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Gastroduodenal ulcer bleeding in elderly patients on low dose aspirin therapy

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Abstract

AIM

To determine the clinical characteristics of elderly patients of hemorrhagic gastroduodenal ulcer on low-dose aspirin (LDA) therapy.

Methods

A total of 1105 patients with hemorrhagic gastroduodenal ulcer treated in our hospital between January 2000 and March 2016 were grouped by age and drugs used, and these groups were compared in several factors. These groups were compared in terms of length of hospital stay, presence/absence of hemoglobin (Hb) decrease, presence/absence of blood transfusion, Forrest I, percentage of *Hp* infection, presence/absence of underlying disease, and percentage of severe cases.

Results

The percentage of blood transfusion (62.6% vs 47.7 %, P<0.001), Hb decrease (53.8% vs 40.8%, P<0.001), and the length of hospital stay (23.5 vs 16.7 days, P<0.001) were significantly greater in those on drug therapy. The percentage of blood transfusion (65.3% vs 47.8%, P<0.001), Hb decrease (54.2% vs 42.1%, P<0.001), and length of

hospital stay (23.3 vs 17.5 days, P<0.001) were significantly greater in the elderly. In comparison with the LDA monotherapy group, the percentage of severe cases was significantly higher in the LDA combination therapy group when elderly patients were concerned (16.1% vs 34.0%, P=0.030). Meanwhile, among those on LDA monotherapy, there was no significant difference between elderly and non-elderly (16.1% vs 16.0%, p=0.985).

Conclusions

A combination of LDA with antithrombotic drugs or NSAIDs contributes to aggravation. And advanced age is not an aggravating factor when LDA monotherapy is used.

Key words: Hemorrhagic gastroduodenal ulcer, low-dose aspirin, antithrombotic drugs, elderly patients, proton pump inhibitor.

Core tip

A total of 1105 patients with hemorrhagic gastroduodenal ulcer were grouped by age and drugs used, and these groups were compared in several factors. Among the elderly

(over 70 years), the rate of severe conditions was significantly higher in patients receiving LDA combination therapy than in those receiving LDA monotherapy. Meanwhile, in the LDA monotherapy group, no significant difference in the rate of severe conditions was observed between elderly and non-elderly patients. This result suggests LDA combination therapy contributes to the aggravation, and advanced age is not an aggravating factor when LDA monotherapy is used.

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Introduction

Japan's population is aging rapidly. According to the White Paper on Aging Society 2016, Cabinet office, Government of Japan, people 65 years of age or older accounted for 27.3% of the total population as of October 1, 2016. Under a situation where cerebrovascular disorder and ischemic heart disease have been increasing, clinical evidence of the usefulness of low-dose aspirin (LDA) as a means of secondary prevention of such diseases has often been reported and the frequency of its use has increased [1-3]. However, Pearson et al. reported that the use of LDA caused an approximately 20% decrease in cardiovascular events in comparison with the control group, but its use was associated with a 2.7-fold higher risk of gastrointestinal hemorrhage [4]. Serious adverse responses to LDA include gastrointestinal mucosal disorder and gastrointestinal hemorrhage; therefore, there is a concern for an increase and aggravation of these conditions [5-9].

Based on the Special Report of Vital Statistics in Japan issued by the Ministry of Health, Labour and Welfare, data in 1996, when the number of patients with gastric ulcer was the greatest after 1990, and the latest available data in 2014 were compared in

113 regard to the number of patients with gastroduodenal ulcer and the number of deaths
114 from gastroduodenal ulcer. The number of patients and the number of deaths in 1996
115 were 1,124,000 and 4,514, respectively, whereas the corresponding numbers were
116 311,000 (28% of the number in October 1996) and 2,770 (61% of the number in 1996)
117 in October in 2014. Although the number of patients with ulcer was decreased to less
118 than one third, there was no marked decrease in the number of deaths from ulcer. This
119 indicates that the clinical picture of ulcer became more severe, presumably reflecting an
120 increase in the incidence of ulcer due to the increased use of antithrombotic drugs
121 including LDA in the aging society, whereas the rate of infection with *Helicobacter*
122 *pylori* (*Hp*) has decreased, and the rate of *Hp* eradication has increased, in the younger
123 generation in recent years [10]. In particular, combined use of LDA and non-steroidal
124 anti-inflammatory drugs (NSAIDs) and advanced age serve as risk factors for the
125 occurrence of LDA-induced ulcer and also increase the risk of hemorrhage and
126 aggravation [11-14]. According to a sub-analysis by Nikolsky et al., who investigated the
127 presence/absence and prognosis of gastrointestinal hemorrhage within 30 days of
128 hospitalization due to acute coronary syndrome, the overall mortality at 1 year was

129 significantly higher in patients who had gastrointestinal hemorrhage within 30 days of
130 hospitalization than in those who did not [15]. In this study, we paid attention to patients
131 who were on oral LDA therapy, a clinically important issue, among elderly patients with
132 hemorrhagic gastroduodenal ulcer due to oral antithrombotic therapy to elucidate the
133 clinical characteristics of this condition and analyzed patients with hemorrhagic
134 gastroduodenal ulcer treated in our hospital in relation to age and medication.
135
136 **Materials and methods**
137 **Patients**
138 This study included 1105 patients who had hematemesis, melena, or acute anemia
139 symptoms due to hemorrhagic gastroduodenal ulcer [801 (72.5%) cases of gastric ulcer
140 and 304 (27.5%) cases of duodenal ulcer] and who underwent emergency endoscopic
141 hemostasis because upper gastrointestinal hemorrhage was suspected in Dokkyo
142 Medical University Hospital between January 2000 and March 2016. These 1105
143 patients comprised inpatients, outpatients at the emergency department, and emergency
144 transport patients.

Patient management

The rules of our response to hemorrhagic gastric and duodenal ulcers are as follows: (1) hemostasis is rapidly and continuously performed by a gastroenterologist; (2) the hemostasis procedure uses clipping or argon plasma coagulation at the operator's discretion, and a local injection of hypertonic saline epinephrine (HSE) and thrombin spray are employed if necessary without restriction to a single technique; (3) blood transfusion is indicated for patients with hemoglobin (Hb) $\leq$ 7.0 g/dL or patients in shock; (4) intravenous administration of a proton pump inhibitors (PPIs) is given promptly after endoscopic hemostasis, and it is switched to oral administration after initiation of oral feeding; (5) oral feeding is begun with thin rice gruel if blood test shows no progression of anemia and if no bleeding is found by second-look endoscopy performed within 0-5 days; and (6) when the patient is on antithrombin drug or anticoagulation drug therapy, discontinuation of the drug therapy is considered in consultation with a doctor of the specialty concerned after evaluating the risk of thrombosis, embolism, and bleeding.

Definition

Patients aged 70 years or older were defined as elderly, and those aged younger than 70 years were defined as non-elderly. A significant decrease in the Hb level was defined as a decrease of at least 2.0 g/dL in comparison with the Hb level in the previous blood examination or as an Hb level of 7.0 g/dL or lower in the absence of available data in the previous blood examination. As for *Hp* infection, it was possible that the urea breath test would provide a false-negative result because of the PPIs administered. Therefore, *Hp*-IgG antibody was measured in all subjects, and antibody titers of 10 U/mL or more were defined as positive. Multiple ulcer was defined by the presence of two or more ulcer lesions. Rebleeding was defined by the endoscopic evidence and additional treatment of hemorrhage within 72 h after the implementation of the initial endoscopic hemostasis. Hemorrhage found after more than 72 h was defined as recurrence. Severe cases were defined as cases with at least two of the following three items: (1) an Hb decrease of 2.0 g/dL or more or blood transfusion; (2) hospital stay of at least 30 days; and (3) rebleeding, surgery, interventional radiology (IVR), or death. The oral drugs examined included antiplatelet drugs, such as LDA, thienopyridines (clopidogrel, ticlopidine, and prasugrel), and cilostazol, and

anticoagulation drugs such as warfarin, heparin, and direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban, and edoxaban). LDA, administered at doses of 70–330 mg/day, reportedly provides an antiplatelet effect [6,11]. In Japan, LDA is usually prescribed at a dose ≤162mg/day. This also applies to the present study. In addition, the use of NSAIDs was also examined. The subjects were also examined for the presence/absence of cardiac disease, cerebrovascular disorder, renal disease, peptic ulcer, and diabetes mellitus as possible underlying diseases.

Data analysis

This was a retrospective study. The medical records of the subjects were examined for patient age, sex, Hb level, presence/absence of blood transfusion, Forrest classification, the number of ulcerative lesions, oral drugs, underlying disease, presence/absence of *Hp* infection, etc. These subjects were divided into those who were on oral drug therapy and those who were not and were also classified as elderly and non-elderly patients. These groups were compared in regard to the percentage of patients with blood transfusion, Hb decrease, rebleeding, surgery, IVR, or fatal outcome, and the length of hospital stay. In addition, among patients on oral drug therapy,

attention was focused on LDA; in each of the LDA monotherapy group and LDA combination therapy group, the percentage of severe cases was analyzed in relation to elderly and non-elderly patients. To investigate factors for aggravation of the condition in elderly patients, the elderly group was further divided into those with and without severe conditions for comparison.

Statistical analysis

For statistical analysis, χ^2 test, *t* test, and Mann-Whitney U test were used. Logistic regression analysis was also performed using hospital stay of 20 days or more as a dependent variable. SPSS version (IBM SPSS Statistics 21; IBM Japan, Ltd.) was used for statistical analysis processing. This study was approved by the life ethics committee of our institution.

Results

Patient characteristics in each group

The numbers (percentages) of patients with gastric ulcer and duodenal ulcer were 801 (72.5%) and 304 (27.5%), respectively. Table 1 shows the characteristics of the

209 patients with gastroduodenal ulcer examined in this study. These patients were classified
210 into those with oral drug therapy (medicated group) and those without oral drug therapy
211 (non-medicated group). The medicated group comprised 474 (42.9%) patients, whereas
212 the non-medicated group comprised 631 (57.1%) patients. These patients were also
213 divided into elderly and non-elderly patients. There were 436 (39.5%) and 669 (60.5%)
214 elderly and non-elderly patients, respectively. Table 2 shows the patient characteristics
215 of each group.

216 **Comparison between the medicated group and non-medicated group**

217 Types of oral medication included 474 patients [113 cases of LDA monotherapy
218 and 157 cases of NSAIDs monotherapy and 113 cases of clopidogrel monotherapy and
219 10 cases of cilostazol monotherapy and 40 cases of warfarin monotherapy and 4 cases
220 of DOACs monotherapy, and 118 cases of combination therapy]. When the medicated
221 and non-medicated groups were compared, the percentage of patients with blood
222 transfusion (62.6% vs. 47.7 %; $p<0.001$) and the percentage of patients with Hb
223 decrease (53.8% vs. 40.8%; $p<0.001$) were significantly higher in the medicated group
224 (Figure 1a). The length of hospital stay after the implementation of endoscopic

225 treatment (23.5 vs. 16.7 days; p<0.001) and the overall length of hospital stay (27.0 vs.
226 18.5 days; p<0.001) were significantly longer in the medicated group. There was no
227 significant difference with regard to rebleeding, surgery, IVR, or mortality between the
228 two groups.

229 **Comparison between elderly and non-elderly patients**

230 The results of the comparison between elderly and non-elderly patients are shown
231 in Figure 1b. The percentage of patients with blood transfusion (65.3% vs. 47.8%;
232 p<0.001), percentage of patients with Hb decrease (54.2% vs. 42.1%; p<0.001), and
233 percentage of patients with rebleeding, surgery, IVR, or death (11.7% vs. 6.6%;
234 p=0.033) were significantly higher among elderly patients. The length of hospital stay
235 after the implementation of endoscopic treatment (23.3 vs. 17.5 days; p<0.001) and the
236 overall length of hospital stay (26.9 vs. 19.0 days; p<0.001) were significantly longer
237 among elderly patients.

238 **Comparison between patients on LDA monotherapy and those on LDA**
239 **combination therapy**

240 Patients in the medicated group were divided into those with LDA monotherapy or

LDA combination therapy and elderly or non-elderly patients, and the percentage of severe cases and the length of hospital stay were examined. Patients in the medicated group were divided into groups A (elderly receiving LDA monotherapy), B (elderly receiving LDA combination therapy), C (non-elderly receiving LDA monotherapy), and D (non-elderly receiving LDA combination therapy). Elderly patients, a population that may have clinical issues, were investigated by comparing groups A and B. In addition, the age-related tendency in the LDA monotherapy group was examined by comparing groups A and C (Table 3). The results are shown in Figures 2 and 3. A comparison between groups A and B revealed that the length of hospital stay tended to be longer in group B than in group A (group A 20.0 vs. group B 25.5 days; p=0.194). Rebleeding, surgery, IVR, and death were more frequent in group B than in group A (group A 3.2% vs. group B 14.6%; p=0.038). In comparison with group A, the percentage of severe cases was significantly higher in group B (group A 16.1% vs. group B 34.0%; p=0.030). A comparison of groups A and C showed no significant difference in the length of hospital stay or the percentage of severe cases between the two groups.

Risk factor for aggravation in elderly patients

In the elderly group, severe cases defined by rebleeding or fatal outcome were compared with non-severe cases ending in discharge in remission to determine risk factors for aggravation (Table 4). There was a significant intergroup difference in regard to Hb decrease (70.0% vs. 52.1%; p=0.017), blood transfusion (88.0% vs. 62.4%; p<0.001), Forrest I (45.1% vs. 22.9%; p=0.001), HSE use (9.6% vs. 21.6%; p=0.010), and diabetes mellitus (29.4% vs. 16.9%; p=0.030). Multivariate logistic regression analysis revealed blood transfusion [odds ratio (95% confidence interval [CI]): 3.59 (1.42-9.06); p=0.007], Forrest I [odds ratio (95% CI): 2.40 (1.07-4.54); p=0.007], and diabetes mellitus [odds ratio (95% CI): 2.02 (1.00-4.06); p=0.049] as independent risk factors.

Discussion

Aspirin exerts an anti-inflammatory action by inhibiting the activity of COX-1 and COX-2 as well as an antiplatelet action by inhibiting intraplatelet COX-1 and suppressing the production of thromboxane A2, a promoter of platelet aggregation. It is known that aspirin inhibits gastric mucosal protection through COX inhibition. In

addition, aspirin takes a lipid-soluble nonionic form under the intragastric acidic condition and accumulates in the cell to cause injury directly, with increased drug permeability. Case-control studies conducted in Europe and North America showed that gastrointestinal mucosal disorder would increase the risk of upper gastrointestinal hemorrhage about 2- to 4-fold [16-17]. Sakamoto et al. reported based on the results of a case-control study in Japanese people that the odds ratio of upper gastrointestinal hemorrhage due to LDA was 8.2 (95% CI: 3.3-20.7) [18]. In addition, studies that examined the prognosis in relation to the presence or absence of the increasingly prevalent gastrointestinal hemorrhage after acute coronary syndrome or acute stroke found that the occurrence of gastrointestinal hemorrhage after acute coronary syndrome or acute stroke would increase the overall mortality at 1 year [15,19]. This should not only alert endoscopists but also alert cardiologists and neurologists. Antiplatelet drugs other than LDA are also associated with the risk of gastrointestinal hemorrhage because they inhibit thrombogenesis, but they cause less injury to the mucosa. Clopidogrel is known to increase the risk of hemorrhage by 1.7-2.8 times; case-control studies with more than 10,000 cases showed that its risk of inducing hemorrhage is not statistically significant

[16,17,20,21]. Because reports on antiplatelet drugs other than LDA are limited, accumulation of data and additional investigations in the future are awaited. The anticoagulant warfarin significantly increases the risk of upper gastrointestinal hemorrhage by about two to four times [16,20-22]. In recent years, the use of DOACs as a new treatment of venous thromboembolism and atrial fibrillation has increased. In a cohort study, Shimomura et al. performed a long-term follow-up of 508 patients on oral anticoagulant therapy in whom peptic ulcer and hemorrhage were denied and calculated the incidence rate of gastrointestinal hemorrhage. As a result, acute gastrointestinal hemorrhage occurred in 8.3% of the patients during an average observation period of 31 months, and the cumulative incidence rates of gastrointestinal hemorrhage at 5 and 10 years were reported to be 13% and 19%, respectively, which were clinically relevant [23]. There was no significant difference in the hemorrhage risk between warfarin and DOACs. In addition, other more recent studies have found no significant difference in the hemorrhage risk between warfarin and DOACs [24,25]. Our present study included only four patients on DOACs therapy, and therefore DOACs were not analyzed. Because the use of DOACs is expected to increase in the future, additional

305 investigations would be necessary.

306 Hallas et al. reported that the risk of hemorrhage was increased 1.8-fold by LDA
307 monotherapy, and the risk was further increased by the combined use of LDA with other
308 drugs, e.g., 7.4-fold by combination with clopidogrel and 5.3-fold by combination with
309 warfarin [16]. Several studies have demonstrated bleeding risk in patients treated with a
310 combination of LDA plus antithrombotic drugs [26,27]. The present study showed that the
311 condition was significantly more severe in elderly patients aged 70 years or older on
312 LDA combination therapy than in those on LDA monotherapy. Although a comparison
313 among different drugs was not made, this study indicated that the combined use of
314 drugs would increase the risk of hemorrhage, requiring due caution. In addition, when
315 LDA monotherapy was used, there was no significant difference in the severity of the
316 condition between elderly and non-elderly patients. Although oral LDA therapy poses a
317 risk of ulceration as mentioned previously, the results of this study suggest that LDA
318 monotherapy does not contribute to aggravation of hemorrhage in elderly patients in
319 comparison with non-elderly patients.

320 Increases in the incidence of rebleeding and mortality in relation to the underlying

321 disease and age have been reported. Rockall et al. have reported that the fatality rate due
322 to upper gastrointestinal hemorrhage was 14% (584/4412) and that the rate increased
323 with the presence of comorbidities such as heart failure, ischemic heart disease, and
324 renal failure [28]. It has also been reported that the mortality within 30 days is
325 proportional to the prevalence of serious comorbidities [29]. In addition, some
326 researchers reported that the Glasgow Blatchford score was the most effective
327 predictive factor for treatment intervention and death [30,31]. Travis et al. investigated the
328 risk factors for rebleeding after endoscopy and reported that non-use of PPIs, hepatic
329 cirrhosis, heparin, and the use of epinephrine were independent factors [32]. In this study,
330 the condition was more likely to be more severe in elderly patients and medicated
331 patients, indicating that aggressive treatment intervention would be necessary in such
332 patients. In addition, when elderly patients aged 70 years or older were concerned, Hb
333 decrease, implementation of blood transfusion, Forrest I, HSE, and a history of diabetes
334 mellitus were found to be risk factors for a severe clinical course (rebleeding, surgery,
335 IVR or other treatment intervention, or death). When multivariate analysis was
336 performed, Hb decrease, implementation of blood transfusion, and a history of diabetes

337 mellitus were identified as independent factors. In these patients, endoscopically and
338 clinically more appropriate management including an adequate endoscopic hemostatic
339 procedure and an aggressive second-look procedure is required.

340 As for management after hemostasis, both the rebleeding risk due to continued oral
341 antithrombotic medication and the risk of developing thromboembolism due to
342 discontinuation of antithrombotic therapy should be considered. Thus, the method of
343 such management is a clinically relevant issue. Discontinuation of antithrombotic drugs
344 was previously reported to be associated with a significantly higher incidence of
345 thromboembolic events and related deaths [5,16,33-35]. The risk of recurrence of
346 underlying disease associated with discontinuation of LDA has also been reported to be
347 significantly higher than the risk of recurrence of hemorrhagic gastric ulcer associated
348 with continuation of LDA therapy [36]. Nagata et al. have reported that a history of
349 thromboembolism, comorbidity score, discontinuation of LDA, discontinuation of
350 antiplatelet drugs other than aspirin, and discontinuation of anticoagulant drugs were
351 identified as risk factors for thromboembolism and that discontinuation of LDA and
352 anticoagulant drugs resulted in a higher risk of thromboembolism [37]. Therefore, when

353 treating patients, it is necessary to consider the propriety of discontinuation of
354 medication and avoid prolonged withdrawal, in consultation with specialists such as a
355 cardiologist or a neurologist. Elderly patients are at a high risk of rebleeding and are
356 more likely to discontinue antithrombotic medication. In such cases, a second-look
357 procedure should be performed aggressively, and antithrombotic medication should be
358 resumed as soon as possible. It is also necessary to ensure that antithrombotic
359 medication is resumed on discharge.

360 With regard to LDA-induced peptic ulcer, several randomized controlled trails
361 demonstrated the secondary preventive effect of PPIs, and in Japan, an additional
362 indication for the use of PPIs to prevent recurrence of LDA-induced ulcer was approved
363 for the first time in 2010 [38-40]. In a randomized controlled trial that included patients
364 aged 60 years or older who had no endoscopic evidence of ulcer, esomeprazole 20 mg
365 proved to be effective for prevention of peptic ulcer (primary prevention) [41]. As
366 mentioned previously, the incidence rates of severe ulcer and drug-induced ulcer are
367 increasing, and administration of more appropriate acid-blocking drugs including PPIs
368 has become important. Japanese guidelines recommend the use of PPIs [42,43]. However,

as demonstrated in the present study, the actual frequency of the use of PPIs is currently low, and therefore further spread of this type of drugs is necessary.

Our present study had several limitations. This was a single-center retrospective study that provided restrictive analysis. Endoscopic skills varied among different endoscopists. The definition of severe ulcer was not based on any well-known scoring system but used unique factors produced from evaluable items. The age difference between elderly and non-elderly subjects was small 54.9 vs 78.5 years. Addition of data and another verification with participation of multiple centers are desirable.

Conclusions

When patients on LDA combination therapy and LDA monotherapy were compared, the percentage of severe cases was high in those on LDA combination therapy among elderly patients, indicating that combined use of LDA with antithrombotic drugs or NSAIDs contributes to the aggravation of hemorrhagic gastroduodenal ulcer. In the LDA monotherapy group, there was no significant difference in the percentage of severe cases between elderly and non-elderly patients,

385 indicating that age is not a risk factor for aggravation of the condition when LDA
386 monotherapy is used.
387
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Conflict of interest

There are no conflicts of interest to disclose in the study.

ARTICLE HIGHLIGHTS

Research background

As the Japanese population ages, the prevalence of cerebrovascular disorders and ischemic heart diseases have been increasing. Under these circumstances, low-dose aspirin (LDA) has increasingly been used for secondary prevention of such conditions in recent years. Severe adverse reactions to LDA include hemorrhagic gastroduodenal ulcer. In the future, the incidences of LDA-induced peptic ulcer and ulcer hemorrhage are expected to rise in the elderly.

Research motivation

As previously reported, the concomitant use of LDA and other antithrombotic drugs increases the risk of ulcer hemorrhage. However, no report of any study that LDA-induced ulcer hemorrhage in elderly patients who expected to become severe. Elucidation of the current status of this condition would thus be useful.

Research objectives

Of patients with hemorrhagic gastroduodenal ulcer caused by oral administration of antithrombotic drugs, those receiving oral LDA, which is likely to be particularly problematic, were targeted. By comparing elderly and non-elderly patients, this study aimed to identify clinical features of the ulcer and factors contributing to its progression to severe conditions. These issues are particularly important in countries that have become aged societies, like Japan, or are aging at a rapid rate.

Research methods

This study included 1105 patients with hemorrhagic gastroduodenal ulcer, who were

433 divided according age (the elderly group consisting of those 70 years of age or older and
434 the non-elderly group consisting of those less than 70 years of age) and orally
435 administered drugs (the LDA monotherapy group and the LDA combination therapy
436 group). We retrospectively compared and analyzed the length of hospital stay, presence
437 or absence of decreased hemoglobin (Hb) level, use of blood transfusion, rate of severe
438 conditions, etc.
439
440 *Research results*
441 When elderly patients were compared between the LDA monotherapy and LDA
442 combination therapy groups, the rate of severe conditions was higher in the LDA
443 combination therapy group. Concomitant use of LDA with antithrombotic drugs or
444 nonsteroidal anti-inflammatory drugs was found to contribute to the progression of
445 severe hemorrhagic gastroduodenal ulcer to severe conditions. Moreover, among the
446 LDA monotherapy group, no significant difference in the rate of severe conditions was
447 observed between elderly and non-elderly patients. Oral administration of LDA alone
448 was not found to be a risk factor for progression to severe conditions in elderly patients.

Research conclusions

This study showed that LDA combination therapy contributes to progression to severe conditions, such as markedly decreased Hb levels, increased frequency of blood transfusion, and prolonged hospital stay, in elderly patients. Meanwhile, in cases receiving LDA monotherapy, advanced age is not a risk factor for progression to severe conditions. Based on these findings, when LDA combination therapy is administered to elderly patients, efforts should be made toward adequate prevention of hemorrhage. In cases with ulcer hemorrhage, while treatment is given, appropriate antithrombotic therapy is required to prevent the occurrence of vascular events. Furthermore, apparently, if LDA monotherapy is administered, even elderly patients may be at a risk of progression to severe conditions similar to that in non-elderly patients.

Research perspectives

The limitations of this study include the single-center retrospective design. In addition, because the analysis in the LDA combination therapy group was not stratified according

to the types of antithrombotic drugs used in combination with LDA, the effects of different combinations of drugs on the risk of hemorrhage should be examined in future studies. Although the use of proton pump inhibitors (PPIs) is preferable for prevention of hemorrhage as described in the guidelines, further accumulation of additional data and studies on effects, adverse events, etc. are needed to use PPIs appropriately. Furthermore, evidence must be accumulated for the prophylactic effect of novel therapeutic drugs, such as vonoprazan, for ulcers in elderly patients.

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Figure legend

Figure 1. Comparison between 2 groups

a. Medicated and non-medicated groups

b. Elderly and non-elderly groups

Figure 2. Comparison between the LDA monotherapy and LDA combination therapy groups in the elderly

Figure 3. Comparison between the elderly and non-elderly groups in patients receiving LDA monotherapy

690 Table 1 Baseline characteristics

Items	All cases (n=1105)
Mean age (years)	64.37
Sex (%)	
Male	823 (74.5)
Female	282 (25.5)
Mean length of hospital stay (days)	
After endoscopic treatment	19.8
Overall	22.1
Hb (mg/dL)	8.74
Hb decrease (%)	509 (46.1)
Blood transfusion (%)	594 (53.8)
Hp positive (%)	857 (77.6)
Endoscopic findings	
Ulcer	
Single	759 (68.7)
Multiple	346 (31.3)
Forrest classification (%)	
Ia	88 (8.0)
Ib	171 (15.5)
IIa	525 (47.5)
IIb	142 (12.8)
III	179 (16.2)
Rebleeding (%)	82 (7.4)
Recurrence (%)	60 (5.4)
Surgery/IVR/death	32 (2.9)
Prophylactic anti-ulcer medication	
None	749 (67.8)
PPI	88 (8.0)
H2RA	117 (10.6)
MP	152 (13.6)
Comorbidity	

Cardiac disease	254 (30.0)
Cerebrovascular disorder	180 (16.3)
Renal failure	125 (11.3)
DM	198 (17.9)
Orthopedic disorder	162 (14.7)
History of ulcer	317 (28.7)

Hb, hemoglobin; *Hp*, *Helicobacter pylori*; IVR, interventional radiology; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonists; MP, mucosal protectant; DM, diabetes mellitus.

703 Table 2 Characteristics of the medicated vs. non-medicated groups and the elderly vs.
704 non-elderly groups

	Medicated group (n =474)	Non-medicated group (n =631)	p	Elderly group (n =436)	Non-elderly group (n =669)	p
Mean age (years)	69.7	60.4	<0.001	78.5	54.9	<0.001
Sex (male:female)	352:122	491:140	<0.001	271:165	552:117	<0.001
Hb (mg/dL)	8.26	9.11	<0.001	8.08	9.19	<0.001
Hp infection (positive:negative)	73.5% (324:117)	89.3% (533:64)	<0.001	77.9% (311:88)	85.4% (546:93)	0.002
Single ulcer	61.4% (291:183)	74.2 (468:163)	<0.001	40.1% (175:261)	25.6% (171:498)	<0.001
Forrest I	25.7% (122:352)	21.7% (137:494)	0.118	25.5% (11:325)	22.1% (148:521)	0.201
Anti-ulcer medication	52.1% (247:227)	17.3% (109:522)	<0.001	41.3% (189:256)	26.3% (176:493)	<0.001
Underlying disease						
Cardiac disease	43.0% (204:270)	7.9% (50:581)	<0.001	33.9% (148:288)	15.8% (106:563)	<0.001
Cerebrovascular disorder	25.9% (123:351)	4.0% (25:606)	<0.001	22.2% (97:339)	7.6% (51:618)	<0.001
Renal disease	16.5% (78:396)	7.4% (47:584)	<0.001	13.1% (57:379)	10.2% (68:601)	0.136
Respiratory disease	13.5% (64:410)	8.1% (51:580)	0.003	14.9% (65:371)	7.5% (50:619)	<0.001
Orthopedic disorder	28.9% (137:337)	4.0% (25:606)	<0.001	21.6% (94:342)	10.2% (68:601)	<0.001
History of ulcer	21.9% (104:370)	28.7% (181:450)	<0.001	18.3% (80:356)	30.6% (205:464)	<0.001
Hypertension	41.4% (196:278)	25.9% (158:473)	<0.001	45.2% (197:239)	23.5% (157:512)	<0.001
DM	21.7% (103:371)	15.1% (95:536)	0.004	18.3% (80:356)	17.6% (118:551)	0.763

Hb, hemoglobin; *Hp*, *Helicobacter pylori*; DM, diabetes mellitus.

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Table 3 Characteristics of LDA therapy

	Elderly patients (n=111)		Non-elderly patients (n=99)			
	Group A: LDA monotherapy (n=63)	Group B: LDA combination therapy (n=48)	Group C: LDA monotherapy (n=49)	Group D: LDA combination therapy (n=50)	p (A vs. B)	p (A vs. C)
Mean age (years)	80	80	58.3	60.7	0.989	<0.001
Sex (male:female)	43:20	34:14	45:4	44:6	0.77	0.003
Mean length of hospital stay (days)						
After endoscopic treatment	20	25.5	20.9	21.9	0.194	0.323
Overall	20.1	28.4	23	27.3	0.12	0.685
Hb (mg/dL)	8.4	8.4	8.9	8.6	0.948	0.307
Hb decrease (present:absent)	43.5% (27:35)	53.2% (25:22)	49.0% (24:25)	67.4% (31:15)	0.702	0.569
Blood transfusion (present:absent)	61.3% (38:24)	66.0% (31:16)	38.8% (19:30)	58.7% (27:19)	0.69	0.018
Hp infection (positive:negative)	77.4% (48:14)	68.3% (28:13)	80.9% (38:9)	68.8% (33:15)	0.303	0.664
Forrest (I:II, III)	23.8% (15:48)	27.1% (13:35)	16.3% (8:41)	20.0% (10:40)	0.694	0.331
Ulcer (multiple:single)	42.9 (27:36)	39.6% (19:29)	22.4% (11:38)	46.0% (23:27)	0.846	0.024
Rebleeding (present:absent)	3.2% (2:61)	12.5% (6:42)	2.0% (1:48)	8.0% (4:46)	0.06	1
Rebleeding/surgery/IVR/death (present:absent)	3.2% (2:61)	14.6% (7:41)	4.1% (2:47)	8.0% (4:46)	0.038	1
Recurrence (present:absent)	0% (0:63)	4.2% (2:46)	8.2% (4:45)	4.0% (2:48)	0.185	0.034
DM	17.5% (11:51)	25.0% (12:36)	36.7% (18:31)	36.0% (18:32)	0.332	0.021
Cardiac disease	52.4% (33:30)	66.7% (32:16)	46.9% (23:26)	78.0% (39:11)	0.13	0.568
Cerebrovascular disorder	38.1% (24:39)	39.6% (19:29)	22.4% (11:38)	34.0% (17:33)	0.873	0.076
Orthopedic disorder	12.7% (8:55)	25.0% (12:36)	6.1% (3:46)	20.0% (10:40)	0.095	0.342
Respiratory disease	17.5% (11:52)	14.6% (7:41)	4.1% (2:47)	4.0% (2:48)	0.684	0.028
Renal disease	12.7% (8:55)	22.9% (11:37)	18.4% (9:40)	24.0% (12:38)	0.157	0.407
History of peptic ulcer	19.0% (12:51)	12.5% (6:42)	28.6% (14:35)	20.0% (10:40)	0.354	0.236
Hypertension	49.2% (31:32)	52.1% (25:23)	36.7% (18:31)	42.0% (21:29)	0.764	0.187
Preceding anti-ulcer medication (present:absent)	38.1% (24:39)	79.2% (38:10)	44.9% (22:27)	58.0% (29:21)	<0.001	0.468
Preceding PPI medication	11.1% (7:56)	22.9% (11:37)	12.2% (6:43)	16.0% (8:42)	0.095	0.853

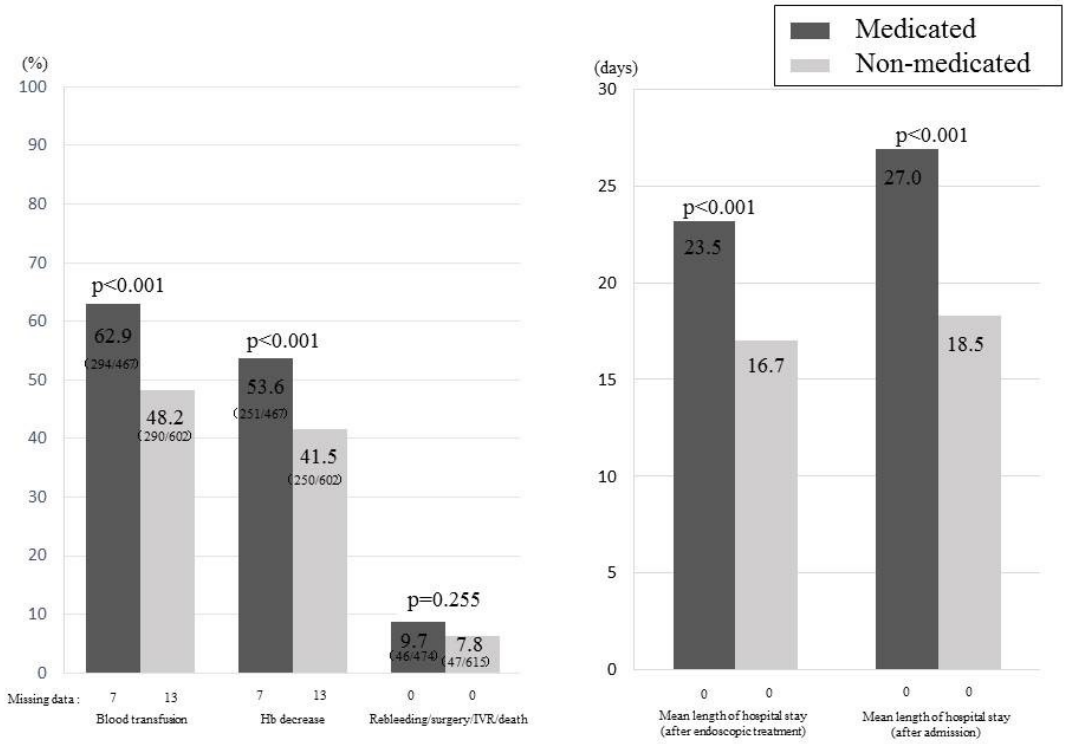
Hb, hemoglobin; LDA, low dose aspirin; *Hp*, *Helicobacter pylori;* IVR, interventional radiology; PPI, proton pump inhibitor; DM, diabetes mellitus.

726 Table 4 Comparison between the severe and non-severe groups in the elderly group

	Elderly group (n=436)		Univariate analysis	Multivariate analysis	
	Severe cases (n=51)	Non-severe cases (n=385)	p	OR（95% CI）	p
Mean age (years)	79	78.8	0.846		
Sex (male:female)	64.7%(33:18)	61.8%(238:147)	0.689		
Mean length of hospital stay (days)					
After endoscopic treatment	21.9	23.5	0.699		
Overall	25.9	27	0.823		
Hb (mg/dL)	7.63	8.14	0.113		
Hb decrease (present:absent)	70.0% (35:15)	52.1% (198:182)	0.017	1.378 (0.693-2.74)	0.361
Blood transfusion (present:absent)	88.0% (44:6)	62.4% (237:143)	<0.001	3.592 (1.423-9.064)	0.007
Hp infection (positive:negative)	69.8% (30:13)	78.9% (281:75)	0.171		
Forrest (I:II, III)	45.1% (23:28)	22.9% (88:297)	0.001	2.395 (1.065-4.537)	0.007
Ulcer (multiple:single)	31.4% (16:35)	41.3% (159:226)	0.174		
HSE use	21.6% (11:40)	9.6% (37:348)	0.01	2.178 (0.975-4.862)	0.058
DM	29.4% (15:36)	16.9% (65:320)	0.03	2.018 (1.002-4.063)	0.049
Cardiac disease	29.4% (15:36)	34.5% (133:252)	0.467		
Cerebrovascular disorder	27.5% (14:37)	21.6% (83:302)	0.342		
Orthopedic disorder	23.5% (12:39)	21.3% (82:303)	0.716		
Respiratory disease	21.6% (11:40)	14.0% (54:331)	0.155		
Renal disease	5.9% (3:48)	14.0% (54:331)	0.105		
History of peptic ulcer	23.5% (12:39)	17.7% (68:317)	0.309		
Hypertension	41.2% (21:30)	45.7% (176:209)	0.541		
Preceding anti-ulcer medication	52.9% (27:24)	39.7% (153:232)	0.072		
Preceding PPI medication	11.8% (6:45)	11.7% (45:340)	0.987		

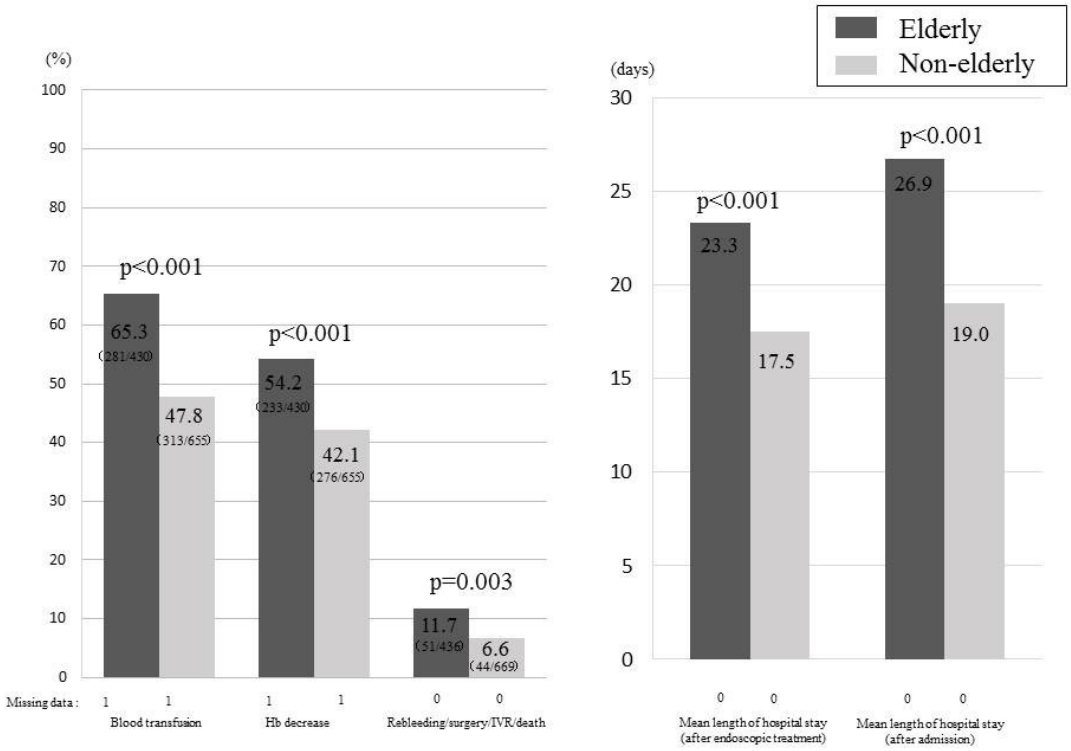
Hb, hemoglobin; Hp, Helicobacter pylori; IVR, interventional radiology; HSE, hypertonic saline epinephrine; DM, diabetes mellitus; PPI, proton pump inhibitor.

Figure 1a



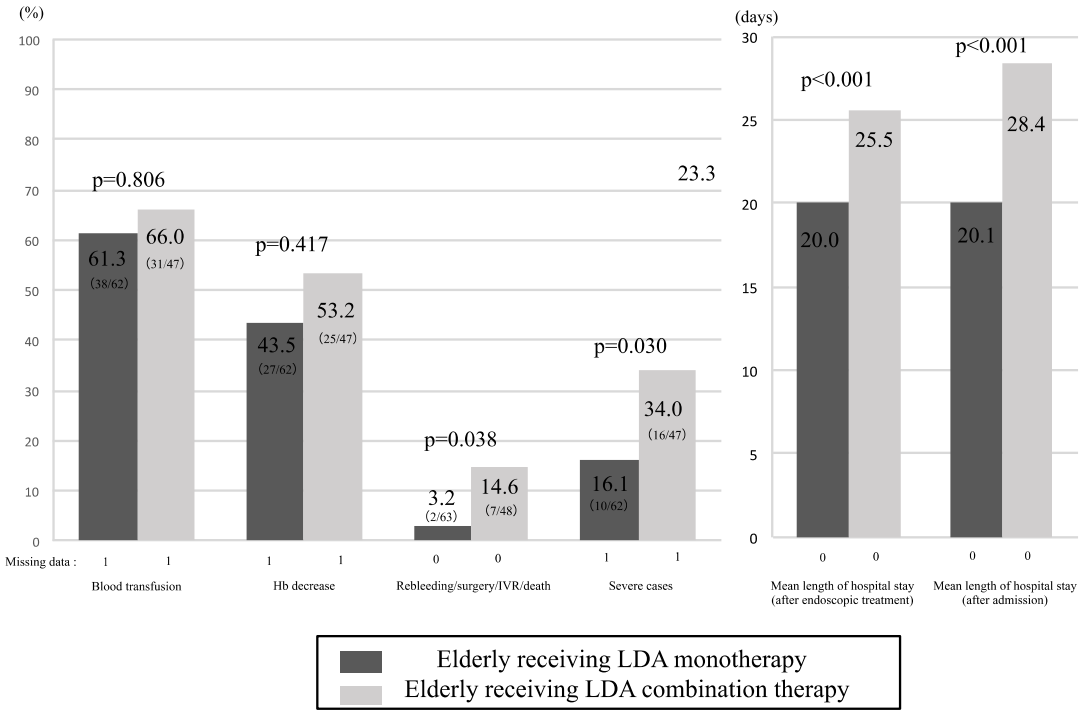
741

Figure 1b



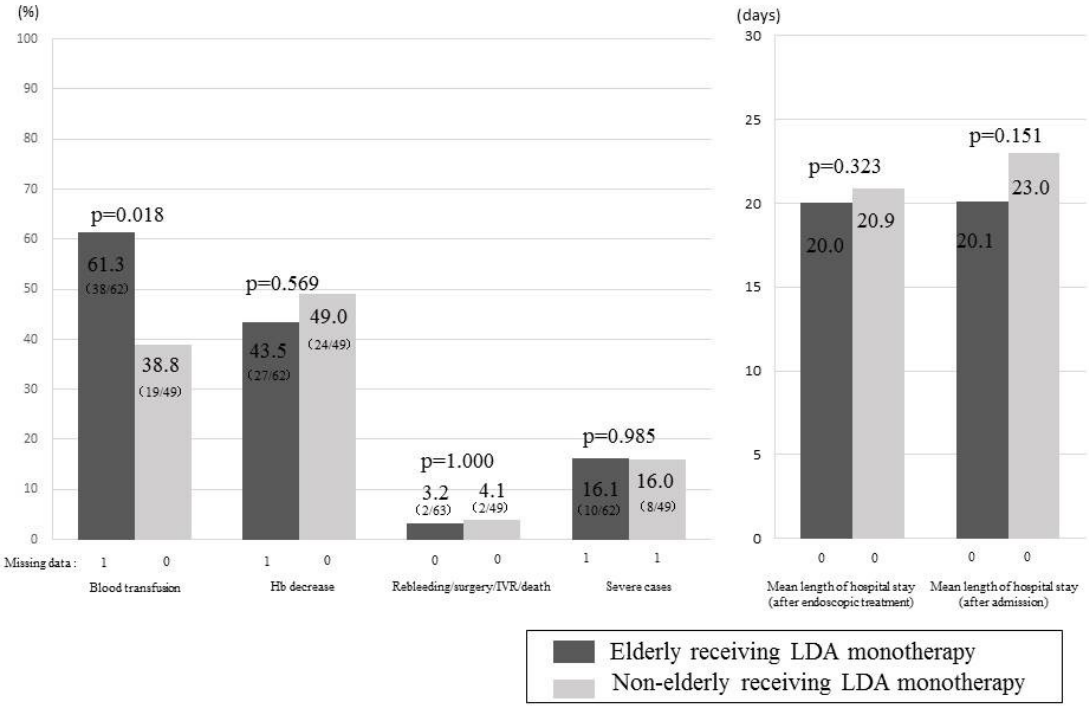
742

Figure 2



743

Figure 3



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