**Table 1** Participants' baseline characteristics ($n$=21,469)

| Variables | ≤5 h ($n$=5,045) | 6 h ($n$=8,678) | 7 h ($n$=5,658) | ≥8 h ($n$=2,088) | Total ($n$=21,469) | $p$ value |
|---|---|---|---|---|---|---|
| Age, mean, $y$ (SD) | 43.3 (11.0) | 46.8 (11.7) | 50.2 (12.8) | 53.6 (14.4) | 47.5 (12.6) | <0.01 |
| Male, $n$ (%) | 2,237 (44.3) | 3,728 (43.0) | 2,525 (44.6) | 959 (45.9) | 9,449 (44.0) | 0.04 |
| Base line BMI | 21.2 (2.2) | 21.2 (2.1) | 21.2 (2.2) | 21.2 (2.2) | 21.2 (2.2) | <0.01 |
| Exercise, $n$(%) | | | | | | <0.01 |
| None per week | 2,326 (46.1) | 3,400 (39.2) | 1,813 (32.0) | 667 (31.9) | 8,206 (38.2) | <0.01 |
| 1–2 days per week | 1,707 (33.8) | 3,278 (37.7) | 2,197 (38.8) | 740 (35.4) | 7,922 (36.9) | <0.01 |
| 3–5 days per week | 593 (11.8) | 1,205 (13.9) | 1,029 (18.2) | 411 (19.7) | 3,238 (15.1) | <0.01 |
| Almost all days | 419 (8.3) | 795 (9.2) | 619 (10.9) | 270 (12.9) | 2,103 (9.8) | <0.01 |
| Alcohol drinker, $n$ (%) | 3,080 (61.1) | 5,183 (59.7) | 3,256 (57.5) | 1,166 (55.8) | 12,685 (59.1) | <0.01 |
| Current smoker | 1,018 (20.2) | 1,463 (16.9) | 868 (15.3) | 356 (17.0) | 3,705 (17.3) | <0.01 |
| Comorbidity | | | | | | |
| Hypertension | 214 (4.2) | 470 (5.4) | 452 (8.0) | 257 (12.3) | 1,393 (6.5) | <0.01 |
| Diabetes | 73 (1.4) | 171 (2.0) | 151 (2.7) | 76 (3.7) | 471 (2.2) | <0.01 |
| Dyslipidemia | 155 (3.1) | 340 (39.2) | 288 (5.1) | 159 (7.6) | 942 (4.4) | <0.01 |
| Past medical history | | | | | | |
| Myocardial infarction | 0 (0.0) | 0 (0.0) | 5 (0.0) | 0 (0.0) | 5 (0.0) | <0.01 |
| Cerebral infarction | 2 (0.0) | 6 (0.0) | 5 (0.0) | 3 (0.0) | 16 (0.0) | 0.50 |

reported past myocardial infarction and 16 reported past cerebral infarction.

Table 2 shows weight and BMI change over 3 years. Those who slept less than 5 h per night demonstrated a BMI increase of 0.10 kg/m$^2$ of (SD 1.02). Those who slept progressively more showed BMI reductions of −0.03, −0.10, and −0.07 kg/m$^2$ (SD 0.94, 0.93, and 0.90), respectively. Excluding those with obesity at baseline, 13,820 participants were included in the linear regression analysis between 2005 and 2008 (Table 3). Multivariate linear regression analysis showed that those who slept less than 5 h per night were more likely to gain weight compared to those who slept 7 h ($\beta$ coefficient=0.03; 95% CI=0.03–1.13). However, there were no significant differences between those who slept 8 h or more and those who slept 7 h.

The results of logistic regression analysis are shown in Table 4. Four hudnred ten (3.7%) participants met the criteria for new obesity during the study period. Multivariate logistic regression model indicated that those who slept less than 5 h per night were more likely to become obese compared to those who reported sleeping 7 h (OR=1.5; 95% CI=1.1–2.0). In contrast, those reporting more than 8 h of sleep had no significant difference compared to those reporting 7 h but have tendency to become obesity more (OR=1.3, 95% CI=0.9–1.8).

**Table 2** Weight and BMI change in 3 years ($n$=13,820)

| Variables | Weight change, kg (SD) | BMI change, kg/m$^2$ (SD) |
|---|---|---|
| Sleep duration | | |
| ≤5 h | 0.28 (0.05) | 0.10 (1.02) |
| 6 h | −0.07 (0.04) | −0.03 (0.94) |
| 7 h | −0.24 (0.04) | −0.10 (0.93) |
| ≥8 h | −0.18 (0.07) | −0.07 (0.90) |

## Discussion

In our study, short sleep duration was associated with weight gain and obesity over a 3-year period in both male and female apparently healthy adults. This association was held true after adjusting for traditional variables associated with obesity, including age, gender, alcohol consumption, frequency of exercise, hypertension, dyslipidemia, diabetes, cerebral infarction, and myocardial infarction. Those reporting less than 5 h of sleep per night tended to have more weight gain and more new-onset obesity compared with those reporting 7 h of sleep.

**Table 3** Results of Linear analysis about BMI change ($n$=13,820) adjusted for age, gender, baseline BMI, alcohol drinking, exercise, hypertension, dyslipidemia, diabetes, cerebral infarction, and myocardial infarction

| Variables | $\beta$ coefficient | 95% CI | $p$ value |
|---|---|---|---|
| Sleep duration | | | <0.01 |
| ≤5 h | 0.03 | 0.03–1.1 | 0.02 |
| 6 h | 0.09 | −0.03–0.06 | 0.49 |
| 7 h | Reference | Reference | |
| ≥8 h | 0.01 | −0.03–0.1 | 0.34 |

**Table 4** Results of logistic analysis about new obesity ($n$=11,136) adjusted for age, gender, baseline BMI, alcohol drinking, exercise, hypertension, dyslipidemia, diabetes, cerebral infarction, and myocardial infarction

| Variables | New obesity, $n$ (%; $n$=410) | Odds ratio | 95% CI | $p$ value |
|---|---|---|---|---|
| Sleep duration | | | | 0.04 |
| ≤5 h | 115 (28.0) | 1.5 | 1.1–2.0 | <0.01 |
| 6 h | 157 (38.3) | 1.1 | 0.9–1.4 | 0.44 |
| 7 h | 94 (22.9) | Reference | Reference | |
| ≥8 h | 44 (10.7) | 1.3 | 0.9–1.8 | 0.22 |

Previous cohort studies demonstrated the association between short sleep duration and weight gain and obesity, though these were conducted in limited populations, namely in the population of men [11] or young adult [15]; these findings are consistent with our results. Also the study in the population of different race and culture had similar result [16]. From these facts, the relationship between sleep duration and obesity seems independent upon ethnicity and cultural habits.

Previous literature, including cross-sectional studies, has suggested physiologic pathways that include induced energy imbalance, hormonal abnormalities, and metabolic behavioral derangements such as increased hunger and reduced physical activity to explain this association [17].

In our study, there was no significant difference in weight gain or new-onset obesity between long sleep duration (more than 8 h) and 7 h sleep duration, but has tendency to weight gain or new-onset obesity. It suggests that long sleep also results in decreased weight/BMI, but perhaps not as strongly as 6–8 h sleep. Maybe sleep over 8 h is like a long tail of diminishing returns. There are some hypotheses about the association between long sleep duration and obesity from previous studies. First, the reduction of active time with longer sleep durations may reduce energy expenditure [11]. Second, obstructive sleep apnea syndrome (OSAS), of which obesity is known to be a primary risk factor, was associated with long sleep duration. The production of proinflammatory cytokines, which cause sleepiness, is increased in OSAS patients. They may be a cause of this increased sleep duration [18]. Third, high leptin resistance may cause obesity and weight gain [19]. Individuals with long sleep durations have higher serum leptin levels, suggesting leptin resistance.

We also analyzed participants characteristics; for example, hypertension, diabetes, and dyslipidemia. The prevalence of those in our study was similar with that of Japanese population [20]. In this aspect, our study was representative of the general Japanese population. However, because annual check-up needs payment, our participants might have high income or education status.

There are some limitations in our study. First, out of the 21,469 participants enrolled, even excluding participants with baseline obesity, only 13,820 participants were finally included in the linear regression analysis and logistic regression analysis due to missing data. Reformatting the health exam survey into a multiple choice questionnaire to facilitate patients' ability to answer questions may be helpful [21]. Second, we did not incorporate data on satisfaction or quality of sleep, nor timing of retiring or awakening, all of which may affect our results [22]. Third, our study was retrospective; large-scale, prospective studies of sufficient duration are needed to further explore the association between sleep duration and obesity. In addition, our data did not include the data of potential confounders such as OSAS. However the prevalence in Japan is about 1%. Moreover those who have OSAS may be eliminated in baseline because of obesity. Therefore it might have small effects for our result.

## Conclusion

Short sleep (≤5 h) may facilitate weight gain and the development of obesity in both male and female adults. Optimal sleep duration to mitigate weight gain in adults appears to be around 7 h.

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**Conflict of interest** None

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ORIGINAL ARTICLE

# Correlation between HIV disease and lipid metabolism in antiretroviral-naïve HIV-infected patients in Japan

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**Abstract** Antiretroviral therapy alters lipid metabolism in HIV-infected patients. However, interpreting the impact of HIV infection on lipid metabolism is difficult because of various associated factors, including antiretroviral drugs and demographic characteristics. A few studies have associated HIV infection with lipid metabolism in antiretroviral-naïve HIV-infected patients. Because there were no data in this regard from Japan, the present study examined the impact of HIV infection, as well as demographic and clinical features, on lipid metabolism in antiretroviral-naïve HIV-infected patients in Japan. We performed a cross-sectional study to examine the impact of HIV disease, demographic and clinical characteristics on lipid metabolism among 168 HIV-infected Japanese men who were antiretroviral naïve and who did not have hemophilia, including patients who took medication for dyslipidemia. The mean age of the patients was 45.7 years; 0.6% of the patients took medication to dyslipidemia. The mean CD4 lymphocyte count was 289/μL, the mean baseline log10 HIV viral load was 4.2 HIV-1 RNA copies/mL, and 22% of the patients had a history of AIDS-defining events. A higher HDL-C concentration was associated with a higher CD4 lymphocyte count ($p = 0.043$). Also, a higher LDL-C concentration was associated with a higher CD4 lymphocyte count ($p = 0.003$). Infection with HIV was associated with dyslipidemia in antiretroviral-naïve patients. More advanced HIV disease was associated with less favorable lipid homeostatic profiles. These results are similar to findings from other countries.

**Keywords** Lipids · HIV infection · Antiretroviral naïve

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## Introduction

The current treatment has significantly prolonged the survival of patients infected with HIV. Accordingly, the frequencies of not only opportunistic infection but also long-term metabolic complications have increased. Several investigators have reported that metabolic syndrome is more common in HIV-infected patients than in HIV-negative individuals, and altered lipid metabolism has also been reported since the start of the HIV epidemic [1–7]. These outcomes have been ascribed to antiretroviral therapy. Studies [8–11] have demonstrated that high total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) concentrations are associated with protease inhibitor (PI) treatment. High TC and TG concentrations have also been identified in patients on non-PI highly active antiretroviral therapy (HAART) regimens.

Some studies have recently demonstrated that HIV infection and demographic characteristics influence lipid metabolism in patients who are antiretroviral naïve [12–15]. Low high-density lipoprotein cholesterol (HDL-C) concentrations and hypertriglyceridemia have been detected in antiretroviral-naïve HIV-infected patients who do not have a history of antiretroviral therapy. However, participants in these studies were derived from predominantly one or two ethnic groups. The impact of HIV infection on lipid metabolism has never been studied in a Japanese population.

The present study determines the impact of demographic and HIV disease characteristics on lipid metabolism in antiretroviral-naïve HIV-infected patients in a Japanese population.

## Patients and methods

### Patient population

A total of 218 HIV-infected nonhemophilic patients were treated at Juntendo University Hospital in Tokyo, Japan between October 1992 and March 2010. We retrospectively reviewed their records and selected 168 Japanese male patients from among them, including patients who took medication for dyslipidemia. Thirty-two patients were excluded because antiretroviral therapy was started at another institution and information about their status before that point was unavailable. Also, 17 patients who were female or not Japanese were excluded.

Patients were eligible if they had evidence of HIV infection, in the form of either positive Western blot findings or measurable plasma HIV-1 RNA. The Research Ethics Committee of Juntendo University School of Medicine approved the study protocol.

### Assessments and measurements

After we obtained their histories, the patients underwent a baseline physical examination to ascertain demographic and clinical characteristics, HIV risk factors, previous HIV disease-related diagnoses, and current medications. Height and weight were measured following a standard procedure, and body mass index (BMI) was calculated as weight in kg/height in $m^2$. We tested for HIV antibody using a chemiluminescence enzyme immunoassay (CLEIA).

Venous blood was drawn from all of the patients, and then concentrations of HDL-C or LDL-C were calculated using the Friedewald formula. The most recent blood data were obtained from patients who had never received antiretroviral therapy, and just before initiating antiretroviral therapy from those who had.

### Statistical methods

Descriptive statistics are reported as mean values with standard SD and median values. Lipid parameters were compared between patients with or without AIDS-defining events using the Mann–Whitney *U* test and the unpaired *t* test. Correlations of HIV RNA level and CD4 cell counts with lipid parameters were assessed by linear analysis.

The level of statistical significance was defined as $p < 0.05$, and all data were analyzed using JMP version 8 (SAS Institute Inc.).

## Results

### Patient population

Of the 168 patients included in this analysis, 27% (17/63) were smokers, 1.8% (3/168) had diabetes, and 0.6% (1/168) had a history of intravenous drug use. 0.6% (1/168) of the patients took medication for dyslipidemia. 60% (100/168) of the patients took antiretroviral therapy that generally consisted of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus either one non-nucleoside reverse transcriptase inhibitor (NNRTI) or a PI (with or without ritonavir boosting), following the guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [16].

The mean age was 45 ± 13 years (mean standard deviation; SD), and 22% (37/167) had AIDS-defining events. The mean baseline CD4 lymphocyte count was 289 ± 249/μL, and the mean baseline log10 HIV RNA was 4.2 ± 0.7 HIV-1 RNA copies/mL (Table 1).

### Lipid parameters and demographic characteristics compared according to HIV stage

Patients were assigned for comparisons to paired groups with or without AIDS-defining events (Table 2). There is

**Table 1** Patient characteristics

| Factor | *n* | Mean ± SD |
|---|---|---|
| Age (years) | 167 | 45.7 ± 13.2 |
| BMI (kg/$m^2$) | 130 | 22.0 ± 3.3 |
| TC (mg/dL) | 145 | 155 ± 35.2 |
| LDL-C (mg/dL) | 43 | 92.2 ± 27.7 |
| HDL-C (mg/dL) | 54 | 38.6 ± 12.4 |
| HIV RNA level (log copies/mL) | 148 | 4.2 ± 0.70 |
| CD4 (cells/μL) | 164 | 289 ± 249 |
| **Factor** | ***n*** | **Number (weighted %)** |
| HIV treatment history | 168 | 100 (59.5) |
| AIDS-defining event (yes) | 167 | 37 (22.2) |
| MSM | 133 | 97 (72.9) |
| Drugs | 168 | 1 (0.6) |
| Smoker | 63 | 17 (27) |
| DM | 168 | 3 (2.9) |

*BMI* body mass index, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *MSM* men who have sex with men, *DM* diabetes mellitus

Value are means ± SD and number (weighted %)

**Table 2** Comparison of the characteristics of patients with or without AIDS-defining events

| Baseline factor | *n* | With AIDS-defining events ($n = 37$) | Without AIDS-defining events ($n = 130$) | *p* value | *Difference | **p* value |
|---|---|---|---|---|---|---|
| TC (mg/dL) | 145 | 152.3 ± 35.1 | 156.5 ± 35.3 | 0.549[b] | 2.32 | 0.2347 |
| LDL-C (mg/dL) | 43 | 99.5 ± 8.33 | 89.7 ± 4.89 | 0.315[b] | −2.09 | 0.4733 |
| HDL-C (mg/dL) | 54 | 32.0 ± 10.5 | 39.9 ± 12.4 | 0.79[a] | 2.17 | 0.1326 |

*BMI* body mass index, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *DM* diabetes mellitus

Value are means ± SD and number (weighted %). Determined by [a]the Mann–Whitney *U* test and [b]the unpaired *t* test

* Adjusted by BMI, age

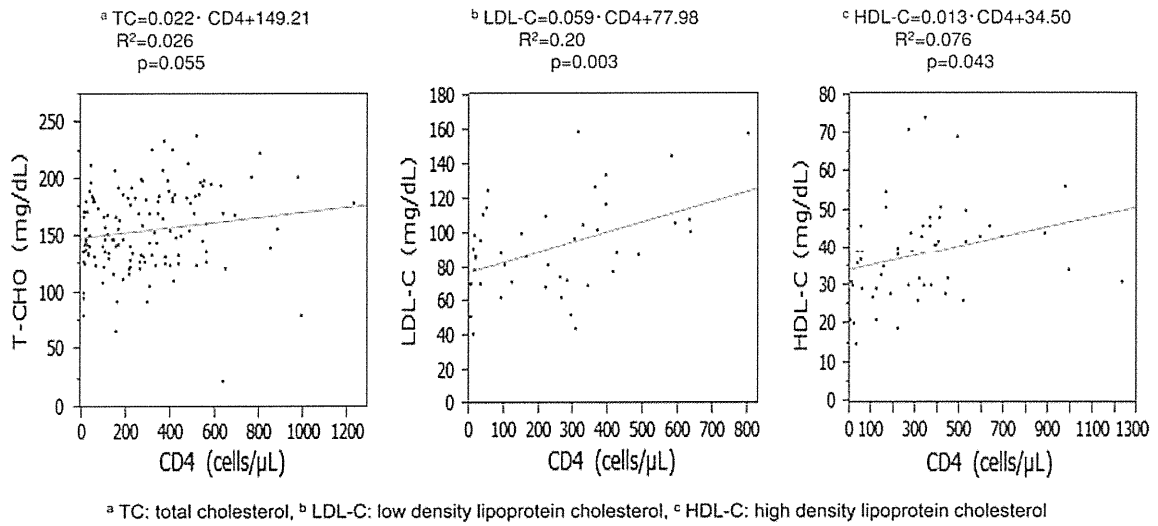



**Fig. 1** Correlation of lipid measures with the $CD4^+$ cell count

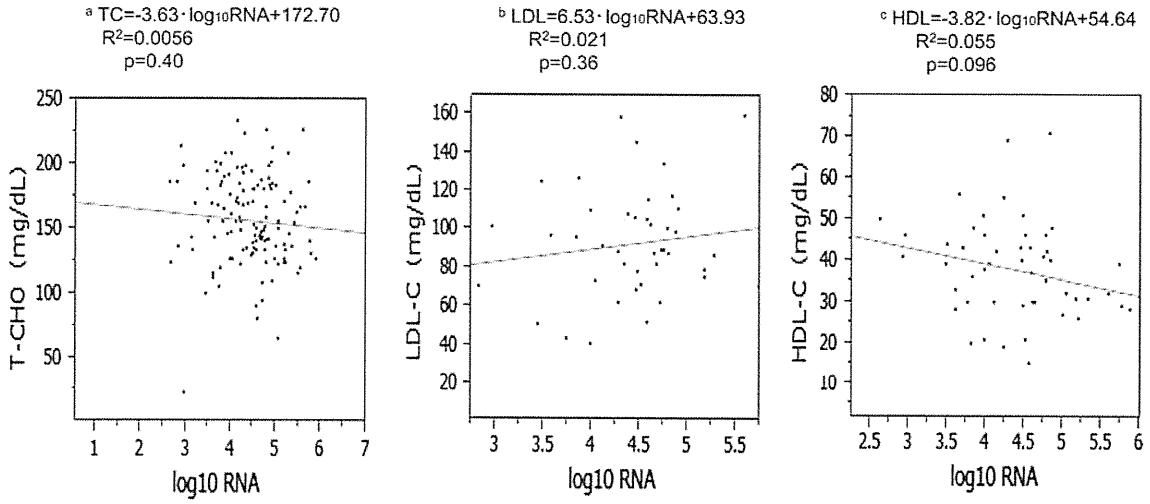
no significant difference in lipid profile between patients with AIDS and those without AIDS.

Higher concentrations of HDL-C and LDL-C were associated with a higher CD4 lymphocyte count. However, HIV RNA levels were not associated with the lipid profile, and CD4 lymphocyte counts were not associated with TC concentrations (Figs. 1, 2).

## Discussion

This study demonstrated the impact of HIV diseases on lipid metabolism in antiretroviral-naïve patients selected from the Japanese male population. The relationships between the markers of HIV infection and lipid parameters in this study were consistent with those of previous reports based on other ethnic populations [12–15]. Patients with lower CD4 lymphocyte counts were more likely to have lower LDL-C and HDL-C levels. A recent study found that HIV seroconversion is associated with decreased TC, HDL-C and LDL-C concentrations [17]. Constans et al. [18] suggested that the alterations in cholesterol metabolism that occur in HIV-infected patients could be explained by lipid peroxidation. The cytokine tumor necrosis factor (TNF)-α plays a role in plasma lipoprotein peroxidation in HIV-infected patients by stimulating the production of reactive oxygen species [19]. These modifications might have major effects on the immune system.

A low HDL-C concentration increases the risk for coronary artery disease [20–22]. Others have found that a lower HDL-C concentration is associated with a higher risk of cardiovascular disease (CVD) in HIV-infected patients in US and European populations [23, 24]. However, no such study had previously been performed for a Japanese population. The HDL-C concentration of HIV-infected patients in this study (38.6 ± 12.4 mg/dL) was <51 mg/dL, which is considered to indicate an increased risk for CVD [25]. There is evidence for relationships between BMI and age to HDL-C concentration [26, 27]. However, small sample size limited our ability to assess causal relationships in this study.




[a] TC: total cholesterol, [b] LDL-C: low density lipoprotein cholesterol, [c] HDL-C: high density lipoprotein cholesterol

**Fig. 2** Correlation of lipid measures with the HIV RNA level

Numerous studies have implicated antiretroviral therapy, and in particular PIs, as an important risk factor for metabolic syndrome including dyslipidemia when controlling for other demographic and traditional risk factors. On the contrary, Mondy et al. [5] showed that metabolic syndrome is closely associated with traditional risk factors rather than with antiretroviral therapy-related effects. Therefore, these and the present findings suggest that the assessment of lipid parameters is an essential component of routine clinical care for HIV-infected patients.

This study has some limitations. The cross-sectional study design and small sample size limited the ability to assess causal relationships between HIV diseases and lipid parameters. Antiretroviral therapy has significantly prolonged the survival of HIV-infected patients, and only lately has more attention has been directed toward long-term metabolic syndrome. Therefore, the lipid data set we obtained was rather small. We also could not always ensure overnight fasting when we took a blood sample because of the retrospective study design. Finally, whether or not lipid data was taken during the treatment of the HIV-infected patient depended on the doctor's subjective judgement, suggesting potential biases.

In conclusion, the present findings indicate that HIV disease itself is associated with lipid metabolism in antiretroviral-naïve patients in the Japanese male population. More advanced HIV disease was also associated with an unfavorable lipid profile. Antiretroviral therapy, together with the stage of HIV disease as well as demographic and clinical characteristics, should be considered when interpreting dyslipidemia in HIV-infected patients.

**Conflict of interest** The authors declare that they have no conflict of interest.

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# Recurrence of colonic diverticular bleeding and associated risk factors

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## Abstract

**Aim** Colonic diverticular bleeding often recurs, but the risk factors remain unclear. Our aim was to identify risk factors for recurrence in patients with diverticular bleeding.

**Method** Seventy-two hospitalized patients who were diagnosed with diverticular bleeding between 2004 and 2008 were analyzed. Rebleeding was considered as the main outcome measure, with the duration until recurrence identified from medical records. Potential risk factors for rebleeding, such as underlying pathologies, medication and smoking and drinking habits, were investigated from the medical records on initial admission.

**Results** Of the 72 patients, 19 had a diverticular disease on the right, 16 on the left side and 37 on both sides of the colon. Recurrence was identified in 27 (38%) patients at a median interval of 1535 days. The cumulative incidence of rebleeding at 6, 12 and 24 months was 15%, 20% and 33%. Multivariate analysis revealed nonsteroid anti-inflammatory drugs (NSAIDs) (hazard ratio (HR), 2.57; 95% confidence interval (CI), 0.89–7.46; $P = 0.08$), antiplatelet drugs (HR, 2.39; 95% CI, 1.01–5.67; $P = 0.05$) and hypertension (HR, 4.16; 95% CI, 1.22–14.2; $P = 0.02$) to be risk factors for rebleeding.

**Conclusion** Patients with colonic diverticular bleeding show high recurrence rates within a short period. Risk factors for recurrence have been identified as the use of NSAIDs or antiplatelet drugs and hypertension.

**Keywords** Colonic diverticular bleeding, recurrence, risk factors, hypertension, NSAIDs, antiplatelet drugs

**What is new in this paper?**

This is the first retrospective cohort study that analyses the recurrence of colonic diverticular bleeding. We report the incidence of rebleeding, the interval between bleeding episodes and the associated risk factors. The use of NSAIDs or antiplatelet drugs and hypertension are risk factors for rebleeding.

## Introduction

The incidence of colonic diverticular disease appears to be increasing [1]. Most patients with colonic diverticular disease are asymptomatic throughout their lifetime, but some can develop serious complications such as colonic bleeding, which is a major cause of bleeding from the lower gastrointestinal tract [2] and occurs in 3–5% of patients with colonic diverticular disease [3]. Past reports have suggested that colonic diverticular bleeding is caused by hard faeces, pharmacotherapy, bleeding tendency and other factors [4]. Previous reports have indicated, furthermore, that risk factors for colonic diverticular bleeding include nonsteroid anti-inflammatory drugs (NSAIDs), antithrombotic agents, steroids, hypertension and hyperuricemia [5,6]. None of these have, however, given information regarding the risk of rebleeding with time.

The present study examined the risk factors for rebleeding in patients presenting with an index episode of colonic diverticular bleeding, with particular attention to the period when rebleeding occurred and the interval between bleeds.

## Method

The records were examined of 72 hospitalized patients who were diagnosed with diverticular bleeding at the

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National Center for Global Health and Medicine between 2004 and 2008. The incidence of rebleeding and the interval to recurrence up to October 2009 were determined. Where medical records were insufficient, telephone interviews were conducted. Possible risk factors studied included associated pathology, medication, smoking and alcohol consumption. For patients who had died, the date and cause of death were determined. Data from patients who died of causes other than bleeding or those who were lost to follow up after discharge were considered censored.

### Diagnosis of colonic diverticular bleeding and recurrence

The diagnosis of colonic diverticular bleeding was based on the painless passage of bloody faeces with haemorrhoids excluded by anorectal examination. All patients underwent colonoscopy or abdominal computed tomography (CT) to exclude other diseases such as colonic cancer or inflammatory bowel disease or other inflammation. CT was performed particularly for patients in a poor systemic condition and in the elderly. Those who underwent colonoscopy were diagnosed based on the criteria described by Jensen [7]. Infectious colitis was excluded by microbiological examination of the stool and cultures. Recurrent bleeding was diagnosed similarly, although re-examination for rebleeding was not performed because these patients had already undergone endoscopic examinations on the initial admission. The bowel was prepared with a cleansing agent containing polyethylene glycol diluted with 2 l of water. A colonoscope using an electronic videoscope (model CFH260; Olympus Optical, Tokyo, Japan) was used.

### Treatment

All patients underwent conservative treatment initially. After making the diagnosis all antithrombotic drugs were stopped. If the bleeding did not stop, an attempt was made to arrest it endoscopically. An attempt at embolization or surgery was performed when an endoscopic approach was unsuccessful. After discharge, any antithrombotic drugs were resumed.

### Risk factors

The use of NSAIDs, steroids and antithrombotic agents has already been investigated in bleeding diverticular disease [5,6]. The patient was regarded to be taking an anticoagulant (warfarin), antiplatelet agent (ticlopidine, clopidogrel, cilostazol, zaltoprofen or dipyridamole) or aspirin if any had been taken for over 1 month or within 2 weeks of the bleed.

A medical history of hypertension, diabetes mellitus, hyperlipidemia, cardio/cerebrovascular disease, chronic hepatic dysfunction or chronic renal failure was ascertained. Diabetes mellitus was diagnosed based on the diagnostic criteria of the American Diabetes Association [8]. Hyperlipidemia was confirmed when a patient was receiving anti-hyperlipidemic medication or showed total serum cholesterol ≥ 240 mg/dl. Cardio/cerebrovascular disease was confirmed when a patient had a history of cardiac infarction, angina pectoris, cerebral infarction or valvular cardiac disease. Chronic hepatic dysfunction was defined as chronic viral hepatitis or alcoholic liver diseases. Chronic renal failure was confirmed in patients receiving haemodialysis or when serum creatinine level was ≥ 2.0 mg/dl. Alcohol and tobacco consumption was quantified.

### Statistical analysis

The interval between the first bleed and recurrence was calculated using the Kaplan–Meier method. Risk factors were evaluated by univariate analysis using the log-rank test. A multivariate analysis using the Cox proportional hazards model was carried out. When developing the final model, we investigated all possible combinations of candidate variables whose $P$ values were $< 0.10$ in univariate analysis, and selected the model where all the variables included had $P$ values $< 0.10$ and minimal Akaike information criterion. All statistical analyses were performed using STATA version 10 software (StataCorp, College Station, Texas, USA).

### Ethics

The study protocol was approved by the ethics committee at the National Center for Global Health and Medicine and was performed in accordance with the Declaration of Helsinki.

## Results

Table 1 shows the characteristics of the first bleeding episode. Among patients with bilateral diverticula, right-sided bleeding occurred in five patients, and left-sided bleeding in eight. The location of bleeding could not be confirmed in 24 patients. Sixty-three patients were treated conservatively and nine underwent endoscopic treatment. Bleeding was difficult to control in only one patient, who underwent right hemicolectomy. Seventeen of the 72 patients required blood transfusion (mean, 2.8 units).

**Table 1** Patient characteristics.

| | $n = 72$ |
|---|---|
| Age, years (mean ± SD) | 72 ± 12 |
| Sex, male/female | 50/22 |
| Location of diverticulum* | |
| Right side | 19 |
| Left side | 16 |
| Bilateral | 37 |
| Type of diverticulum† | |
| Sporadic/scatter type | 19 |
| Cluster type | 53 |

*Right side, proximal and transverse colon; Left side, descending and sigmoid colon; Bilateral, entire colon.
†Sporadic type, 1; Scatter type, 2–9; Cluster type, ≥ 10.

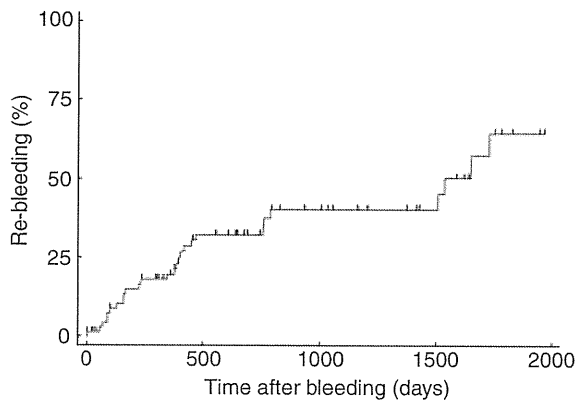


**Figure 1** Cumulative incidence of rebleeding.

The incidence of recurrent bleeding was 38% (27/72), and the median duration to recurrent bleeding was 1535 days. The incidence of recurrent bleeding at 6, 12 and 24 months was 15%, 20% and 33%, respectively (Fig. 1). Eleven patients died during the observation period from causes unrelated to colonic diverticular bleeding.

The results of the log-rank testing indicated that the use of antiplatelet drugs ($P = 0.02$), hypertension ($P < 0.01$) and chronic renal failure ($P = 0.03$) were significant risk factors for rebleeding (Table 2). The results of the multivariate analysis indicated that NSAIDs (hazard ratio (HR), 2.57; 95% confidence interval (CI), 0.89–7.46; $P = 0.08$), antiplatelet drugs (HR, 2.39; 95% CI, 1.01–5.67; $P = 0.05$) and hypertension (HR, 4.16; 95% CI, 1.22–14.2; $P = 0.02$) were significant risk factors for recurrent bleeding (Table 3).

## Discussion

The incidence of recurrent colonic diverticular bleeding was as high as 38%, in line with previous studies that describe rates from 10.8% to 43.4% [9,10]. We also

**Table 2** Risk factors for diverticular rebleeding: univariate analysis.

| | Rebleeding/none | $P$ |
|---|---|---|
| Age (years) | | |
| ≤ 75 | 14/26 | 0.40 |
| > 75 | 13/19 | |
| Sex | | |
| Male | 18/32 | 0.59 |
| Female | 9/13 | |
| Alcohol | | |
| Yes | 8/15 | 0.20 |
| No | 15/19 | |
| Smoking | | |
| Yes | 12/16 | 0.58 |
| No | 11/18 | |
| Location of diverticulum* | | |
| Right side | 6/13 | 0.43 |
| Left side | 5/11 | |
| Bilateral | 16/21 | |
| Type of diverticulum† | | |
| Sporadic/scatter type | 4/15 | 0.06 |
| Cluster type | 23/30 | |
| Warfarin | | |
| Yes | 3/3 | 0.39 |
| No | 24/42 | |
| Antiplatelet drugs | | |
| Yes | 17/18 | 0.02 |
| No | 10/27 | |
| NSAIDs | | |
| Yes | 5/2 | 0.05 |
| No | 22/43 | |
| Steroids | | |
| Yes | 1/1 | 0.50 |
| No | 26/44 | |
| Hypertension | | |
| Yes | 24/22 | < 0.01 |
| No | 3/23 | |
| Diabetes mellitus | | |
| Yes | 9/9 | 0.19 |
| No | 18/36 | |
| Hyperlipidemia | | |
| Yes | 3/6 | 0.68 |
| No | 24/39 | |
| Cardiocerebral disease | | |
| Yes | 10/16 | 0.85 |
| No | 17/29 | |
| Chronic renal failure | | |
| Yes | 5/2 | 0.03 |
| No | 22/43 | |
| Liver disease | | |
| Yes | 2/3 | 0.95 |
| No | 25/42 | |

Data were calculated using the log-rank test.
*Right side, proximal and transverse colon; Left side, descending and sigmoid colon; Bilateral, entire colon.
†Sporadic type, 1; Scatter type, 2–9; Cluster type, ≥10.
NSAIDs, nonsteroidal anti-inflammatory drugs; antiplatelet drugs, including aspirin and other antiplatelet drugs.

**Table 3** Risk factors for diverticular rebleeding: multivariate analysis.

| | Hazard ratio | 95% CI | *P* |
|---|---|---|---|
| NSAIDs | 2.57 | 0.89–7.46 | 0.08 |
| Antiplatelet drugs | 2.39 | 1.01–5.67 | 0.05 |
| Hypertension | 4.16 | 1.22–14.2 | 0.02 |

Hazard ratios were calculated using Cox proportional hazard modelling adjusted for age, sex, hypertension, NSAIDs, antihypertensive drugs, chronic renal failure and type of diverticulum. NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval.

report a 15% recurrence rate within the first year, which doubles by the end of the second year, emphasizing the short interval between bleeds.

Although the risk factors for colonic diverticular bleeding have been studied [5,6], specific risk factors for recurrent bleed have not been reported. We identified NSAIDs, antiplatelet drugs and hypertension as risk factors for recurrent bleeding. Patients with these risk factors had a significantly shorter time to recurrent bleeding.

Several studies have reported associations between NSAIDs and colonic diverticular bleeding [11]. The mechanism by which NSAIDs injure the mucous membrane of the gastrointestinal tract is through cyclooxygenase (COX) inhibition, leading to increased prostaglandin levels, which in turn damage the mucosa, rendering it prone to ulceration [12].

The present study also identified antiplatelet drugs as a risk factor for recurrent diverticular bleeding. These drugs have previously been suggested as a potential risk factor [5], and an odds ratio of 2.4–3.0 for colonic diverticular bleeding was demonstrated in patients on aspirin [5]. A bleeding tendency may also affect the likelihood of recurrent bleeding.

Diverticular bleeding is thought to be caused by a rupture of small vessels in the vicinity of a diverticulum [4]. This explains why hypertension might also be a risk factor [5] through increased pressure in small vessels. We speculate that hypertension might exert a synergistic effect on the likelihood of bleeding in patients on NSAIDs or antiplatelet drugs [5].

The results of the present study should assist in management due to the identification of risk factors, certainly at the time of an initial bleed. Adjustment of the patient's medication might then reduce the risk of rebleeding, or if this is not possible, then at least it would identify patients at increased risk of a rebleed, allowing a degree of increased surveillance in this group.

The location of diverticula is different in Western and Eastern countries. We consider it significant that, in contrast to studies from Western countries, most of the patients in the present study had diverticula on the right. Diverticula on either side can bleed [5,6], which makes location even more difficult with bilateral diverticula.

A limitation of this study was that it was a single-centre, retrospective investigation of a relatively small patient group. Some risk factors might thus have been missed due to the small numbers. In addition, the individual effects of medication on hypertension were not evaluated. A prospective cohort study involving several institutions is required to generalize the results of this study.

In conclusion, we found that colonic diverticular bleeding often recurs within a short period of time and patients taking NSAIDs and antiplatelet drugs and hypertensive patients are at a higher risk of such a recurrence.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

# Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial

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## Abstract

*Background* The efficacy of low-dose lansoprazole has not been established for the prevention of recurrent gastric or duodenal ulcers in those receiving long-term low-dose aspirin (LDA) for cardiovascular and cerebrovascular protection. This study sought to examine the efficacy of low-dose lansoprazole (15 mg once daily) for the secondary prevention of LDA-associated gastric or duodenal ulcers.

*Methods* Patients were randomized to receive lansoprazole 15 mg daily ($n = 226$) or gefarnate 50 mg twice daily ($n = 235$) for 12 months or longer in a prospective, multicenter, double-blind, randomized active-controlled trial, followed by a 6-month follow-up study with open-label lansoprazole treatment. The study utilized 94 sites in Japan and 461 Japanese patients with a history of gastric or duodenal ulcers who required long-term LDA therapy for cardiovascular and cerebrovascular disease.

*Results* The primary endpoint was the development of gastric or duodenal ulcers. The cumulative incidence of gastric or duodenal ulcers on days 91, 181, and 361 from the start of the study was calculated by the Kaplan–Meier method as 1.5, 2.1, and 3.7%, respectively, in the lansoprazole group versus 15.2, 24.0, and 31.7%, respectively, in the gefarnate group. The risk of ulcer development was

For the Lansoprazole Ulcer Prevention Study Group (Low-Dose Aspirin Therapy).

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significantly (log-rank test, $P < 0.001$) lower in the lansoprazole group than in the gefarnate group, with the hazard ratio being 0.099 (95% confidence interval [CI] 0.042–0.230).

*Conclusion* Lansoprazole was superior to gefarnate in reducing the risk of gastric or duodenal ulcer recurrence in patients with a definite history of gastric or duodenal ulcers who required long-term LDA therapy.

**Keywords** Low-dose aspirin · Gastric or duodenal ulcers · Lansoprazole · Cardiovascular diseases · Cerebrovascular diseases

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin (LDA), are known to disrupt the mucosal resistance to gastric acid through mechanisms including the decreased production of endogenous prostaglandin in the gastric mucosa, and are thus associated with adverse events such as gastric or duodenal ulcers. In one Japanese study of patients presenting with a bleeding ulcer, 7.6% were taking LDA [1]. Another study found the point prevalence of ulcers in LDA users to be 11.9–15.2%, irrespective of the aspirin formulation [2]. Furthermore, several observational studies have suggested that the increasing use of LDA is becoming a major cause of bleeding ulcers [3]. In a Japanese single-institution report, ulcer lesions were endoscopically identified in 38 (12.4%) of 305 patients taking LDA [4].

When patients present with gastrointestinal bleeding, discontinuation of LDA is recommended according to various guidelines [5]. However, discontinuation of LDA can be associated with a recurrence of disease, and this can result in serious outcomes [6]. Thus, it is vitally important to ensure prophylaxis of gastric or duodenal ulcers in patients on LDA therapy.

In this context, a number of controlled studies have reported on the prevention of gastric or duodenal ulcers with regular-dose H2-receptor antagonists or proton pump inhibitors (PPIs) in patients during LDA therapy [7–10]. Based on the evidence obtained to date, a clinical expert consensus statement [5] recommends PPIs as the preferred agents for the prophylaxis of LDA-associated gastrointestinal injury. However, to date, low-dose lansoprazole has not been evaluated in a clinical trial for its prophylactic efficacy in patients with definitive evidence of previous ulcer development.

This study thus aimed to examine the preventive effect of low-dose lansoprazole (15 mg daily) against the recurrence of gastric or duodenal ulcer associated with long-term LDA therapy in patients with definitive evidence of previous ulcer history. Ulcer recurrence was defined as endoscopically confirmed ulcers, and the occurrences of gastric or duodenal bleeding with or without hospitalization were also evaluated. Appendix 1 shows the list of investigators for the Lansoprazole Ulcer Prevention Study Group (low-dose aspirin therapy).

Given that no drug has been proven to be effective for the prevention of gastric or duodenal ulcer associated with LDA therapy in Japan, and given that it is unethical to conduct a placebo-controlled trial in patients at high risk of developing gastric or duodenal ulcers, the present study was designed to compare the efficacy of lansoprazole 15 mg once daily and gefarnate 50 mg twice daily [11, 12]. Gefarnate is a cytoprotective anti-ulcer agent which is approved for the treatment for gastric or duodenal ulcers. These cytoprotective anti-ulcer agents are commonly prescribed as prophylactic drugs to reduce NSAID- or LDA-induced gastrointestinal injury, although they have not been investigated in a controlled trial for the latter indication.

## Methods

### Design overview

The study protocol was approved by the Ethics Committee of each participating institution, and all patients gave written informed consent to participate in the study. The Independent Data Monitoring Committee planned an interim analysis in advance to investigate whether or not to continue the study on the basis of interim efficacy and safety findings, based on the predefined criteria. An independent statistician performed the interim analysis on behalf of the Independent Data Monitoring Committee. After the committee made the decision to discontinue the double-blind trial, the patients at the 68 participating healthcare institutes were invited to move on to the follow-up trial with open-label lansoprazole treatment lasting up to 6 months. This trial was registered with ClinicalTrials.gov, number NCT00762359.

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### Setting and participants

Patients were enrolled in the study if they met the following criteria: those who were being given LDA when they gave informed consent, and who required long-term LDA therapy after the start of the study (day 1) with the investigational drug; and those in whom a history of gastric or duodenal ulcer (or gastroduodenal ulcer) was confirmed by endoscopy, i.e., those who were confirmed to have an ulcer scar on day 1 or were confirmed to have an ulcer or ulcer scar in an endoscopic examination performed prior to day 1 (e.g., photographs, films).

Patients were excluded if they were confirmed to have an open gastric or duodenal ulcer or an active upper gastrointestinal hemorrhage by endoscopy on day 1; aspirin-induced asthma or hypersensitivity to NSAIDs including aspirin, or a history of hypersensitivity; a history of surgery or a planned operation which affects gastric secretion (e.g., upper gastrointestinal tract resection, vagotomy); clinically significant liver or kidney disorder (including liver tests demonstrating aspartate aminotransferase [AST]/alanine aminotransferase [ALT] values 2.5 times or higher than their upper limit of normal, or creatinine levels 2.0 times or higher than its upper limit of normal); or an active cancer.

All patients confirmed to be eligible at each trial site were reassessed for their eligibility, based either on endoscopic images on films or data submitted after randomization, by an independent panel of expert endoscopists.

### Randomization and intervention

Patients who met the inclusion criteria were randomly assigned to one of the following two treatment groups: a group receiving the investigational drug (lansoprazole 15 mg orally given once daily) and the cytoprotective anti-ulcer agent, gefarnate placebo (twice daily) or a group receiving gefarnate [11, 12] (50 mg orally given twice daily) and a lansoprazole placebo (once daily), in combination with LDA (81–324 mg given once daily) for a duration of 12 months or longer (up to 30 months). Lansoprazole and gefarnate placebos were used to ensure that all patients followed the same regimen and that blinding was maintained. The treatment-group assignment was done by computer-generated random sequence numbers. Patients were randomly assigned by investigators to receive lansoprazole or gefarnate at a 1:1 ratio according to the unique sequential numbers for the study drugs, which were pre-assigned to each study site before the start of the treatment. When the onset of ulcer was diagnosed endoscopically or LDA was changed to different drugs, the subjects were excluded from the study at that time point.

### Outcomes and measurements

The primary endpoint was the recurrence of gastric or duodenal ulcers, defined as patients confirmed to have active-stage or healing-stage ulcers associated with a mucosal defect with whitish exudates measuring 3 mm or greater. All ulcers confirmed on endoscopy and reported from each study site were reconfirmed by the independent expert panel, based on submitted films. The secondary endpoints were the development of gastric and/or duodenal hemorrhagic lesions as observed with endoscopy, treatment discontinuations due to lack of efficacy, gastric and/or duodenal mucosal damage as assessed with a modified Lanza score [13], and gastrointestinal symptoms.

### Follow-up procedures

Endoscopy was scheduled every 12 weeks until 12 months of treatment and every 24 weeks after 12 months. Non-scheduled endoscopy was also performed if patients were suspected of having symptoms associated with ulcers or signs and symptoms indicative of gastrointestinal bleeding.

Every 4 weeks, clinical laboratory tests (chemistry, hematology, and urinalysis) were performed, blood pressure was measured, compliance checks (returned tablet counts) were conducted, and patients were asked about any adverse effects they experienced. All patients were scheduled to receive the study treatments in a double-blind fashion until 12 months after the start of the study in the last enrolled patient. After the termination of the double-blind trial, patients at the 68 study sites were invited to participate in the follow-up study, in which all patients were treated once daily with lansoprazole 15 mg. If onset of an ulcer was confirmed on endoscopy in a patient, the patient discontinued their medication, and antiulcer treatment – such as full-dose PPI therapy – was offered for ulcer healing.

### Statistical analysis

The 1-year cumulative incidences of ulcer events in patients treated with lansoprazole and gefarnate, in addition to LDA therapy, were assumed to be 6 and 13%, respectively, which suggested that the hazard ratio (HR) of the lansoprazole-treated group relative to the gefarnate-treated group was 0.44 under an exponential assumption of event distributions. We required a total of 64 ulcer events (endpoints) for the two treatment groups to ensure a statistical power of 90% using a log-rank test with a two-sided alpha of 5%. To observe 64 events, we required the enrollment of 406 patients for each treatment group at randomization, for a total of 812 patients for the study, assuming a mean follow-up duration of 1 year and a 1-year dropout rate of 20%.

One interim analysis was planned in advance for the Independent Data Monitoring Committee to perform when half of the required number of ulcer events was observed. The O'Brien-Fleming boundary, based on the information fraction of 0.5, was employed for an overall significance level of $\alpha = 0.05$. To avoid unnecessary trial hazard to subjects assigned to either arm, we planned to discontinue the double-blind trial if the difference in the primary endpoint reached significance at $P = 0.0038$ at the interim analysis.

The cumulative incidences of the primary and secondary endpoints were estimated by using the Kaplan–Meier method and compared between the treatment groups by using the log-rank test. For event-free cases the event times were censored either at the point of the last endoscopy performed or at the point of early withdrawal. We also performed multivariate Cox regression analyses to adjust for possible effects of baseline variables on event times. The final analyses were conducted for the full-analysis set (FAS), defined as all patients who were randomized and received one or more doses of the study medication. In the survival analysis, the patients at risk were defined as all event-free FAS patients who had at least one post-randomization assessment with endoscopy.

Differences in adverse events between the lansoprazole and gefarnate groups were tested for significance by using the $\chi^2$ test.

Analyses were conducted using SAS software (version 9.1.3; SAS Institute, Cary, NC, USA). One and the same statistician (S.M.) had full access to all the trial data and conducted statistical analyses independently of the sponsoring company.

### Role of the funding source

Takeda Pharmaceutical Company Limited (the Sponsor) and its contractor provided all financial and material support for the study design, data collection, data analysis, data interpretation, and preparation and review of manuscripts. The Sponsor was also responsible for consultations with the authors and the members of this study group about the study design and about monitoring of the study. The principal investigator (K.S.) was responsible for the study design and for preparation of the manuscript. All co-authors reviewed the manuscript, and necessary revisions were made to accommodate their suggestions and opinions.

## Results

### Study patients

This prospective, double-blind, randomized, active-controlled trial with an open-label 6-month follow-up study was conducted at a total of 94 healthcare institutions in Japan, in accordance with the principles of good clinical practice and the Declaration of Helsinki. The Independent Data Monitoring Committee performed an interim analysis, based on data that had become available from 414 patients. The cumulative number of ulcer events at the interim analysis was 30 in the gefarnate group and three in the lansoprazole group. The HR was estimated as 0.080 (95% CI 0.023–0.264; $P < 0.001$, 2-sided log-rank test), verifying the efficacy of lansoprazole compared with gefarnate and, accordingly, the Independent Data Monitoring Committee made the decision to terminate the initial part of the study early. Data completion and analysis were performed based on data collected at the termination of the trial. The results discussed here are based on the final data.

Figure 1 shows the flow diagram of this trial. Of the 771 patients enrolled, 461 patients were randomized, while the remaining 310 patients were excluded, primarily because they were not confirmed to have evidence of past gastric or duodenal ulcers on baseline endoscopy after enrollment. Of the 461 patients randomized, 226 were assigned to receive lansoprazole and 235 to receive gefarnate. Of the 235 patients assigned to gefarnate, the study medication was not given to one patient, because malignancy was found in this patient (a violation of the study protocol). Thus, the FAS population comprised a total of 460 patients, with 226 and 234 patients in the lansoprazole group and the gefarnate group, respectively. The numbers of withdrawals were similar in the treatment groups, with 59 withdrawals (26.1%) in the lansoprazole group and 57 (24.3%) in the gefarnate group. The most frequent reasons for withdrawal were adverse events, which occurred in 20 (33.9%) patients in the lansoprazole group and 23 (40.4%) patients in the gefarnate group; followed by protocol deviations (including failure to take the medication) and consent withdrawals in 21 (35.6%) and 13 (22.0%) patients in the lansoprazole group, and 13 (22.8%) and 10 (17.5%) patients, respectively, in the gefarnate group. Additionally, four patients in the gefarnate group withdrew due to lack of efficacy or suspected ulcer-related symptoms/diagnoses. The median duration of follow-up was 7.5 months (range 0.1–17.0) for the lansoprazole group and 5.7 months (range 0.0–16.5) for the gefarnate group. Compliance with the study medication and LDA therapy was similarly high in the two treatment groups. There was no difference between the treatment groups in the frequency distribution of baseline variables (Table 1).

### Efficacy

In the FAS population, the cumulative number of gastric or duodenal ulcer recurrences, i.e., the primary endpoint, at the end of the study was 6/226 (2.7%) in the lansoprazole

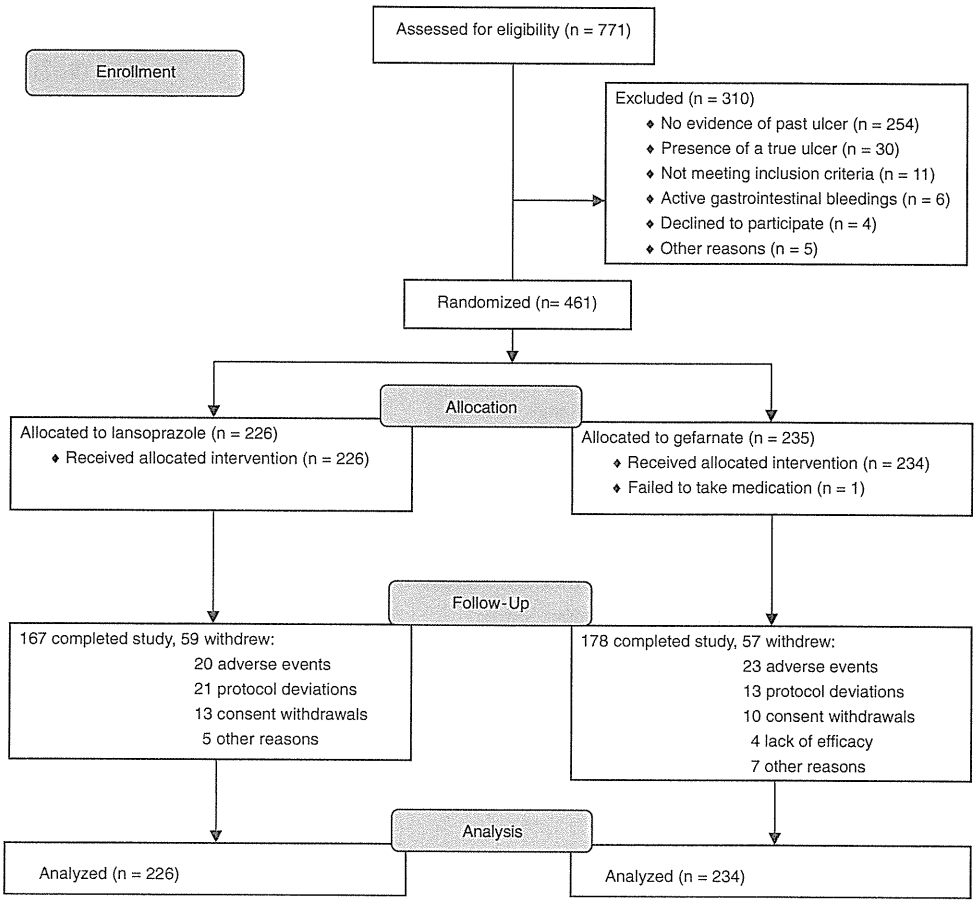


**Fig. 1** Patient disposition in this trial (2010 CONSORT flow diagram)

group and 53/234 (22.6%) in the gefarnate group (Table 2). The cumulative recurrences on days 91, 181, and 361 from the start of the study were estimated as 1.5% (95% CI 0.00–3.20), 2.1% (95% CI 0.06–4.08), and 3.7% (95% CI 0.69–6.65), respectively, for the lansoprazole group, compared to 15.2% (95% CI 10.17–20.22), 24.0% (95% CI 17.84–30.21), and 31.7% (95% CI 23.86–39.57), respectively, for the gefarnate group. The HR of the lansoprazole group relative to the gefarnate group was estimated as 0.099 (95% CI 0.042–0.230)—a 90.1% risk reduction, and the difference was highly significant (log-rank test, $P < 0.001$) (Table 2; Fig. 2).

As to the secondary endpoints (Table 2), the risk of developing gastric/duodenal ulcers or hemorrhagic lesions in the lansoprazole group was significantly lower than that in the gefarnate group (log-rank test, $P < 0.001$). Similarly, the risk of having gastric/duodenal ulcers, hemorrhagic lesions, or treatment discontinuations due to lack of efficacy was significantly lower in the lansoprazole group than in the gefarnate group (log-rank test, $P < 0.001$).

The magnitude of risk reduction for gastric or duodenal ulcers (primary endpoint) was generally stable for all subgroups as defined by each baseline variable (Table 3). The analyses in both *Helicobacter pylori*-positive and -negative subgroups showed ulcer risk reductions, with an HR of 0.061 (95% CI 0.019–0.197; $P < 0.001$) and an HR of 0.206 (95% CI 0.060–0.710; $P = 0.02$), respectively, in each of the subgroups in the lansoprazole group as compared to the gefarnate group. Furthermore, the risk reduction, in terms of HR, was estimated as 0.085 (95% CI 0.034–0.216; $P < 0.001$ by a Wald test) after adjustment for the baseline variables, *H. pylori* status, CYP2C19 polymorphism, age, gender, smoking, alcohol consumption, and concomitant use of anticoagulants in a multivariate Cox regression analysis (Table 4).

We also analyzed the sites of the recurrent ulcers to examine whether the ulcer recurred at sites similar to those of the scars observed at the start of the study. Whitish or red scars were reported in 397 patients (86.1% of total). We further obtained data on the location of the scars from all 59 patients in whom ulcers had relapsed. In 36 (61.0%) of these patients, ulcer recurrence was observed at sites similar to those of the scars seen at the start of the study.

Gastrointestinal damage, as assessed by a modified Lanza score [13], from the start of treatment tended to improve in the lansoprazole group, but to worsen in the gefarnate group, throughout the course of treatment (Supplemental Fig. 1).

In the FAS population, the cumulative number of patients who developed gastric or duodenal hemorrhagic

**Table 1** Demographic and baseline characteristics of Japanese patients randomized to treatment

| | Lansoprazole ($n$ = 226) | Gefarnate ($n$ = 235) |
|---|---|---|
| Mean age (SD), years | 69.3 (8.57) | 68.7 (8.79) |
| Sex | | |
| Males | 175 (77.4) | 192 (81.7) |
| Females | 51 (22.6) | 43 (18.3) |
| Current smoking status | 52 (23.0) | 53 (22.6) |
| Alcohol consumption | 102 (45.1) | 123 (52.3) |
| Mean duration (SD) of prior LDA (months)[a] | 25.4 (13.34) | 24.9 (13.54) |
| Status of concomitant aspirin use | | |
| Aspirin dialminate | 27 (11.9) | 28 (11.9) |
| 81 mg | 26 (11.5) | 26 (11.1) |
| 162 mg | 1 (0.4) | 3 (1.3) |
| Aspirin | 199 (88.1) | 207 (88.1) |
| 100 mg | 193 (85.4) | 194 (82.6) |
| 200 mg | 7 (3.1) | 13 (5.5) |
| Underlying disease[b] | | |
| Ischemic heart disease | 109 (48.2) | 120 (51.1) |
| Ischemic stroke | 96 (42.5) | 97 (41.3) |
| Others | 50 (22.1) | 49 (20.9) |
| *H. pylori* status[c] | | |
| Positive | 137 (60.6) | 125 (53.2) |
| Negative | 89 (39.4) | 109 (46.4) |
| CYP2C19 polymorphism[d] | | |
| EM | 163 (72.1) | 181 (77.0) |
| PM | 40 (17.7) | 34 (14.5) |
| Mean compliance rate (SD), % | | |
| Study drug | 99.03 (2.268) | 98.17 (7.073) |
| LDA therapy | 93.84 (3.319) | 93.12 (7.400) |

Data are numbers (and % of total) except where otherwise indicated

*LDA* low-dose aspirin, *EM* Extensive metabolizers, *PM* poor metabolizers

[a] Those who reported taking LDA for >3 years prior to the start of the study medication were construed as having taken it for 3 years

[b] Some patients were included in more than 1 disease category. The category "Others" includes treatments such as carotid arteriosclerosis or carotid artery occlusion

[c] Unknown in 1 patient

[d] Unknown in 46 patients for whom consent was not obtained for the CYP2C19 polymorphism test

**Table 2** Effect of lansoprazole on each component of the primary and secondary endpoints

| | Lansoprazole[a] ($n$ = 226) | Gefarnate[b] ($n$ = 234) | Hazard ratio (95% CI) | $P$ value[c] |
|---|---|---|---|---|
| Number at risk at baseline[d] | 213 | 227 | | |
| Primary endpoint | | | | |
| Gastric or duodenal ulcer | 6 | 53 | 0.099 (0.042–0.230) | <0.001 |
| Secondary endpoints | | | | |
| Gastric/duodenal ulcer or hemorrhagic lesion | 7 | 56 | 0.109 (0.050–0.239) | <0.001 |
| Gastric/duodenal ulcer, hemorrhagic lesion or treatment discontinuation due to lack of efficacy | 7 | 59 | 0.104 (0.047–0.228) | <0.001 |
| Component | | | | |
| Gastric ulcer | 6 | 40 | | |
| Duodenal ulcer | 0 | 15 | | |
| Hemorrhagic lesion | 2 | 9 | | |
| Treatment discontinuation due to lack of efficacy | 0 | 4 | | |

*CI* confidence interval

[a] Patients received lansoprazole 15 mg daily

[b] Patients received gefarnate 50 mg twice daily

[c] Log-rank test

[d] The number of patients at risk included all full-analysis set patients who received at least 1 endoscopy assessment post-randomization, and had no acute-stage or healing-stage gastric or duodenal ulcer as confirmed by the Independent Adjudication Committee

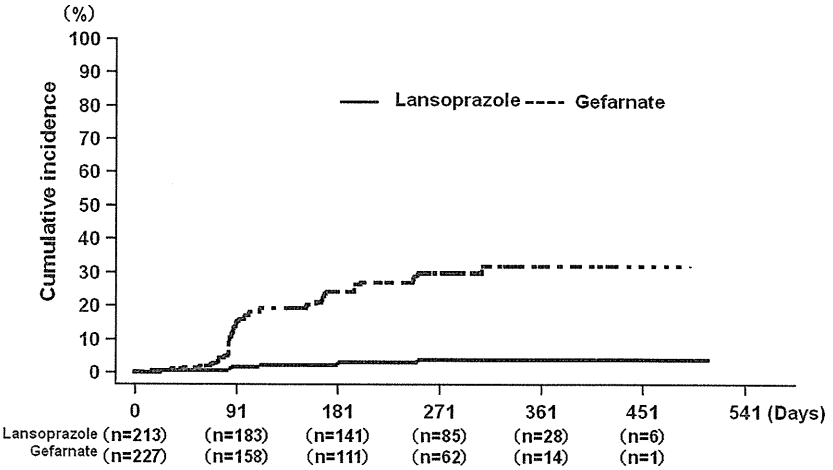


**Fig. 2** Kaplan–Meier estimates of the cumulative incidence of gastric or duodenal ulcers and hemorrhagic lesions in the treatment groups

**Table 3** Analysis of subgroups as defined by each baseline variable

| Baseline characteristics | Recorded number of patients with gastric or duodenal ulcer | | Cox regression analysis | |
|---|---|---|---|---|
| | Lansoprazole | Gefarnate | Hazard ratio (95% CI) | *P* value |
| *H. pylori* status | | | | |
| Positive | 3/128[a] | 38/122[b] | 0.061 (0.019–0.197) | <0.001 |
| Negative | 3/85[a] | 15/105[b] | 0.206 (0.060–0.710) | 0.02 |
| CYP2C19 | | | | |
| PM | 0/38[c] | 9/33[d] | 0.000 (0.000 to –[e]) | – |
| EM | 5/155[c] | 39/175[d] | 0.125 (0.049–0.317) | <0.001 |
| Age | | | | |
| 32–64 years | 1/57 | 14/72 | 0.072 (0.009–0.550) | 0.02 |
| 65–88 years | 5/156 | 39/155 | 0.106 (0.042–0.268) | <0.001 |
| Gender | | | | |
| Male | 5/168 | 43/184 | 0.104 (0.041–0.264) | <0.001 |
| Female | 1/45 | 10/43 | 0.082 (0.011–0.643) | 0.02 |
| Smoker | | | | |
| Yes | 1/49 | 16/51 | 0.048 (0.006–0.365) | 0.01 |
| No | 5/164 | 37/176 | 0.122 (0.048–0.311) | <0.001 |
| Alcohol consumption | | | | |
| Yes | 4/96 | 24/120 | 0.170 (0.059–0.491) | 0.01 |
| No | 2/117 | 29/107 | 0.052 (0.012–0.219) | <0.001 |
| Concomitant use of anticoagulants | | | | |
| Yes | 2/47 | 19/69 | 0.127 (0.029–0.546) | 0.01 |
| No | 4/166 | 34/158 | 0.091 (0.032–0.256) | <0.001 |

Data are *n*/at risk; at risk: the number of patients at risk included all full-analysis set patients who had at least 1 post-randomization endoscopy assessment, and had no acute-stage or healing-stage gastric or duodenal ulcer as confirmed by the Independent Adjudication Committee

*EM* Extensive metabolizers, *PM* Poor metabolizers

[a, b, d] Results of Cox regression analyses; hazard ratio (95% CI), and *P* value: [a] 0.6746 (0.1361–3.3426), $P = 0.63$; [b] 2.2665 (1.2451–4.1258), $P = 0.01$; [d] 0.6970 (0.3373–1.4405), $P = 0.33$

[c] Hazard ratio relative to these subgroups could not be estimated

[e] Could not be estimated

lesions at the end of the study was two of the 226 patients in the lansoprazole group versus nine of the 234 patients in the gefarnate group. The cumulative incidence rate was calculated by the Kaplan–Meier method (Supplemental Fig. 2) and the risk of hemorrhage was shown to be significantly lower in the lansoprazole group than in the gefarnate group. Bleeding ulcers occurred in one patient in the lansoprazole group and five in the gefarnate group. Other gastric or duodenal bleeding was primarily related to erosions. The number of patients who were hospitalized with serious adverse events leading to gastric or duodenal bleeding was one in the lansoprazole group and five in the gefarnate group.

Of the 460 patients randomized to lansoprazole or gefarnate in this trial, 262 who had received lansoprazole or gefarnate were included in an open-label follow-up trial to examine the outcome after another 24 weeks of treatment with lansoprazole, in addition to LDA. During this open-label follow-up trial period, no gastric or duodenal ulcer recurrence was observed in the study participants

**Table 4** Results of multivariate Cox regression analysis using baseline variables

| Baseline characteristics | Direction estimation | Multivariate analysis | |
|---|---|---|---|
| | | Hazard ratio (95% CI) | *P* value |
| Treatment group | Lansoprazole/gefarnate | 0.085 (0.034–0.216) | <0.001 |
| *H. pylori* status | Positive/negative | 2.057 (1.137–3.720) | 0.02 |
| CYP2C19 | PM/EM | 1.434 (0.668–3.076) | 0.36 |
| Age | 10 years' increase | 1.459 (1.045–2.036) | 0.03 |
| Gender | Male/female | 0.893 (0.437–1.823) | 0.76 |
| Smoking status | Yes/no | 1.532 (0.820–2.863) | 0.19 |
| Alcohol consumption | Yes/no | 1.047 (0.588–1.866) | 0.88 |
| Concomitant use of anticoagulants | Yes/no | 1.200 (0.665–2.166) | 0.55 |

*EM* Extensive metabolizers, *PM* Poor metabolizers

(Supplemental Table 1). Importantly, compared to the ulcer recurrence in the double-blind phase, no ulcer recurrence was observed from the gefarnate group during the 6 months of the lansoprazole open study, indicating the potent preventive effect of lansoprazole.

Adverse events

With respect to adverse events observed in the double-blind study period (Table 5), diarrhea was noted significantly more frequently in the lansoprazole group than in the gefarnate group, while reflux esophagitis occurred significantly more frequently in the gefarnate group. No serious adverse drug reactions occurred in the lansoprazole group, versus one (liver disorder) in the gefarnate group. No deaths occurred in either group. Of the 21 patients who discontinued lansoprazole, four were suspected of having possible adverse drug reactions, which included stomatitis, abnormal liver function tests, diarrhea, constipation, and palpitation. In the gefarnate group, six patients experienced possible adverse drug reactions, which included dyspepsia, Mallory–Weiss syndrome, eczema, tinnitus, toxic skin eruption, and liver disorder.

From the start of the double-blind study through the continued follow-up trial, four bone fractures were observed in four patients in the lansoprazole group, with three events occurring during the double-blind trial period ($P = 0.08$, $\chi^2$ test, vs. gefarnate group), and the other one event occurring in the open-label follow-up period. Investigators reported the causes of the bone fractures to be factors such as aging, accidental fall occurring as a result of a subject's inattentiveness, and the like; hence, their causal relationship to lansoprazole was denied. No bone fracture occurred in the gefarnate group during the double-blind period.

During the entire study, including the follow-up trial, two deaths occurred, due to ventricular fibrillation and acute myocardial infarction, respectively; their causal relationship to lansoprazole was denied by the investigators. Serious adverse reactions occurred in 51/339 (15.0%) patients, of which 26 occurred in the follow-up trial. Of these, melena occurred in one patient (0.3%) and this was the only event whose causal relationship to lansoprazole could not be denied. Thirty-nine treatment discontinuations occurred in the entire period; of these, 16 occurred in the follow-up period, where the most common event was diarrhea, which occurred in four patients (1.2%).

## Discussion

Given that no drug has been proven to be effective for the prevention of gastric or duodenal ulcer associated with LDA therapy in Japan, and given that it is unethical to conduct a placebo-controlled trial in patients at high risk of developing gastric or duodenal ulcers, the present study was designed to compare the efficacy of lansoprazole 15 mg once daily and gefarnate 50 mg twice daily [11, 12]. Gefarnate is a cytoprotective anti-ulcer agent which is approved for the treatment of gastric or duodenal ulcers. These cytoprotective anti-ulcer agents are commonly prescribed as prophylactic drugs to reduce NSAID- or LDA-induced gastrointestinal injury, although they have not been investigated in a controlled trial for the latter indication.

To minimize risks to the patients enrolled in this trial, they were strictly assessed by endoscopic examination for eligibility. In addition, unlike most long-term clinical trials conducted to date in a similar patient population, frequent endoscopic examinations (every 3 or 6 months) were scheduled by the protocol to closely monitor the study subjects for early detection of ulcer recurrence.

While there are arguments for and against *H. pylori* eradication in long-term NSAID users [14], one study showed that *H. pylori* eradication prior to LDA therapy was equivalent to omeprazole therapy in preventing recurrent gastrointestinal bleeding [15], although the study was underpowered to demonstrate such equivalence. However, in other studies, the ulcerogenic effect of LDA was not abolished by *H. pylori* eradication in high-risk patients [7], and 20% of an entire cohort of patients who had developed dyspeptic or bleeding ulcers/erosions during prophylactic