

Effect of Folate and Mecobalamin on Hip Fractures in Patients With Stroke

A Randomized Controlled Trial

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THE RISK OF A HIP FRACTURE IN patients after stroke is 2 to 4 times higher than that in age-matched healthy control patients.¹ These fractures usually occur relatively late after stroke onset and affect the paretic side of the body.²⁻⁵ Hip fractures are associated with more deaths, disabilities, and medical costs than all other osteoporosis-related fractures combined.⁶ We previously measured the bone mineral density (BMD) in patients with stroke in the second metacarpal bone and demonstrated a decrease in the bone mass in the hemiplegic limb that corresponded to the degree of palsy and vitamin D deficiency,⁷ which may explain why hip fractures in patients poststroke occur almost exclusively on the hemiplegic side of the body.

A close association between plasma homocysteine and risk of ischemic stroke has been reported,⁸⁻¹¹ and plasma homocysteine levels are higher in patients with ischemic stroke in both acute^{12,13} and convalescent phases.¹⁴⁻¹⁷ In patients with homocysteinuria, a rare autosomal recessive biochemical abnormality, there is an increased preva-

Context Stroke increases the risk of subsequent hip fracture by 2 to 4 times. Hyperhomocysteinemia is a risk factor for both ischemic stroke and osteoporotic fractures in elderly men and women. Treatment with folate and mecobalamin (vitamin B₁₂) may improve hyperhomocysteinemia.

Objective To investigate whether treatment with folate and vitamin B₁₂ reduces the incidence of hip fractures in patients with hemiplegia following stroke.

Design, Setting, and Patients A double-blind, randomized controlled study of 628 consecutive patients aged 65 years or older with residual hemiplegia at least 1 year following first ischemic stroke, who were recruited from a single Japanese hospital from April 1, 2000, to May 31, 2001. Patients were assigned to daily oral treatment with 5 mg of folate and 1500 µg of mecobalamin, or double placebo; 559 completed the 2-year follow-up.

Main Outcome Measure Incidence of hip fractures in the 2 patient groups during the 2-year follow-up.

Results At baseline, patients in both groups had high levels of plasma homocysteine and low levels of serum cobalamin and serum folate. After 2 years, plasma homocysteine levels decreased by 38% in the treatment group and increased by 31% in the placebo group ($P < .001$). The number of hip fractures per 1000 patient-years was 10 and 43 for the treatment and placebo groups, respectively ($P < .001$). The adjusted relative risk, absolute risk reduction, and the number needed to treat for hip fractures in the treatment vs placebo groups were 0.20 (95% confidence interval [CI], 0.08-0.50), 7.1% (95% CI, 3.6%-10.8%), and 14 (95% CI, 9-28), respectively. No significant adverse effects were reported.

Conclusion In this Japanese population with a high baseline fracture risk, combined treatment with folate and vitamin B₁₂ is safe and effective in reducing the risk of a hip fracture in elderly patients following stroke.

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lence of skeletal abnormalities,¹⁸⁻²⁰ including osteoporosis, a primary risk factor for hip fracture. Thus, elevated plasma homocysteine concentrations may be associated with osteoporosis and increase the risk of a hip fracture. An increased homocysteine level appears to be a strong and independent risk factor for an osteoporotic fracture of the bones, including the hip, in older men and women.^{21,22}

In the remethylation cycle, homocysteine is salvaged for methionine synthesis by the addition of a methyl group

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by methionine synthase.²³ Vitamin B₁₂ (cobalamin) is an essential cofactor for methionine synthase and N⁵-methyltetrahydrofolate serves as the methyl donor. Therefore, there are close relationships between plasma homocysteine and cobalamin and folate.^{8,9,24-26}

We previously demonstrated a reduction in plasma homocysteine levels by combination therapy with folate and vitamin B₁₂ in patients with ischemic stroke.²⁶ Our goal for this study was to investigate the efficacy of the combined therapy for decreasing the risk of fractures, particularly in the hip, in a 2-year trial in elderly patients with hemiplegia following ischemic stroke.

METHODS

Study Population

We compared the occurrence of hip fractures in patients with stroke who were administered either folate and vitamin B₁₂ in the form of mecobalamin or double placebos. A total of 628 consecutive poststroke outpatients were recruited from the Futase Social Insurance Hospital, Iizuka, Japan, from April 1, 2000, to May 31, 2001; follow-up occurred until May 30, 2003. Inclusion criteria were patients aged 65 years or older, having first-ever noncardioembolic ischemic stroke more than 1 year before, and being in a convalescent stage with poststroke hemiplegia. Exclusion criteria were past history of fracture; impairment of hepatic, renal, cardiac, or thyroid function; known causes of osteoporosis, such as primary hyperparathyroidism, renal osteodystrophy, and familial osteoporosis; or use of any drug known to alter bone and methionine metabolism for 3 months or more during the 12 months preceding the study, including corticosteroids, anticonvulsants, estrogens, calcitonin, bisphosphonates, calcium, folate, or vitamins B₆, B₁₂, D, and K. The diagnosis of ischemic stroke was based on clinical evaluation, magnetic resonance imaging brain scans, and magnetic resonance imaging angiography. The study neurologist (Y.S.), who was blinded to the results of homocys-

teine and vitamin assays, classified strokes into 2 major etiological subtypes: atherothrombotic and lacunar infarction.

Baseline demographic data, duration of illness, body mass index (calculated as weight in kilograms divided by the square of height in meters), current smoking status, history of vascular risk factors, and previous vascular events were recorded. At baseline, we determined Barthel Index, a functional dependence score in which a score of 100 represents independence, while a score of 0 represents total dependence.²⁷ The clinical severity of the hemiplegia was evaluated using the Scandinavian Stroke Scale,²⁸ in which a score of 0 represents complete paralysis of the hand or leg, and a score of 6 represents healthy strength. Patients who fell at least once in the 3 months before recruitment were defined as *fallers*.

The study was approved by the local ethics committee, and written informed consent was obtained from all study participants in the presence of a witness.

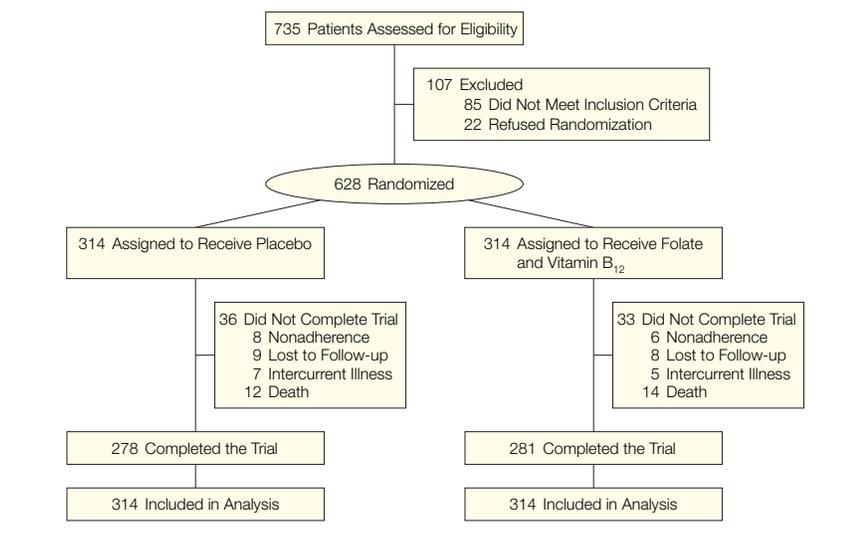
Study Protocol

Patients were assigned to 1 of 2 study groups by means of computer-generated random numbering. Random allocation sequence was implemented by using numbered containers and the sequence was concealed until interventions were assigned. Patients were randomized to the 2 groups by using a permuted block size of 4. No other restrictions were used in the randomization procedure. Patients received a daily dose of 5-mg folate (Foliamin; Nihon Pharmaceuticals, Tokyo, Japan) and 1500- μ g mecobalamin (Methycobal; Eisai Pharmaceuticals, Tokyo, Japan) (n=314), or double placebos (n=314). Patients were blinded to group assignment, and the effectiveness of the blinding was assessed by a questionnaire at the end of the study in which patients were asked to guess their assignment; there was no difference from chance in the frequency of correct guesses ($\kappa=0.009$). No dose adjustments were made at any time dur-

ing the study. Patients were not allowed to take any other drugs that could affect bone and methionine metabolism. Adherence to study medication was assessed by pill count of returned tablets. Follow-up assessment of the patients was performed by 2 physicians who did not participate in the initial randomization and who were blinded to treatment assignment.

Both groups were observed for 2 years. General medical evaluation, metacarpal BMD measurements, and laboratory values were assessed on entry and after 1 and 2 years. For the purpose of our study, *hypertension* was defined as systolic blood pressure of more than 140 mm Hg, diastolic blood pressure of more than 90 mm Hg, or use of antihypertensive medication. *Diabetes mellitus* was defined as a fasting blood glucose level of more than 125 mg/dL (>6.94 mmol/L) or use of diabetic medication. *Hypercholesterolemia* was defined as a serum total cholesterol level of more than 220 mg/dL (>5.70 mmol/L). The patients' clinical status was assessed at baseline, and all patients were observed every 4 weeks in the outpatient clinic, at which time all fractures were recorded. Falls were registered by means of "fall calendars." The participants were instructed to complete the calendar daily, marking an X for each fall on the date that the fall occurred.

Metacarpal BMD measurements on the hemiplegic and nonhemiplegic sides and laboratory values were assessed on study entry to obtain baseline values. Computed x-ray densitometry (Teijin Diagnostics, Tokyo, Japan)²⁹ using a microdensitometric method was used to quantify BMD in the bilateral second metacarpals of each patient as described previously.³⁰ The computer algorithm for computed x-ray densitometry compares bone radiodensity with the gradations of an aluminum step wedge, calculating bone thickness as an aluminum equivalent (mm Al) showing the same x-ray absorption. A BMD value (mm Al) relative to the mean for young adults (T score) was also calculated. The healthy range for BMD for patients aged 65 to 75 years was 2.36

Figure 1. Flow of Participants Through the Study

to 2.96 mm Al,³¹ which corresponds to a T score of -2.1 to 0.7 .

Fasting venous blood was obtained, and homocysteine in plasma was determined using an LC-9A high-performance liquid chromatograph (Shimadzu Co Ltd, Tokyo, Japan) equipped with a fluorescent detector (Hitachi Co Ltd, Tokyo, Japan; healthy range for 66 to 88 years, 7.7 - 14.3 $\mu\text{mol/L}$ ³²). Serum cobalamin and folate were determined by using a competing protein binding assay kit (Bayer Medical Co Ltd, Osaka, Japan) and the values were compared with the reference values in healthy patients aged 65 to 75 years (614 - 1766 pg/mL for cobalamin and 1.9 - 4.3 ng/mL for folate²⁶).

Study End Points and Statistical Analysis

The primary end point was defined as the incidence of a hip fracture. An intention-to-treat analysis was performed on all randomized participants to determine relative risk (RR) and relative risk reduction, absolute risk reduction, and the number needed to treat (NNT). Data satisfied proportional hazards assumptions, and these measures were adjusted for presence of dementia, cardiovascular events, and subsequent strokes by Cox proportional hazards regression model analy-

sis. Patients were censored for nonadherence with study drugs leading to withdrawal, intercurrent illnesses leading to withdrawal, withdrawal of consent, loss to follow up, trauma-related fracture by causes other than fall, and death. For the all-fracture analysis, censoring was at the time of first fracture. For the hip-fracture analysis, patients were included until the time of first hip fracture even if there had been an earlier non-hip fracture. Fracture incidence was analyzed by the Kaplan-Meier method, and the difference between the 2 groups was analyzed by the log-rank test.

Group differences for the categorical data were tested by χ^2 analyses. Spearman rank correlation coefficients were calculated to determine the relationships between BMD and plasma homocysteine or between plasma homocysteine and each variable. For the analyses comparing BMD, homocysteine, and vitamin concentrations between each treatment group, an analysis of covariance model, with age and sex as covariates, was applied to rank-transformed data. SAS software version 8.2 (SAS Institute Inc, Cary, NC) was used for all analyses and $P < .05$ was considered statistically significant.

It was estimated that a study population of 560 patients had an 80% power

to detect a 64% decrease in the risk of hip fractures, given a 10% fracture rate in an untreated group, with a 2-sided α level of .05.

RESULTS

Baseline Characteristics of the Study Participants

Of 735 assessed patients, 628 were randomized into 2 treatment groups (FIGURE 1). Thirty-three patients in the folate and vitamin B₁₂ group and 36 in the placebo group dropped out or withdrew from the study due to nonadherence, loss to follow-up, intercurrent illness, or death. A total of 559 patients (281 in the folate and vitamin B₁₂ group and 278 in the placebo group) completed the trial. We included 314 patients in each treatment group in the final intention-to-treat analysis.

TABLE 1 lists the baseline characteristics of the participants. There was no significant difference between the placebo group and folate and vitamin B₁₂ group in duration of illness, type of stroke, Barthel Index, degree of hemiplegia, numbers of fallers, and prevalence of vascular risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, and previous vascular events.

Compared with the reference range of the healthy Japanese population between ages 50 and 88 years,^{26,32} the 2 stroke groups had high plasma homocysteine and low serum cobalamin levels. Combining the placebo and folate and vitamin B₁₂ groups together, total homocysteine concentration correlated negatively with serum cobalamin ($r = -0.681$, $P < .001$) and serum folate ($r = -0.745$, $P < .001$). The BMD on the hemiplegic side did not correlate with plasma homocysteine concentration ($r = 0.032$, $P = .43$) but correlated positively with degree of hand paralysis ($r = 0.489$, $P < .001$) and negatively with duration of illness ($r = -0.884$, $P < .001$).

Fracture Incidence

Hip Fractures. There were 6 hip fractures in the treatment group and 27

hip fractures in the placebo group (FIGURE 2A); this difference was statistically significant (log-rank $P < .001$). The number of hip fractures per 1000 patient-years was 10 and 43 for the folate and vitamin B₁₂ and placebo groups, respectively. The unadjusted RR, relative risk reduction, and absolute risk reduction in the folate and vitamin B₁₂ group vs placebo group for hip fractures were 0.22 (95% confidence interval [CI], 0.09-0.53), 0.78 (95% CI, 0.47-0.91), and 6.7% (95% CI, 3.2%-10.1%), respectively. The NNT for hip fracture was 15 (95% CI, 10-31). The adjusted RR (adjusted for presence of dementia, cardiovascular events, and subsequent stroke), absolute risk reduction, and NNT for hip fractures in the treatment vs placebo groups were 0.20 (95% CI, 0.08-0.50), 7.1% (95% CI, 3.6%-10.8%), and 14 (95% CI, 9-28), respectively.

All Fractures. There were 8 fractures in the treatment group and 32 fractures in the placebo group (Figure 2B); this difference was statistically significant (log-rank $P < .001$). The unadjusted RR, relative risk reduction, and absolute risk reduction in the folate and vitamin B₁₂ vs placebo groups for all fractures were 0.25 (95% CI, 0.12-0.53), 0.75 (95% CI, 0.47-0.88), and 7.6% (95% CI, 3.9%-11.4%), respectively. The NNT for all fractures was 13 (95% CI, 9-26). The adjusted RR (adjusted for presence of dementia, cardiovascular events, and subsequent stroke), absolute risk reduction, and NNT for all fractures in the treatment vs placebo groups were 0.24 (95% CI, 0.11-0.53), 7.7% (95% CI, 3.9%-11.6%), and 13 (95% CI, 9-25), respectively.

There was no significant difference between the 2 groups in the number of falls per patient during the 2 years (mean, 2.2 [SD, 1.8] in the placebo group and mean, 2.3 [SD, 1.9] in the treatment group).

Bone Changes and Blood Biochemical Markers

The mean (SEM) percentage change from the baseline in the metacarpal

BMD on the hemiplegic side after 2 years was -3.0 (0.2) in the placebo group and -2.9 (0.2) in the folate and vitamin B₁₂ group (TABLE 2). The differences between the treatment groups were not statistically significant ($P = .69$). Plasma homocysteine decreased significantly in the folate and vitamin B₁₂ group (after 1 year, -36.1 [1.7]; after 2 years, -38.1 [1.7]) but increased in the placebo group (after 1 year, 18.2 [1.1]; after 2 years, 31.2 [1.4]). Serum cobalamin and serum folate increased significantly in the folate and vitamin B₁₂ group but de-

creased in the placebo group. These differences between the placebo and folate and vitamin B₁₂ groups were statistically significant (all $P < .001$).

Adverse Effects

Twelve patients in the folate and vitamin B₁₂ group experienced anorexia and nausea, and 1 patient in the folate and vitamin B₁₂ group experienced itching, but these symptoms subsided within a week without discontinuing folate or mecobalamin. Three patients in the placebo group experienced abdominal discomfort. All adverse effects oc-

Table 1. Baseline Characteristics of the Study Population*

Characteristic	Received Placebo (n = 314)	Received Folate and Vitamin B ₁₂ (n = 314)
Age, y	71.2 (4.2)	71.6 (5.1)
Sex, No. (%)		
Female	169 (53.8)	169 (53.8)
Male	145 (46.2)	145 (46.2)
Duration of illness, mo	16.9 (3.6)	16.9 (4.4)
Lacunar infarction/atherothrombotic infarction, No. of patients	217/97	212/102
Barthel Index†	67 (16)	68 (16)
Degree of hemiplegia‡		
Hand	4.5 (1.3)	4.5 (1.3)
Leg	4.5 (1.5)	4.5 (1.4)
Body mass index	22.3 (1.9)	22.3 (1.6)
Fallers, No. (%)§	70 (22)	70 (22)
Prevalence of vascular risk factors, No. (%)		
Hypertension	182 (58)	175 (56)
Diabetes mellitus	70 (22)	68 (22)
Hypercholesterolemia	59 (19)	59 (19)
Current smoker	64 (20)	64 (20)
Previous vascular event	62 (20)	58 (18)
BMD, mm Al		
Hemiplegic side	2.30 (0.24)	2.30 (0.25)
T score¶	-2.9 (1.0)	-2.9 (1.0)
Intact side	2.41 (0.24)	2.42 (0.24)
T score¶	-1.8 (1.0)	-1.8 (0.9)
Concentration levels		
Plasma homocysteine, $\mu\text{mol/L}$	19.9 (20.4)	19.9 (21.3)
Serum cobalamin, pg/mL	590 (332)	606 (382)
Serum folate, ng/mL	2.4 (1.5)	2.4 (1.5)

Abbreviations: Al, aluminum; BMD, bone mineral density.

SI conversion factors: To convert serum cobalamin to pmol/L, multiply by 0.7378; and serum folate to nmol/L, multiply by 2.266.

*Data are presented as mean (SD) unless otherwise specified. Body mass index is calculated as weight in kilograms divided by the square of height in meters. Reference range: BMD, 2.36 to 2.96 mm Al³¹; homocysteine, 7.7 to 14.3 $\mu\text{mol/L}$ ³²; cobalamin, 614 to 1766 pg/mL²⁶; and folate, 1.9 to 4.3 ng/mL²⁶.

†Activities of daily living was evaluated by Barthel Index.²⁷

‡Evaluated by the Scandinavian Stroke Scale.²⁸

§Fallers were defined as patients who fell at least once in the 3 months before recruitment.

|| $P < .001$ vs intact side.

¶Defined as the individual BMD value relative to the standard mean BMD for young adult population. According to the World Health Organization, a T score of less than -2.5 SD is diagnostic of osteoporosis, and a score between -1.0 and -2.5 SD is diagnostic of osteopenia.

curred within 6 months after the initiation of the study.

COMMENT

Treatment with folate and mecobalamin was effective in reducing the risk of the serious poststroke complication of fractures. The high incidence of hip fractures in elderly patients with stroke may be attributed to frequent falls,^{7,30} as well as osteoporosis due to disuse as suggested by our findings and a study on vitamin D deficiency.⁷ In our study, the number of falls was similar in both groups during the follow-up period and the combined therapy with folate and mecobalamin prevented hip fractures in patients with stroke despite frequent falls.

The RR for fractures was extremely low in the folate and vitamin B₁₂ group

compared with the placebo group. Previous studies on the prevention of fracture in women by drug intervention demonstrated that alendronate reduced the incidence of hip fracture with an NNT of 15,³³ and raloxifene reduced the incidence of nonvertebral fracture with an NNT of 18.³⁴ In our study, NNT for hip and all fractures was 14 and 13, respectively, similar to other types of treatment. The therapy was safe during chronic administration.

The loss of BMD in the femoral neck, spine, and total body in an untreated, community-dwelling elderly population of both sexes has been reported to be less than 1% over 3 years.³⁵ In our study, we found more pronounced bone loss on the hemiplegic side in elderly patients following stroke; over 2 years,

BMD decreased by 3.0% in the placebo group and by 2.9% in the folate and vitamin B₁₂ group. We excluded any patient who had taken commonly used agents to prevent osteoporosis, such as calcium and vitamin D. This may have made our study population a high-risk group and may explain the unexpectedly high rate of decline in BMD.

An increased plasma homocysteine level has been found to be a strong and independent risk factor for osteoporotic fracture in older men and women.^{21,22} The age-adjusted incidence rates per 1000 person-years for hip fractures in the lowest and the highest quartiles of total homocysteine levels was 1.96 and 8.14, respectively, for men, and 9.42 and 16.57, respectively, for women.²² The placebo group in our

Figure 2. Kaplan-Meier Plot of Incidence of New Hip Fractures and All Fractures in Patients Receiving Placebo or Folate and Vitamin B₁₂

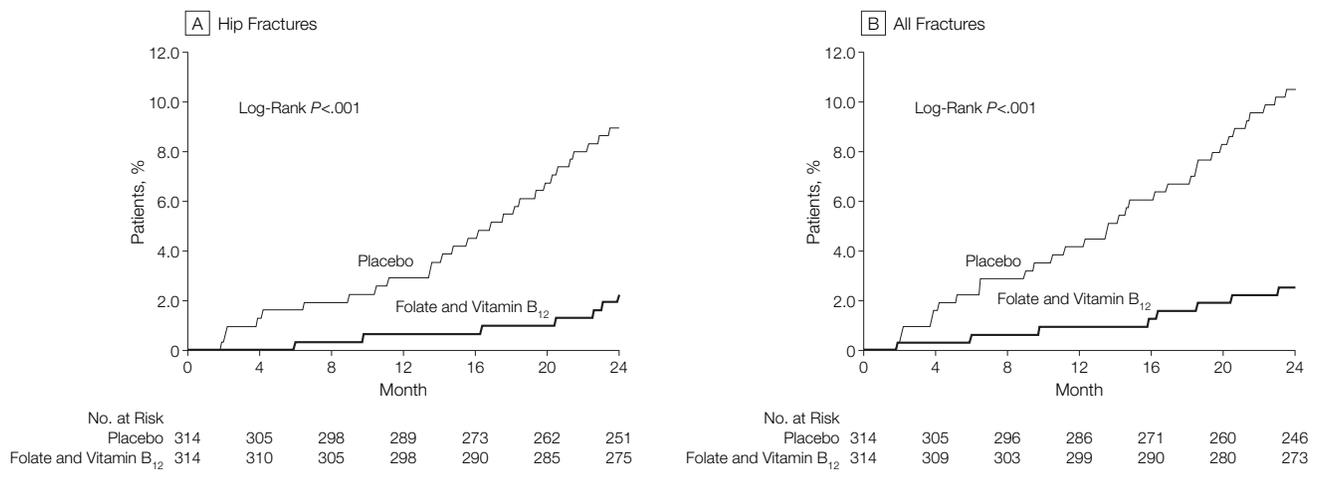


Table 2. Percentage Change of Bone Mineral Density, Plasma Homocysteine, and Serum Vitamins

	Percentage Change, Mean (SEM)					
	After 1 Year			After 2 Years		
	Received Placebo (n = 298)	Received Folate and Vitamin B ₁₂ (n = 299)	P Value*	Received Placebo (n = 278)	Received Folate and Vitamin B ₁₂ (n = 281)	P Value*
Bone mineral density†						
Hemiplegic side	-1.8 (0.2)	-1.7 (0.2)	.89	-3.0 (0.2)	-2.9 (0.2)	.69
Intact side	-1.0 (0.1)	-0.9 (0.1)	.85	-1.9 (0.2)	-1.9 (0.2)	.92
Concentration levels						
Plasma homocysteine	18.2 (1.1)	-36.1 (1.7)	<.001	31.2 (1.4)	-38.1 (1.7)	<.001
Serum cobalamin	-9.1 (3.2)	209.5 (14.6)	<.001	-20.5 (3.0)	214.4 (17.0)	<.001
Serum folate	-12.1 (1.4)	47.2 (3.2)	<.001	-30.1 (1.8)	51.2 (3.8)	<.001

*Comparison between treatment and placebo groups. Based on analysis of covariance model applied to rank-transformed data.
†Bone thickness as an aluminum equivalent measured by computed x-ray densitometry.

study had a much higher incidence rate for hip fracture of 43 per 1000 patient-years, suggesting that homocysteine level may have greater impact on hip fracture risk in patients who have had stroke than in those without stroke, although our patient group may have been a particularly high-risk study population.

In spite of the lack of difference in BMD between the 2 groups, the incidence of hip fractures in the placebo group was higher than in the folate and vitamin B₁₂ group. In accordance with these findings, 2 previous studies failed to find a relationship between homocysteine concentrations and BMD.^{21,36} There is only limited evidence for the direct effect of homocysteine on bone, including its density. The mechanism underlying the association between increased homocysteine levels and the risk of fractures may involve interference of collagen cross-linking by homocysteine,³⁷ which has been shown to specifically interfere with the formation of collagen cross-links and fibrils in solution.³⁸ Because collagen cross-links are important for the stability and strength of the collagen network, interference in their formation may alter bone matrix which, in turn, may enhance bone fragility. However, there are currently no data on bone turnover or bone collagen cross-links in hyperhomocysteinemia, and the combined therapy may be also beneficial in a mechanism independent of homocysteine. Future studies should investigate whether prevention of fractures with folate and vitamin B₁₂ is associated with changes in the markers of bone turnover and collagen cross-linking.

Previous studies reported a hip fracture incidence of 1.75% to 4.65% per year in patients with stroke.^{7,31} The incidence in our placebo group (8.6% in 2 years) was substantially higher, which may have been related to a low intake of vitamin D and calcium in a traditional Japanese diet, particularly common among the elderly Japanese population. Reduced sunlight exposure with decreased active 1,25-dihydroxyvitamin D may also have contributed to the

high prevalence of fractures in the present series.^{7,31} Furthermore, decreased BMD on the hemiplegic side depends on the degree of motor palsy,³⁹ and the severity of the neurological condition may have affected the prevalence of fractures through an effect on osteoporosis.

There are some limitations that need to be considered in the interpretation of our study. First, one of the major risk factors for low BMD at the femoral neck in postmenopausal women is family history of osteoporosis⁴⁰ and many patients with osteoporosis have a familial predisposition⁴¹; this group was excluded from the study population. Our study was conducted at only a single site, which suggests that generalization to broader non-Japanese populations should be performed with caution. Moreover, even assuming that the RR is valid in other groups, the absolute risk reduction would be lower in populations with a lower baseline fracture risk; therefore, NNT would be higher. Finally, the minimal clinically significant difference detectable in our study was a 64% risk reduction. Although our results are statistically significant, given the relatively low power of this study it is important to emphasize that the true RR reduction may be as low as 0.5 (the lower end of the CI).

In conclusion, combined treatment in our population with folate and vitamin B₁₂ is safe and effective in reducing the risk of a hip fracture in elderly patients of both sexes following stroke. Further research is needed to validate these findings in other populations.

Author Contributions: Dr Sato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Satoh.

Acquisition of data: Sato, Honda, Kanoko, Satoh.

Analysis and interpretation of data: Sato, Iwamoto, Satoh.

Drafting of the manuscript: Satoh.

Critical revision of the manuscript for important intellectual content: Sato, Honda, Iwamoto, Kanoko.

Statistical analysis: Honda, Iwamoto.

Administrative, technical, or material support: Kanoko.

Study supervision: Sato.

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Character—the willingness to accept responsibility for one's own life—is the source from which self-respect springs.

—Joan Didion (1934-)