Introduction

The Japanese Atherosclerosis Society (JAS) published new guidelines for the diagnosis and treatment of atherosclerotic cardiovascular diseases in 2002 (1, 2). Hypercholesterolemia is one of the major risk factors that contributes to the development of coronary atherosclerosis (3). Recent clinical practice guidelines recommend that physicians and patients make decisions regarding coronary heart disease (CHD) prevention on assessment of underlying global CHD risk (3–9).

It has been reported that the incidence of CHD is lower in Japanese, compared with North American and European peoples (10, 11). The Japan Lipid Intervention Trial (J-LIT) was undertaken and reported in 2002 (12, 13). The J-LIT involved 52,421 patients with simvastatin treatment, and the results showed a positive relationship between LDL-C levels and CHD events, and a negative relationship between HDL-C levels and CHD events. The results from the studies in Japan such as the Hisayama study (14), NIPPON DATA (15), KLIS (16) as well as those from J-LIT, were incorporated into the new JAS guidelines, considering the clinical decision making according to the person's absolute risk.

Our purpose in this study is to evaluate the JAS guidelines as a risk assessment tool in Japanese patients with hypercholesterolemia, using the cohort of the Holicos-PAT study (17). The Holicos-PAT study was designed in 1989 in the Hokuriku district, as a prospective observational study. 2039 patients were followed with or without pravastatin for 5 years. The primary endpoints were CHD, and the secondary endpoints were CVD and total mortality. CHD event includes onset and worsening of angina pectoris in the Holicos-PAT, in contrast to the other studies.

Patients and Methods

We assessed CHD and cerebrovascular disease (CVD) risks by the patient categories, in the 2,039 patients of Holicos-PAT study. The main outcome measures were CHD events and CVD events, identified in the Holicos-PAT study. The event rates were calculated by the person-years method. The patient category was described in the JAS guidelines. In brief, Category A is absence of CHD and absence of atherosclerosis risk factors other than hypercholesterolemia, B1, B2, B3 and B4 are absence of CHD but presence of one to four atherosclerosis risk factors other than hypercholesterolemia, and C is presence of CHD.

The results of the Holicos-PAT study are described in full elsewhere (17). The patients with hypercholesterolemia (total cholesterol was greater than 220 mg/dl) were registered, and followed up by 132 physicians at 70 facilities. 2,232 patients were recruited and 193 patients were excluded. 1290 patients received pravastatin and 749 patients were followed without pravastatin (Diet group) for 5 years. Baseline characteristics are shown in Table 1. About 60% were women, and the mean age was 56.8 years. Hypertension was present in 37% and diabetes mellitus in about 15%. 82% had no history of CHD, and 18% had a history of CHD. The primary endpoints were CHD, and the secondary endpoints were CVD and total mortality. Coronary heart event includes onset and worsening of angina pectoris, performing CABG or PTCA, non-fatal and fatal myocardial infarction, and death from CHD including heart death and sudden death. Cerebrovascular events: CVD events are onset or recurrence of cerebral infarction, onset of cerebral hemorrhage, and death from cerebral infarction or hemorrhage.

Statistical Analysis

As for the incidence of events, the number of occurrences per 1,000 patients-years was calculated. Data of the patients with or without pravastatin treatment were combined in the groups of whole patients, men and women, because there were no significant differences in the event rates between them that was described in the previous paper (17). Baseline imbalances were compared between men and women by using either t test or chi-square test according to the type of variables. In comparisons of the event rates with person-year data between two groups, chi-square test assuming a Poisson model was used. The significance level was 5%, and the statistical package SAS version 6.12 (SAS Institute, NC) was used.

Results

The patient background was shown in Table 1. There were the significant differences between men and women, in the variables of age ($p < 0.001$), angina pectoris ($p < 0.001$), myocardial infarction ($p < 0.001$), cerebral infarction ($p = 0.022$), hypertension ($p = 0.002$), diabetes mellitus ($p < 0.001$), current smoking ($p < 0.001$), body mass index ($p < 0.001$) and serum lipids ($p < 0.001$). LDL-C and HDL-C levels in men were significantly lower than those in women ($p < 0.001$), but triglyceride level in men was significantly higher than that in women ($p < 0.001$). The percent pravastatin treatment in men (56.9%) was significantly lower than that in women (67.1%) ($p < 0.001$). The number of patients in each category group was shown in Table 2. The percent secondary prevention, Category C was 18%. Category B4 was only 123 patients.

In the whole patients group, the event rates of CHD in Category A, B1, B2, B3, B4 and C, were 1.1, 4.0, 2.8, 5.7, 18.2 and 38.8 per 1,000 person-years (Table 3). When the event rates of CHD in the Category B4 and C groups

Table 1. Baseline characteristics of the Holicos-PAT study.

Variable	Whole (n = 2,039)	Men (n = 758)	Women (n = 1,281)	Diet (n = 749)
Gender (men%/women%)	37.2 / 62.8	–	–	43.7 / 56.3
Age (year)	56.8 ± 9.2	53.5 ± 9.9	58.7 ± 8.2***	55.1 ± 9.4
Angina pectoris (%)	14.0	17.6	11.9***	13.5
Myocardial infarction (%)	4.4	8.8	1.8***	3.7
Cerebral infarction (%)	2.8	3.8	2.1*	2.3
Cerebral hemorrhage (%)	0.2	0.3	0.2	0.1
Hypertension (%)	37.4	33.0	40.0**	35.8
Diabetes mellitus (%)	15.0	18.6	12.9***	18.6
Current smoking (%)	25.0	57.5	5.8***	29.2
Family history of CHD (%)	7.4	7.9	7.1	7.2
Systolic BP (mmHg)	133.6 ± 20.6	130.0 ± 20.0	135.7 ± 20.6***	132.0 ± 21.9
Diastolic BP (mmHg)	79.8 ± 12.0	80.0 ± 12.8	79.7 ± 11.5	78.8 ± 12.6
Body mass index (Kg/m^2)	23.7 ± 2.9	23.9 ± 2.6	23.5 ± 3.0***	23.5 ± 2.8
Total cholesterol (mg/dl)	250.3 ± 28.6	247.1 ± 28.4	252.2 ± 28.5***	236.1 ± 24.1
LDL choresterol (mg/dl)	169.0 ± 29.5	166.2 ± 30.4	170.7 ± 28.9***	156.8 ± 25.9
HDL choresterol (mg/dl)	51.6 ± 14.7	47.3 ± 13.5	54.2 ± 14.7***	51.8 ± 14.7
Triglycerides (mg/dl)	155.7 ± 97.9	181.2 ± 111.9	140.6 ± 85.1***	139.3 ± 76.9

Statistical differences between men and women are shown by P values: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Diet: the patients with diet only therapy.

were compared to that in the combined category groups A + B1 + B2, the rates of CHD events in the higher risk category groups, Category B4 group ($p = 0.004$ in whole patients) and C group ($p < 0.001$ in whole patients), were significantly higher than that in the lower risk category group. The event rates of CHD in men were significantly higher than those in women, in the category B4 ($p < 0.001$) and C ($p < 0.001$).

The event rates of CVD in Category A, B1, B2, B3, B4 and C, were 2.1, 1.8, 1.8, 0.6, 10.8 and 6.4 per 1000 person-years, in the whole patients group (Table 4). When the event rates of CVD in the category B4 and C groups were compared to that in the combined category groups A + B1 + B2, the rates of CVD events in the higher risk category groups: Category B4 group ($p = 0.027$ in whole patients) and C group ($p = 0.142$ in whole patients), were higher than that in the lower risk category group. The event rates of CVD in men showed the same tendency as those in women.

Table 2. Number of the patients in each patient category.

Patient category	Whole	Men	Women	Diet
A	212 (10.4%)	33 (4.4%)	179 (14.0%)	81 (10.8%)
B1	502 (24.6%)	126 (16.6%)	376 (29.4%)	192 (25.6%)
B2	482 (23.6%)	170 (22.4%)	312 (24.4%)	154 (20.6%)
B3	348 (17.1%)	164 (21.6%)	184 (14.4%)	144 (19.2%)
B4	123 (6.0%)	80 (10.6%)	43 (3.4%)	43 (5.7%)
C	372 (18.2%)	185 (24.4%)	187 (14.6%)	135 (18.0%)
Total	2,039 (100%)	758 (100%)	1,281 (100%)	749 (100%)

Discussion

This study examined the risk of CHD and CVD in Japanese patients with hypercholesterolemia, classified by the categories in JAS guidelines, using the cohort of the

Table 3. The event rate of coronary heart disease.

Patient category	Whole	Men	Women	Diet
A	1.1	8.2	0.0	2.8
B1	4.0	3.7	4.1	4.8
B2	2.8	5.3	1.4	3.0
B3	5.7 ^{ns}	9.7 ^{ns}	2.3 ^{ns}	4.8 ^{ns}
B4	18.2¶	25.4§	5.1***	5.4 ^{ns}
C	38.8§	55.4§	23.6***§	50.7§
Total	10.5	19.8	5.3	11.7

Statistical differences between men and women are shown by P values: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Statistical differences of category B3, B4 and C, to the combined category groups A + B1 + B2, are shown by P values: $^{†}p < 0.05$, $^{¶}p < 0.01$, $^{§}p < 0.001$, ^{ns} no significance.
Numbers are per 1,000 person-years.

Table 4. The event rate of cerbrovascular disease

Patient category	Whole	Men	Women	Diet
A	2.1	0.0	2.5	0.0
B1	1.8	3.7	1.2	3.6
B2	1.8	0.0	2.8	1.5
B3	0.6 ^{ns}	1.3 ^{ns}	0.0 ^{ns}	1.6 ^{ns}
B4	10.8†	8.3 ^{ns}	15.4¶	10.9†
C	6.4 ^{ns}	9.4†	3.5 ^{ns}	6.9 ^{ns}
Total	3.0	4.2	2.4	3.4

Statistical differences between men and women are shown by P values: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.
Statistical differences of category B3, B4 and C, to the combined category groups A + B1 + B2, are shown by *P* values: $^{\dagger}p < 0.05$, $^{¶}p < 0.01$, $^{§}p < 0.001$, ^{ns} no significance.
Numbers are per 1,000 person-years.

Holicos-PAT study. The JAS guidelines reported the absolute and relative risk of CHD classified by accumulation of risk factors, calculated according to the data from J-LIT. In J-LIT, the relative rate of CHD is 2 in one risk factor group, 4 in two risk factors group, 8 in three risk factors group, and 15 in four risk factors group (1). The relative risk of CHD from the Holicos-PAT is 4 in one risk factor group, 3 in two risk factors group, 5 in three risk factors group, and 17 in more than four risk factors group. The relative risk was similar between the two trials. The absolute risk was not compared directly, because of the different endpoints. The endpoints in Holicos-PAT include the onset and worsening of angina pectoris, but the J-LIT does not include these. Angina pectoris accounted for 49.5% of the whole CHD events. In the Holicos-PAT study, CHD events occurred in 55.4 per 1,000 patients-year for men and 23.6 per 1,000 patients-year for women with a history of CHD, and myocardial infarction occurred in 8.4 per 1,000 patients-year for men, and 5.7 per 1,000 patients-year for women with a history of CHD (17). CHD events including nonfatal/fatal myocardial infarction and cardiac sudden death in the J-LIT, was 4.45 per 1,000 patients-year in the patients with a history of CHD (12). The interpretation of the results from the Holicos-PAT may be limited, because of the small number of the events.

The incidence of CHD events was 3.5 times higher than that of CVD events in this study. The CVD event rate in the Holicos-PAT (3.0 per 1,000 patients-year in whole patients) was lower than that in the KLIS (5.2 per 1,000 patients-year in the control group). CHD and CVD event rates in the KLIS showed 6.0 and 5.2 per 1,000 patients-year in the control group, respectively, in a 5-year follow-up (16). There were 249 deaths from CHD, and 174 deaths from CVD in Nippon Data (15). The difference may be accounted by the different endpoints: the endpoints in KLIS did not include onset and worsening of angina pectoris. From other points, the events of CVD were defined in Holicos-PAT as the onset and recurrence of cerebral infarction, the onset of cerebral hemorrhage, or death from the clinical findings and CT scanning. The events of CVD may have been underestimated because of lack of autopsy. The number of CHD death gradually increased, in comparison with CVD death, in Japan.

Current guidelines in the world recommend lipid-lowering therapy by specific drugs, if the absolute risk exceeds a certain threshold (18). The threshold is 20% over 10 years according to the joint European Societies guidelines (4, 5) and 15% over 10 years according to the joint British guidelines (6). Most Japanese patients are of low risk for CHD, but 16% of Japanese die of cardiac disease, and 13% of cerebrovascular disease (19). The number of CHD deaths has exceeded that of CVD deaths, since 1990. As a result, substantial number of Japanese die of atherosclerotic diseases. To make a strategy for prevention of the atherosclerotic diseases in Japan, we have to consider the traits in patient preference regarding the lipid-lowering therapy and cost-effectiveness.

Various guidelines use different risk assessment methods. There are a lot of Framingham-based risk calculation tools (20). The Framingham Scores, originally developed in a white, middle-class population, overestimated CHD risk in Japanese-American and Hispanic men and Native American women (10). These results suggest that the Framingham Score should be used after recalibration, which requires data on each cohort's CHD risk factor prevalence and CHD event rates (11).

The event rate of CHD was analyzed in the male and female groups. The event rate of CHD in men was higher than that in women, even though the factor of gender was considered when the patients were categorized. The factor of gender may be more potent than one risk factor for CHD, and the risk may be underestimated in men and overestimated in women. We have to consider the differences between men and women when using the JAS guidelines.

From these results, we thought that the categories in the Japanese guidelines are useful to assess CHD and CVD risk in Japanese patients with hypercholesterolemia.

Acknowledgments: The authors are indebted to H. Kodama (Sankyo Co., Ltd.) for statistical analysis, and T. Matsukura and H. Nomura (General Medicine, Kanazawa University Hospital) for helpful discussion.

References

(1) Japan Atherosclerosis Society: Japan atherosclerosis society (JAS) guidelines for diagnosis and treatment of atherosclerotic cardiovascular disease.

2002
(2) Saito Y: Editorial. J Atheroscler Thromb, 11: 101–103, 2004
(3) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA, 285: 2486–2497, 2001
(4) Pyorala K, De Backer G, Graham I, Poole-Wilson P, and Wood D: Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J, 15: 1300–1331, 1994
(5) Pyorala K and Wood D: Prevention of coronary heart disease in clinical practice. European recommendations revised and reinforced. Eur Heart J, 19: 1413–1415, 1998
(6) Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. Heart, 80 Suppl 2: S1–S29, 1998
(7) Ramsay LE, Haq IU, Jackson PR, Yeo WW, Pickin DM, and Payne JN: Targeting lipid-lowering drug therapy for primary prevention of coronary disease: an updated Sheffield table. Lancet, 348: 387–388, 1996. Erratum in: Lancet, 348: 1251, 1996
(8) Assmann G, Cullen P, and Schulte H: Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation, 105: 310–315, 2002. Erratum in: Circulation, 105: 900, 2002
(9) Durrington PN, Prais H, Bhatnagar D, France M, Crowley V, Khan J, and Morgan J: Indications for cholesterol-lowering medication: comparison of risk-assessment methods. Lancet, 353: 278–281, 1999. Erratum in: Lancet, 354: 166, 1999
(10) Kent DM and Griffith J: The Framingham scores overestimated the risk for coronary heart disease in Japanese, Hispanic, and Native American cohorts. ACP Journal Club, 136: 36, 2002
(11) D'Agostino RB Sr, Grundy S, Sullivan LM, and Wilson P; CHD Risk Prediction Group: Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA, 286: 180–187, 2001
(12) Mabuchi H, Kita T, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, and Itakura H; J-LIT Study Group: Japan Lipid Intervention Trial. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: secondary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). Circ J, 66: 1096–1100, 2002
(13) Matsuzaki M, Kita T, Mabuchi H, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, and Itakura H; J-LIT Study Group: Japan Lipid Intervention Trial. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia. Circ J, 66: 1987–1095, 2002
(14) Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, and Yoshitake T: Diabetes and cardiovascular disease in a prospective population survey in Japan: The Hisayama Study. Diabetes, Suppl 3: S14–S16, 1996
(15) Sakata K, Hashimoto T, Ueshima H, and Okayama A; NIPPON DATA 80 Research Group: Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980-1994. National Integrated Projects for Prospective Observation of Non-communicable Diseases and its Trend in the Aged. Eur J Epidemiol, 17: 461–468, 2001
(16) Pravastatin use and risk of coronary events and cerebral infarction in japanese men with moderate hypercholesterolemia: the Kyushu Lipid Intervention Study. J Atheroscler Thromb, 7: 110–121, 2000
(17) Koizumi J, Shimizu M, Miyamoto S, Origasa H, and Mabuchi H: Effect of pravastatin-induced LDL-cholesterol reduction on coronary heart disease and cerebrovascular disease in Japanese: Hokuriku lipid coronary heart disease study-pravastatin atherosclerosis trial (Holicos-PAT). J Atheroscler Thromb, 9: 251–259, 2002
(18) Broedl UC, Geiss HC, and Parhofer KG: Comparison of current guidelines for primary prevention of coronary heart disease: risk assessment and lipid-lowering therapy. J Gen Intern Med, 18: 190–195, 2003
(19) Statistics and Information Department, Minister's Secretariat, Ministry of health, labour and Welfare: Vital statistics of Japan 2003, http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei03/index.html
(20) Sheridan S, Pignone M, and Mulrow C: Framingham-based tools to calculate the global risk of coronary heart disease: a systematic review of tools for clinicians. J Gen Intern Med, 18: 1039–1052, 2003

J Neurosurg 102:882–887, 2005

Decrease in platelet count as an independent risk factor for symptomatic vasospasm following aneurysmal subarachnoid hemorrhage

YUTAKA HIRASHIMA, M.D., HIDEO HAMADA, M.D., MASANORI KURIMOTO, M.D., HIDEKI ORIGASA, PH.D., AND SHUNRO ENDO, M.D.

Department of Neurosurgery; and Division of Biostatistics, Toyama Medical and Pharmaceutical University, Toyama, Japan

Object. Increased platelet consumption is expected in patients with cerebral vasospasm, according to data from clinical and experimental studies. The authors investigated sequential changes in platelet counts in patients with subarachnoid hemorrhage (SAH) and the difference in platelet consumption between patients with and those without symptomatic vasospasm (SV). Variables related to platelet count as well as other clinical and radiological variables were analyzed as independent predictors of SV.

Methods. One hundred consecutive patients who had undergone surgery within 48 hours after SAH onset were entered in the study. Clinical and radiological variables and blood cell counts, including red blood cells, white blood cells, and platelets, after SAH were retrospectively examined. Twenty of these variables were entered into univariate and multivariate analyses to determine predictors for SV.

After SAH, the platelet count decreased to a minimum and then increased rapidly to levels greater than those recorded on admission. This change was specific to SAH, and platelet consumption was more severe in patients with SV than in those without. There were three independent predictors of SV: a ratio of the lowest platelet count and the admission count greater than 0.7 (odds ratio [OR] 0.322, 95% confidence interval [CI] 0.124–0.834, p = 0.0196) and a history of hypertension (OR 0.338, 95% CI 0.126–0.906, p = 0.0311) were negatively significant (that is, decreases the occurrence of SV), and a Fisher Grade 3 (OR 4.42, 95% CI 1.48–13.2, p = 0.0077) was positively significant (that is, increases the occurrence of SV).

Conclusions. The association between a decrease in platelet count and the occurrence of SV indicates the important role of platelets in the pathophysiology of vasospasm following SAH.

KEY WORDS • subarachnoid hemorrhage • vasospasm • platelet • risk factor

CEREBRAL vasospasm following SAH remains a notable cause of poor outcome in patients suffering from this disease. Its origin and pathogenesis are still poorly understood. Ischemia due to cerebral vasospasm after SAH may be due to factors other than constriction of main arteries; that is, luminal narrowing of main arteries does not always correlate with symptoms and reduced cerebral blood flow.[18,26] For example, distal artery constriction and microcirculatory dysfunction are also noteworthy contributors to cerebral vasospasm.[22,25] Many factors may contribute to circulatory pathology at any level of the vasculature in patients with vasospasm after SAH, including the following: 1) infiltration of leukocytes into the wall of arteries together with injury of the endothelium;[4,30] 2) aggregation of platelets on the injured endothelium of arteries;[7] 3) release of substances from leukocytes and platelets with vasoactive or aggregation-inducing effects;[12,16] and 4) microthrombi in peripheral vessels.[29] Subsequently, intraluminal platelet consumption may occur in patients with cerebral vasospasm.[10] In the present study, we investigated sequential changes in platelet count following SAH as well as the difference in platelet consumption between patient groups with and without cerebral vasospasm. In addition, we assessed whether serological variables related to platelet consumption, in addition to clinical and radiological variables, can be used to identify patients at increased risk for SV.

Abbreviations used in this paper: CI = confidence interval; CT = computerized tomography; DM = diabetes mellitus; Hb = hemoglobin; Ht = hematocrit; OR = odds ratio; RBC = red blood cell; SAH = subarachnoid hemorrhage; SV = symptomatic vasospasm; WBC = white blood cell.

Clinical Material and Methods

Patient Population and Data Collection

We studied 100 consecutive patients with ruptured aneurysms who had undergone surgery (clip and wrap application) within 48 hours after SAH onset at the Department of Neurosurgery, Toyama Medical and Pharmaceutical University, between January 1995 and October 2001. The clinical data in these 100 patients are summarized in Tables 1 and 2. In addition, nine patients with SAH who had been observed within 18 days after onset of SAH and nine patients who had undergone cranioplasty after decompressive craniotomy were used as control groups. All patient charts were retrospectively reviewed. Neuroimaging and intensive care unit records were available for all patients.

Noted variables included patient sex and age, Hunt and Hess grade,[14] Fisher grade,[8] location of ruptured aneurysm, and acute hydrocephalus in patient groups with and without SV. Symptomatic vasospasm following SAH was de-

TABLE 1

*Summary of characteristics in 100 consecutive patients with or without SV following SAH**

Variable	No. of Patients (%) w/ SV	w/o SV	p Value
sex			
M	14 (35.0)	19 (31.7)	0.829
F	26 (65.0)	41 (68.3)	
mean age (yrs)†	60.3 ± 14.1	59.1 ± 13.5	0.678
Hunt & Hess grade			
I–II	19 (47.5)	41 (68.3)	0.0372
III–V	21 (52.5)	19 (31.7)	
Fisher grade			
3	32 (80.0)	34 (56.7)	0.0158
other	8 (20.0)	26 (43.3)	
site of ruptured aneurysm			
ICA	12 (30.0)	16 (26.7)	0.265
ACoA	13 (32.5)	14 (23.3)	
ACA	13 (32.5)	19 (31.7)	
MCA	2 (5.00)	5 (8.33)	
VBA	0 (0.0)	6 (10.0)	
acute hydrocephalus			
present	1 (2.5)	3 (5.0)	0.648
absent	39 (97.5)	57 (95.0)	
lowest mean platelet count ($\times 10^4$)	15.2 ± 4.68	16.7 ± 5.29	0.324
ratio of lowest platelet count & admission count			
>0.7	19 (47.5)	42 (70.0)	0.0359
≤0.7	21 (52.5)	18 (30.0)	
mean no. of days post-SAH to lowest platelet count†	4.43 ± 3.34	4.01 ± 2.80	0.733
mean no. of days to recover admission platelet count†	9.33 ± 4.29	8.13 ± 3.99	0.0954
highest WBC count			
$>150 \times 10^2$	26 (65.0)	31 (51.7)	0.220
$\leq 150 \times 10^2$	14 (35.0)	29 (48.3)	

* ACA = anterior cerebral artery; ACoA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery; VBA = vertebrobasilar artery.

† Values are presented as the means ± standard deviation.

TABLE 2

Summary of risk factors and treatment in 100 consecutive patients with or without SV following SAH

Variable	No. of Patients (%) w/ SV	w/o SV	p Value
hypertension			
yes	17 (42.5)	36 (60.0)	0.104
no	23 (57.5)	24 (40.0)	
tobacco smoking			
yes	15 (37.5)	19 (31.7)	0.667
no	25 (62.5)	41 (68.3)	
alcohol use			
yes	16 (40.0)	19 (31.7)	0.402
no	24 (60.0)	41 (68.3)	
DM			
yes	2 (5.00)	5 (8.33)	0.699
no	38 (95.0)	55 (91.7)	
cerebrovascular disease			
yes	1 (2.50)	1 (1.67)	0.999
no	39 (97.5)	59 (98.3)	
cardiac disease			
yes	4 (10.0)	3 (5.0)	0.433
no	36 (90.0)	57 (95.0)	
glycerol administration			
yes	32 (80.0)	27 (45.0)	0.0008
no	8 (20.0)	33 (55.0)	
steroid administration			
yes	26 (65.0)	37 (61.7)	0.834
no	14 (35.0)	23 (38.3)	
hemostatic drug administration			
yes	38 (95.0)	54 (90.0)	0.471
no	2 (5.0)	6 (10.0)	

fined as significant transient or permanent neurological deterioration, such as hemiparesis or aphasia. We monitored vasospasm every day by performing transcranial Doppler ultrasonography studies in all patients and confirmed it on digital subtraction angiography when transcranial Doppler velocities increased (flow velocities > 150 cm/second) or symptoms were indicative of vasospasm. Although CT scanning, magnetic resonance imaging, and/or ^{99m}Tc–hexamethylpropyleneamine oxime single-photon emission computerized tomography scanning were also performed, results of these examinations offered only supporting data for the presence or absence of vasospasm. Calcium channel blockers were not used prophylactically. When SV occurred, patients were usually treated with induced hypertension. Steroid agents, glycerol, and other medicines were occasionally administered (Table 2). Some patients underwent percutaneous transluminal angioplasty and intraarterial administration of papaverine hydrochloride.

A Hunt and Hess grade was assigned by the primary neurosurgeons. Computerized tomography scanning of the brain was performed immediately after admission by using a unit (YCT-900S; Toshiba, Tokyo, Japan) that displayed pictures on a 512 × 512 matrix. From the resultant scans we determined the Fisher classification. The presence of acute hydrocephalus was determined using the admission CT scan. Fisher grade on admission and the presence of acute hydrocephalus were evaluated independently by two observers blinded to the data in the medical charts. When the two observers disagreed, a diagnosis other than a Fisher Grade 3 SAH and acute hydrocephalus was rendered. Cerebral angiography studies were performed in all patients and used to determine the location of the aneurysm. A history of hypertension, tobacco smoking, alcohol use, DM, cerebrovascular disease, and cardiac disease were noted from patient charts. The postoperative administration of glycerol, steroid agents, and hemostatic drugs was recorded.

Blood was drawn from a peripheral vein. The WBC count, RBC count, Hb concentration, Ht, and platelet count from Days 0 through 20 were compared in patients with and those without SV. Sequential changes in platelet count were also observed in four groups: patients with SV, patients without SV, patients with SAH who had been observed for 18 days after SAH without any intervention, and patients who had undergone cranioplasty after surgery for a disease other than SAH. In 100 patients with SAH and with or without SV, we noted the following details: lowest platelet count, ratio of the lowest and the admission platelet count, number of days post-SAH to reach the lowest platelet count, number of days required for the platelet count to recover to admission levels, and WBC count greater than 150×10^2.

Statistical Analysis

Values are represented as the means ± standard devia-

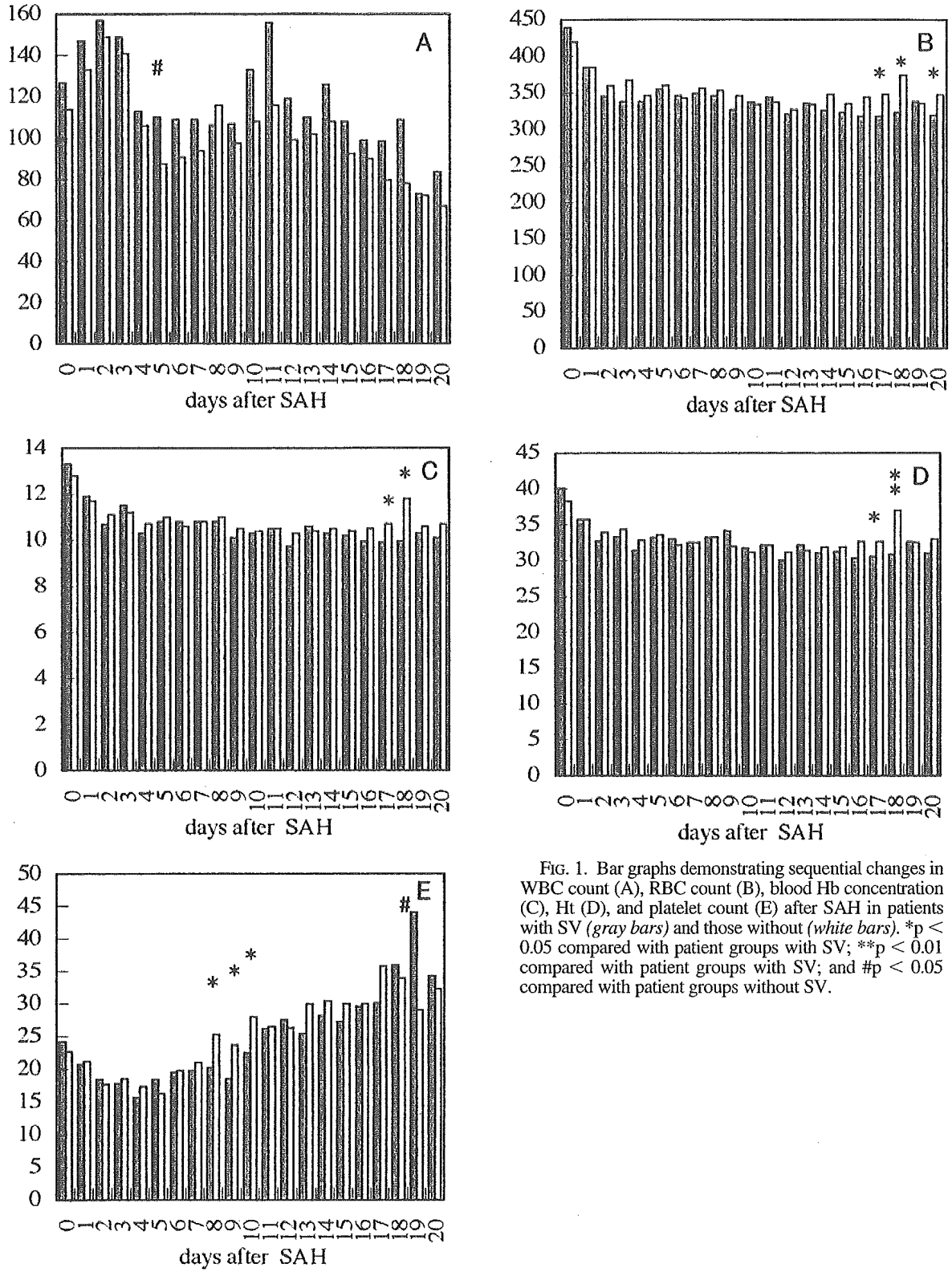

FIG. 1. Bar graphs demonstrating sequential changes in WBC count (A), RBC count (B), blood Hb concentration (C), Ht (D), and platelet count (E) after SAH in patients with SV *(gray bars)* and those without *(white bars)*. *$p < 0.05$ compared with patient groups with SV; **$p < 0.01$ compared with patient groups with SV; and #$p < 0.05$ compared with patient groups without SV.

tion. Univariate analysis was performed to assess the relationships between each variable and the occurrence of SV by using the Student t-test for continuous variables and the Mann–Whitney U-test, Fisher exact test, and chi-square test for categorical data. After eliminating spurious variables that were closely related, some demographic variables and factors involved in the occurrence of SV were analyzed further by performing multiple logistic regression analyses. Variables in the final model were selected according to a stepwise method. Odds ratios were calculated for associations between each risk factor and the occurrence of vasospasm. Interobserver agreement was estimated using the kappa coefficient for classifying Fisher Grade 3 or other grade on admission, and the presence or absence of acute hydrocephalus on admission CT studies. Probability values less than 0.05 were considered significant.

Results

For Fisher grade and acute hydrocephalus, the index of agreement was very high (kappa coefficients 0.91 and 0.96, respectively).

Forty patients (40%) experienced SV after SAH, whereas 60 (60%) did not. Demographic variables such as patient sex ($p = 0.829$) and age ($p = 0.678$) did not differ between patients with and those without SV (Table 1). No significant difference in either the site of ruptured aneurysm ($p = 0.265$) or the presence of acute hydrocephalus on admission ($p = 0.648$) was observed between these two groups, although the Hunt and Hess grade ($p = 0.0372$) and Fisher grade ($p = 0.0158$) were worse in patients with SV than in those without.

The distribution of the presence or absence of a blood examination on each day after SAH did not differ between patients with SV and those without for any of the 21 days (data not shown). The WBC count was greater in the patients with SV than in those without only on Day 5 ($p = 0.0206$; Fig. 1A). The RBC count, Hb concentration, and Ht were lower in the group with SV than in the group without SV in the late phase, that is, on Days 17 (RBC, $p = 0.0338$; Hb, $p = 0.0393$; and Ht, $p = 0.0492$), 18 (RBC, $p = 0.0377$; Hb, $p = 0.0175$; and Ht, $p = 0.0089$), and 20 (RBC, $p = 0.0452$) after SAH (Fig. 1B, C, and D). Nevertheless, the platelet count was smaller in the group with SV than in the group without on Days 8 ($p = 0.0332$), 9 ($p = 0.0342$), and 10 ($p = 0.0382$) and greater in the group with than in the group without SV on Day 19 ($p = 0.0480$; Fig. 1E). Individual sequential changes in platelet count exhibited a gradual decrease followed by an increase and surpassing the initial level, followed by another decrease. The minimum count occurred between Days 1 and 13 in the group with SV (4.43 ± 3.34 days) and between Days 1 and 14 in the group without SV (4.01 ± 2.80 days; Table 1). In patients with SAH who had been conservatively observed for approximately 2 weeks without any intervention, the change in platelet count was exactly the same as that in patients who had undergone surgery within 48 hours after SAH (data not shown). Furthermore, these changes were very small in patients who had undergone cranioplasty alone after surgery for a disease other than SAH (data not shown). Thus, these changes appeared to be specific to SAH. Various factors related to platelet count were examined, such as the lowest platelet count, the ratio of the lowest count and the admission count, the ratio—greater than 0.7—of the lowest count and the admission count, the number of days elapsed to the lowest count after SAH, and the number of days after SAH to recovery of the admission platelet count. The ratio of the lowest count and the admission count was greater than 0.7 more frequently in the group without SV ($p = 0.0359$; Table 1). When, by univariate analysis, we evaluated the association between the occurrence of SV and each risk factor or medical treatment, a significant association was found between glycerol use and patients in the group with SV ($p = 0.0008$; Table 2). After eliminating variables that were closely related to others or considered likely to be effects, rather than causes, of SV, the following items were adopted as confounders in the multiple logistic regression analysis: 1 year of age, male sex, Fisher Grade 3, ratio of the lowest platelet count and the admission count greater than 0.7, history of hypertension, history of tobacco smoking, DM, and alcohol use. Interestingly, results of this analysis revealed that the ratio of the lowest platelet count and the admission count greater than 0.7 (OR 0.322, 95% CI 0.124–0.834, $p = 0.0196$) was negatively significantly associated with the occurrence of SV. Furthermore, a history of hypertension (OR 0.338, 95% CI 0.126–0.906, $p = 0.0311$) and Fisher Grade 3 (OR 4.42, 95% CI 1.48–13.2, $p = 0.0077$) were negatively and positively, respectively, significantly associated with the occurrence of SV (Table 3).

TABLE 3

Results of multiple logistic regression analysis of variables related to SV

Variable	Adjusted OR (95% CI)	p Value
1 yr of age	1.02 (0.98–1.06)	0.363
male sex	1.18 (0.333–4.19)	0.797
Fisher Grade 3	4.42 (1.48–13.2)	0.0077
ratio of lowest platelet count/ admission platelet count >0.7	0.322 (0.124–0.834)	0.0196
hypertension	0.338 (0.126–0.906)	0.0311
tobacco smoking	0.863 (0.249–2.98)	0.816
DM	0.701 (0.102–4.81)	0.718
alcohol use	1.75 (0.480–6.40)	0.395

Discussion

The incidence of SV after SAH has previously been reported to be less than 40%.[5,17,24,28] After reviewing 296 publications, Dorsch[6] reported a mean incidence of SV of 32.4% (10,472 of 32,284 patients with SAH). The incidence of SV in the present series—40%—is somewhat higher. We diagnosed SV conservatively, that is, even when a patient exhibited transient minimal neurological symptoms.

In this series of 100 consecutive patients, a Fisher Grade 3 SAH and a history of hypertension were independent risk factors for SV following SAH. Note that this is the first report in which a variable related to platelet count was determined to be an independent predictor of SV after SAH (Table 3). The ratio of the lowest platelet count and the admission count of greater than 0.7 was independently associated with a reduced risk of SV. Patient age and sex, history of tobacco smoking, DM, and alcohol use were not asso-

ciated with SV after adjusting for variables in the logistic regression model.

The risk of SV is associated with the extent of hemorrhage demonstrated on CT scanning.[20] This conclusion is based on data from many prior studies.[1,2,8,19,21] Similarly, a Fisher Grade 3 SAH was the strongest risk factor for SV in the present study.

The relationship between a history of hypertension and vasospasm is controversial. Although a history of hypertension has been demonstrated to be a predictor of an unfavorable outcome,[27] many investigators have not detected an effect of hypertension on the risk of vasospasm.[1–3,13,21] Nonetheless, other researchers have demonstrated an association between preexisting hypertension and the likelihood of an occurrence of SV.[20,23] Interestingly, our data demonstrated a beneficial association between preexisting hypertension and SV. Note that we also considered patients to have SV when transient neurological symptoms were quickly reversed by induced hypertension. Thus, hypertension may be beneficial in reversing cerebral blood flow at the critical level in some patients without SV.

Recently, McGirt, et al.,[21] demonstrated that leukocytosis for 5 days after SAH is an independent risk factor for cerebral vasospasm following aneurysmal SAH. Note, however, that a WBC count greater than $150 \times 10^2/mm^3$ even 21 days after SAH was not an independent predictor for SV in the present study, although a WBC count tended to be higher in patients with SV than in those without ($p = 0.220$; Table 1). Juvela, et al.,[16] reported sequential changes in platelet count and function in patients with SAH. These authors found that platelet count increased for 3 weeks after SAH and that patients with delayed ischemic deterioration, that is, SV, had greater increases in platelet count. Regarding changes in platelet count after SAH, some discrepant and some coincident points were revealed in a comparison of our findings and those of Juvela and colleagues. In our study within 21 days after SAH, the platelet count decreased but then increased rapidly to a level higher than that demonstrated on admission. Patients with SAH who had not undergone surgery exhibited exactly the same early changes in platelet count, whereas patients with SAH who had undergone cranioplasty did not. The number of days to recover a platelet count from a minimal level tended to be greater in patients with SV than in those without ($p = 0.0954$). In comparing patients with and those without SV, platelet consumption appeared to be more severe in the former than in the latter group from 8 to 10 days after SAH. On the other hand, platelet count was greater in patients with than in patients without SV in the late phase after SAH, that is, approximately 18 days post-SAH ($p = 0.0480$; Fig. 1E). This is a point of agreement in the two studies.[16] The group with SV exhibited anemia that was more severe than that in the group with asymptomatic vasospasm. On multiple logistic regression analysis, platelet consumption, that is, a decrease in the platelet count of more than 30% compared with the level on admission, was found to be an independent predictor of the occurrence of SV. Microcirculatory dysfunction plays an important role in the pathogenesis of vasospasm. During vasospasm, an increased tendency of platelets to aggregate,[9,11] an increased release of substances from platelets and leukocytes (which enhance platelet aggravation),[9,12,15,16] and an increased injury of the endothelium and subendothelium[4,30] may promote platelet consumption.

In a large series Macdonald, et al.,[20] demonstrated other predictors for vasospasm including a patient age of 40 to 59 years, larger aneurysm size, intraventricular hemorrhage, and the prophylactic use of induced hypertension. Some variables were not estimated in the present study and thus additional studies with a large sample size as well as many other variables are required to better understand the mechanism of the occurrence of vasospasm after SAH.

Conclusions

In summary, the association between a decrease in platelet count and the occurrence of SV indicates the important role of platelets in the pathophysiology of vasospasm after SAH.

References

1. Brouwers PJ, Dippel DW, Vermeulen M, Lindsay KW, Hasan D, van Gijn J: Amount of blood on computed tomography as an independent predictor after aneurysm rupture. **Stroke 24:**809–814, 1993
2. Charpentier C, Audibert G, Guillemin F, Civit T, Ducrocq X, Bracard S, et al: Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage. **Stroke 30:**1402–1408, 1999
3. Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, et al: Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. **Stroke 32:**2012–2020, 2001
4. Clatterbuck RE, Gailloud P, Ogata L, Gabremariam A, Dietsch GN, Murphy KJ, et al: Prevention of cerebral vasospasm by a humanized anti-CD11/CD18 monoclonal antibody administered after experimental subarachnoid hemorrhage in nonhuman primates. **J Neurosurg 99:**376–382, 2003
5. Conway JE, Tamargo RJ: Cocaine use is an independent risk factor for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. **Stroke 32:**2338–2343, 2001
6. Dorsch NWC: Cerebral arterial spasm—a clinical review. **Br J Neurosurg 9:**403–412, 1995
7. Feil JM, Flor WJ, Cohan SL, Parkhurst J: Sequential changes of vascular ultrastructure in experimental cerebral vasospasm. Myonecrosis of subarachnoid arterties. **J Neurosurg 41:**49–58, 1974
8. Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. **Neurosurgery 6:**1–9, 1980
9. Hirashima Y, Endo S, Kurimoto M, Tsukamoto E, Takaku A: Platelet-activating factor and antiphospholipid antibodies in subarachnoid haemorrhage. **Acta Neurochir 128:**144–149, 1994
10. Hirashima Y, Hayashi N, Endo S, Takaku A: Sequential changes in the platelet count in patients with symptomatic vasospasm after subarachnoid hemorrhage. **Neurol Med Chir 33:**220–224, 1993
11. Hirashima Y, Kurimoto M, Tsukamoto E, Endo J, Takaku A: Anti-phospholipid antibodies and cerebral vasospasm following subarachnoid haemorrhage. **Acta Neurochir 135:**191–197, 1995
12. Hirashima Y, Nakamura S, Endo S, Kuwayama N, Naruse Y, Takaku A: Elevation of platelet activating factor, inflammatory cytokines, and coagulation factors in the internal jugular vein of patients with subarachnoid hemorrhage. **Neurochem Res 22:** 1249–1255, 1997
13. Hop JW, Rinkel GJ, Algra A, van Gijn J: Initial loss of consciousness and risk of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. **Stroke 30:**2268–2271, 1999
14. Hunt WE, Hess RM: Surgical risk as related to time of intervention in the repair of intracranial aneurysms. **J Neurosurg 28:** 14–20, 1968
15. Juvela S, Hillbom M, Kaste M: Platelet thromboxane release and

delayed cerebral ischemia in patients with subarachnoid hemorrhage. **J Neurosurg 74:**386–392, 1991
16. Juvela S, Kaste M, Hillbom M: Platelet thromboxane release after subarachnoid hemorrhage and surgery. **Stroke 21:**566–571, 1990
17. Kassell NF, Sasaki T, Colohan AR, Nazar G: Cerebral vasospasm following aneurysmal subarachnoid hemorrhage. **Stroke 16:** 562–572, 1985
18. Kelly PJ, Gorten RJ, Grossmann RG, Eisenberg HM: Cerebral perfusion, vascular spasm, and outcome in patients with ruptured intracranial aneurysms. **J Neurosurg 47:**44–49, 1977
19. Lasner TM, Weir RJ, Riina HA, King JT Jr, Zager EL, Raps EC, et al: Cigarette smoking-induced increase in the risk of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. **J Neurosurg 87:**381–384, 1997
20. Macdonald RL, Rosengart A, Huo D, Karrison T: Factors associated with the development of vasospasm after planned surgical treatment of aneurysmal subarachnoid hemorrhage. **J Neurosurg 99:**644–652, 2003
21. McGirt MJ, Mavropoulos JC, McGirt LY, Alexander MJ, Friedman AH, Laskowitz DT, et al: Leukocytosis as an independent risk factor for cerebral vasospasm following aneurysmal subarachnoid hemorrhage. **J Neurosurg 87:**1222–1226, 2003
22. Ohkuma H, Manabe H, Tanaka M, Suzuki S: Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. **Stroke 31:**1621–1627, 2000
23. Ohman J, Servo A, Heiskanen O: Risk factors for cerebral infarction in good-grade patients after aneurysmal subarachnoid hemorrhage and surgery: a prospective study. **J Neurosurg 74:**14–20, 1991
24. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, Ogilvy CS, et al: Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. **Neurology 56:**1299–1304, 2001
25. Park KW, Metais C, Dai HB, Comunale ME, Sellke FW: Microvascular endothelial dysfunction and its mechanism in a rat model of subarachnoid hemorrhage. **Anesth Analg 92:**990–996, 2001
26. Petruk KC, Weir BK, Overton TR, Marriott MR, Grace MG: The effect of graded hypocapnia and hypercapnia on regional cerebral blood flow and cerebral vessel caliber in the rhesus monkey: study of cerebral hemodynamics following subarachnoid hemorrhage and traumatic internal carotid spasm. **Stroke 5:**230–236, 1974
27. Rosen DS, Macdonald RL: Grading of subarachnoid hemorrhage: modification of the world World Federation of Neurosurgical Societies scale on the basis of data for a large series of patients. **Neurosurgery 54:**566–576, 2004
28. Shimoda M, Takeuchi M, Tominaga J, Oda S, Kumasaka A, Tsugane R: Asymptomatic versus symptomatic infarcts from vasospasm in patients with subarachnoid hemorrhage: serial magnetic resonance imaging. **Neurosurgery 49:**1341–1350, 2001
29. Suzuki S, Kimura M, Souma M, Ohkima H, Shimizu T, Iwabuchi T: Cerebral microthrombosis in symptomatic cerebral vasospasm—a quantitative histological study in autopsy case. **Neurol Med Chir 30:**309–316, 1990
30. Tanabe Y, Sakata K, Yamada H, Ito T, Takada M: Cerebral vasospasm and ultrastructual changes in cerebral arterial wall. An experimental study. **J Neurosurg 49:**229–238, 1978

Manuscript received July 21, 2004.
Accepted in final form January 14, 2005.
Address reprint requests to: Yutaka Hirashima, M.D., Department of Neurosurgery, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama-shi, Toyama 930-0194, Japan. email: yhira @ms.toyama-mpu.ac.jp.

Clinical Trials Methods and Design

Rationale and Design of a Randomized Trial to Assess the Effects of β-blocker in Diastolic Heart Failure; Japanese Diastolic Heart Failure Study (J-DHF)

THE J-DHF PROGRAM COMMITTEE

Suita, Japan

ABSTRACT

Background: Heart failure consists of two phenotypes: systolic heart failure and diastolic heart failure (DHF). A growing body of evidence demonstrated benefits of β-blocker, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blocker in systolic heart failure; however, evidence leading to therapeutic strategy of DHF is lacking.

Methods and Results: The Japanese Diastolic Heart Failure Study (J-DHF) is a multicenter, prospective, randomized trial designed to assess effects of β-blocker in patients with DHF. A total of 800 patients (400 patients in each group) will be enrolled. The primary outcome is a composite of cardiovascular death and unplanned admission to hospital for congestive heart failure. Other outcomes include all-cause mortality, worsening of the symptoms of heart failure, or a need for modification of the treatment for heart failure. Serial assessment of echocardiographic and neurohumoral parameters and cost analysis of the treatment regimen will be conducted. The follow-up period is a minimum of 2 years.

Conclusion: This study will provide important evidences for the treatment of DHF.

Key Words: Diastolic heart failure, β-blocker.

The clinical syndrome of congestive heart failure occurs over a broad range of underlying left ventricular (LV) systolic function.[1–4] Epidemiologic studies have revealed that 40% to 50% of patients with heart failure have normal or minimally impaired systolic function.[1,2,5,6] Experimental and clinical studies demonstrated that diastolic dysfunction such as relaxation abnormality and chamber stiffening plays a crucial role in the development of this type of heart failure[7,8] and is termed *diastolic heart failure* (DHF). DHF primarily affects the elderly and females and leads to poor prognosis.[1,2,9,10] The rate of hospitalization and the cost of health care associated with DHF rival those associated with heart failure with systolic dysfunction (systolic heart failure).[5,11] As the age of the world population is increasing, the incidence and the economic impact of DHF will continue to increase.

Our understanding about the therapeutic approach to systolic heart failure has progressed in the past 2 decades. The benefits of angiotensin-converting enzyme (ACE) inhibitor and β-blocker in this type of heart failure have been demonstrated by a number of prospective clinical trials,[12–16] and the treatments with these agents are recommended unless contraindicated. In patients intolerant to ACE inhibitor, angiotensin II type 1 receptor blocker (ARB) is recommended as a substitute based on recent clinical studies.[17–19] However, we have failed to address the therapeutic strategy of nearly half of the epidemic of heart failure, DHF.

Animal experiments with a DHF model demonstrated beneficial effects of β-blocker or a blockade of renin-angiotensin system with ACE inhibitor or ARB,[20–24] and several retrospective clinical studies supported the animal studies.[25–28] A recent clinical trial, CHARM-Preserved trial,[29] demonstrated that ARB decreased a rate of hospitalization from congestive heart failure in patients with DHF; however, the ARB administration did not significantly affect

From the Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, Suita, Japan.

Manuscript received October 7, 2004; revised manuscript received March 31, 2005; revised manuscript accepted April 7, 2005.

Reprint requests: Masatsugu Hori, MD, PhD, FACC, Department of Internal Medicine and Therapeutics (A8), Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita 565-0871, Japan.

Supported in part by the Research Grant for Cardiovascular Diseases (15C-2) from the Ministry of Health, Labour and Welfare.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2005.04.003

the primary end points, cardiovascular death, or unplanned admission to hospital for the management of worsening congestive heart failure. Dauterman et al demonstrated a lack in benefits of ACE inhibitor for patients with DHF in a retrospective clinical study.[30] The Swedish Doppler-Echocardiographic study, a prospective and randomized study in 113 DHF patients, demonstrated an increase in a ratio of peak transmitral E to A wave velocities (E/A) after a 6-month administration of carvedilol, suggesting the improvement of diastolic function; however, overall assessment of diastolic function or heart failure symptoms failed to prove benefits of β-blocker in this type of heart failure.[31] Thus a current consensus is that there is no established therapeutic strategy of DHF, and we designed a multicenter prospective study, J-DHF (Japanese Diastolic Heart Failure Study).

Aims

The aim of this trial is to assess the effects of the β-blocker, carvedilol, as an addition to conventional treatment in patients with DHF (Fig. 1). Carvedilol was chosen as is an only β-blocker approved as a therapeutic regimen for heart failure in Japan.

This study first started to assess effects of ACE inhibitor (if intolerant to ACE inhibitor, switched to ARB) as well as β-blocker in May 2004. However, continuously growing evidence about benefits of ACE inhibitor or ARB in patients with hypertension in our and other countries[32,33] facilitated prescription of ACE inhibitor or ARB at an earlier stage of hypertension in Japan.

Because hypertension is a major underlying cardiovascular disease of DHF,[1,2] a clinical significance to assess effects of ACE inhibitor or ARB prescribed after the onset of DHF has decreased in our country. Thus the study enrollment was not promoted, and a protocol was revised to the current version in February 2005.

Study Design

The study used a multicenter, prospective, randomized, open, blinded endpoint design.

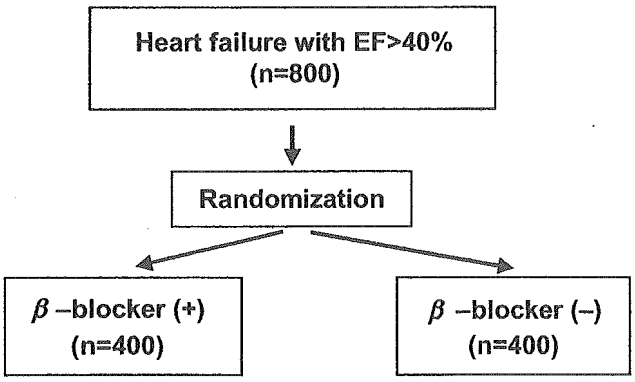

Fig. 1. The Japanese Diastolic Heart Failure Study program design.

Ethical Issues

This study will be conducted in accordance with the principles stated in the Declaration of Helsinki, 1964, as revised in South Africa in 1996. The Ethical Committee in Osaka University Graduate School of Medicine approved this study on December 2, 2003 (no. 318), and the revision of the protocol was approved on February 9, 2005. The study protocol will be also submitted to an ethical committee of each participating hospital. Written informed consent is given by all patients before entry to the study.

Outcome Measures

The primary outcome is a composite of cardiovascular death and unplanned admission to hospital for congestive heart failure. The secondary outcomes are listed as follows: all-cause mortality; worsening of the symptoms (defined by either a decrease by ≥1 Mets in the SAS questionnaire score or an increase by ≥1 class in the New York Heart Association functional class for at least 3 months compared with the baseline); an increase in brain natriuretic peptide by ≥30% of the value at the randomization in patients with brain natriuretic peptide ≥200 pg/mL at the randomization; unplanned admission to hospital for congestive heart failure; or a need for modification of the treatment for heart failure (changes in oral medicine for at least 1 month or addition of intravenous inotropes for at least 4 hours). Outcomes will be assessed by the endpoint committee in which the allocated group was blinded to all the committee members.

Eligibility

- Inclusion criteria
- 20 years of age or older
- Clinical diagnosis of heart failure based on a slight modification the Framingham criteria[34] as previously described[1] within 12 months before the entry (Table 1)
- Documentation of LV ejection fraction >40% by quantitative echocardiography or radionuclide ventriculography when diagnosed as heart failure
- No change in baseline therapy and symptoms of heart failure within 1 month
- Clinical diagnosis of heart failure and LV ejection fraction will be confirmed on hospitalization records or physician practice data. The current status of heart failure will not be considered at the study entry

Table 1. Definition of Heart Failure

Major	Minor
Paroxysmal nocturnal dyspnea	Edema
Orthopnea	Night cough
Abnormal jugular venous distention	Dyspnea on exertion
Pulmonary rales	Hepatomegaly
Cardiomegaly	Pleular effusion
Pulmonary edema	Tachycardia (>120 bpm)
Presence of a third heart sound	Weight loss of ≥4.5 kg in 5 days
Central venous pressure of >16 cmH_2O	(Considered a major criterion if it occurs during therapeutic interventions for heart failure)
Hepatojugular reflux	

A patient is considered to have heart failure if 2 major criteria are present or if 1 major and 2 minor criteria are present concurrently.

Exclusion Criteria

- Current symptomatic hypotension
- Hypertension that has not been controlled to the satisfaction of the investigator by drugs other than β-blocker
- Hemodynamically significant (in the investigators opinion) LV outflow tract obstruction (from either aortic stenosis or ventricular hypertrophy) or mitral valve stenosis
- Important aortic or mitral regurgitation in the investigator's opinion
- Heart rate <50 beats/min
- Second- or third-degree heart block without permanent pacemaker in situ
- Acute coronary syndrome
- Arrhythmogenic right ventricular cardiomyopathy
- Primary pulmonary hypertension or pulmonary hypertension not from LV dysfunction
- Serious cerebrovascular disease
- Acute myocardial infarction within the last 3 months
- Patients who require intravenous inotropes
- Cerebrovascular accident within the last 6 months
- Percutaneous coronary intervention or open heart surgery within the last 3 months
- On the waiting list for percutaneous coronary intervention or open heart surgery
- Serum creatinine >3.0 mg/dL or creatinine clearance ≤30 mL/min
- Known bilateral renal artery stenosis
- Serum potassium >5.5 mEq/L
- Serious liver disease
- Prescription of β-blocker within the last month or a history of a life-threatening adverse event induced by β-blocker
- Any change in cardiovascular drug therapy within a month before randomization
- History of chronic obstructive pulmonary disease or restrictive lung disease
- Diabetes mellitus that has not been controlled to the satisfaction of the investigator
- History of any life-threatening noncardiac disease (eg, cancer) within 5 years
- Other diseases likely to cause death or serious disability within 1 year
- Patients unable to walk without personal aid
- Arteriosclerosis obliterans with Fontaine Grade II or more.
- Severe anemia (hemoglobin ≤6.0 g/dL)
- Uncontrolled thyroid dysfunction

Randomization, Up-Titration, and Maintenance Phase

After screening for eligibility and obtaining written informed consent, patients will be randomized to either arm with or without β-blocker treatment with the stratification according to age (<75, ≥75) and ejection fraction (≤50, >50) in a 1:1 ratio (Fig. 1). In any arms, patients are treated with standard therapy, including diuretics, digitalis, spironolactone, and vasodilators such as ACE inhibitor, ARB, and calcium-channel blockers.

In the β-blocker arm, carvedilol will be up-titrated from 1.25 mg twice daily to the target dose of 10 mg twice daily within 8 weeks based on tolerability. Patients will be maintained at the target dose or the maximum tolerated dose for the rest of the study.

Thereafter, patients are reviewed every 2 to 8 weeks. The planned minimum follow-up period for each patient is 2 years, and electrocardiography, Doppler echocardiography, chest X-ray, and blood sample will be conducted at the study entry and every 12 months after the randomization.

Statistical Considerations

Sample Size

Estimation of cardiovascular death or unplanned admission to hospital for congestive heart failure in patients with DHF was based on the epidemiologic study in Japan.[5] We estimated that a composite outcome of cardiovascular death and unplanned admission to hospital for congestive heart failure will occur in 30% per annum in heart failure patients with ejection fraction >40%. We have planned for a recruitment period of 2 years and a follow-up of 3 years. The risk reduction was assumed to be 20% for treatment with β-blocker.

The power calculation was based on a 2-sided log-rank test for comparing the cumulative incidence curves between the groups treated with and without β-blocker at a significance level of 0.05.[35] A total of 800 patients (400 patients in each group) will be necessary to achieve the power greater than 80%.

Statistical Analysis

All the analyses will be performed according to the intention to treat principle. All study data will be presented stratified by treatment group. All baseline variables will be presented using appropriate descriptive summary tables. The primary outcome will be presented by Kaplan-Meier curves for the treatment groups followed by the stratified log-rank test using the stratification variables. The risk reduction and its 95% confidence interval will be estimated by using Cox proportional hazards model. Similar analyses will be performed for all-cause mortality and the time to either unplanned hospital admission or additional medication. For worsening symptoms and brain natriuretic peptide elevation, chi-square tests will be applied for the analysis. A two-sided P value <.05 will be considered statistically significant. Statistical analysis will be performed using the SAS version 9.1.

Cost Analysis

This study also aims cost analysis of the treatment regimen. To determine costs for outpatient treatments, medication fees for the treatment of DHF are calculated in each patient, and the following assumptions are applied. Patients with DHF are assumed to see cardiologists once per month and to undergo plasma brain natriuretic peptide assay once every 4 months, other blood examination (general peripheral blood test, sodium, potassium, creatinine, urea nitrogen, aspartate aminotransferase, alanine aminotransferase), and chest X-ray once every 9 months, 12-lead electrocardiogram at rest once every 11 months, and Doppler echocardiography once per year. The assumption of the examination schedule was derived from the averaged opinions of 7 cardiologists at different institutes who are specified in the management of heart failure. When the cardiologists answered the questionnaire, they were blind to the answers of the others. Hospitalization costs and inpatient medical expenses in the cardiovascular events are calculated based on the Diagnosis Procedure Combination system (inclusive payment system) in Japan every time a patient is hospitalized. Whenever the cardiovascular events that do not require hospitalization occur, additional medical fees for the modified treatment or unexpected examinations at outpatient clinic are calculated on the basis of fee schedule from fee-for-service.

Safety Monitoring

Two interim analysis will be performed with adjustment by the Lan and DeMets method for multiple comparison.[36] The first is planed for the date on which the planned number of patients has been enrolled. The second is planned 1 year after all the patients have been enrolled. The O'Brien-Fleming type alpha spending function will be used. The independent data safety and monitoring committee will be only responsible for the reviewing these interim results and make recommendations to the Executive and Steering committee members during the course of the trial.

Status of the Study

The first patient was enrolled in May 2004. However, the study protocol was revised in February 2005, and the study is expected to finish in 2009.

Discussion

A lack of evidence about the effects of pharmacologic interventions on DHF is responsible for empirical therapeutic strategies for this type of heart failure.

The CHRAM-Preserved trial was the first prospective and randomized trial to address this issue and the suggested benefits of ARB in DHF.[29] However, administration of ARB did not provide statistically significant effects on the primary endpoint. The Swedish Doppler-Echocardiographic trial was the first prospective and randomized trial to assess the effects of β-blocker on DHF; however, there was no significant effects of β-blocker on severity of heart failure symptoms or LV diastolic function except E/A,[31] which may be partly explained by a small number of the study subjects and a short follow-up period. Currently, several clinical trials that compare the effects of ACE inhibitor or ARB or β-blocker versus placebo are ongoing.[37–40] A total of 2000 patients will be enrolled in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure trial, but it includes patients with both systolic and diastolic heart failure to assess effects of nebivolol.[38] This study may be at least 1 of the largest trials to assess effects of β-blocker on DHF.

The target dose of carvedilol is smaller than that in previous studies conducted in Western countries[14,41]; however, we adopted the standard dose used in Japan.

Previous studies demonstrated that the smaller dose of carvedilol showed the equivalent pharmacologic effect in Japanese patients as larger doses in Western people.[42] In addition, the target dose is a maximum dose that is allowed to be prescribed in Japan.

This study is an open-label design that must be of less statistical power than a double-blind trial. However, an open-trial design may enhance participant recruitment and retention and thus improve generalizability and statistical power.[43] There is a concern that withdrawal rates may differ between the study allocations and may threaten the internal validity of the trial in an open-trial design. We will carefully watch the balance in withdrawal rates. If it is greatly violated, we will perform an adjusted analysis to improve the internal validity.

The initial protocol of this study was designed to assess the effects of ACE inhibitor and β-blocker as compared with the standard therapy without ACE inhibitor, β-blocker, and ARB in patients with DHF. Before the revision of the protocol, 14 patients were enrolled. Five patients in the β-blocker arm of the initial protocol will be followed as a β-blocker group of the revised protocol. Three patients who were assigned to the treatment without ACE inhibitor, β-blocker, and ARB in the initial protocol will be followed as a group treated without β-blocker in the revised protocol. Six patients in the ACE inhibitor arm of the initial protocol will be followed as a group treated without β-blocker in the revised protocol. In any patient, the prescription of ACE inhibitor or ARB was allowed at the revision of the protocol. The inclusion of the patients enrolled before the revision of the study protocol may provide a bias to results of this study; however, the number of the patients was less than 2% of the study subjects, and the inclusion of the patients may not affect the conclusion of this study.

In addition to the assessment of the primary and secondary outcomes, substudies will determine the effects of β-blocker on LV structure and diastolic filling dynamics as assessed with Doppler echocardiography. These are well known to determine prognosis of patients with heart failure, and their assessment may provide a deep insight into the mechanisms of the effects of carvedilol. The subanalysis to assess effects of some combination therapies such as the treatment with β-blocker and ACE inhibitor will be conducted. Cost analysis of the treatment regimen for the management of DHF patients will be also conducted to address economic impact.

In spite of recent progress in treatment of systolic heart failure after a number of prospective clinical trials during the past decades, the prognosis of patients with heart failure is still poor.[44] This may be at least in part attributed to a lack of clinical evidence about the treatment of DHF and thus of appropriate guidelines for DHF. This clinical study will contribute to advances in the treatment of heart failure.

Acknowledgments

The authors gratefully acknowledge the support from Ms. Sonoko Ishizuka, Ms. Aki Sato, and Ms. Tomoko Kobayashi (Japan Clinical Research Assist Center [JCRAC], Tokyo, Japan) as data manager and the secretarial assistance of Ms. Marie Kusaka (Osaka University Graduate School of Medicine, Suita, Japan).

References

1. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282–9.

2. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction. J Am Coll Cardiol 1999;33:1948–55.
3. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144–50.
4. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2001;37:1042–8.
5. Tsutsui H, Tsuchihashi M, Takeshita A. Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. Am J Cardiol 2001;88:530–3.
6. Cleland JGF, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The European Failure survey programme—a survey on the quality of care among patients with heart failure in Europe, part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442–63.
7. Masuyama T, Yamamoto K, Sakata Y, Doi R, Nishikawa H, Kondo H, et al. Evolving changes in Doppler mitral flow velocity pattern in rats with hypertensive hypertrophy. J Am Coll Cardiol 2000;36:2333–8.
8. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953–9.
9. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, et al. Prevalence of heart failure and left ventricular dysfunction in the general population: the Rotterdam Study. Eur Heart J 1999;20:447–55.
10. Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. Ann Intern Med 2002;137:631–9.
11. Vasan RS, Benjamin EJ. Diastolic heart failure—no time to relax. N Engl J Med 2001;344:56–8.
12. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
13. Cohn JN, Johnson G, Zilsche S. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
14. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349–55.
15. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–7.
16. CIBIS-II Investigators. The Cardiac Insufficiency Bisoprolol Study II: a randomized trial. Lancet 1999;353:9–13.
17. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345: 1667–75.
18. McMurray JJV, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767–71.
19. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772–6.
20. Kobayashi M, Machida N, Mitsuishi M, Yamane Y. Beta-blocker improves survival, left ventricular function and myocardial remodeling in hypertensive rats with diastolic heart failure. Am J Hypertens 2004; 17:1112–9.
21. Sakata Y, Masuyama T, Yamamoto K, Doi R, Mano T, Kuzuya T, et al. Renin angiotensin system-dependent hypertrophy as a contributor to heart failure in hypertensive rats: different characteristics from renin angiotensin system-independent hypertrophy. J Am Coll Cardiol 2001; 37:293–9.
22. Kim S, Yoshiyama M, Izumi Y, Kawano H, Kimoto M, Zhan Y, et al. Effects of combination of ACE inhibitor and angiotensin receptor blocker on cardiac remodeling, cardiac function, and survival in rat heart failure. Circulation 2001;103:148–54.
23. Sakata Y, Yamamoto K, Mano T, Nishikawa N, Yoshida J, Miwa T, et al. Temocapril prevents transition to diastolic heart failure in rats even if initiated after appearance of LV hypertrophy and diastolic dysfunction. Cardiovasc Res 2003;57:757–65.
24. Yoshida J, Yamamoto K, Mano T, Sakata Y, Nishikawa N, Nishio M, et al. AT1 receptor blocker added to ACE inhibitor provides benefits at advanced stage of hypertensive diastolic heart failure. Hypertension 2004;43:686–91.
25. Philbin EF, Rocco TA Jr. Use of angiotensin-converting enzyme inhibitors in heart failure with preserved left ventricular systolic function. Am Heart J 1997;134:188–95.
26. Philbin EF, Rocco TA Jr, Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. Am J Med 2000;109:605–13.
27. Chen HH, Lainchbury JG, Senni M, Bailey KR, Redfield MM. Diastolic heart failure in the community: clinical profile, natural history, therapy, and impact of proposed diagnostic criteria. J Card Fail 2002;8:279–87.
28. Lenzen MJ, Scholte op Reimer WJM, Boersma E, Vantrimpont PJMJ, Follath F, Swedberg K, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J 2004;25:1214–20.
29. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.
30. Dauterman KW, Go AS, Rowell R, Gebretsadik T, Gettner S, Massie BM. Congestive heart failure with preserved systolic function in a statewide sample of community hospitals. J Card Fail 2001;7:221–8.
31. Bergstrom A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-Echocardiographic study (SWEDIC). Eur J Heart Fail 2004;6:453–61.
32. Wing LMH, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GLR, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med 2003;348:583–92.
33. Iino Y, Hayashi M, Kawamura T, Shiigai T, Tomino Y, Yamada K, et al. Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension—a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. Hypertens Res 2004;27: 21–30.
34. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441–6.
35. Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics 1982;38:163–70.
36. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.
37. Cleland JGF, Tendera M, Adamus J, Freemantle N, Gray CS, Lye M, et al. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. Eur J Heart Fail 1999;1:211–7.
38. Shibata MC, Flather MD, Bohm M, Borbola J, Cohen-Solal A, Dumitrascu D, et al. Study of the effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure (SENIORS). Rationale and design. Int J Cardiol 2002;86:77–85.
39. Sanderson JE. Re: The PEP-CHF study. Eur J Heart Fail 2000;2:117.
40. Shinozaki T, Watanabe J, Kikuchi J, Tamaki K, Hoshi N, Hayashi M, et al. Rationale, design, and organization of the Diastolic Heart Failure Assessment Study in Tohoku District (DIAST). Circ J 2004;68:660–4.

41. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
42. Hori M, Sasayama S, Kitabatake A, Toyo-oka T, Handa S, Yokoyama M, et al. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. Am Heart J 2004;147:324–30.
43. Avenell A, Grant AM, McGee M, McPherson G, Campbell MK, McGee MA. The effects of an open design on trial participant recruitment, compliance and retention—a randomized controlled trial comparison with a blinded, placebo-controlled design. Clin Trials 2004;1: 490–8.
44. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397–402.

Appendix

The J-DHF Program Committee

Executive committee members. Masatsugu Hori (Chair). Osaka University Graduate School of Medicine: Akira Kitabatake, Hiroyuki Tsutsui, Hiroshi Okamoto, Hokkaido University Graduate School of Medicine; Kunio Shirato, Tohoku University Graduate School of Medicine; Ryozo Nagai, University of Tokyo; Toru Izumi, Kitasato University School of Medicine; Hiroyuki Yokoyama, Shizuoka National Hospital; Yoshio Yasumura, Osaka National Hospital; Yoshio Ishida, National Cardiovascular Center; Masunori Matsuzaki, Yamaguchi University School of Medicine; Takashi Oki, Higashitokushima National Hospital; Michihito Sekiya, Ehime National Hospital.

Endpoint subcommittee members. Toru Izumi (Chair), Kitasato University School of Medicine; Jun Watanabe, Tohoku University Graduate School of Medicine; Koichiro Kinugawa, University of Tokyo; Yoshio Yasumura, Osaka National Hospital; Masafumi Yano, Yamaguchi University School of Medicine; Hiroyuki Tsutsui, Hokkaido University Graduate School of Medicine; Kazuhiro Yamamoto, Osaka University Graduate School of Medicine.

Data management, statistics, cost analysis. Tsutomu Yamazaki, University of Tokyo and Japan Clinical Research Assist Center (JCRAC); Hideki Origasa, Toyama Medical and Pharmaceutical University; Shunya Ikeda, Keio University School of Medicine; Naoki Ishizuka, International Medical Center of Japan.

Steering committee members. Kenjiro Kikuchi, Asahikawa Medical College; Kazuaki Shimamoto, Sapporo Medical University; Katsuhiko Hiramori, Iwate Medical University; Yukio Maruyama, Fukushima Medical University School of Medicine; Hiroshi Ito, Akita University School of Medicine; Isao Kubota, Yamagata University School of Medicine; Ken Okumura, Hirosaki University School of Medeicine; Hiroshi Kasanuki, Tokyo Women's Medical University; Tsutomu Yoshikawa, Keio University School of Medicine; Kazuyuki Shimada, Jichi Medical School; Hiroyuki Daida, Juntendo University School of Medicine; Iwao Kuwajima, Tokyo Metropolitan Geriatric Medical Center; Noboru Takegoshi, Kanazawa Medical University; Hitoshi Hishida, Fujita Health University School of Medicine; Hisayoshi Fujiwara, Gifu University School of Medicine; Genjiro Kimura, Nagoya City University Graduate School of Medical Sciences; Junichi Yoshikawa, Osaka City University School of Medicine; Mitsuhiro Yokoyama, Kobe University Graduate School of Medicine; Tohru Masuyama, Hyogo College of Medicine; Yoshihiko Saito, Nara Medical University; Toru Ohe, Okayama University Graduate School of Medicine and Dentistry; Yoshinori Doi, Kochi Medical School; Jitsuo Higaki, Ehime University School of Medicine; Kenji Sunagawa, Kyushu University Faculty of Medicine; Tsutomu Imaizumi, Kurume University School of Medicine; Koichi Node, Saga University Faculty of Medicine.

Data safety and monitoring committee. Shin-ichi Kimata, Tokyo Kosei-nenkin Hospital; Hirohide Matsuo, Shikoku Electric Power Co. Inc.; Akira Takeshita, Aso Iizuka Hospital.

調査報告

高齢者のQuality of Life（QOL）調査票開発プロジェクトにおける予備調査結果

WHOQOL-OLD調査票日本語版開発グループ

田崎美弥子[*1]・石井八重子[*2]・海老原良典[*3]・折笠秀樹[*4]・高山美智代[*3]・広瀬信義[*3]
角間辰之[*5]・加藤芳朗[*6]・国吉　緑[*7]・Jung Won Lee[*8]・鈴木千智[*9]・長谷川恵美子[*10]
藤井美和[*11]・畑田けい子[*12]・松田正巳[*13]

＊1　東京理科大学理学部教養，＊2　東京女子医科大学看護学部，＊3　慶應義塾大学医学部老年内科
＊4　富山医科薬科大学医学部統計情報学教室，＊5　日本赤十字九州国際看護大学，＊6　大和村国民健康保険診療所
＊7　琉球大学医学部保健学科，＊8　関西福祉科学大学，＊9　日本赤十字豊田看護大学
＊10　聖学院大学人間福祉学部人間福祉学科，＊11　関西学院大学社会学部，＊12　道ノ尾病院精神神経科
＊13　静岡県立大学看護学部

抄録

WHOはEUと共同で2000年度から，高齢者の全体的なQOLを計測するためのWHOQOL調査票の高齢者版開発を目的とした国際共同研究を実施した．本稿では，この高齢者版の日本語版開発における予備調査の，国内における結果について報告する．対象は2002年3～4月に全国7か所に在住する60歳以上の男女410人である．調査票はWHOQOL-100日本語版，WHOQOL-OLD予備調査票日本語版，重要性の調査票，健康状態に関する調査票，社会背景因子に関する調査票の5種類である．結果は，高齢者の全体的QOLに有意に影響を与える社会的背景因子としては性別，居住環境，仕事があげられた．重要性に関しては「身体的領域」に属するものが上位を占めていた．全体のQOL平均値は3.04であった．IRT項目反応理論による解析ではほとんどのWHOQOL-OLDに含まれる項目は識別度が高いと評価されることが確認された．

Key words：QOL，WHOQOL，高齢者，日本人高齢者，WHOQOL-OLD

老年精神医学雑誌 16：221－227，2005

はじめに

QOL概念については，尺度開発をとおしてさまざまな研究がなされてきた．しかし，その多くはがん患者や特定の疾病をもつものを対象としたものであり，「生活者としての人」を対象とした普遍的概念としてのQOLや，高齢の特性を考慮した高齢者QOL尺度の開発は少なかった．そこでWHO本部精神保健部は1992年にWHOQOLプロジェクト[10]を開始し，現在までにWHOQOL基本調査票（WHOQOL-100）[2]，そこに含まれる26の下位項目からなる臨床版（WHOQOL-BREF）[7,8]，WHOQOL Spiritual/Religious/and Personal belief（WHOQOL-SRPB）[1]調査票を開発した．さらに2000年度からはEuropean Union（EU）と共同でWHOQOL調査票の高齢者版を開発することとなった[9]．エジンバラ大学のPower教授をコーディネーターとして世界23か国のセンターが参加し，日本センターもEU加盟諸国以外の国として参加招聘を受けた．そこで，国内9か所の医療機関に所属する研究者の共同研究グループが組織された．

本稿は，WHOQOL-OLD日本語版の開発にあたり実施した予備調査のなかで，高齢者のQOLに

（受付日　2004年7月28日）
Miyako Tazaki, Yaeko Ishii, Yoshinori Ebihara, Hideki Origasa, Michiyo Takayama, Nobuyoshi Hirose, Tatsuyuki Kakuma, Yoshiro Kato, Midori Kuniyoshi, Jung Won Lee, Chika Suzuki, Emiko Hasegawa, Miwa Fujii, Keiko Hatada, Masami Matsuda
＊1　〒162-8601　東京都新宿区神楽坂1-3

影響を与える因子，予備調査にあたり作成されたWHOQOL-OLD予備調査票日本語版の質問項目の妥当性について，日本国内の結果と若干の考察を加え報告するものである．

Ⅰ．対象および調査方法

対象は2002年3～4月の2か月間に，東京（3か所），静岡，神戸，広島，長崎，福岡，沖縄に在住する高齢者とし60～69歳，70～79歳，80歳以上の3つの年齢層で男性と女性ができるだけ同数であるようサンプルの設定を行った．がんの末期患者や痴呆症などの認知的欠損がみられる患者は，調査対象とはしなかった．すべての対象者に各医療機関から調査説明とインフォームド・コンセントを行い調査協力への同意を文書にて得た．調査は原則として面接調査であったが，地域の特性などから一部，事前に調査に関する十分な説明を対面にて行い，協力の承諾を文書にて得たうえで，自己記入式の調査票については自宅にて記入後，郵送で回収する方法がとられた．調査実施期間は2002年8月から12月で，2003年2月にはすべてのデータはコード化され，エジンバラ大学へメールで送付された．

調査票は，①WHOQOL-100日本語版（100問）[6]，②WHOQOL-OLD予備調査票日本語版（46問）（以下，WHOQOL-OLD），③重要性の調査票（高齢者が生活するうえで質問項目の重要度を問う調査で，「あなたにとって健康はどれくらい重要ですか」など40問），④調査対象者の健康状態に関する調査票（23問），⑤調査対象者の社会背景因子に関する調査票（18問）の5種類である．②，③については，まず2回の国際会議を経て質問項目を選択し英語版が完成され，それをもとに英語から日本語への翻訳，さらに翻訳された日本語をもとに英語への逆翻訳を実施して，エジンバラ大学との間で言語等価性を保つためのやりとりを数回経たあとに作成した．WHOQOL-OLDには高齢者特有のものとして「感覚能力」「威厳」「現在・過去・未来の活動性」「時間の使い方」「社会参加」「死と死にいくこと」（40問）が含まれている．①～③は自己記入式で，過去2週間について，それぞれ「まったくない」「少しだけ」「多少は」「かなり」「非常に」の5段階で評価するもので，結果をリッカート法にて得点化した．

●解析方法

以下の手続きに従って処理を行った．

(1) WHOQOL-OLDのQOL平均値を算出した．

(2) すべての調査票に含まれる変数の度数分布を算出したのち，社会背景因子，重要性の因子，健康状態（罹病状況）の因子をそれぞれ説明変数とし，WHOQOL-OLDの領域/下位項目を反応変数として一元配置分散分析を行った．

a）データ入力エラーは，欠損値に変換し，分散を伴わない変数や，分散がきわめて少ない変数は，データ解析から除外することで対処した．

b）WHOQOL-OLDの高齢者特有のものとして加えられた項目については，データ解析においてそれぞれの質問の反応変数に個々の質問を変数として扱うと解析が非常に多くなってしまうので，反応変数としてあらたに領域と下位項目を設定した．

(3) 各項目がどれだけ重要であるかを問う重要性の調査票の各項目の平均値を算出した．

(4) 高齢者特有の質問項目に対し，項目反応理論（Item Response Theory；IRT）の識別力パラメータを用いてそれぞれの質問が妥当なものかどうかについて検討した．5段階の尺度妥当性については，同じく困難度パラメータを用いて，質問の答えにくさを検討した．5段階なので困難度パラメータが4となり，隣り合う同士の差の値は3つ生じる．そこで，30点満点の下位項目では3つの差とも6点未満，35点満点の下位項目では7点未満，40点満点の下位項目では8点未満を妥当と判定した．また，高齢者領域の全体での得点と下位項目内得点との相関については，Pearsonの相関係数を用いた．

Ⅱ．結　果

1．対象者

調査対象者は410人（男性182人，女性228人）であった．地域差によるQOL平均値の有意差はみられなかった．対象者を4つの年齢群に分けるとその内訳は，60～65歳群119人，66～70歳群112人，71～79歳群89人，80歳以上群67人，不明23人である．

2．WHOQOL-100とWHOQOL-OLDの各項目の平均値

WHOQOL-100とWHOQOL-OLDのQOL平均値を表1に示す．各領域の平均値は5点満点で，身体的領域が2.70，心理的領域3.10，社会的関係2.91，環境3.23，信念・精神性2.77，高齢者特有の領域3.16という結果となった．項目として平均QOL値が高かったのは，家庭環境と余暇の時間であった．全体の平均値は3.04であった．

表1　WHOQOL-100とWHOQOL-OLD予備調査票のQOL平均値

身体的領域	**2.70**
F1：痛みと不快	2.55
F2：活力と疲労	3.02
F3：睡眠と休養	2.77
F9：移動能力	2.77
F10：日常活動	2.68
F11：医薬品への依存	2.42
心理的領域	**3.10**
F4：積極的感情	3.34
F5：思考，学習，記憶，集中	3.19
F6：自己評価	3.12
F7：容姿と外見	2.76
社会的関係	**2.91**
F14：社会的支援	2.91
環境	**3.23**
F16：身体的安全	3.29
F17：家庭環境	3.69
F18：経済的状況	2.73
F19：健康と社会的サービス	3.27
F20：新しい情報と技術	3.29
F21：余暇	3.57
F22：身体的環境	3.20
F23：交通手段	2.81
信念・精神性	**2.77**
F24：個人的信念	2.77
高齢者特有のものとして加えられたもの	**3.16**
F25：感覚能力	3.09
F26：威厳	3.30
F27：現在・過去・未来の活動性	3.41
F28：時間の使い方	3.13
F29：社会参加	2.98
F30：死と死にいくこと	3.04
全体の平均値	3.04

3．高齢者の全体的QOLに影響を与える因子（一元配置分散分析の結果）

分散分析の結果，高齢者の全体的QOL（WHOQOL-OLD合計点，200点満点）に有意に影響を与える因子は以下のとおりであった．

1）社会的背景因子

性別では，全体的QOLは，男性（126.6）よりも女性（129.6）のほうが有意に高かった（$F=3.88$，$p<0.05$）．

居住環境では，自宅で生活している高齢者の全体的QOL（130.2）は，施設入所中や長期入院中の高齢者の全体的QOL（119.7）より高かった（$F=2.64$，$p<0.05$）．

仕事では，何らかの仕事をもつ高齢者は，仕事をもたない高齢者（退職者や主婦など）よりも全体的QOLが高かった（$F=2.59$，$p<0.05$）．

主観的健康状態は，全体的QOLに有意な影響を与えなかった．下位項目別の検討では，高齢者の現在・過去・未来の活動性（以下，活動性，7項目，35点満点）に関するQOLに有意な影響を与え，「現在自分は健康である」と考えている人の活動性のQOL（25.28）は「現在自分は健康ではないと思う」と考えている人の活動性のQOL（24.02）よりも高かった（$F=12.15$，$p<0.001$）．

2）重要性の因子

感覚機能の重要性は全体的QOLに有意に影響していた（$F=5.30$，$p<0.05$）．感覚機能を保つことが「非常に重要である」と考えている人は，全体的QOLが高かった（132.4）．この傾向は，とくに活動性に関するQOLと心理に関するQOLにおいて顕著であった（活動性：$F=11.73$，$p<0.0001$，心理：$F=7.33$，$p<0.0001$）．

表2　WHOQOL-OLD 重要性上位10項目

順位	項目		平均値
1	ImpG2	健康	4.47
2	Imp11	痛みがないこと	4.28
3	Imp101	日常生活動作の自立	4.27
4	Imp21	活力があること	4.22
5	Imp91	家のまわりを自由に出歩けること	4.18
6	Imp31	十分な睡眠をとること	4.17
6	Imp261	自立していること	4.17
8	Imp41	幸福を感じたり，人生を楽しむこと	4.13
8	Imp251	感覚（視覚・聴覚・味覚・嗅覚・触覚）があること	4.13
10	Imp191	適切な医療サービスが受けられること	4.10

自由と自立の重要性は，全体的QOLに有意に影響していた（$F=5.31$，$p<0.05$）．自由と自立が「非常に重要である」と考える人は全体的QOL（131.1）が高かった．とくに，活動性の下位項目の検討では，重要性の程度が強いほどQOLが高かった（活動性：$F=15.92$，$p<0.0001$）．

達成感の重要性は，全体的QOLに有意に影響していた（$F=9.41$，$p<0.0001$）．達成感が「非常に重要である」と考える人は全体的QOL（135.3）が高かった．

時間の管理能力の重要性は，全体的QOLに有意に影響していた（$F=6.41$，$p<0.0001$）．時間の管理能力が「非常に重要である」と考えている人は全体的QOL（134.1）が高かった．

社会参加能力の重要性は，全体的QOLに有意に影響していた（$F=4.20$，$p<0.05$）．社会参加能力が「非常に重要である」と考えている人は全体的QOL（135.3）が高かった．

死と死にいくことへの前向きな姿勢の重要性は，活動性と心理的領域に関するQOLに有意な影響を与えていたが，全体的QOLには有意な影響を与えなかった．

3）健康状態（罹病状況）の因子

全体的QOLに有意な影響を与える疾病は，狭心症，腎疾患，心臓ペースメーカーであった（狭心症：$F=5.93$，$p<0.05$，腎疾患：$F=6.69$，$p<0.05$，心臓ペースメーカー：$F=5.13$，$p<0.05$）．このうち，狭心症と腎疾患は，死と死にいくことに関するQOLにも有意な影響を与えていた（狭心症：$F=5.40$，$p<0.05$，腎疾患：$F=5.91$，$p<0.05$）．がん，心筋梗塞，心不全は，すべてのQOLの領域に有意差を認めなかった．

4．重要性の調査票における各項目の平均値

重要性の調査票における各項目の平均値を算出し，高順位10項目を表2に示す．このなかには「身体的領域」に属するものが多く，全体的にみても「感覚」や「動作」に関係するものが高順位であった．「心理的領域」に属するものは全体に散らばっているが，そのなかでも肯定的なもの（「幸福感」や「希望」）が比較的高順位である．「環境」領域に属すると思われるものも全体に散らばっているが，そのなかでも比較的高順位なもの（「医療サービス」「身体的安全保障」「交通手段」）は「身体的領域」に近縁なものが多かった．これらの質問項目に対するQOL反応パターンと，各個人の社会背景因子との間に相関がみられるかどうかを検証したが，全般的に明確な相関はみられなかった．

5．高齢者特有の質問項目の妥当性

IRT解析結果は表3に示す．項目の識別度は，0.2～0.3以上であれば十分と評価されるため，ほとんどのWHOQOL-OLDに含まれる項目は識別度が高いと判断できる．しかし，識別力パラメータの値が負の値であった質問F30.5（「あなたは死ぬことをどのぐらい心配していますか？」）は，項目「死と死にいくこと」に正しく寄与していないといえる．つまり，人によって答えのばらつきが多く，この質問はQOL評価には不適切であると