8	網膜芽細胞腫	外科手術 放射線療法	質問紙調査（YSR, ASR）
29)	Zebrack et al（2007）	2778	2925	27.1±6.0	記載なし	固形腫瘍	放射線療法 化学療法	質問紙調査（BSI）

Peds-QL: Pediatric Quality of Life Inventory **BASC:** Behavioral Assessment System for Children **MHI:** Mental Health Inventory **SPPA:** Self-Perception Profile for Adolescents **SADS-L:** Schedule for affective disorder and schizophrenia lifetime **DSM-Ⅲ-R:** Diagnostic and Statistical Manual for Mental Disorders,version Ⅲ,revised **AGHDA:** Adult GH-Deficient Assessment **PGWB:** Psychological General Well-Being **RCP:** Revised Class Play **SEI:** Self-Esteem Inventory **HSA:** Hopefulness Scale for Adolescents **CDI:** Children's Depression Inventory **BDI:** Beck's Depression Inventory **POMS:** Profile of Mood States **PCL-C:** The Posttraumatic Stress Disorder Checklist-Civilian Version **SF-36:** The 36-item Short-form Health Survey **CES-D:** The Center for Epidemiological Studies Depression Scale **SWLS:** The Satisfaction with Life Scale **Harter ASPP:** Harter Adult self-perception profile **STAI:** The State-Trait Anxiety Inventory **BCSEI:** The Battle Culture-free Self-esteem Inventory **QoLQ:** Quality of Life Questionnaire **RAND-36:** Rand 36 Health Survey Questionnaire **CCSS:** the Cognitive Control Strategies Scale **YSR:** Youth Self-report **ASR:** Adult Self-report **BSI:** Brief Symptom Inventory-18

NII-Electronic Library Service

表2　1999-2009年に出されたがん患者と健常者を比較した研究の結果

カテゴリー		結果		
		＋	±	－
社会機能の問題	社会生活	10)	15), 18), 21), 26), 28), 29)	20), 26), 28)
	婚姻，出産状況		27)	16), 19), 25)
	教育水準	10)	11), 12), 18), 29)	16), 19), 27)
	雇用状態		12), 17), 19), 27)	16), 25)
	他者との関係	10)	11), 18)	14), 17)
情動の問題	抗うつ	10), 23)	11), 28), 24)	29)
	不安		11)	26), 29)
	気分状態	23), 24)	28), 29)	20)
健康の問題	心身の問題	10)	24), 29)	12), 28), 9), 29)
	メンタルヘルス，PTSR		26), 28)	24)
個人内の問題	自尊感情		11), 22)	26)
	自己認識		12), 25)	
行動の問題	問題行動	9)	21)	
	向社会行動	21)		
	コーピングレパートリー	26)		14), 17), 26)

（＋）：健常群と比較してがん患者群の方が良好な状態，望ましい状態である．（±）：健常群とがん患者群の間に明らかな差が見られない状態である．（－）：健常群と比較してがん患者群の方が劣悪な状態，望ましくない状態である．

間に有意な差は見られなかったが，対象患者の診断時および治療時の年齢の幅が広く，これらを考慮した検討をすべきだと指摘した．

4．健常者との比較

全体を概観すると，小児がん患者の方が健常者よりも結果が良いとする研究は少数であった[10,24]．健常者と有意な差がみられないとする研究と，健常者よりも結果が良くないとする研究がほぼ同数あり，一貫した結果が得られていないことが明らかになった（Table 2）．しかし，“婚姻，出産状況”や“身体の不調”に関しては，健常者よりも結果が良くないとする研究が多く，病気や治療による副作用や晩期障害が患者の身体状況や婚姻，出産に悪い影響を及ぼしていることが示唆された．

Ⅳ　考　察

今回複数の論文をレビューすることにより，小児がん患者が退院後に直面する心理社会的問題として，社会的機能，情動，身体的健康，個人内の認識，行動の問題などが検討されており，小児がん患者が健常児と同等の状態であるという結論を導き出している論文も多く見られることが示された．これらの研究結果だけをみると，小児がん患者は一見心理社会的問題に直面していないかのように見受けられる．しかしこれらの研究のほとんどが，進学率や雇用率，既婚率など客観的な結果のみで検討した量的記述的研究であり，結果に至るプロセスが十分に反映されていないことが問題である．すなわち，進学や就職，婚姻状況が健常者と同程度であっても，そこに至るまでのプロセスが健常者と同様であるとは限らない．全般的な適応状態が良くても，より細かな，特定の領域において，小児がん患者は明らかに心理社会的問題を抱えていることが指摘されている[5,31]ため，小児がん患者がどのような困難に直面し，乗り越えてきたのかを考慮する必要があるだろう．また，治療内容，副作用や晩期障害，発症年齢などについても考慮する必要がある．これらの点を考慮して研究を行うことにより，小児がん患者の抱える心理社会的問題を，より明らかにすることができると考える．治療の副作用による抜毛や体型の変化，さまざまな晩期障害は，患者にとって，短期的および長期的に大きなストレスになりうる[32]．

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また，受験期や単位制である高校時代に入院や外来治療で学校を休むことは，その後の患者の進路に大きな影響を及ぼしかねない．したがって今後は，患者の受けた治療，それによる副作用や晩期障害，患者の　ライフステージを考慮した研究，支援を行う必要があるだろう．

小児がんの治癒率の向上に伴い，治療終了後に長期生存する患者が増加しつつある．これらの患者に対しては医学的問題に対するサポート以外に，心理的，社会的な問題に対しても長期にわたるサポートが必要である．そのために，小児がん治療終了後に患者が直面する様々な問題点に対して，今後さらなる研究，臨床実践を行っていくことが重要である．

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Psychosocial problems in survivors of childhood cancer: Systematic Review

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The purpose of this study is to report the results of a systematic review to determine the psychosocial problems associated with childhood cancer. Searches were conducted using Pub Med, PsychINFO, and the Web of Science and twenty-one studies were identified. They were considered to be related to: social functioning, emotional, behavioral, intrapersonal and mental health problems. Furthermore, a majority of the results indicated that survivors didn't differ from comparison groups. We should consider the types of children and how they adjust to daily life.

Key Words: childhood cancer, psychosocial problems, systematic review

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臨床精神医学　38 (9) : 1359 − 1372, 2009

植込み型除細動器（ICD）患者の抑うつおよび不安に対する精神科的支援の現状と展望

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抄録：植込み型除細動器（ICD）は，致死性不整脈による心臓突然死を予防する機器として発展している。しかし，ICD患者は，ショック作動などの特異的な経験により心理社会的問題を抱えているとされている。そこで本研究においては，ICDにおけるショック作動が抑うつや不安などの精神症状に及ぼす影響についての観察研究，およびICD患者に対する心理社会的介入研究について検討し，ICD患者の精神科的支援の現状と展望について論じることを目的とする。方法としては，観察研究および介入研究を収集したうえで，適格基準に当てはまる論文を選定した。その後，それらの研究の特徴を抽出し，介入研究に関してはメタ分析を行い，効能の検討を行った。その結果，まず観察研究においては，ショック作動と抑うつや不安などの精神症状との関連について一致した結論は得られなかった。また，介入研究においてもメタ分析の結果，効能は認められなかった。今後の研究への展望として，まず観察研究では，ショック作動と精神症状の関連に関与する交絡変数を考慮したうえで，知見を重ねる必要がある。また，介入研究では，研究の質を高めて効能を検討し直す必要があり，今後は精神症状を呈した患者に対するターゲット・アプローチの開発も期待される。

臨床精神医学38：1359～1372

Key words：植込み型除細動器（implantable cardioverter defibrillator），心理社会的介入（psycho-social intervention），抑うつ（depression），不安（anxiety），作動（shock）

（2009年8月29日受理）

1 はじめに

心臓突然死の原因となる心室細動や心室頻拍などの致死性不整脈の治療法として，植込み型除細動器（Implantable Cardioverter Defibrillators；以下ICDと略記）が1980年に米国で初めて使用された。ICDはペースメーカーに電気ショックの機能を加えた機器であり，重篤な不整脈が発生した際に電気ショックが流れることにより突然死を防ぐものである。メタ分析の結果から，ICD植込みは，抗不整脈薬の使用と比較して，不整脈による突然

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Psychiatric supports for depression and anxiety of patients with an implantable cardioverter defibrillators; A review and future recommendations
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死を50％低減させることが明らかとなっている（HR 0.50, 95％ CI 0.37～0.67）[9)]。また本邦においても，ICD植込みに関する研究が積極的に進められ，1996年には保険償還がなされた。近年では，手術の簡便化や機器の軽量化がなされたこともあり，ICDの症例数も，90年代までは500件以内にとどまっていたのに対し，2005年には3,000件にまで増加している[29)]。さらにICDは，心不全や拡張型心筋症，また心筋梗塞後の患者に対して致死性不整脈の一次予防としての適用の有効性も示されている[30)]。

以上のように，ICD植込みは患者にとって生命予後の改善という恩恵があるが，その一方でICDのショック作動は胸痛や衝撃，恐れなどを招くため[16)]，ICD患者の心理社会的問題に焦点が当てられるようになってきている[5,35,40)]。そこで本稿では，ICDのショック作動と抑うつや不安との関連を検討した観察研究，およびICD患者の呈する抑うつと不安に対する介入研究を展望し，今後のICD患者に対する有益な精神科的支援のあり方について考察することを目的とする。

2 観察研究

ICD患者のうち24～46％が抑うつ症状，24～87％は不安症状を呈していることが，系統的展望により示されている[37)]。このような精神症状を呈する一因として，特にICDショックの作動経験があると考えられている。ICD患者に対してその特徴を横断的に検討した研究では，約半数が致死性の不整脈が発生した際のショック作動を経験しており，このようなショック作動は，胸痛や強い衝撃を伴い，患者に恐怖心を与えるものであると報告されている[16,20)]。また，24時間以内に3回以上の作動を起こす頻回作動（storm）を経験した患者は，植込み後の2年間に10％存在していることが示されており，これらの頻回作動が抑うつや不安に影響を及ぼすとの知見も得られている[11,28)]。そこで本節では，ICD患者におけるショック作動と抑うつや不安との関連についての研究を展望し，今後の研究の課題を考察する。

1. 方法

1）文献収集

1980年1月～2009年4月までに行われた，ICD患者におけるショック作動と抑うつおよび不安の関連について検討している研究を，文献データベースとしてMEDLINEとPsycINFOを用いて検索した。

2）適格基準

適格基準として，以下の5つの基準を採用した：(1)調査対象は，ICD患者である，(2)ショック作動経験の有無による群分けを行って分析をしている，(3)目的変数として抑うつまたは不安を測定している，(4)出版されている論文である，(5)英語の論文である。

3）情報の抽出

著者の2人（K.I., Y.O.）が，適格基準に合致している文献を収集し，おのおのの文献から，下記の情報を抽出した：(1)研究法，(2)適格基準，(3)標本サイズ，(4)評価項目，(5)群ごとの抑うつまたは不安に関する指標の差異。

2. ICD患者の抑うつ症状

上記の手続きの結果，ICD患者におけるショック作動と抑うつの関連について検討した研究は5編であり（表1），そのうち2編において，群間で得点差がみられた。Jacqら（2009）[21)]は，作動を経験していない患者と比較して，作動を経験している患者で有意に抑うつ得点が高いことを示している。また，Prudenteら（2006）[34)]は，実際には作動が起きていないが，作動が起きていると患者が思い込んでいる「疑似作動」に注目し，疑似作動を経験している患者は，本当の作動を経験している患者および作動を経験していない患者と比較して，有意に抑うつ得点が高いことを示している。

3. ICD患者の不安症状

上記の手続きの結果，ICDのショック作動と不安に関する検討を行った観察研究は6編であり（表1），そのうち4編において，群間で得点差がみられていた。Prudenteら（2006）[34)]は，不安と同様に，疑似作動を経験している患者は，本当の作動を経験している患者および作動を経験していない患者と比較して，有意に不安得点が高いことを示している。一方，Bilgeら（2006）[2)]とJacqら

(2009)[21]は，作動を経験していない患者と比較して，作動を経験している患者で有意に不安得点が高いことを示している。また，Van den Broekら(2008)[41]は，縦断的な調査を行い，植込み後2カ月後に作動を経験している患者は，作動を経験していない患者と比較して，植込み時から2カ月後までの不安得点が有意に上昇していることを示している。

4. ICD患者の抑うつおよび不安に関する今後の研究への展望

観察研究においては，ICDのショック作動と抑うつや不安との関連について一致した結論は得られていない。有意差がみられなかった研究では，限界点として，作動経験の有無を自己報告により測定しているためバイアスが生じる可能性が指摘されている[32]。さらに，今回検討した先行研究では，作動経験からの期間を測定しているものは，1編のみであった[2]。そのため，作動経験からの期間の影響について交絡している可能性も考えられる。

Searsら(1999)[37]の系統的展望によると，ICD患者においては，死への恐れ，作動への恐れ，デバイスに対する依存心が抑うつや不安の症状を上昇させることが示されている。また，作動と破局的認知(たとえば，「次に作動が起きたら死んでしまうのではないか」といった認知[31])や抑うつ的な対処行動[17]との関連も示されている。これらのことから，今後研究を進めていくうえで，さまざまな交絡変数の存在を考慮に入れ，作動と抑うつや不安との関連を検討する必要があるといえる。

先行研究では，ショック作動が抑うつと関連することを検討する研究ばかりでなく，逆の因果として，重篤な抑うつ症状がショック作動を引き起こすとの知見が得られている。Whangら(2005)[44]は，ICD患者を対象に，ショック作動の予測因子を検討した結果，重篤な抑うつ症状が心室細動や心室頻拍の予測因子となることを示している。また，その他のネガティブな感情に関しても，不整脈発作を引き起こすことが示されている[13,20]。したがって，ICD患者の抑うつ症状を予防・管理していくことは疾病管理においても重要な課題であるといえる。今後は先に述べた問題点を考慮したうえで，観察研究による知見がさらに積み重ねられることで，精神症状による作動の誘発を軽減し，作動の悪循環を断ち切ることが期待できる。

3 介入研究

近年，ICD患者が呈する精神症状に対する無作為化比較試験も蓄積されつつある。本節では，メタ分析により精神症状に対する介入法の効能の程度を検討することを目的とする。

1. 方法

1)文献収集

Pedersenら(2007)[33]は，文献データベースとしてMEDLINEとPsycINFOを用いて，1980年1月～2007年4月までに行われた，ICD患者への心理社会的介入法の効能を検討している研究を系統的に収集している。本研究では，Pedersenら(2007)[33]が収集した9編のうち，評価項目として抑うつまたは不安を測定し，研究法が無作為化比較試験である5編を分析対象とした。さらに，2009年6月時点までに出版された，ICD患者への抑うつまたは不安への介入法の効能を，無作為化比較試験により検討している研究を，文献データベースとしてMEDLINEとSocial Science Citation Indexを用いて検索した。

2)適格基準

適格基準として，以下の5つの基準を採用した：(1)調査対象は，ICD患者である，(2)研究法は無作為化比較試験(クラスター無作為化試験を含む)である，(3)評価項目として抑うつまたは不安を測定している，(4)出版されている論文である，(5)英語の論文である。

3)情報の抽出

著者の2人(K.I., Y.O.)が，適格基準に合致している文献を収集し，おのおのの文献から，下記の情報を抽出した：(1)国，(2)調査対象，(3)標本サイズ，(4)最終追跡症例数，(5)適格基準，(6)介入内容，(7)介入の実施者，(8)介入期間，(9)介入時期，(10)介入頻度，(11)対照群の設定，(12)研究終了時の群ごとの抑うつまたは不安に関する指標の値，(13)評価時点，(14)研究の質にかかわる情報。

表1 ICD患者の作動と抑うつおよび不安の関連

研究	研究法	適格基準
Pauli et al (2001)[32]	横断研究	収集基準：ICD患者のうち，60歳未満の者 除外基準：(1) 精神的問題で回答が難しい者，(2) ドイツ語が話せない者，(3) 話番号が入手不可な者
Kamphuis et al (2003)[22]	横断研究	収集基準：ICD患者132名，非ICD患者35名（1998～1999年の間に大学病院3施設もしくは一般病院1施設のいずれかに来院した患者） 除外基準：NA
Prudente et al (2006)[34]	横断研究	収集基準：ICD患者のうち，18歳以上の者（2001～2003年の間に来院した患者） 除外基準：NA
Bilge et al (2006)[2]	横断研究	収集基準：ICD患者のうち，心室性不整脈により適用となった者（1995～2005年の間に来院した患者） 除外基準：(1) 状態の悪い精神疾患を併発している者，(2) 植込み3カ月以内の者
Van den Broek et al (2008)[41]	縦断研究	収集基準：ICD患者のうち，18～80歳の者(2003～2007年の間に来院した患者) 除外基準：オランダ語の読みと理解のできない者
Jacq et al (2009)[21]	横断研究	収集基準：ICD患者のうち，16歳以上の者で同意を得た者 除外基準：医学的あるいは，手術の問題で，インタビュー調査への参加が困難な者

注）STAI=State-Trait Anxiety Inventory[39]；BAI=Beck Anxiety Inventory[1]；BDI=Beck Depression Inventory[19]；CES-D=Centre for Epidemiologic Studies Depression scale[43]；HAD=Hospital Anxiety and Depression Scale[38]；STAI#=ドイツ語版STAI[24]；STAI##=オランダ語版STAI[42]；STAI-S=STAI-State anxiety; STAI-T=STAI-Trate anxiety; NA=Not Available（論文中未記入）；NS=Not Significiant
a=p<.01
b=p<.05
c=p<.10

4)研究の質の評価

非薬物療法の無作為化比較試験のための報告の質の基準[3,4]を参考にして作成した，以下の基準を用いて，適格基準に該当した研究の質を評価した。

a)乱数生成の方法として乱数生成器または乱数表を使用しているか，また，無作為化に制限(置換ブロック法，層別無作為化法，最小化法など)を加えている場合は具体的に記述しているか。

b)検定力分析の記述をしているか。

c)介入法の標準化の詳細を記載しているか。例えば，介入者が均質な治療を行うようにするための訓練に用いた，マニュアル，ガイドラインや教材などを引用しているか。

5)統計解析

各研究について，研究の終了時点(終了時点の値が欠損の場合は，値が記載されている中で最も終了時点に近いもの)の抑うつまたは不安に関する平均値，標準偏差および標本サイズから，Hedgesのg値およびその標準誤差を算出した。母数モデルのメタ分析により，おのおのの研究の効果量および標準誤差から，統合された効果量およびその95％信頼区間を求めた[10]。なお，母数モデルの妥当性を評価するため，有意水準を5％として，等質性の検定を行った。等質性が満た

表1 ICD患者の作動と抑うつおよび不安の関連

群	評価項目	結果
(1) 作動群 (n=12) (2) 未作動群 (n=12)	STAI #	NS
	BAI	NS
	BDI	NS
(1) A∩B群 (n=6) (2) A群 (n=9) (3) B群 (n=20) (4) C群 (n=97) (A：前の作動から6カ月以内に作動があった人，B：前の作動から6～12カ月の間に作動があった人，C：ここ1年は作動がない人)	STAI#-T	NS
	STAI#-S	NS
	CES-D	NS
(1) 疑似作動群 (n=19) (2) 作動群 (n=28) (3) 未作動群 (n=28)	CES-D	a (1>3)
	STAI-T	b (1>3，1>2)
	STAI-S	b (1>3，1>2)
(1) 作動群 (n=56) (2) 未作動群 (n=35)	HAD (depression)	NS
	HAD (anxiety)	b (1>2)
(1) 作動群 (n=16) (2) 未作動群 (n=160)	STAI##	a (1>2) * 植込み2カ月後
(1) 作動群 (n=40) (2) 未作動群 (n=25)	HAD (depression)	b (1>2)
	HAD (anxiety)	c (1>2)

されない場合は，変量モデルのメタ分析を行った[10]。

2. 無作為化比較試験の特徴

上記の手続きの結果，ICD患者が呈する抑うつおよび不安への介入法の効能を検討した無作為化比較試験は8編であった(表2)。無作為化比較試験で効能が検討されている介入法は，薬物療法ではなく，認知行動療法などの心理社会的介入法に限定される。また，これらの心理社会的介入法は，ICD患者の一部である気分障害や不安障害を呈する患者を対象とするのではなく，ICD患者の全症例を対象としている。すなわち，現在のところ効能が検討されている介入法は，ポピュレーション・アプローチによる心理社会的介入法である。

また，これらの心理社会的介入法の実施者および介入期間は多様であった。介入の実施者が，心理士(大学院生を含む)である研究が5編(62.3%)，看護師である研究が3編(37.5%)，精神科医または研究者である研究が1編(12.5%)であった。介入期間は，1～3カ月のものが6編(75.0%)，1日または9カ月のものが1編(12.5%)であった。さらに介入内容に用いられた技法については，ICD機器や疾患に関する心理教育が6編(75.0%)，認知再構成法が1編(12.5%)，ストレスマネジメントが4編(50.0%)，リラクセーションなどのセルフヘルプが4編(50.0%)であった。

3. メタ分析

まず，メタ分析に必要な統計量が報告されている5編(62.5%)の研究の統計量を基に，ICD患者が呈する抑うつおよび不安への心理社会的介入法の効能を検討した。各研究の効果量は図1のとおりである。次に，研究間の等質性の検定を行ったところ，不安において，研究間の異質性がみられたため(Q17.97，df 4, p<.05)，変量モデルのメタ分析を行った。分析の結果，抑うつ(g0.17，95% CI-0.09 to 0.43)，および不安(g0.38，95 % CI -0.10 to 0.86)ともに効果量に差は認められなかった。

表2 ICD患者への心理的社会的介入の抑うつ及び不安への効能①

研究	調査対象
Kohn et al (2000) [23]	国：アメリカ合衆国 対象：2つの大都市の病院において，1998年10月から1998年5月にICDが適用となった61症例を連続登録 標本サイズ：25（介入群）vs 24（対照群） 最終追跡症例数：18（介入群）vs 18（対照群） 適格基準：(1) 研究参加に同意，(2) 認知機能の障害が重篤でない，(3) 基準時まで生存している
Fitchet et al (2003) [15]	国：イギリス 対象：ICDを植込み，心臓リハビリテーションが必要な73症例を連続登録 標本サイズ：8（介入群）vs 8（対照群） 最終追跡症例数：7（介入群）vs 4（対照群） 適格基準：(1) 運動が可能，(2) NYHA心機能分類がIV度ではない，(3) 狭心症ではない，(4) 同意能力がある
Dougherty et al (2004) [12]	国：アメリカ合衆国 対象：突然心停止または致死性の心室性不整脈の蘇生患者のうち，初めてICDを植込み，2000年2月から2001年12月の間に入院していた243症例 標本サイズ：84（介入群）vs 84（対照群） 最終追跡症例数‡：79（介入群）vs 79（対照群） 適格基準：(1) 英語の読み，書き，会話ができる，(2) 電話での連絡が可能，(3) 1年後の追跡調査への協力意志がある，(4) 外来診療できる程度の病状，(5) 21歳以上，(6) 認知機能の障害が重篤でない
Frizelle et al (2004) [18]	国：イギリス 対象：ICD植込みにより生存している85症例 標本サイズ：12（介入群）vs 10（対照群） 最終追跡症例数：12（介入群）vs 9（対照群） 適格基準：(1) 慢性心疾患から不整脈が発症したICD患者（ICD植込み前に冠動脈バイパス術などの手術経験のある患者を含む），(2) 冠動脈バイパス術や心移植を待機している症例ではない，(3) 心室性不整脈ではない，(4) 病状が深刻で，共同作業が不可能ではない，(5) 英語の読み書きができる

注）ICD=Implantable Cardioverter Defibrillators; BDI=Beck Depression Inventory[19]；STAI=State-Trait Anxiety Inventory[39]；NA=Not Available（論文中未記入）；HAD=Hospital Anxiety and Depression scale[38]；NYHA=New York Heart Association; CES-D=Center for Epidemiologic Studies Depression scale[43]]；DASS=Depression Anxiety Stress Scales[27]；HAM-A=HAMilton Anxiety scale in French[8]；CCS=Canadian Cardiovascular Society.
†特性不安（STAI-T）の評価も行っているが，メタ分析では状態不安（STAI-S）の結果を用いた。
‡内訳は不明であるが，両群の標本サイズが等しいと仮定した。
§標本サイズの内訳は不明であるが，最終追跡症例数の内訳は合併した集団の平均値の公式より，両群が同数であることが確認できる。
¶研究法は，クラスター無作為化試験である。
a) 乱数生成および制限を加えている場合の記述をしている。
b) 検定力分析の記述をしている。
c) 介入法の標準化の詳細を記載している。

表2 ICD患者への心理的社会的介入の抑うつ及び不安への効能①

介入法	評価と結果	研究の質
介入：認知行動療法（不安，回避行動，作動への恐怖，ストレスマネジメント，復職支援，ICDの安全性などの認知のゆがみ） 実施者：心理学の博士課程の大学院生1名 介入期間：約9カ月 介入時期：ICD植込み前，退院前，外来診療時 介入頻度：ICD植込み前と退院前は30～60分，初めの4週間は毎週1回15～30分，追跡期間（1，3，5，9カ月時）は15～30分の介入 対照：未治療（介入群と同様に，外来診療として1，3，5，9カ月時に追跡）	抑うつ（BDI-II）：M6.9，SD5.9（介入群）vs M15.0，SD13.0（対照群） 不安（STAI-S）†：M32.3，SD9.8（介入群）vs M39.9，SD15.4（対照群） 評価時点：退院後9カ月時	
介入：運動療法，心理教育，心理療法（ICDに関する知識，不安・怒り・抑うつのマネジメント，セルフヘルプ） 実施者：循環器疾患の治療経験のある健康心理士1名 介入期間：12週間 介入時期：ICD植込み後 介入頻度：NA 対照：通常診療	抑うつ（HAD）：NA 不安（HAD）：NA 評価時点：介入後12週間後	
介入：小冊子（回復期の経験談，回復期に成功した技術の説明），電話相談（ICDの知識と行動技術，疾患への対処に関するセルフ・エフィカシーの向上，感情の浮き沈みおよび不安の抑制），緊急相談窓口 実施者：循環器科の臨床経験が5年以上であり，電話相談の訓練を受けた看護師 介入期間：2カ月 介入時期：ICD植込みの退院後 介入頻度：小冊子は退院後1週間以内に読む，電話相談は毎週1回15～20分の介入，緊急相談窓口は24時間無料で電話相談可能 対照：通常診療（ICDに関する教育）	抑うつ（CES-D）：M 9.2，SD 9.3（介入群）vs M 8.6，SD 8.8（対照群） 不安（STAI-S）：M 32.0，SD 11.7（介入群）vs M 33.0，SD 11.2（対照群） 評価時点：退院後3カ月時	b，c
介入：認知行動療法（運動療法，心理教育，心理療法，リラクセーション） 実施者：健康心理士1名 介入期間：3カ月 介入時期：NA 介入頻度：リハビリテーション・プログラムは6週間目までは毎週1回120分の介入，9週目に電話相談，12週目に最終ミーティング 対照：治療待機	抑うつ（HAD）：NA 不安（HAD）：NA 評価時点：介入後12週間後	

表2 ICD患者への心理的社会的介入の抑うつ及び不安への効能②

研究	調査対象
Chevalier et al（2006）[6]	国：フランス 対象：臨床試験の前にICDを植込んだ患者および，臨床試験の間にICDを植込んだ253症例を連続登録 標本サイズ：35（介入群）vs 35（対照群） 最終追跡症例数：13（介入群）vs 16（対照群） 適格基準：（1）致死的な心室頻拍の既往歴がある，（2）18～75歳，（3）住居が病院から遠方ではない，（4）心理療法を受けた経験がない，（5）睡眠作用のある向精神薬を使用していない
Sears et al（2007）[36]	国：アメリカ合衆国 対象：ICD患者の中で，過去1年間に少なくとも1回は作動を経験した症例 標本サイズ§：15（介入群）vs 15（対照群） 最終追跡症例数§：10（介入群）vs 10（対照群） 適格基準：NA
Edelman et al（2007）[14]	国：オーストラリア 対象：ICD植込み予定の27症例 標本サイズ：13（介入群）vs 9（対照群） 最終追跡症例数：NA（介入群）vs NA（対照群） 適格基準：（1）精神病症状を示す疾患ではない，（2）認知機能の障害が重篤でない，（3）英語能力が十分である
Lewin et al（2009）[25] ¶	国：イギリス 対象：2004年2月から2005年5月の間に初めてICDを植込んだ268症例を連続登録 標本サイズ：71（介入群）vs 121（対照群） 最終追跡症例数：54（介入群）vs 97（対照群） 適格基準：（1）ICDを1カ月に5例以上植込んでいる施設，（2）介入法の訓練に参加できる施設，（3）18歳以上の症例，（4）同意能力があり，研究参加に同意した症例，（5）循環器医により症状が安定していると判断されている症例，（6）冠動脈バイパス術や心移植を待機している症例ではない，（7）運動誘発性不整脈を患っていない，（8）CCSの狭心症重症度分類でクラスⅢまたはⅣではない，（9）精神病症状を示す疾患の既往歴がない

注 ）ICD=Implantable Cardioverter Defibrillators; BDI=Beck Depression Inventory[19]；STAI=State-Trait Anxiety Inventory[39]；NA=Not Available（論文中未記入）；HAD=Hospital Anxiety and Depression scale[38]；NYHA=New York Heart Association; CES-D=Center for Epidemiologic Studies Depression scale[43]］；DASS=Depression Anxiety Stress Scales[27]；HAM-A=HAMilton Anxiety scale in French[8]；CCS=Canadian Cardiovascular Society.

†特性不安（STAI-T）の評価も行っているが，メタ分析では状態不安（STAI-S）の結果を用いた。

‡内訳は不明であるが，両群の標本サイズが等しいと仮定した。

§標本サイズの内訳は不明であるが，最終追跡症例数の内訳は合併した集団の平均値の公式より，両群が同数であることが確認できる。

¶研究法は，クラスター無作為化試験である。

a）乱数生成および制限を加えている場合の記述をしている。

b）検定力分析の記述をしている。

c）介入法の標準化の詳細を記載している。

表2 ICD患者への心理的社会的介入の抑うつ及び不安への効能②

介入法	評価と結果	研究の質
介入：認知行動療法（ストレスマネジメント，リラクセーション，認知再構成法，コミュニケーション，問題解決療法） 実施者：認知行動療法を実施する資格を持ち，不安障害の治療経験のある，臨床心理士と精神科医各1名 介入期間：3カ月 介入時期：NA 介入頻度：2週間に1回，120分の介入 対照：通常診療	抑うつ（BDI-13）：M 4.9, SD 3.5（介入群）vs M 6.1，SD 4.5（対照群） 不安（HAM-A***）：M 2.6，SD 1.5（介入群）vs M 9.0, SD 4.3（対照群） 評価時点：介入開始後12カ月時	a, b
介入：ストレスマネジメント 実施者：ICD植込み患者へのストレスマネジメントと認知行動療法の経験を持つ研究代表者1名と研究補助者 介入期間：6週間 介入時期：NA 介入頻度：1週間に1回，90分の介入 対照：介入群に行う内容を圧縮した講義を，1日4時間をかけて行う	抑うつ（CES-D）：M 6.3, SD 6.3（介入群）vs M 7.9，SD 4.4（対照群） 不安（STAI-T）：M 32.8, SD 4.9（介入群）vs M 31.3, SD 5.5（対照群） 評価時点：介入終了直後	
介入：心理教育（ICD，作動，生活習慣，コミュニケーション） 実施者：循環器科の看護師と臨床心理士各1名 介入期間：1日 介入時期：ICD植込みの2週間後 介入頻度：60～90分の介入 対照：通常診療（循環器医からの口頭説明と小冊子の配布）	抑うつ（DASS）：NA 不安（DASS）：NA 評価時点：介入後6カ月後	
介入：セルフヘルプ（患者用の小冊子，家族用の小冊子，目標管理用の日記，リラクセーションのテープまたはCD），電話相談（経過の検討，成功体験の強化，新しい目標設定） 実施者：臨床心理士による訓練を受けた看護師 介入期間：12週間 介入時期：ICD植込み前，退院後 介入頻度：ICD植込み前の小冊子は20分の説明，退院後（1, 3, 6週間時）の電話相談は15分の介入 対照：通常診療（ICDに関する小冊子を配布し，手術後の経過を観察する）	抑うつ（HAD）：M 3.9, SD 4.3（介入群）vs M 4.3，SD 4.3（対照群） 不安（HAD）：M 5.3，SD 0.4（介入群）vs M 5.5，SD 3.5（対照群） 評価時点：ICD植込み後6カ月時	a, b, c

4 介入研究の問題点と今後の展望

メタ分析により，ICD患者が呈する抑うつおよび不安への心理社会的介入法の効能が認められないことが示されたものの，この結果の解釈には注意を要する。先行研究の課題として，(1)検定力，(2)介入方法，(3)脱落率の3点がある。

第1に，対応のないt検定（両側検定，有意水準5%）を行う際に検定力が80%以上となるための標本サイズを求めると，母集団効果量が大きい（δ=0.8）と仮定した場合は各群26，中程度（δ=0.5）と仮定した場合は各群64以上の症例が必要となる[7]。つまり，これまでの先行研究は，仮に大きい母集団効果量を期待しても，Doughertyら（2004）[12]とLewinら（2009）[25]を除き，検定力が80%に満たないという問題が残される。したがって，今後の研究では，適切な標本サイズを設計したうえで，効能を検討する必要があると考えられる。

第2に，介入方法については，治療者に対する教育を行っていることを明記している研究は，2編（25.0%）[12,25]にとどまっているという問題がある。そのため，多くの研究は，介入の標準化が十全ではないといえるであろう。

第3に，脱落率について，多くの先行研究の限界として指摘されていた。先行研究における，脱落率は研究間の散らばりが大きく，中央値が26.5%，最小値が4.5%，最大値が58.6%であった。

以上のような問題を考慮したうえで，今後の研究ではより質の高い無作為化比較試験を蓄積する必要がある。その際，自己記入式尺度による評価ばかりでなく，再入院率などを評価指標として含め，費用対効果を求めていく試み[25]も重要になると思われる。さらに，現在のところ効能が検討されている介入法は，ICD患者の全症例を対象とする心理社会的介入法であるが，気分障害や不安障害を呈する患者を対象とするようなターゲット・アプローチによる介入の効能も検討していく必要があると考える。例えば，アメリカ心臓協会は，循環器疾患の通常診療の中で，自己記入式尺度を用いてうつ病をスクリーニングし，重症度が中等症以上の患者は精神科に紹介するように勧告を提出している[26]。このような精神科と循環器科の連携を強化するような試みの効能を検討していくことが求められるであろう。

なお，このメタ分析は，(1)系統的な文献検索をしていないこと，(2)未出版の文献を含めて網羅的な文献検索をしていないこと，(3)複数の評価者により，情報を抽出していないという3点の限界が残される。

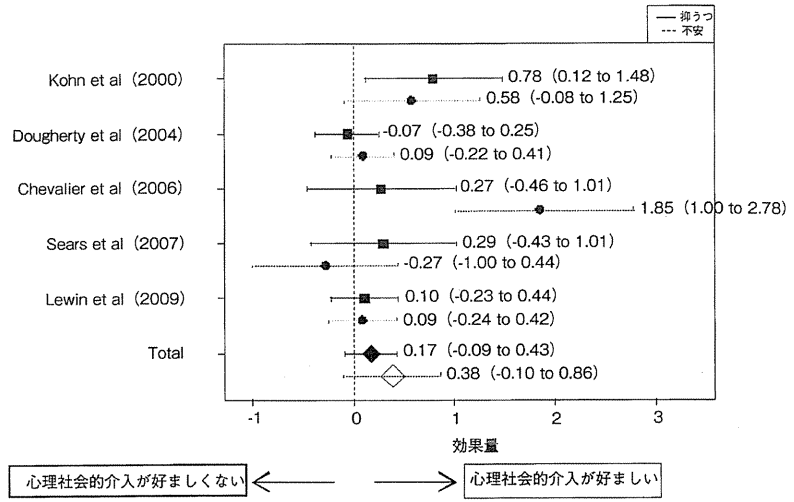

図1 フォレストプロット
四角（■）および丸（●）はHedgesのg値であり，その両脇の線は95%信頼区間を示す。実線は抑うつ，点線は不安の値を示す。Hedgesのg値は，正の値が高いほど対照群よりも心理社会的介入の方が好ましいこと，負であるとその逆を意味する。

5 まとめ

本稿の目的は，ICDのショック作動により引き起こされる抑うつや不安に関する観察研究，およ

びその予防や管理のための介入研究の知見から，今後のICD患者に対する有益な精神科的支援について考察することであった。その結果，第1に観察研究においては，ICD特有の心理社会的問題であるショック作動との関連についての一貫した知見は得られていなかった。また，ICD患者が呈する抑うつおよび不安への心理社会的介入法の効能は認められず，従来の無作為化比較試験には，検定力，介入方法，脱落率の点に課題が残されることが示された。

したがって，今後の展望として，(1)作動と精神症状の関連における交絡変数を検討すること，(2)より質の高い無作為化比較試験により，ICD患者に対する心理的社会的介入法の効能を検討することが求められる。このような点に関する検討を行うことで，ICD患者の精神症状発症のメカニズムが明らかとなり，ICD患者が呈する精神症状に対する診断・治療のために精神科と循環器科との緊密な連携が促進されることが期待される。

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Summary

Psychiatric supports for depression and anxiety of patients with an implantable cardioverter defibrillators: A review and future recommendations

ICHIKURA Kanako et al

Background: The implantable cardioverter defibrillator (ICD) has proved effective in preventing sudden cardiac death. However, ICD patients potentially face significant psychosocial issues because of their risk for life-threatening arrhythmias and the occurrence of ICD shock.

Objective: This review provides an overview of (1) relationship between ICD shock and psychological status including depression and anxiety, and (2) current evidence on the efficacy of psychological intervention in ICD patients.

Method: We carried out a narrative and meta-analytic review of the literature using general bibliographic database: MEDLINE, PsycINFO, and Social Science Citation Index.

Results: First, we found five studies investigating the relationship between ICD shock and depression, and six studies investigating the relationship between ICD shock and anxiety. However, there was no significant relationship between ICD shock and psychological status. In addition, a random effect meta-analysis of five randomized controlled trials produced overall effect sizes of $g = 0.17$ (95% CI = –0.09 to 0.43) for depression and $g = 0.38$ (95% CI = –0.10 to 0.86) for anxiety.

Conclusion: There was no significant relationship between ICD shock and psychological status including depression and anxiety, and no significant efficacy of psychological intervention in ICD patients. In the future studies, we should focus on confounding variable, and increase the methodological quality of the trial.