Risk factors and management strategy for ulcer hemorrhage following gastric endoscopic submucosal dissection in patients on antithrombotic therapy

Toshihisa Takeuchi¹, Kazuhiro Ota¹, Satoshi Harada¹, Shoko Edogawa¹, Yuichi Kojima¹, Satoshi Tokioka¹, Eiji Umegaki¹, Kazuhide Higuchi¹

1) 2nd Department of Internal Medicine, Osaka Medical College

Please address correspondence to: Toshihisa Takeuchi, 2nd Department of Internal Medicine, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki Osaka 569-8686, Japan.
Tel: +81-72-684-6432
E-mail: in2097@poh.osaka-med.ac.jp

Short title: Relations of antithrombotic agents and the after-bleeding of ESD
Abstract

**Background:** There is a lack of consensus regarding the risk of postoperative hemorrhage in patients on antithrombotic therapy who undergo endoscopic submucosal dissection (ESD). We examined postoperative bleeding rates and risk factors for postoperative hemorrhage from post-ESD gastric ulcers in patients on antithrombotic therapy.

**Methods:** The subjects of this study were 833 patients who underwent ESD of gastric tumors. Of these, 743 were not on antithrombotic therapy (NA group), and 90 were on some form of antithrombotic therapy (A group: 46 on low dose aspirin (LDA) only, 23 on LDA + thienopyridine, and 21 on LDA + warfarin). All patients commenced proton pump inhibitor (PPI) therapy immediately postoperatively. Antiplatelet agents were ceased for 7 days preoperatively and postoperative Day 1, and anticoagulants for 5 days preoperatively and postoperative Day 1.

**Results:** The postoperative bleeding rate in the A group was 23.3%, significantly higher than that of 2.0% in the NA group. Significant differences were seen in patients in the A group with and without postoperative bleeding according to ESD duration, Proton pump inhibitor (PPI) + mucosal protective agent combination therapy, and LDA + warfarin combination therapy. Multivariate analysis of these factors yielded odds ratios of 1.04 for ESD duration, 14.83 for LDA + warfarin combination therapy, and 0.27 for PPI + mucosal protective agent combination therapy.

**Conclusions:** LDA + warfarin combination therapy was an extremely strong risk factor for postoperative bleeding. We recommend combination therapy with a mucosal protective agent and a PPI to prevent post-ESD bleeding.

Key words: antithrombotic agents, endoscopic submucosal dissection, gastroprotective agent, peptic ulcer, proton pump inhibitor
Background

Endoscopic submucosal dissection (ESD) is a technique modality increasingly used worldwide in the treatment of gastric tumors. However, postoperative complications of ESD, perforations of the upper gastrointestinal tract and post-ESD ulcer bleeding (postoperative hemorrhage), are increasingly becoming a problem. Whereas perforations are mainly a problem with technique, postoperative hemorrhage is a serious complication that occurs in a certain proportion of patients irrespective of technical considerations. Studies concerning post-ESD ulcer healing and postoperative hemorrhage have reported that proton pump inhibitor (PPI) therapy gives good healing rates for post-ESD ulcers, and is also effective in preventing postoperative hemorrhage\(^1,2\), so PPIs are widely administered post-ESD.

On the other hand, along with the ageing society, we are increasingly likely to perform ESD in patients with concurrent medical conditions, in particular heart conditions and cerebrovascular disease. Many of these patients are on long term antithrombotic therapy (antiplatelet agents or anticoagulants). Patients on antiplatelet agents such as low-dose aspirin (LDA) have a greater risk and frequency of upper gastrointestinal hemorrhage, and in 2011 Luis et al. reported adjusted relative risks for upper gastrointestinal hemorrhage of 1.79 for LDA monotherapy, 3.71 for LDA + thienopyridine, and 3.62 for LDA + anticoagulant combination therapy\(^3\).

Furthermore, inhibitors of acid secretion such as PPIs have been reported to be effective in reducing the incidence and prevalence of upper gastrointestinal hemorrhage\(^4-6\).

For less invasive endoscopic procedures, such as biopsies, the risk of bleeding increases very little in patients taking antiplatelet agents\(^7-9\), and even in patients on anticoagulant therapy, the risk of postoperative hemorrhage is unchanged as long as the prothrombin time-international normalized ratio (PT-INR) is under 3.0\(^10,11\). There is, however, a lack of consensus regarding more invasive procedures such as ESD.

In this study, we examined postoperative bleeding rates and risk factors for postoperative hemorrhage from post-ESD gastric ulcers following ESD for gastric tumors in accordance with a protocol specifying uniform rules for cessation and recommencement of antithrombotic therapy, in a retrospective study.
Methods

Patients

The subjects of this study were 833 patients who underwent ESD for gastric tumors (616 with early gastric cancers, 217 with gastric adenomas) at the Osaka Medical College Hospital between June 2002 and October 2012. We use the overall term antithrombotic therapy to include antiplatelet agents (LDA, thienopyridines) and anticoagulants (warfarin potassium). Antiplatelet agents were administered as monotherapy (one or two agents) or in combination with an anticoagulant. This study included patients with a history of cerebral infarction following surgery for valvular disease. Accordingly, all patients on anticoagulants were also on antiplatelet agents, and none were on anticoagulant monotherapy. We compared hemorrhage rates between the antithrombotic (A) and non-antithrombotic (NA) groups, and examined risk factors for postoperative hemorrhage from post-ESD gastric ulcers in the A group.

ESD

We used a VIO 300D (ERBE) high frequency electrosurgical unit. Approximately 5 mm outside the lesion margin, we placed markings with a needle knife (KD-1L, Olympus Medical Systems Co. Ltd, Tokyo, Japan)\(^\text{12}\), using a coagulation wave (Soft Coag 60 W Effect 7). Next we injected 0.05% adrenaline in physiological saline into the area to be excised, between the muscularis propria and mucosa to give adequate mucosal elevation. The precut was performed using mainly the needle knife and a cutting wave (Endo Cut I Effect 2 Duration 3 Interval 3), and the circumferential cut using mainly an IT-knife 2 (KD-611L, Olympus)\(^\text{13}\) and a cutting wave (Endo Cut Q Effect 2 Duration 4 Interval 3). Submucosal dissection was performed similarly using the IT-knife 2, essentially using a coagulation wave (Swift Coag Effect 2 60–70 W), in conjunction with a cutting wave (Endo Cut Q Effect 2 Duration 4 Interval 3) for difficult to dissect areas with marked fibrosis. For intraoperative bleeding, if oozing, hemostasis was achieved using a coagulation wave (Swift Coag 60–80 W Effect 3), still using the IT-knife 2. If this was ineffective, hemostasis was achieved by pin-point grasping the bleeding source with hemostasis forceps (FD-410LR, Olympus) and a soft coagulation wave (Soft Coag 80 W Effect 6). Similarly for arterial spurting, the hemostasis forceps were used, and if with soft coagulation the heat was not adequately transferred to the bleeding vessel, hemostasis forceps with a larger contact area (Radial Jow 3 HOT Boston Scientific, Marlborough, USA) were substituted, and
hemostasis achieved with a high output coagulation wave (Forced Effect 2 40 W) for 1-2 s. Following resection of the lesion, to prevent postoperative hemorrhage all blood vessels visible in the ulcer base were treated with a coagulation wave (Soft Coag 80 W Effect 6) using hemostasis forceps.

_Treatment of post-ESD ulcer_

For all patients, perioperative management was conducted in accordance with the ESD clinical protocol of this hospital. Setting the day of the ESD procedure as Day 1, whether they were on antithrombotic therapy or not, patients were fasted until Day 2, and allowed to eat from Day 3. Intravenous PPI therapy (omeprazole 40 mg/day) was commenced immediately postoperatively. Patients underwent EGD on Day 2 to confirm hemostasis, and if necessary any blood vessels visible in the ulcer base were cauterized using a soft coagulation wave (Soft Coag 80 W Effect 6). After resumption of oral feeding on Day 3, patients were commenced on an oral PPI (rabeprazole 10 mg/day). Patients regularly taking mucosal protective agents prior to undergoing ESD, e.g. for chronic gastritis, were asked to cease them on Days 1 and 2, and recommence them on Day 3 (Figure 1).

_Guidelines for cessation and recommencement of antithrombotic therapy_

After confirming with the prescribing physician whether it could be ceased, ESD was performed only on patients able to cease antithrombotic therapy. The protocol for antiplatelet agents was to cease them from Day -6 to Day 2, and for anticoagulants to cease them from Day -4 to Day 2. Heparin (unfractionated heparin 10000-20000 U continuous venous infusion) was substituted for anticoagulants while the latter were ceased, measuring the activated partial thromboplastin time (APTT) as appropriate, maintaining the APTT at roughly twice the preheparinization level. Considering the risk of thromboembolic disease, antiplatelet agents were recommenced as soon as possible on postoperative Day 3, following confirmation of hemostasis by EGD on Day 2. Anticoagulants were similarly recommenced on postoperative Day 3, and heparin ceased once the PT-INR returned to a therapeutic level (Figure 1).
Definition of postoperative hemorrhage

Postoperative hemorrhage was defined as hematemesis and/or melena or a sudden drop in hemoglobin (Hb) ≥ 2 mg/dL occurring after recommencing eating on Day 3, requiring an unscheduled EGD, at which bleeding was confirmed to be from the post-ESD ulcer.

Statistical analysis

Categorical data were compared using the χ² test (with Yates’ correction) or Fisher’s exact test. Differences in the means of continuous data were compared using Student’s t test or the Mann-Whitney U test. To identify important risk factors for post-ESD bleeding, predictors with p values < 0.2 in the univariate analysis were included in a backward stepwise multiple logistic regression model. P values < 0.05 were considered significant, and all tests were two-sided.

Results and Discussion

Results

There were 743 patients in the NA group, and 90 in the Antithrombotic group. The underlying disease in the A group was a cardiac condition in 77.8% (70/90), and cerebrovascular disease in 22.2% (20/90). There were 46 patients on LDA (Bayaspirin®) monotherapy, 23 on LDA + thienopyridine (Panaldine®, clopidogrel), and 21 on LDA + warfarin (Figure 2).

No significant differences were seen between the NA and A groups in any background factors: age, gender, Helicobacter pylori (H. pylori) infection rate, tumor size, tumor site, tumor morphology, prevalence of concurrent disease (diabetes, renal failure or cirrhosis), or use of mucosal protective agents (p>0.05). However, the postoperative bleeding rate in the A group was 23.3% (21/90) at a median 5.5 days (range 2-15 days), significantly higher than that of 2.0% (15/743) in the NA group at a median 3.5 days (2-10 days) (p<0.001). There was only one reported thromboembolitic episode (1.1%), a case of cerebral infarction (Table 1).

Comparison of the 21 patients who experienced postoperative hemorrhage and the 69 who did not out of the 90 patients on antithrombotic therapy revealed no significant differences in any background factors, age, gender, tumor size, tumor site, H. pylori infection rate, prevalence of concurrent disease (diabetes, renal failure or cirrhosis), or number of antiplatelet agents (LDA
only or LDA + thienopyridine) (p>0.05). However, significant differences were seen according to ESD duration, LDA + warfarin combination therapy, and PPI + mucosal protective agent combination therapy (13 patients on rebamipide 300 mg/day, 13 on teprenone 150 mg/day, 13 on ecabet sodium hydrate 2.0 g/day) (Table 2). Multivariate analysis of these factors yielded odds ratios of 1.04 for ESD duration (95% CI 1.01-1.08, p=0.025), 14.83 for LDA + warfarin combination therapy (95% CI 3.91-56.26, p<0.001), and 0.27 for PPI + mucosal protective agent combination therapy (95% CI 0.07-1.02, p=0.054) (Table 3).

Discussion

In this study, we found that the risk of postoperative bleeding was higher in patients on antithrombotic therapy undergoing gastric ESD than in patients not on antithrombotic therapy. Although there was no significant difference between postoperative bleeding rates in the LDA monotherapy and LDA + thienopyridine combination therapy groups, LDA + warfarin combination therapy was an extremely strong risk factor for post-ESD bleeding. In this pioneering study, we investigated the risk of hemorrhage following gastric ESD in patients on antithrombotic therapy, based on a protocol setting out the timing of their discontinuation and recommencement, as well as the risk associated with different antithrombotic agents.

The American Society for Gastrointestinal Endoscopy (ASGE) Guidelines released in 2009 recommend that LDA therapy should be continued for gastrointestinal endoscopy, even procedures with a high risk of hemorrhage 14. On the other hand, the 2011 European Society of Gastrointestinal Endoscopy (ESGE) guidelines state that, in principle, LDA should be continued for most endoscopies, but recommend cessation of LDA for 5 days, if the risk of thromboembolic events is low, for ESD and other procedures with a high risk of hemorrhagic complications 15.

In this study, after confirming with the prescribing physician that antithrombotic agents could be discontinued, we performed ESD on patients at low risk of thromboembolic events following a set period of discontinuation. There was only one reported thromboembolystic episode (1.1%) attributable to cessation of antithrombotic therapy. When a patient on LDA therapy ceases aspirin for about 4 weeks, the reported odds ratio for stroke or transient ischemic attack (TIA) is 3.29 (95% CI 1.07-9.80, P<0.005) 16. In this study, we ceased LDA for a shorter period or not at all, keeping the incidence of cerebral infarction to a relatively low level. However, the
postoperative bleeding rate in the A group was 23.3%, significantly higher than that of 2.0% in the NA group.

On the other hand, there is a lack of clear evidence of the extent to which hemorrhagic complications are increased in patients on antiplatelet + anticoagulant combination therapy undergoing gastrointestinal endoscopic procedures with a high risk of bleeding. In a retrospective study of 5593 patients undergoing colorectal polypectomy, postoperative hemorrhage was significantly more common in patients on warfarin therapy\(^\text{17}\). From this, it goes without saying for colorectal polypectomy, and the recommendation is for ESD with its high incidence of hemorrhagic complications, to discontinue warfarin and replace it with heparin\(^\text{18}\). We also replace warfarin with heparin, monitoring APTT as we perform the procedure. Patients on warfarin therapy undergoing ESD in this study included some with a history of cerebral infarction following surgery for valvular disease, so all patients on warfarin were also on LDA. There were no patients on warfarin monotherapy in this study, so it is uncertain whether the risk of postoperative bleeding is increased by LDA + warfarin combination therapy, or by warfarin monotherapy. However, the postoperative bleeding rate was significantly higher in patients on LDA + warfarin combination therapy, with an odds ratio of 14.83 \((p<0.001)\), confirming combination therapy to be an extremely strong risk factor. The odds ratio for postoperative bleeding in patients taking mucosal protective agents in addition to a PPI was 0.27 \((p=0.054)\), suggesting that the addition of a mucosal protective agent may be effective in preventing postoperative hemorrhage, although the difference was not significant.

Until now, only four studies worldwide have examined the relationship between antithrombotic therapy and bleeding following gastric ESD. In 2009, Ono et al. conducted a retrospective study of gastric ESD in patients on antithrombotic therapy. They reported a postoperative bleeding rate of 10.7% \((6/56)\) in patients on antithrombotic therapy, and 5.2% \((20/388)\) in patients not on antithrombotic therapy, with no significant difference between groups. All patients on antithrombotic therapy were taking an antiplatelet agent, with 5 on combination therapy with an anticoagulant. Of these, only 3 were heparinized. All patients ceased antithrombotic therapy for 1 week before and after ESD\(^\text{19}\). The reason for a lack of a significant difference in the postoperative bleeding rate between patients on antithrombotic therapy and not on antithrombotic therapy may be because the drug withdrawal period was longer than for this study. Considering the risk of thromboembolic

8
events, however, antithrombotic therapy should be recommenced as soon as possible, once hemostasis has been confirmed endoscopically. The standards for cessation and recommencement of antithrombotic therapy, as well as heparinization, are vague and ambiguous.

In 2010, Mannen et al. conducted a retrospective study of risk factors for complications following ESD in 436 patients with gastric tumors. They reported a postoperative bleeding rate of 3% (1/33) in patients on antithrombotic therapy, and 9.4% (38/403) in patients not on antithrombotic therapy, with no significant difference between groups.\(^{20}\)

In a similar study, in 2011 Okada et al. conducted a retrospective study of risk factors for post-ESD bleeding in 582 patients with gastric tumors. They reported a postoperative bleeding rate of 14.2% (4/28) in patients on antithrombotic therapy, and 12.6% (70/554) in patients not on antithrombotic therapy, with no causal relationship between postoperative bleeding and antithrombotic therapy (p=0.7732).\(^{21}\)

However, these studies have not reported in detail whether patients were on antiplatelet agents only, or in combination with an anticoagulant, the timing of cessation and recommencement, or if heparin was substituted.

A study that found that antithrombotic therapy increases the risk of postoperative bleeding was the 2010 retrospective study by Tsuji et al. of gastric ESD in patients on antithrombotic therapy, as well as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs). They reported a postoperative bleeding rate of 34.8% (8/15) in patients on antithrombotic therapy, and 16% (60/315) in patients not on antithrombotic therapy, significantly higher in the former with an odds ratio of 2.76 (95% CI 1.09-6.98).\(^{22}\) As in this study, they followed a protocol with set timing of cessation and recommencement of antithrombotic therapy, and heparinization for patients on anticoagulant therapy, and they reported an increased risk of post-ESD bleeding in patients on antithrombotic therapy. However, corticosteroids and NSAIDs are included in the antithrombotic agents, and antithrombotic agents are not examined separately, so simple comparisons cannot be made.

Moreover, suppressors of acid secretion, H2RAs and PPIs, were used to treat post-ESD ulcers in the above four studies, but gastroprotective agents were not used.

In this study, for the first time we added a mucosal protective agents to PPI therapy, lowering the odds ratio for postoperative bleeding to 0.27 (p=0.054), suggesting that the addition of a
mucosal protective agent may be effective in preventing post-ESD hemorrhage in patients on antithrombotic therapy, although the difference was not statistically significant.

In the treatment of hemorrhagic peptic ulcers, suppressors of acid secretion such as PPIs promote ulcer healing as well as reducing the risk of hemorrhage. On the other hand, in the treatment of post-ESD ulcers, PPI + mucosal protective agent combination therapy is reported to yield better healing rates and similar postoperative bleeding rates as PPI monotherapy. These studies reported no significant difference between postoperative bleeding rates in the PPI group and PPI + mucosal protective agent group, but they are studies conducted with patients not on antithrombotic therapy. In this study, we included patients on antithrombotic therapy, and the fact that our results show a reduction in postoperative bleeding to a certain extent can be attributed to superior promotion of ulcer healing with PPI + mucosal protective agent combination therapy as demonstrated in the earlier studies.

Asian people are generally considered to have lower gastric acid levels than Westerners, and furthermore differentiated type gastric cancers, one of the indications for ESD, show a markedly atrophic background mucosa associated with *H. pylori* infection. From this we can assume impairment of gastric mucin and other protective factors, as well as reduced acid secretory function. We can also infer that the pharmacological properties of mucosal protective agents exert favorable effects on the post-ESD healing process, including prevention of postoperative hemorrhage.

The tendency towards higher postoperative bleeding rates with longer ESD durations can be explained in terms of a longer time taken to achieve hemostasis while resecting the lesion. When multiple vessels require cautery, it follows that a number of vessels are present in the ulcer floor following ESD, and we can assume that this influences the postoperative bleeding rate.

The limitations of this study are that it was a retrospective study, that we did not perform ESD while continuing antithrombotic therapy, the absence of a warfarin monotherapy group, and the possibility of a bias in the administration of mucosal protective agents. We are a tertiary referral center, resulting in a relatively high proportion of patients with background factors such as cerebral infarction following valvular surgery. All patients on warfarin therapy were also taking LDA, and we had no warfarin monotherapy group for comparison. However, despite being a retrospective study, we were unable to identify any earlier studies that examined this area in
detail based on a consistent protocol, and we believe the next step should be to conduct a prospective study based on our results. PPI monotherapy is the standard treatment for post-ESD ulcers, but the risk of postoperative hemorrhage cannot be avoided through a PPI alone in patients on antithrombotic therapy. Our results indicate that the addition of a mucosal protective agent to PPI therapy may reduce the risk of postoperative hemorrhage, potentially an extremely useful finding. We intend to conduct a large-scale prospective trial to confirm this.

Conclusions

we found that the risk of postoperative hemorrhage following gastric ESD is higher in patients on antithrombotic therapy than in those not on antithrombotic therapy. Among patients on antithrombotic therapy, LDA + warfarin combination therapy was an extremely strong risk factor for postoperative bleeding. Considering the risk of thromboembolic events, it is difficult to discontinue antithrombotic therapy, and it is clear that PPI therapy alone is inadequate, although it is presently the standard treatment for post-ESD ulcers and the prevention of postoperative hemorrhage. We recommend combination therapy with a mucosal protective agent and a PPI to prevent post-ESD bleeding.

List of Abbreviations

ESD; endoscopic submucosal dissection
LDA; low-dose aspirin
PPI; Proton pump inhibitor
PT-INR; prothrombin time-international normalized ratio
APTT; activated partial thromboplastin time
Hb; hemoglobin

H. pylori; *Helicobacter pylori*

Competing interests

The authors have no conflicts of interest to declare.

Author details

2nd Department of Internal Medicine, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka, Japan
Authors’ contributions

Guarantor of the article: Toshihisa Takeuchi, MD.,PhD

Specific author contributions: Principal investigator, subject evaluation, data collection and manuscript preparation:Toshihisa Takeuchi; manuscript preparation and statistical analysis: Kazuhide Higuchi; subject evaluation and data collection: Kazuhiro Ota, Satoshi Harada, Shoko Edogawa, Satoshi Tokioka and Eiji Umegaki

Funding

This research did not receive any specific grant from any fundings agency in the public, commercial, or not-for-profit sector.
References


8) Shiffman ML, Farrel MT, Yee YS. Risk of bleeding after endoscopic biopsy or polypectomy in patients taking aspirin or other NSAIDS. *Gastrointest Endosc* 1994; 40: 458-462.


pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001; 119 (1 Suppl): 64S-94S.


Figure legends

Figure 1 Endoscopic submucosal dissection protocol
Setting the day of the ESD procedure as Day 1, whether they were on antithrombotic therapy or not, patients were fasted until Day 2, and allowed to eat from Day 3. After resumption of oral feeding on Day 3, patients were commenced on an oral PPI. Patients regularly taking mucosal protective agents prior to undergoing ESD, e.g. for chronic gastritis, were asked to cease them on Days 1 and 2, and recommence them on Day 3. The protocol for antiplatelet agents was to cease them from Day -6 to Day 2, and for anticoagulants to cease them from Day -4 to Day 2. Heparin was substituted for anticoagulants while the latter were ceased, measuring the APTT as appropriate, maintaining the APTT at roughly twice the preheparinization level. Antiplatelet agents were recommenced as soon as possible on postoperative Day 3, following confirmation of hemostasis by EGD on Day 2. Anticoagulants were similarly recommenced on postoperative Day 3, and heparin ceased once the PT-INR returned to a therapeutic level.

Figure 2 Study outline
There were 743 patients in the NA group, and 90 in the Antithrombotic group. The underlying disease in the A group was a cardiac condition in 77.8% (70/90), and cerebrovascular disease in 22.2% (20/90). There were 46 patients on LDA monotherapy, 23 on LDA + thienopyridine and 21 on LDA + warfarin
Table 1 Characteristics of NA and A groups

<table>
<thead>
<tr>
<th></th>
<th>Non antithrombotic (n=743)</th>
<th>Antithrombotic (n=90)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.3±12.3</td>
<td>64.8±13.7</td>
<td>0.719</td>
</tr>
<tr>
<td>Gender (M/F) (% M)</td>
<td>423/320 (56.9)</td>
<td>54/36 (60.0)</td>
<td>0.578</td>
</tr>
<tr>
<td>H. pylori infection (+/-) (% positive)</td>
<td>587/156 (79.0)</td>
<td>73/17 (81.1)</td>
<td>0.642</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>15.5±5.2</td>
<td>15.7±5.5</td>
<td>0.731</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>430</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>IIa + IIc</td>
<td>112</td>
<td>14</td>
<td>0.976</td>
</tr>
<tr>
<td>IIc</td>
<td>201</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Duration of ESD (min)</td>
<td>46.6±17.6</td>
<td>44.0±16.1</td>
<td>0.182</td>
</tr>
<tr>
<td>Location of tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>325</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Angular</td>
<td>185</td>
<td>22</td>
<td>0.944</td>
</tr>
<tr>
<td>Corpus</td>
<td>233</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Concurrent disease (diabetes, renal failure, cirrhosis) (+/-) (% positive)</td>
<td>240/503 (32.3)</td>
<td>28/62 (31.1)</td>
<td>0.819</td>
</tr>
<tr>
<td>Gastroprotective agent (+/-) (% positive)</td>
<td>315/428 (42.4)</td>
<td>39/51 (43.3)</td>
<td>0.865</td>
</tr>
<tr>
<td>Post-ESD bleeding (+/-) (% positive)</td>
<td>15/728 (2.0)</td>
<td>21/69 (23.3)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

NA: no antithrombotic; A: antithrombotic; ESD: endoscopic submucosal dissection

*P < 0.05 vs non-bleeding. Ratios were analysed using the $\chi^2$ test.
Table 2 Background characteristics in relation to bleeding status

<table>
<thead>
<tr>
<th></th>
<th>Bleeding (n=21)</th>
<th>Non-bleeding (n=69)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.4 ± 13.4</td>
<td>64.7 ± 13.8</td>
<td>0.838</td>
</tr>
<tr>
<td>Gender (M/F) (%) M</td>
<td>12/9 (57.1)</td>
<td>42/27 (60.9)</td>
<td>0.760</td>
</tr>
<tr>
<td>H. pylori infection (+/-) (%) positive</td>
<td>17/4 (81.0)</td>
<td>56/13 (81.2)</td>
<td>0.983</td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>15.8 ± 6.1</td>
<td>15.7 ± 5.4</td>
<td>0.942</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>11</td>
<td>40</td>
<td>0.411</td>
</tr>
<tr>
<td>IIa + IIc</td>
<td>2</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>IIc</td>
<td>8</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Duration of ESD (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anteprule</td>
<td>50.3 ± 18.8</td>
<td>42.1 ± 14.9</td>
<td>0.041*</td>
</tr>
<tr>
<td>Antrum</td>
<td>5</td>
<td>32</td>
<td>0.528</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>7</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Corpus</td>
<td>5</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Concurrent disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+/-) (diabetes, renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>failure, cirrhosis)</td>
<td>3/18 (14.3)</td>
<td>25/44 (36.2)</td>
<td>0.057</td>
</tr>
<tr>
<td>Gastroprotective agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+/-) (positive)</td>
<td>5/16 (23.8)</td>
<td>34/35 (49.3)</td>
<td>0.039*</td>
</tr>
<tr>
<td>LDA + warfarin (+/-) (%) positive</td>
<td>12/9 (57.1)</td>
<td>9/60 (13.0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>LDA + thienopyridine (+/-) (%) positive</td>
<td>3/18 (14.3)</td>
<td>20/49 (29.0)</td>
<td>0.176</td>
</tr>
</tbody>
</table>

ESD: endoscopic submucosal dissection; LDA: low dose aspirin.

*P < 0.05 vs non-bleeding. Ratios were analysed using the χ² test.
Table 3 Significant predictors of post-ESD bleeding identified using multiple logistic regression

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of ESD</td>
<td>1.04</td>
<td>1.01-1.08</td>
<td>0.025*</td>
</tr>
<tr>
<td>LDA+warfarin</td>
<td>14.83</td>
<td>3.91-56.26</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PPI</td>
<td>gastroprotective agent</td>
<td>0.27</td>
<td>0.07-1.02</td>
</tr>
</tbody>
</table>

*P < 0.05.

ESD: endoscopic submucosal dissection; LDA: low dose aspirin; PPI: proton pump inhibitor.
Figure 1 Endoscopic submucosal dissection protocol

ESD: endoscopic submucosal dissection; EGD: esophagogastroduodenoscopy
Figure 2 Study outline

Patients with gastric cancer who underwent ESD (n=833)

NA (no antithrombotic) (n=743)

A (antithrombotic) (n=90)

LDA only (n=46)

LDA + thienopyridine (n=23)

LDA + warfarin (n=21)

LDA: low dose aspirin