

Low-Dose Aspirin Continuation During Gastric Endoscopic Submucosal Dissection in Patients With Low Thrombotic Risk: A Randomized Trial

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Background

- ESD - Standard treatment for intramucosal EGC
- Delayed bleeding after ESD - approximately 4-9%
- Aging population - more EGC patients on antiplatelet tx undergoing ESD
- Rationale for continuing LDA
 - > bleeding during/after ESD - usually controllable, rarely fatal
 - > thrombotic stroke - lifelong disability or death
- several observational studies & meta-analysis: non-significant increase in delayed bleeding with continued LDA
 - > mostly retrospective, small sample, heterogeneous timing of interruption

내시경 검사 및 시술시 항혈전제&항응고제 중단 기준

항혈전제				항응고제			
»EGD, sig, mini(상), mini(하), ERCP(외래), (전자식) 내시경 초음파, PEG removal 검사시 혈전제 1가지는 중단없이 검사 진행가능(※단 2가지 성분 복합약물 처방의와 중단시기 상의(클로스원등)). »그 외 검사는 약물 처방의사와 복용 중단 시기에 대해 상의하도록 안내함. *약물 중단 시기 미충족(처방의와 상의 되지 않은 경우) 검사진행 여부는 검사시행의와 상의후 결정한다. *현 처방시점 부터 적용되는 기준입니다.(23.08.23)				»EGD, sig, mini(상), mini(하), ERCP(외래), (전자식) 내시경 초음파, PEG removal 검사시 항응고제 중단없이 검사 진행가능 »그 외 검사는 약물 처방의사와 복용 중단 시기에 대해 상의하도록 안내함. *약물 중단 시기 미충족(처방의와 상의 되지 않은 경우) 검사진행 여부는 검사시행의와 상의후 결정한다. *현 처방시점 부터 적용되는 기준입니다.(23.08.23)			
약품코드	성분명	상품명	중단여부	약품코드	성분명	상품명	중단여부
ASP	Aspirin 100mg	아스피린 정 100mg	용종제거술 및 시술시 : 처방의와 상의후 5~7일 중단	APIXA	Apixaban 2.5mg	엘리퀴스 정 2.5mg	72시간
ASPC	Aspirin coated 100mg	아스트릭스캡셀 100mg		APIXA5	Apixaban 5mg	엘리퀴스	72시간
CLOPI	cloPIDOgrel 75mg	플라빅스		DABI11	Dabigatran 110mg	프라닥사 캡슐 110mg	72시간
CLOPID	cloPIDOgrel 75mg	플라비톨정 75mg		DABI15	Dabigatran 150mg	프라닥사 캡슐 150mg	72시간
CILO	ciloSTAzol 50mg	프레탈정 75mg		RIVA2.5	Rivaroxaban 2.5mg	자렐토 정 2.5mg	72시간
CILO1	ciloSTAzol 100mg	프레탈 정 100mg		RIVAR15	Rivaroxaban 15mg	자렐토 정 15mg	72시간
CIOSR	ciloSTAzol 100mg (서방캡슐)	프레탈 서방캡슐		RIVAR20	Rivaroxaban 20mg	자렐토 정 20mg	72시간
TFLU	Triflusal 300mg	명인디스크렌캡셀 300mg		RIVARX	Rivaroxaban 10mg	자렐토 정 10mg	72시간
TICL	Ticlopidine 250mg			WARF	warfarin 2mg	와르파린나트륨 정 2mg	5일 중단
TICL1	Ticlopidine 100mg	유유 크리드정 100mg		WARF5	warfarin 5mg	와르파린나트륨 정 5mg	
BERAP	beraprost 20mcg	베라실정 20mcg	중단 설명하지 않음	EDOX15	Endoxaban 15mg	릭시아나 정 15mg	72시간
SARPO	Sarpogrelate 100mg(반감기1~2시간)	안플라그정 100mg	중단 설명하지 않음	EDOX3	Endoxaban 30mg	릭시아나 정 30mg	72시간
SARPSR3	Sarpogrelate 300mg(반감기1~2시간)	안플원 서방정 300mg	중단 설명하지 않음	EDOX6	Endoxaban 60mg	릭시아나 정 60mg	72시간
ASPCLO	Closone® 75mg/100mg (clopidogrel 75mg/Aspirin 100mg)	클로스원 캡슐75 mg/100mg	2가지성분복합약물로 처방의와 중단시기 상의				

Hypothesis

- If any increase in ESD-related bleeding with LDA continuation remains within acceptable limits, patients may benefit from maintained antithrombotic effect

Method

Item	Description
Design	Multicenter, randomized, open-label, <u>noninferiority trial</u>
Setting	67 Japanese institutions
Enrollment	June 2014 – March 2020
Randomization	1:1, minimization method
Stratification	Institution, lesion location (antrum/corpus), size (≤ 2 / > 2 cm), UL0/UL1
Blinding	None (neither endoscopists nor patients)
Amendment (2016.7)	Allowed non-thienopyridine antiplatelets (e.g., cilostazol, EPA)

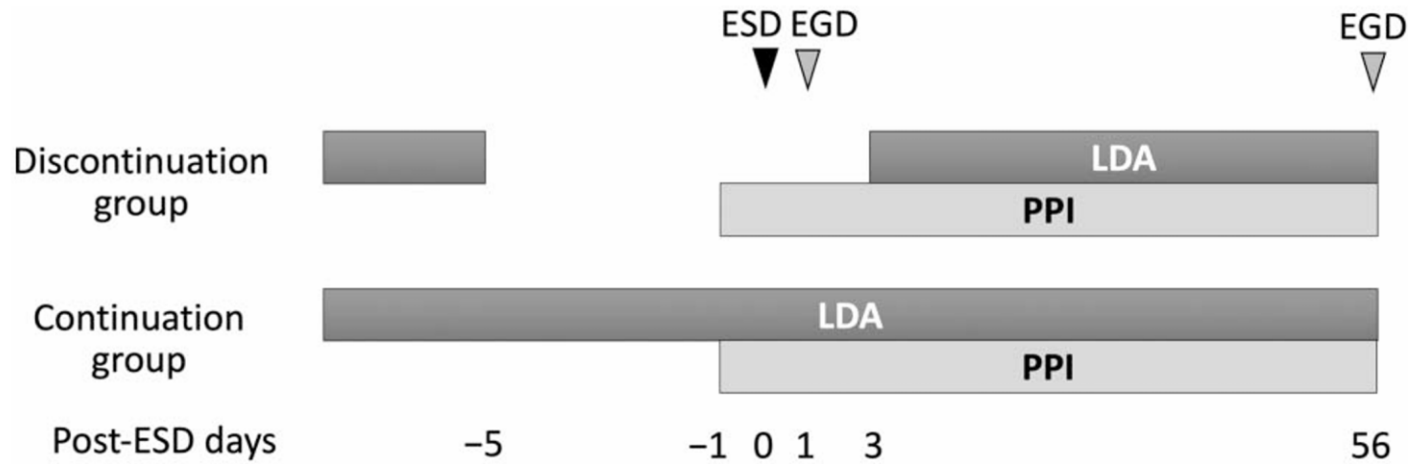
Inclusion criteria

- | |
|---|
| <ul style="list-style-type: none">• Gastric adenoma or cT1a EGC within endoscopic resection indication<ul style="list-style-type: none">– Differentiated, ≤ 2 cm, UL0 / > 2 cm, UL0 / ≤ 3 cm, UL1– Undifferentiated, ≤ 2 cm, UL0 |
| <ul style="list-style-type: none">• Single lesion |
| <ul style="list-style-type: none">• Continuous LDA intake(81-100mg) |
| <ul style="list-style-type: none">• Age ≥ 20 years, ECOG PS 0-2 |
| <ul style="list-style-type: none">• Lab<ul style="list-style-type: none">- $Hb \geq 9$ g/dL- $Plt \geq 100,000/mm^3$- $AST/ALT \leq 100$ IU/L- $Cr \leq 2.0$ mg/dL- $PT-INR \leq 1.5$ |
| <ul style="list-style-type: none">• Approval from prescribing physician for temporary aspirin discontinuation |

Exclusion criteria

- | |
|---|
| <ul style="list-style-type: none">• High thromboembolic risk (JGES 기준)<ul style="list-style-type: none">- within 2 months after coronary BMS / 12 month after DES- within 2 months after carotid endarterectomy or stenting- Ischemic stroke/TIA with >50% major intracranial stenosis, recent ischemic stroke/TIA- obstructive PAD $\geq$ Fontane grade 3, high risk on carotid US or MRA |
| <ul style="list-style-type: none">• Continuous thienopyridine, anticoagulant, systemic steroid, NSAID |
| <ul style="list-style-type: none">• Residual/recurrent lesion after previous endoscopic resection |
| <ul style="list-style-type: none">• Prior epigastric radiotherapy |
| <ul style="list-style-type: none">• simultaneous esophageal/duodenal endoscopic treatment, other UGI treatment within 28 days |
| <ul style="list-style-type: none">• etc: pregnancy & Lactation, Psychiatric disorder, Active infection, Poorly controlled HTN |

Intervention



	Discontinuation	Continuation
LDA	Withhold from day -5 to day +3	Daily throughout
PPI	Lansoprazole 30 mg from day -1, for 56 days	Same

Figure 1. Schedule of drug administration. EGD, esophagogastroduodenoscopy; ESD, endoscopic submucosal dissection; LDA, low-dose aspirin; LPZ, lansoprazole; PPI, proton pump inhibitor.

- 2nd look endoscopic on post-ESD day 1
- Follow up endoscopy at 8 ± 1 weeks

Endoscopic procedure

- JGES-associated endoscopists or supervised trainees
- Device & injection solution($\pm$ epinephrine) - operator
- All exposed vessels in the post-ESD ulcer base cauterized with hemostatic forceps
- No additional prophylaxis(no endoscopic closure, no gel)
- Second look endoscopy the next day
 - hemostasis if active bleeding, NBVV or adherent clot
 - second look endoscopy findings not counted as ESD-related bleeding
- Emergency endoscopy when post-ESD bleeding clinically suspected

Primary End points

- **ESD-related major bleeding**

= massive intraprocedural bleeding + post-ESD bleeding

- Massive intraprocedural bleeding

Bleeding during ESD requiring transfusion, surgery, or Interventional radiology

- Post-ESD bleeding (within 28 days)

(1) clinical signs (hematemesis, melena, SBP ≤ 100 mmHg or PR ≥ 100) AND
(2) endoscopic intragastric blood retention or active bleeding from the ulcer

Secondary end points

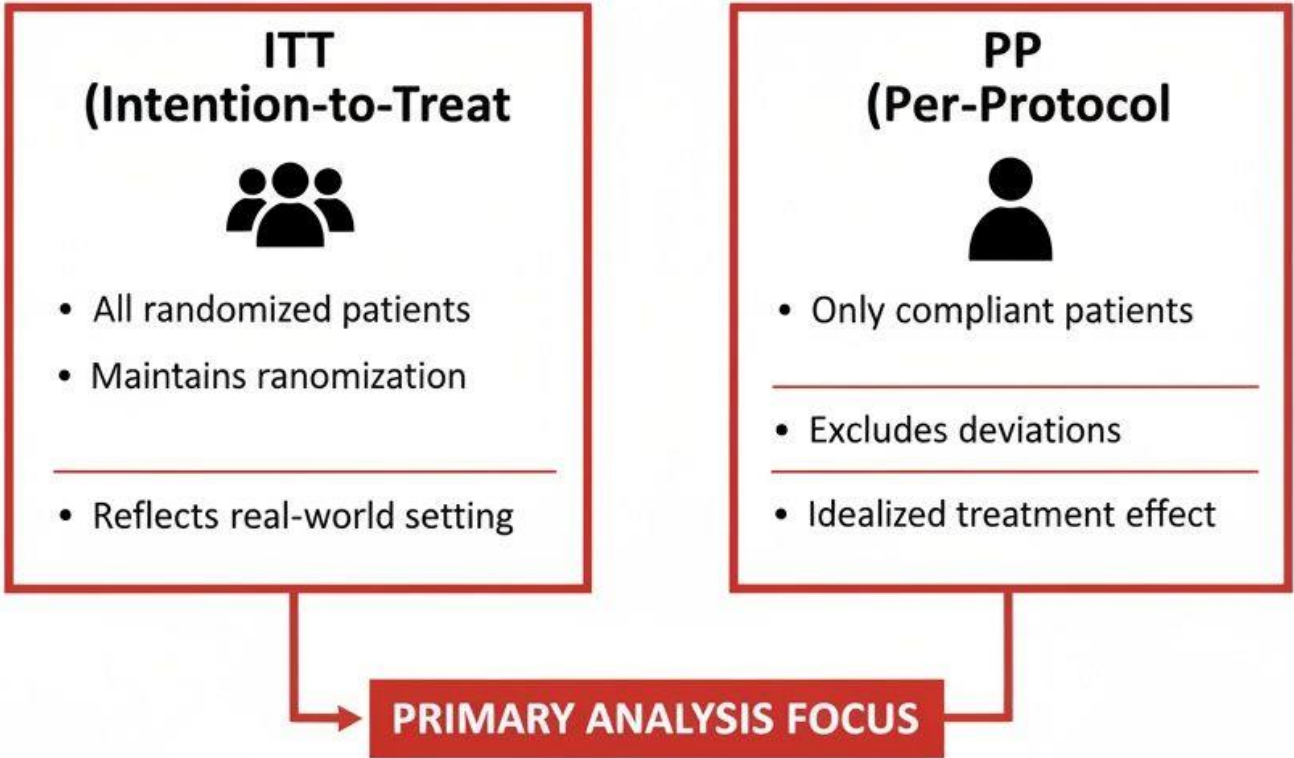
Supplementary Table 1. Secondary endpoints and definitions

1. Incidence of either of the following thromboembolic events	(a) Myocardial infarction (b) Myocardial ischemia requiring percutaneous coronary intervention (c) Cerebral infarction (d) Ischemic cerebral events associated with neurological symptoms lasting ≥ 24 h
2. Procedure time for ESD	Time interval between the start of submucosal injection and the completion of tumor removal
3. Procedure time for prophylactic coagulation	Time interval between the completion of lesion removal and the final endoscope withdrawal
4. Healing of post-ESD ulcer at 8-week follow-up endoscopy according to Sakita-Miwa classification	A1 (Active stage 1): Surrounding mucosa is edematous with no visible regenerating epithelium. A2 (Active stage 2): Surrounding edema decreases and the ulcer margin becomes distinct, showing partial epithelial regeneration, a red halo, and a white slough ring. H1 (Healing stage 1): The white coating thins, regenerative epithelium extends into the ulcer base and height difference between margin and floor flattens. The ulcer remains visible, with sharp margins;

Statistical methods

Parameter	Setting
Expected bleeding rate	5% in both groups (under PPI)
Noninferiority margin	<u>Absolute risk difference 5%</u>
α / β	0.05 / 0.20
Sample size	280
Primary analysis	m-ITT; noninferiority if upper limit of 2-sided 90% CI $\leq 5\%$
Sensitivity analysis	Per-protocol (PP)
Time-to-event	Kaplan-Meier, log-rank test
Subgroups	Age, vascular disease history, H. pylori, lesion size, SLE treatment

CLINICAL TRIAL DATA ANALYSIS: ITT vs. PP



	Effectiveness	Efficacy
포함 대상	무작위 배정 사전 정의된 최소 충족자	프로토콜을 위반없이 완수한 자
분석 군	배정된 군 기준	실제 받은 치료 기준
의미	실제 임상 적용시 효과(effectiveness)	프로토콜대로 했을 때 효과(efficacy)

Results

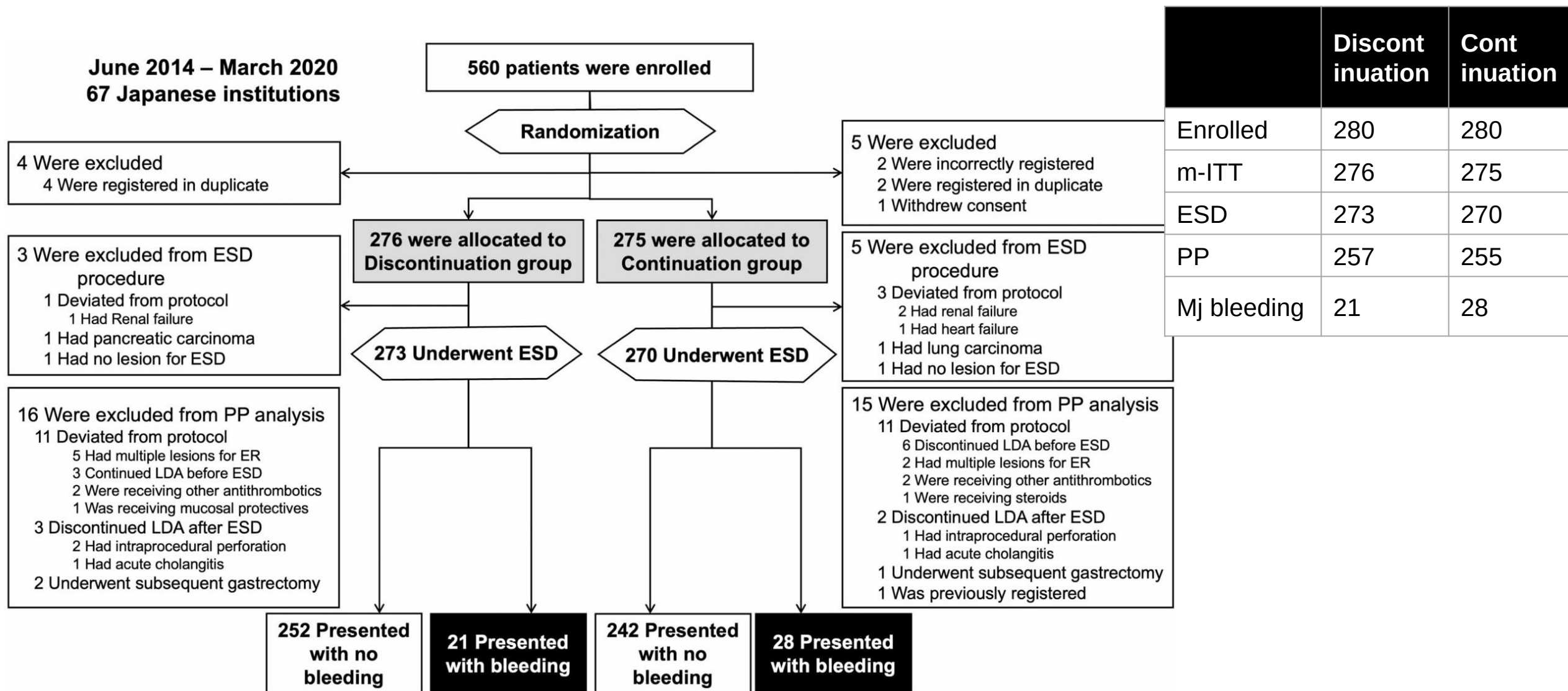


Table 1. Baseline data of patients in the full analysis set

Item	Discontinuation group (n = 276)	Continuation group (n = 275)
Age, yr, mean (SD)	75 (6.8)	75 (6.8)
Sex, n (%)	215 (79)	217 (79)
Height, cm, mean (SD)	161 (8.6)	160 (9.1)
Weight, kg, mean (SD)	60.7 (11)	61.0 (11)
Performance status, n (%)		
0	254 (92)	256 (93)
1	22 (8.0)	18 (6.5)
2	0	1 (0.36)
Drinking, n (%)	108 (39)	96 (35)
Smoking, n (%)	49 (18)	31 (11)
History of peptic ulcer, n (%)	18 (6.5)	19 (6.9)
<i>H. pylori</i> infection, n (%)		
Positive	89 (32)	82 (30)
Negative	155 (56)	162 (59)
Unknown	32 (12)	31 (11)
History of <i>H. pylori</i> eradication therapy, n (%)		
Yes	92 (33)	101 (37)
No	178 (65)	170 (62)
Unknown	6 (2.1)	4 (1.5)
Coronary arterial disease, n (%)	107 (39)	102 (37)
Angina pectoris	60 (22)	55 (20)
Myocardial infarction	37 (13)	34 (12)
Other	10 (3.6)	13 (4.7)
Coronary stenting, n (%)	59 (21)	50 (18)
Drug-eluting stent	26 (9.4)	24 (8.7)
Metal stent	20 (7.2)	20 (7.3)
Other	13 (4.7)	6 (2.2)
Cerebrovascular disease, n (%)	72 (26)	85 (31)
Brain infarction	52 (19)	59 (22)
Internal carotid artery stenosis	4 (1.5)	8 (2.9)
Transient ischemic attack	7 (2.5)	8 (2.9)
Cerebral aneurism	3 (1.1)	5 (1.8)
Subarachnoid hemorrhage	0	3 (1.1)
Cerebral artery stenosis	3 (1.1)	1 (0.36)
Brain hemorrhage	1 (0.36)	0
Other	2 (0.72)	1 (0.36)

Item	Discontinuation group (n = 276)	Continuation group (n = 275)
Peripheral arterial disease, n (%)	13 (4.7)	12 (4.4)
Obstructive arteriosclerosis	12 (4.3)	9 (3.3)
Varicose vein	1 (0.36)	2 (0.73)
Other	0	1 (0.36)
Hypertension needing drug treatment, n (%)	75 (27)	86 (31)
Diabetes mellitus needing drug treatment, n (%)	57 (21)	52 (19)
Hemoglobin, g/dL, mean (SD)	13.7 (1.7)	13.6 (1.6)
Platelet count, 10 ³ /mm ³ , mean (SD)	215 (58)	221 (60)
Aspartate aminotransferase, IU/L, mean (SD)	24 (9.4)	26 (10)
Alanine aminotransferase, IU/L, mean (SD)	20 (11)	21 (11)
Total bilirubin, mg/dL, mean (SD)	0.7 (0.3)	0.7 (0.3)
Serum creatinine, mg/dL, mean (SD)	0.89 (0.28)	0.94 (0.57)
Prothrombin time-international normalized ratio, mean (SD)	1.00 (0.07)	1.00 (0.06)
Longitudinal tumor location, n (%)		
Upper third	54 (20)	50 (18)
Middle third	107 (39)	103 (37)
Lower third	115 (42)	122 (44)
Endoscopic tumor size, mm, mean (SD)	15 (9.2)	15 (8.8)
Main tumor morphology, n (%)		
Protruding	6 (2.2)	5 (1.8)
Superficial elevated	104 (38)	125 (46)
Superficial flat	13 (4.7)	14 (5.1)
Superficial depressed	153 (55)	129 (47)
Excavated	0	2 (0.72)
Endoscopic ulcer/scar, n (%)	21 (7.6)	23 (8.4)
Tumor histology in biopsy, n (%)		
Differentiated type	220 (80)	208 (76)
Undifferentiated type	8 (2.9)	8 (2.9)
Suspicious for adenocarcinoma or indefinite for neoplasia	15 (5.4)	22 (8.0)
Adenoma	33 (12)	37 (13)

H. pylori, *Helicobacter pylori*.

- mean 75 yrs old
- male 78.4%
- LDA indication
CAD 209
CVD 157
PAD 25
- mean tumor size
15mm
- Smoking
18% vs. 11%

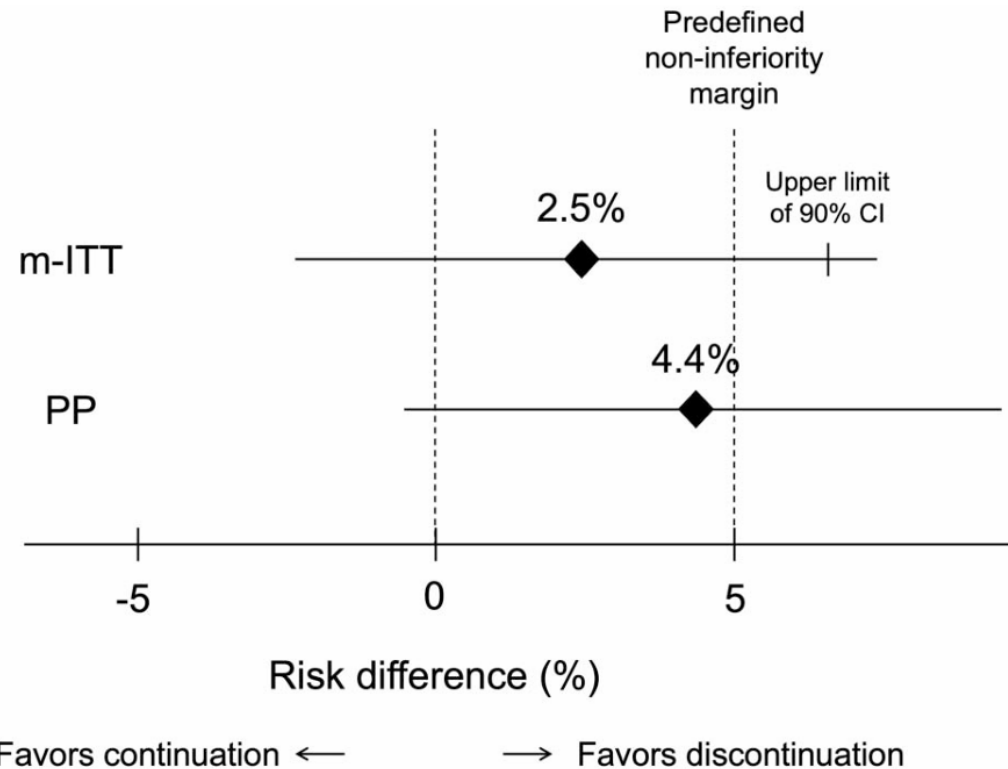
Results - primary endpoints

	Discontinuation (n=276)	Continuation (n=275)
ESD-related major bleeding, n (%)	21 (7.6)	28 (10)
95% CI	4.8–11	6.9–14
Massive intraprocedural	0	0
Post-ESD bleeding	21	28

Analysis	Risk difference	90% CI	95% CI	P (noninferiority)
m-ITT	2.5%	-1.5 to 6.6 상한 5.0 이상	-2.3 to 7.4	0.157
PP	4.4%	–	-0.5 to 9.5	0.400

▶ Noninferiority NOT demonstrated

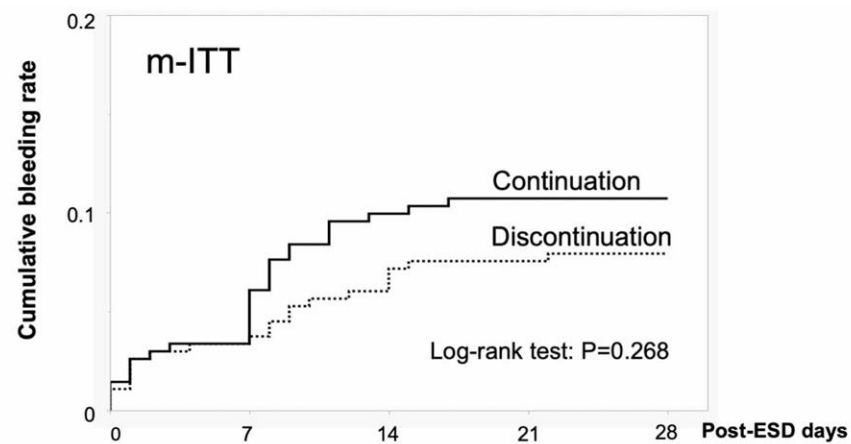
Results - primary endpoints



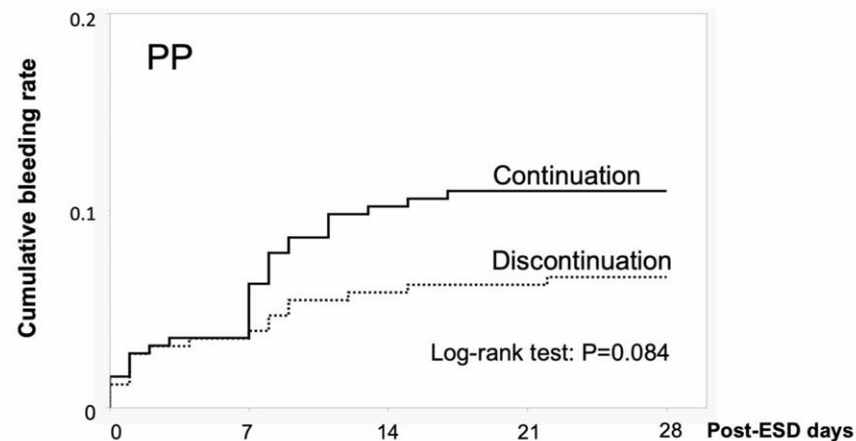
Risk difference
m-ITT upper limit : 6.6%
PP : 4.4%
0 in CI interval in both analysis >> Not significantly worse

Figure 3. Primary outcome of the trial (risk difference in the incidence of ESD-related major bleeding between the groups). CI, confidence interval; m-ITT, modified intent-to-treat; PP, per protocol.

Results - cumulative incidence of major bleeding



No. at Risk					
Continuation	275	257	240	239	239
Discontinuation	276	258	251	248	247



No. at Risk					
Continuation	255	246	229	239	227
Discontinuation	257	248	242	241	240

- Separate from post-ESD day 6
- Difference most marked in day 6 & 13
- Separation more in PP analysis

Table 2. Study outcomes

	Discontinuation group (n = 276)		Continuation group (n = 275)	P value
Primary end point				
ESD-related major bleeding, n (%) [95% CI]	21 (7.6) [4.8–11]		28 (10) [6.9–14]	$P_{\text{noninferiority}} = 0.157, P = 0.369$
Massive intraprocedural bleeding, n	0		0	
Post-ESD bleeding, n	21		28	
Secondary end points				
Thromboembolic events	0		2	0.249
ESD procedure time, min, mean (SD)	59 (48)		60 (46)	0.687
Prophylactic coagulation time, min, mean (SD)	10 (15)		9.0 (8.5)	0.209
Ulcer findings at 8-wk endoscopy, n (%)				0.035
A1 (active stage 1)	0		3 (1.1)	
A2 (active stage 2)	3 (1.1)		1 (0.37)	
H1 (healing stage 1)	4 (1.5)		10 (3.7)	
H2 (healing stage 2)	49 (18)		38 (14)	
S1 (scarring stage 1)	131 (48)		154 (57)	
S2 (scarring stage 2)	66 (2.4)		49 (1.8)	
Adverse events, n (%)				0.431
Intraprocedural perforation	5 (1.8)		1 (0.37)	
Delayed perforation	1 (0.36)		1 (0.37)	
Fever	8 (2.9)		10 (3.7)	
Stomach pain	11 (4.0)		16 (5.9)	
Peritoneal infection	2 (0.73)		2 (0.74)	
Lung infection	2 (0.73)		3 (1.1)	

Results

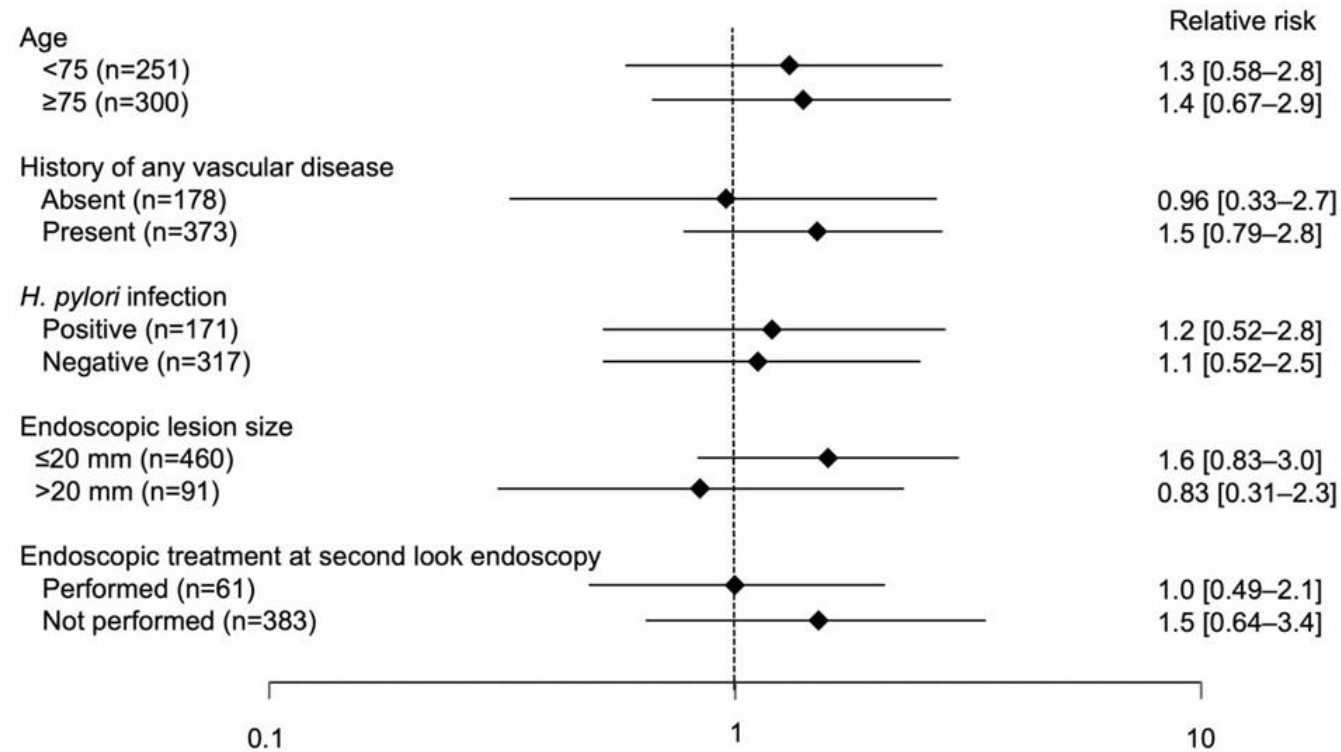
Table 3. Profile and outcome of patients with thromboembolic events

Group	Age	Sex	Lesion location	Lesion size (mm)	History of vascular diseases	<i>H. pylori</i> infection	ESD-related major bleeding	Onset	Thromboembolic event
Continuation	73	Female	Middle third	30	Old myocardial infarction (drug-eluting stent)	Unknown	No	Post-ESD day 2	Cerebral infarction
Continuation	86	Female	Lower third	20	Obstructive arteriosclerosis	Negative	Yes (surgery)	Post-ESD day 10	Cerebral infarction with hemiplegia

ESD, endoscopic submucosal dissection; *H. pylori*, *Helicobacter pylori*.

- No thromboembolic event in discontinuation
- Case 2
bleeding → surgery → stroke - bleeding itself may lead to thrombotic harm

Results - subgroup analysis



► No significant difference in any subgroup

Discussion

- Noninferiorty not shown;
small difference(2.5%) > margin is too strict
- Prior study
 - retrospective, selection bias
- Bleeding gap at 6-13 day $\approx$ plt lifespan 7-10 days
→ may longer interruption (7-10 days) need

Strengths

- First large multicenter RCT
- Hard end point - clinical & endoscopic bleeding
- Standardized ESD, PPI, SLE protocol
- m-ITT & PP analysis

Limitations

- Open-label
 - 6 years recruitments, evolving practice
 - Concomitant cilostazol/EPA not recorded
- Hard end point
 - still meaningful
 - not risky in used alone

Take-home messages

- First RCT comparing LDA continuation vs discontinuation in gastric ESD (low thrombotic risk)
- Major bleeding: 10% (continuation) vs 7.6% (discontinuation)
- Noninferiority of continuation NOT demonstrated (upper 90% CI 6.6% > 5%)
- Authors recommend periprocedural discontinuation in low thrombotic risk patients