Japan since 1960's as the nationwide mass screening for stomach cancer [3,4,5]. Many previous studies suggested that regularly-scheduled UGI-XR may lead to a reduced risk of mortality from gastric cancer [4,6,7,8]. Therefore, UGI-XR is at present the only one method of gastric cancer screening officially authenticated in Japan [9], though other screening methods with endoscopy or serum pepsinogens are gradually spreading [10,11].

Nowadays, an issue to be solved for UGI-XR-based gastric cancer screening is coming about. UGI-XR has been mainly performed to find gastric cancer and other lesions such as erosion, ulcer, polyp, and so on. But regrettably, atrophic gastritis detected by UGI-XR has not been usually assessed. One of the reasons for that is probably the time when UGI-XR-based gastric cancer screening began: around 1960's in Japan, the prevalence of *Helicobacter pylori* (*H. pylori*)-induced gastritis was extremely high [3,5]. In the past several decades, however, the infection rate of *H. pylori* has been decreased worldwide [12,13,14,15]: consequently, clinical significance of evaluating UGI-XR-based atrophic gastritis become relatively higher today. Another more important reason is inadequate validation of the meaning of "atrophic gastritis" diagnosed by UGI-XR. At present, it is well established that chronic *H. pylori* infection mostly causes pathological gastritis with mucosal atrophy and precancerous intestinal metaplasia [16,17,18,19,20]. However, there is no clear evidence that "UGI-XR-based" atrophic gastritis coincides with *H. pylori*-induced "pathological" gastritis or "endoscopy-based" atrophic gastritis.

Based on these backgrounds, the purpose of this study is evaluating associations of "UGI-XR-based" atrophic gastritis with several causative factors including chronic *H. pylori* infection. Through the large-scale analysis of healthy adults in Japan, we have challenged the unsolved but important problem: the meaning of "atrophic gastritis" diagnosed by UGI-XR. We further expect that our results will improve the efficacy of gastric cancer screening via establishing precise evaluation of premalignant UGI-XR-based atrophic gastritis. Prediction of future cancer risk based on UGI-XR-based atrophic gastritis should increase the value of gastric cancer screening with barium X-ray.

Materials and Methods

Study Subjects

The study population was 20,773 subjects who received medical checkup at Kameda Medical Center Makuhari (Chiba-shi, Chiba, Japan) in 2010 and agreed with participating in our study. In cases where health checkup was performed twice in 2010, the former data was used. Criteria for exclusion were insufficient data for analysis or history of gastrectomy. This study was approved by the ethics committee of the University of Tokyo, and written informed consents were obtained from all the study participants according to the Declaration of Helsinki.

Double-contrast Upper Gastrointestinal Barium X-ray Radiography (UGI-XR)

Five minutes after intramuscular injection of spasmolytic agent (10 mg of scopolamine butylbromide), the subject drank 150 ml of barium (220 w/v %) in one gulp. X-ray images were then taken as follows; 1) double-contrast right anterior oblique view of the upper and lower esophagus in the near-supine standing position, 2) single-contrast frontal view of the stomach in the supine standing position, 3) double-contrast frontal image of the stomach in the supine position, 4) double-contrast right anterior oblique view of the stomach in the near-supine position, 5) double-contrast left anterior oblique view of the stomach in the near-supine position, 6) double-contrast right lateral view of the stomach in the horizontal position, 7) single-contrast frontal view of the stomach in the prone position, 8) double-contrast frontal view of the stomach in the prone position with the head down, 9) double-contrast frontal view of the stomach in the prone standing position, 10) double-contrast left anterior oblique view of the stomach in the prone position with the head down, 11) double-contrast left lateral view of the stomach in the horizontal position, 12) double-contrast left anterior oblique view of the stomach in the near-supine half-standing position (Schatzki's position), 13) double-contrast left anterior oblique view of the stomach in the near-supine position ("Barium divided" image), and 14) double-contrast right anterior oblique view of the stomach in the near-supine half-standing position.

Definition of Atrophic Gastritis Based on the Double-contrast Barium X-ray Radiography (UGI-XR-based atrophic gastritis)

The characteristics of gastritis in the double-contrast barium X-ray images have been described by a few reports [21,22]. By referring to them, in our previous report [23], we diagnosed gastritis based on the enlarged areae gastricae and/or hypertrophic gastritis with thickened folds on the greater curvature. It is also well known that atrophic gastritis usually extends from the antrum to body and fornix [19]. Taken these into consideration, we classified the double-contrast barium X-ray images of stomach into four types, on the basis of the irregular shapes of areae gastricae and their expansion as follows;

(A: normal) No atrophic change can be observed in stomach. The areae gastricae cannot be detected or can be recognized as small, round, and regular shapes in all the mucosal surface of stomach (Figure 1a).

(B: mild) The mucosal atrophy is mostly limited to gastric antrum. The enlarged areae gastricae with slight angularity and irregularity are observed in the restricted mucosal surface of stomach (Figure 1b).

(C: moderate) The mucosal atrophy extends from gastric antrum to body (corpus) and/or fornix. The obviously enlarged areae gastricae with considerable angularity and irregularity are observed in most or all mucosal surface of stomach (Figure 1c).

(D: severe) The severe atrophic change entirely covers the mucosal surface of stomach. The small or even absent areae gastricae diffusely extend in stomach, accompanied with irregularly rugged mucosal surface (Figure 1D).

Disgnosis of Atrophic Gastritis by Endoscopy

Atrophic patterns of gastric mucosa by endoscopy were classified into seven classes according to the Kimura-Takemoto classification [24,25]: no atrophic change (C0), three closed type atrophy patterns (C1, C2, C3), and three open type atrophy patterns (O1, O2, O3).

Evaluation of Serum anti-*Helicobacter pylori* IgG, Serum Pepsinogens (PGs), Alcohol Intake, and Smoking

Serum anti-*H. pylori* IgG, pepsinogen I, and pepsinogen II were measured using commercial kits (E-plate "EIKEN" Helicobacter pylori antibody and E-Plate "EIKEN" Pepsinogen I and II, Eiken Chemical Co LTD., Tokyo, Japan) as we had previously reported [26,27,28]. According to the manufacture's instruction, titer of *H. pylori* IgG $\geq$10 U/ml was considered as *H. pylori*-positive. Recently, it has been suggested that titer of *H. pylori* IgG $<$ 10 U/ml should be reconsidered from the standpoint of mucosal

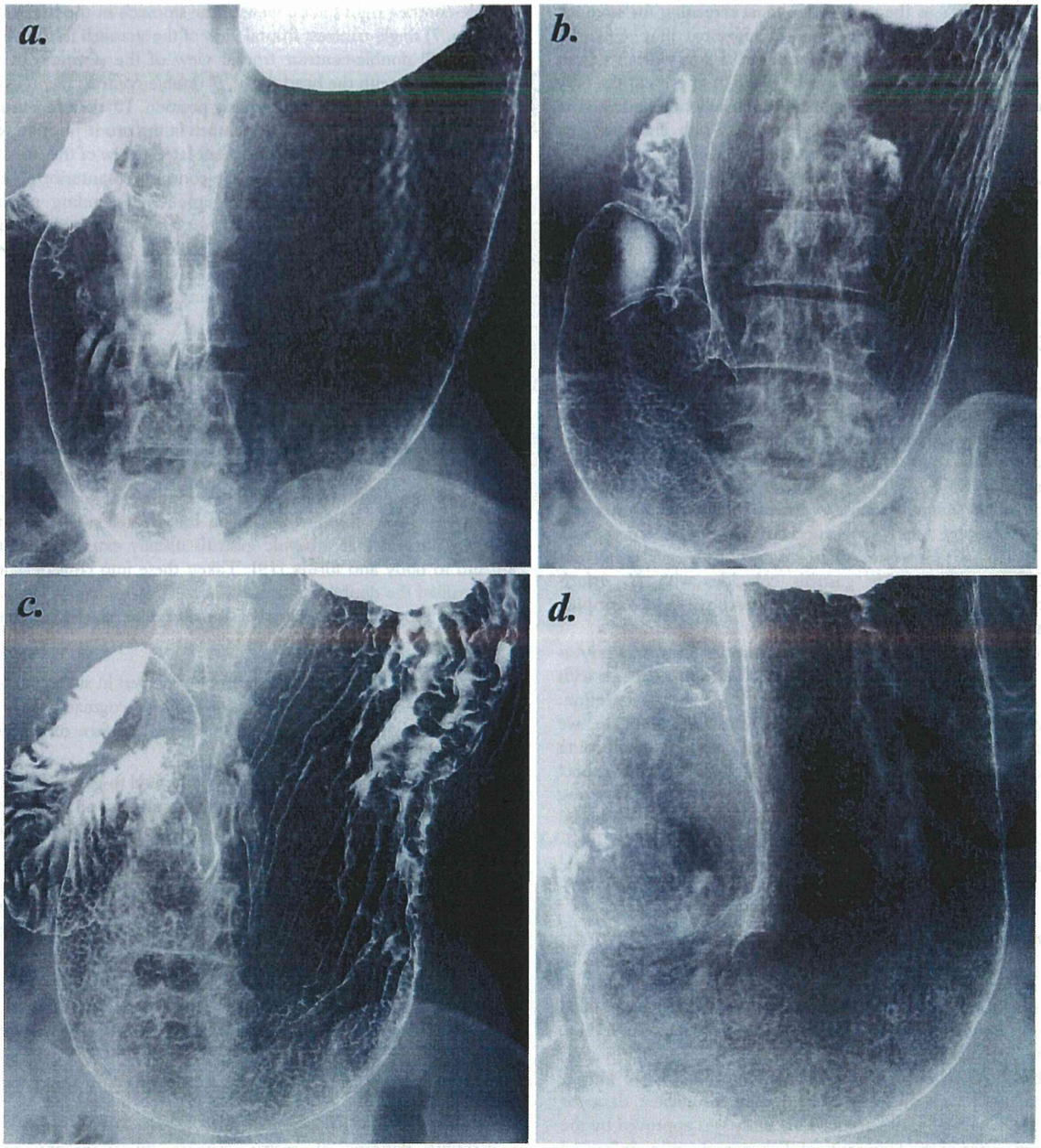

Figure 1. Typical four images of stomach by double-contrast upper gastrointestinal barium X-ray radiography (UGI-XR). (a) Normal stomach with no atrophic change of gastric mucosa. (b) Mild gastritis in which atrophic change mostly exists in gastric antrum and angle, accompanied with slightly enlarged irregular areae gastricae. (c) Moderate gastritis in which atrophic change extends from gastric antrum to body and/or fornix, accompanied with obviously enlarged irregular areae gastricae. (d) Severe gastritis in which atrophic change covers the entire stomach, accompanied with obscured small or even absent areae gastricae.
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atrophic change or gastric cancer risk [29,30]. Therefore, we further divided "*H. pylori*-negative" subjects into "≥3 and < 10 U/ml (gray-zone titer of *H. pylori* IgG)" and "<3 U/ml (absolutely negative for *H. pylori* IgG)". In accordance with previous reports [28,31,32], ratios of serum pepsinogen I and II (pepsinogen I [ng/ml]/pepsinogen II [ng/ml]) were classified into ">3", ">2 and ≤3", and "≤2".

For alcohol intake, the study subjects were scored according to the 5-grade scale (never, seldom, sometimes, often, and always), and further categorized into "rarely drinking" group (never or seldom) and "usually drinking" group (sometimes, often, or always). For smoking, the subjects were classified into three groups: "current smoker" group, "past habitual smoker" group, and "lifelong nonsmoker" group.

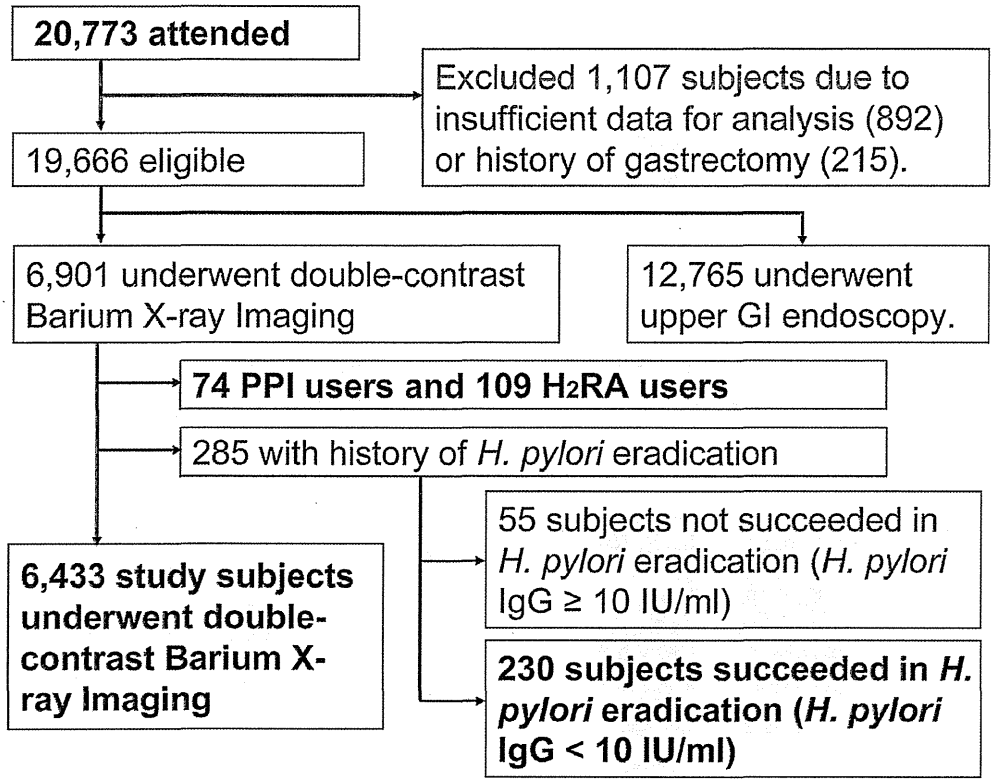


Figure 2. Study flowchart of the present study.
doi:10.1371/journal.pone.0111359.g002

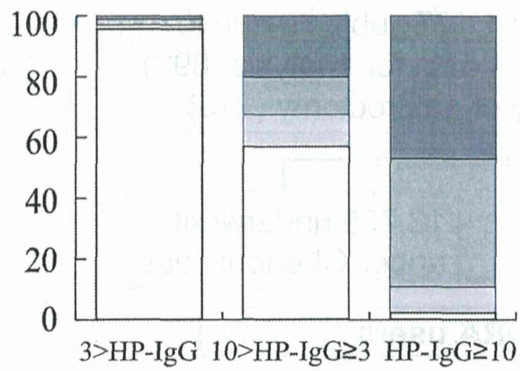
UGI-XR-based atrophic gastritis

Endoscopy-based atrophic gastritis (Kimura-Takemoto classification of mucosal atrophic change in stomach)		Normal	Mild	Moderate	Severe	Total
-	C0	84	1	3	0	88
+	C1	6	0	1	1	8
	C2	4	2	5	4	15
	C3	1	0	3	1	5
	O1	0	0	9	7	16
	O2	0	0	3	11	14
	O3	0	0	0	4	4
	Total	95	3	24	28	150

(Polychoric correlation coefficient: r=0.9330)

Figure 3. Relationship between the four grades of UGI-XR-based atrophic gastritis and the extent of endoscopy-based atrophic gastritis classified into seven categories according to the Kimura-Takemoto classification (C0 with no atrophic change and C1-O3 with various degrees of endoscopy-based atrophic change of gastric mucosa).
doi:10.1371/journal.pone.0111359.g003

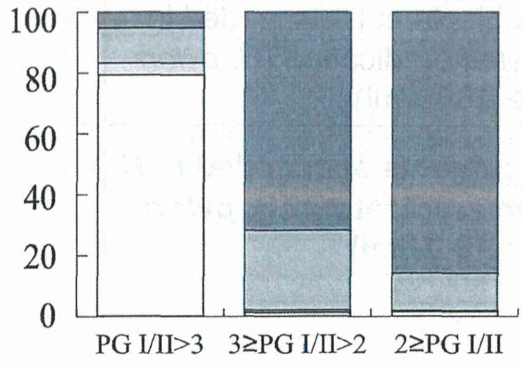
a.



UGI-XR-based Gastritis	A	B	C	D	Total
3 > HP-IgG	4337 (95.5%)	66 (1.5%)	90 (2.0%)	48 (1.1%)	4541
10 > HP-IgG ≥ 3	124 (56.9%)	23 (10.6%)	27 (12.4%)	44 (20.2%)	218
HP-IgG ≥ 10	36 (2.2%)	145 (8.7%)	705 (42.1%)	788 (47.1%)	1674
Total	4497 (69.9%)	234 (3.6%)	822 (12.8%)	880 (13.7%)	6433

(p value<0.0001 by Cochran-Mantel-Haenszel trend test)

b.



UGI-XR-based Gastritis	A	B	C	D	Total
PG I/II > 3	4486 (79.2%)	229 (4.0%)	656 (11.6%)	293 (5.2%)	5664
3 ≥ PG I/II > 2	7 (1.4%)	4 (0.8%)	135 (26.2%)	369 (71.7%)	515
2 ≥ PG I/II	4 (1.6%)	1 (0.4%)	31 (12.2%)	218 (85.8%)	254
Total	4497 (69.9%)	234 (3.6%)	822 (12.8%)	880 (13.7%)	6433

(p value<0.0001 by Cochran-Mantel-Haenszel trend test)

Figure 4. Distribution of our proposed four types of atrophic gastritis by double-contrast upper gastrointestinal barium X-ray radiography (A: normal, B: mild, C: moderate, D: severe) with titer of serum *Helicobacter pylori* IgG (a) or serum pepsinogen I/II ratio (b).

doi:10.1371/journal.pone.0111359.g004

Statistical Analyses

We used JMP 10 software or SAS 9.1.3 (SAS Institute Inc. Cray, NC, USA) for statistical analyses and matching process. In the univariate analysis, associations between the presence of UGI-XR-based atrophic gastritis and seven variables were compared using the χ^2 test and Cochran-Mantel-Haenszel trend test. In the multivariate analysis, standardized coefficient and odds ratio of each variable were calculated using multiple logistic regression analysis. In the both analyses, p values <0.05 were considered as statistically significant.

To estimate the association between UGI-XR-based atrophic gastritis (normal, mild, moderate, and severe) and endoscopy-based atrophic gastritis (C0, C1, C2, C3, O1, O2, and O3 according to Kimura-Takemoto classification) [24,25], the polychoric correlation coefficient was calculated.

To evaluate the effect of *H. pylori* eradication on UGI-XR-based atrophic gastritis, the matching was performed to control age (±2 years), sex, smoking (current, past habitual, or lifelong non-smoking), and drinking ("rarely" or "usually") between the successfully *H. pylori*-eradicated subjects (negative for serum *H. pylori* IgG with history of eradication therapy) and the chronically *H. pylori*-infected subjects (positive for serum *H. pylori* IgG with no history of eradication therapy). Using the matched pairs of subjects, we applied Cochran-Mantel-Haenszel trend test, in which p value <0.05 was considered as statistically significant.

To evaluate the influence of gastric acid suppressants (proton pump inhibitors (PPI) and histamine H_2-receptor antagonist (H_2RA)) upon UGI-XR-based atrophic gastritis, we used Fisher's exact test in which p value <0.05 was considered as statistically significant.

Results and Discussion

Characteristics of the Study Subjects

Of the 20,773 subjects who participated in the study (Figure 2), we excluded 1,107 subjects with insufficient data or history of gastrectomy, and also excluded 12,765 subjects who underwent upper gastrointestinal (GI) endoscopy. Of the residual 6,901 subjects, we further excluded 74 PPI users, 109 H_2RA users, and 285 subjects who had underwent eradication therapy for *H. pylori*. The eligible 6,433 subjects comprised of 3,405 men and 3,028 women (a mean age of 47.4±8.8 years; range 20–83 years) were mainly analyzed in our present study (Figure 2).

Among the 6,433 main subjects for this study, only 1,674 (26.0%) were positive for *H. pylori*, which is consistent with the rapid decrease in prevalence of *H. pylori* infection in Japan [12,33]. Actually, for the data of healthy adults in our institutes located at Chiba prefecture in Japan, the seropositivity of *H. pylori* infection has markedly reduced from 47.0% (2,695 of 5,732

Table 1. Characteristics of the study subjects from the standpoint of atrophic gastritis diagnosed by double-contrast upper gastrointestinal barium X-ray radiography (UGI-XR-based atrophic gastritis).

Factor	Total 6,433 study subjects	1,936 subjects with UGI-XR-based atrophic gastritis	234 subjects with mild UGI-XR-based atrophic gastritis	822 subjects with moderate UGI-XR-based atrophic gastritis	880 subjects with severe UGI-XR-based atrophic gastritis	Residual 4,497 subjects without UGI-XR-based atrophic gastritis (normal)	*p* value
Age	47.7±8.8 y.o.	51.1±8.9 y.o.	48.4±8.4 y.o.	49.8±8.8 y.o.	53.0±8.7 y.o.	45.8±8.3 y.o.	<.0001*
<30	53 (0.8%)	5 (0.3%)	0 (0.0%)	3 (0.4%)	2 (0.2%)	48 (1.1%)	
≥30 and <40	1,274 (19.8%)	212 (11.0%)	40 (17.1%)	107 (13.0%)	65 (7.4%)	1,062 (23.6%)	
≥40 and <50	2,579 (40.1%)	600 (31.0%)	94 (40.2%)	286 (34.8%)	220 (25.0%)	1,979 (44.0%)	
≥50 and <60	1,909 (29.7%)	774 (40.0%)	76 (32.5%)	304 (37.0%)	394 (44.8%)	1,135 (25.2%)	
≥60 and <70	558 (8.7%)	308 (15.9%)	22 (9.4%)	111 (13.5%)	175 (19.9%)	250 (5.6%)	
≥70	60 (0.9%)	37 (1.9%)	2 (0.9%)	11 (1.3%)	24 (2.3%)	23 (0.5%)	
Sex							<.0001*
female	3,028 (47.1%)	828 (42.8%)	77 (32.9%)	366 (44.5%)	385 (43.8%)	2,200 (48.9%)	
male	3,405 (52.9%)	1,108 (57.2%)	157 (67.1%)	456 (55.5%)	495 (56.3%)	2,297 (51.1%)	
BMI	22.8±3.4	23.0±3.3	23.3±3.4	22.9±3.3	22.8±3.4	22.8±3.4	0.0079*
<18.5	451 (7.0%)	120 (6.2%)	17 (7.3%)	42 (5.1%)	61 (6.9%)	331 (7.4%)	
≥18.5 and <25	4,508 (70.1%)	1,337 (69.1%)	147 (62.8%)	587 (71.4%)	603 (68.5%)	3,171 (70.5%)	
≥25	1,474 (22.9%)	479 (24.7%)	70 (29.9%)	193 (23.5%)	216 (24.5%)	995 (22.1%)	
H. pylori IgG							<.0001*
<3	4,541 (70.6%)	204 (10.5%)	66 (28.2%)	90 (10.9%)	48 (5.5%)	4,337 (96.4%)	
<10 and ≥3	218 (3.4%)	94 (4.9%)	23 (9.8%)	27 (3.3%)	44 (5.0%)	124 (2.8%)	
≥10	1,674 (26.0%)	1,638 (84.6%)	145 (62.0%)	705 (85.8%)	788 (89.5%)	36 (0.8%)	
PG I/II ratio							<.0001*
>3	5,664 (88.0%)	1,178 (60.9%)	229 (97.9%)	656 (79.8%)	293 (33.3%)	4,486 (99.8%)	
≤3 and >2	515 (8.0%)	508 (26.2%)	4 (1.7%)	135 (16.4%)	369 (41.9%)	7 (0.2%)	
≤2	254 (3.9%)	250 (12.9%)	1 (0.4%)	31 (3.8%)	218 (24.8%)	4 (0.1%)	
Smoking							<.0001*
non smoker	3,511 (54.6%)	950 (49.1%)	92 (39.3%)	422 (51.3%)	436 (49.5%)	2,561 (57.0%)	
former smoker	1,622 (25.2%)	548 (28.3%)	73 (31.2%)	197 (24.0%)	278 (31.6%)	1,074 (23.9%)	
current smoker	1,300 (20.2%)	438 (22.6%)	69 (29.5%)	203 (24.7%)	166 (18.9%)	862 (19.2%)	
Alcohol							0.8881
rarely drinking	2,567 (39.9%)	770 (39.8%)	75 (32.1%)	319 (38.8%)	376 (42.7%)	1,797 (40.0%)	
usually drinking	3,866 (60.1%)	1,166 (60.2%)	159 (67.9%)	503 (61.2%)	504 (57.3%)	2,700 (60.0%)	

BMI, body mass index; *H. pylori*, *Helicobacter pylori*; PG, pepsinogen. The levels of significance (*p* value) for analyzing associations between UGI-XR-based atrophic gastritis and the seven causative factors were set at <0.05 (*), which were calculated by χ^2 test or Cochran-Mantel-Haenszel trend test.

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Table 2. Multivariate analysis of the 6,433 study subjects evaluating associations of the seven background factors with UGI-XR-based atrophic gastritis (atrophic gastritis diagnosed by double-contrast upper gastrointestinal barium X-ray radiography).

Factor	Standardized coefficients	Odds ratio (95% C.I.)	*p* value
Age	0.401	1.49 (1.31–1.70)	<.0001*
Sex			
female	reference	reference	reference
male	0.306	1.36 (1.16–1.59)	0.0002*
BMI	−0.100	0.90 (0.80–1.03)	0.124
H. pylori IgG			
<3	reference	reference	reference
<10 and ≥3	0.479	1.61 (1.52–1.72)	<.0001*
≥10	1.499	4.48 (4.12–4.91)	<.0001*
PG I/II ratio			
>3	reference	reference	reference
≤3 and >2	0.270	1.31 (1.18–1.48)	<.0001*
≤2	0.339	1.40 (1.26–1.59)	<.0001*
Smoking			
non smoker	reference	reference	reference
former smoker	0.137	1.15 (0.98–1.33)	0.0773
current smoker	0.526	1.69 (1.49–1.93)	<.0001*
Alcohol			
rarely drinking	reference	reference	reference
usually drinking	0.051	1.05 (0.92–1.20)	0.449

BMI, body mass index; *H. pylori*, *Helicobacter pylori*; PG, pepsinogen. The level of significance in each factor was set at $p<0.05$ (*).
doi:10.1371/journal.pone.0111359.t002

subjects in 1996–1997 [34]) to 26.0% (1,674 of 6,433 subjects in the present study) in only 14 short years.

The 285 subjects after *H. pylori* eradication therapy comprised of 230 subjects with serum *H. pylori* IgG <10 U/ml (certainly succeeded in *H. pylori* eradication) and 55 subjects with serum *H. pylori* IgG ≥10 U/ml (probably not succeeded in *H. pylori* eradication or on the way of negative conversion of serum *H. pylori* IgG). Aside from the main 6,433 study subjects, we additionally analyzed the above-mentioned 74 PPI users, 109 H_2RA users, and 230 "successfully *H. pylori*-eradicated" subjects (Figure 2).

Validation of our defined "UGI-XR-based" Atrophic Gastritis by comparing "Endoscopy-based" Atrophic Gastritis

In our previous work [23], 29 (97%) of 30 subjects positive for serum anti-*H. pylori* IgG were diagnosed as gastritis by UGI-XR, which convinced us the sufficient detection of *H. pylori*-induced chronic gastritis by barium X-ray. In the present study, we classified the UGI-XR-based atrophic gastritis into four types as above-mentioned (Figure 1). To validate this classification, the extent of endoscopy-based atrophic gastritis were simultaneously evaluated among the 150 subjects randomly selected (Figure 3).

Table 3. Comparison between the matched pairs of 227 subjects with chronic infection of *H. pylori* and after successful eradication of *H. pylori*, focusing on the presence of UGI-XR-based atrophic gastritis (atrophic gastritis diagnosed by double-contrast upper gastrointestinal barium X-ray radiography).

	Presence of UGI-XR-based atrophic gastritis (mild, moderate, severe)	Absence of UGI-XR-based atrophic gastritis (normal)	Total
The 227 matched subjects after successful eradication of *H. pylori*	135 (59.5%)	92 (40.5%)	227 (100%)
The 227 matched subjects with chronic *H. pylori* infection	225 (99.1%)	2 (0.9%)	227 (100%)

($p<0.0001$ by Cochran-Mantel-Haenszel test).
doi:10.1371/journal.pone.0111359.t003

Table 4. Comparison between the *H. pylori*-positive gastric acid suppressant (PPI or H_2RA) users and *H. pylori*-positive gastric acid suppressant-free subjects, focusing on the presence of UGI-XR-based gastritis (gastritis diagnosed by double-contrast upper gastrointestinal barium X-ray radiography).

	Presence of UGI-XR-based atrophic gastritis (mild, moderate, severe)	Absence of UGI-XR-based atrophic gastritis (normal)	Total	*p* value
H. pylori-positive and gastric acid suppressant-free subjects among the 6,433 main study subjects	1,638 (97.8%)	36 (2.1%)	1,674 (100%)	reference
H. pylori-positive subjects among the 74 PPI users	13 (92.9%)	1 (7.1%)	14 (100%)	0.2677
H. pylori-positive subjects among the 109 H_2RA users	33 (97.1%)	1 (2.9%)	34 (100%)	0.5286

For the PPI and H_2RA users each, the level of significance was set at $p<0.05$ (*) by Fisher's exact test.

doi:10.1371/journal.pone.0111359.t004

On the basis of endoscopy-based atrophic gastritis, sensitivity and specificity of UGI-XR-based atrophic gastritis were 82.3% (51/62) and 95.5% (84/88) respectively. In addition, the four-grade categories of UGI-XR-based atrophic gastritis showed significant association with seven-grade classes of endoscopy-based atrophic gastritis (polychoric correlation coefficient: $r = 0.9330$). Actually, all the subjects (34/34) with severe endoscopy-based atrophic gastritis (namely, open type (O1–O3) atrophy according to Kimura-Takemoto classification [24,25]) were diagnosed as UGI-XR-based atrophic gastritis (Figure 3). Based on these results, we concluded that UGI-XR-based diagnosis used in this study can certainly reflect the atrophic mucosa of stomach.

The Four-grade Types of UGI-XR-based Atrophic Gastritis are Significantly Associated with the Titer of Serum *H. pylori* IgG and the Ratio of Serum Pepsinogen I and II

Based on the UGI-XR-based mucosal atrophy of stomach, the total 6,433 subjects with no history of *H. pylori* eradication and free from gastric acid suppressants were classified into four classes (Figure 4): 234 subjects with mild gastritis, 822 subjects with moderate gastritis, 880 subjects with severe gastritis, and residual 4,497 subjects without atrophic gastritis (normal).

We first evaluated associations of the four-grade UGI-XR-based atrophic gastritis with two serum markers: the titer of *H. pylori* IgG and the ratio of pepsinogen I and II reflecting the mucosal atrophy of stomach [32,35]. As shown in Figure 4a, UGI-XR-based atrophic gastritis significantly extends in proportion to rise in serum *H. pylori* IgG titer ($p<0.0001$). And as also shown in Figure 4b, the grade of UGI-XR-based atrophic gastritis meaningfully advances accompanied with decline in pepsinogen I/II ratio ($p<0.0001$). Though the effects of other causative factors should not be groundlessly underestimated, these results suggest that the four-grade categorization of UGI-XR-based atrophic gastritis strongly reflects chronic *H. pylori* infection and consequent mucosal atrophy of stomach.

Associated Background Factors of UGI-XR-based Atrophic Gastritis

The detailed characteristics of the 6,433 study subjects focusing on UGI-XR-based atrophic gastritis and the seven putative background factors are shown in Table 1. The results of univariate analyses concerning the seven factors are also denoted. It is clear that old age, male gender, a high titer of serum *H. pylori* IgG, low ratio of serum pepsinogen I/II, and a habit of smoking show strongly positive association with the presence of UGI-XR-based atrophic gastritis.

We next executed multivariate analyses with these seven causative factors (Table 2). As was expected, a high titer of serum *H. pylori* IgG is the strongest associated factor for UGI-XR-based atrophic gastritis. Current smoking, old age, low ratio of serum pepsinogen I/II, and male gender also show significant association. In contrast, drinking as well as BMI (body mass index) has no meaningful association with UGI-XR-based atrophic gastritis: this unexpected but clear difference between drinking and smoking should be noted when considering the establishment of atrophic gastritis.

Eradication of *Helicobacter pylori* Seems to Superficially Improve UGI-XR-based Atrophic Gastritis

We next tried to evaluate the effect of *H. pylori* eradication upon UGI-XR-based atrophic gastritis. For this purpose, the matching was performed to control age (within±2 years), sex, smoking, and drinking between the 230 subjects succeeded in *H. pylori* eradication (negative for serum *H. pylori* IgG with history of eradication therapy) and the 1,674 subjects with chronic *H. pylori* infection (positive for serum *H. pylori* IgG with no history of eradication therapy).

Between the 227 matched pairs of subjects, prevalences of UGI-XR-based atrophic gastritis were markedly different with statistical significance (Table 3): it was detected in only 59.5% of the *H. pylori*-eradicated subjects but was detected in 99.1% of the chronically *H. pylori*-infected subjects ($p<0.0001$). These suggest that eradication of *H. pylori* diminishes the typical images of UGI-XR-based atrophic gastritis. In other words, chronic infection of *H. pylori* in the past cannot be efficiently detected by UGI-XR, after eradication therapy has been completed.

It has been reported that eradication of *H. pylori* can improve gastritis both pathologically [20,36,37] and endoscopically [38]. The result of our present study suggests that eradication of *H. pylori* can also relieve UGI-XR-based atrophic gastritis, which is defined by the irregular shapes of areae gastricae and their expansion in the stomach. However, this is not always a preferable result, since the superficial improvement of chronic gastritis does not considerably reduce the risk of gastric tumorigenesis [39,40,41,42]. It can be otherwise considered that UGI-XR cannot adequately distinguish the lifelong *H. pylori*-negative stomach (having a very low risk of gastric cancer [17,30,43]) from

the *H. pylori*-eradicated stomach keeping a considerable risk for gastric canceration [40]. We are apprehensive that the difficulty in detecting *H. pylori*-eradicated stomach will be a formidable problem for UGI-XR-based gastric cancer screening.

Intakes of PPI and H_2RA Mostly do not Affect UGI-XR-based Atrophic Gastritis

We further evaluated the influence of gastric acid suppressants upon UGI-XR-based atrophic gastritis. Among the gastric acid suppressant users positive for serum *H. pylori* IgG (Table 4), UGI-XR-based atrophic gastritis was detected in 13 of 14 PPI users (92.9%) and 33 of 34 H_2RA users (97.1%). Though the statistical evaluation cannot be accurately calculated due to the small number of subjects, there seems to be no obvious differences compared to the *H. pylori*-positive 1,674 subjects free from gastric acid suppressants. To say the least, our results indicate that intakes of PPI and H_2RA mostly do not deteriorate the diagnostic quality of UGI-XR-based atrophic gastritis.

Conclusions

The presence of atrophic gastritis diagnosed by double-contrast upper gastrointestinal barium X-ray radiography (UGI-XR-based atrophic gastritis) is positively associated with *Helicobacter pylori* infection, current smoking, old age, decreased pepsinogen I/II ratio, and male gender. Eradication of *Helicobacter pylori* seems to superficially improve UGI-XR-based gastritis whereas intake of proton pump inhibitors or histamine H_2-receptor antagonist does not.

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Author Contributions

Conceived and designed the experiments: NY CH TS TM MI. Performed the experiments: NY CH CM Y. Takahashi CN RM MKS. Analyzed the data: NY TS SK SO KN SM Y. Tsuji YS IAH CT SY HK RW. Contributed reagents/materials/analysis tools: NY CH TM. Contributed to the writing of the manuscript: NY CH TS MF JK MI KK.

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Guideline

Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment

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Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment have been produced by the Japan Gastroenterological Endoscopy Society in collaboration with the Japan Circulation Society, the Japanese Society of Neurology, the Japan Stroke Society, the Japanese Society on Thrombosis and Hemostasis and the Japan Diabetes Society. Previous guidelines from the Japan Gastroenterological Endoscopy Society have focused primarily on prevention of hemorrhage after gastroenterological endoscopy as a result of continuation of antithrombotic therapy, without considering the associated risk of thrombosis. The new edition of the guidelines includes discussions of gastroenterological hemorrhage associated with continuation of antithrombotic therapy, as well as thromboembolism associated with withdrawal of antithrombotic therapy.

Key words: anticoagulant, antiplatelet agent, gastroenterological endoscopic examination and treatment, gastroenterological hemorrhage, thromboembolism

INTRODUCTION

IN THE MIDST of rapid advances in the medical and healthcare fields, Japan has achieved impressive progress in the development of gastroenterological endoscopy techniques that have been adopted around the world. The history of research in this field shows major breakthroughs in recent years in both endoscopic diagnosis and treatment, driven mainly by advances in medical equipment. These breakthroughs are dependent on rising standards in endoscopic diagnosis and treatment, and in the field of endoscopy in general.

The above developments have prompted a complete revision of the Guidelines for Gastroenterological Endoscopy issued by the Japan Gastroenterological Endoscopy Society along with other guidelines appearing in academic journals. The fundamental expertise built up over many years of work on gastroenterological endoscopy in Japan will now be presented as a Handbook on Gastroenterological Endoscopy, while the latest advances in the rapidly evolving field of endoscopic treatment will be issued in the form of legitimate guidelines based on evidence based medicine (EBM) and consensus.

The Guidelines for Gastroenterological Endoscopy in Patients undergoing Antithrombotic Treatments represents the first set of Guidelines issued in accordance with this new approach. I would like to take this opportunity to express my appreciation to the editorial team led by Professor Kazuma Fujimoto and the evaluation team led by Professor Yoshikazu Kinoshita, whose tireless efforts helped bring the Guidelines to fruition. I should also like to extend my thanks to Professor Shinichiro Uchiyama of Tokyo Women's Medical University Department of Neurology, Professor Atsunori Kashiwagi of Shiga University Hospital, and Professor Hisao Ogawa of Kumamoto University Department of Cardiovascular Medicine for their invaluable contributions.

We are planning to produce many more Guidelines in areas such as endoscopic mucosal resection and endoscopic submucosal dissection of the esophagus, stomach and bowel; anesthetics and sedatives; and training and education. Given that guidelines are designed to present both standard medical

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knowledge and recent developments, they are subject to periodical reassessment, review and revision as required. The Handbook on Gastroenterological Endoscopy, meanwhile, presents the fundamental principles and established understandings of gastroenterological endoscopy. The Handbook and the various Guidelines are thus equivalent to 'pure' and 'applied' endoscopic theory respectively, and should be read in conjunction rather than in isolation. In this way, we hope to enhance the standards of gastroenterological endoscopy in this country.

Finally, I would like to once again extend my heartfelt thanks to Professor Masao Ichinose, Director, and Professor Toshiyuki Matsui, Chair of the Steering Committee, for their work in the production of the Guidelines.

Michio Kaminishi
The then Chair of Board of Directors, The Japan Gastroenterological Endoscopy Society (JGES)

BASIC PRINCIPLES UNDERPINNING THE JAPAN GASTROENTEROLOGICAL ENDOSCOPY SOCIETY GUIDELINES

WITH THE INCREASING need for endoscopic examination and treatment, and the increasing complexity of procedures, there is a need to standardize protocols to raise overall standards of endoscopic examination and treatment, and thus improve patient outcomes. A committee was established by the Japan Gastroenterological Endoscopy Society (JGES) in January 2010 to produce an updated version of its evidence-based guidelines. The six basic principles of the guidelines are:

1. They should be based on solid scientific foundations.
2. Where the literature does not provide sufficient evidence – for example, in relation to endoscopic techniques – the guidelines should be supplemented through consensus (formation of a joint position based on scientific methodology to make recommendations when the level of evidence is low).
3. They should make clear and specific recommendations about therapeutic options, especially in high-priority areas.
4. Given the wide scope of the literature, the criteria and methodology for literature searches will be determined by individual working committees.
5. Because the guidelines are intended for Japanese readers, Japanese and English language versions should be produced.
6. They should provide a general overview.

The guidelines have been produced in accordance with the approach espoused by the Medical Information Network Distribution Service (MINDS), using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument for the research and evaluation process. Care has been taken to ensure consistency with other guidelines in related areas. Given the rapid pace of change in this field, the guidelines will need to be reviewed in several years to reflect the latest developments in diagnostic and therapeutic techniques. The guidelines are intended as a decision-making tool for use by medical professionals in clinical practice.

HISTORY AND BACKGROUND

IN 2010, THE JGES decided to produce and/or update a number of guidelines related to gastroenterological endoscopy. The 1999 version of the *Guidelines for Gastroenterological Endoscopy*[1] provided general guidance for the conduct of gastroenterological endoscopy in patients taking antithrombotic therapy. These were followed in 2005 by guidelines on the *Use of Anticoagulants and Antiplatelet Agents During Endoscopic Procedures*,[2] which formed the basis of the third version of the *Guidelines for Gastroenterological Endoscopy*[3] released in 2006. The latter was used as a key source of information concerning gastroenterological endoscopy in patients taking antithrombotics, and the principles were adopted in other guidelines from academic associations published in Japan, including the *Guidelines on Anticoagulant and Antiplatelet Therapy for Cardiovascular Illnesses*[4] (revised edition, 2009) and the *2009 Stroke Therapy Guidelines*.[5]

The 2010 update to the guidelines was prompted by recent advances in gastroenterological endoscopic examination and treatment techniques. Some of the updated information has been adapted from similar guidelines in the USA[6–8] and Europe.[9,10]

In July 2010, the board of directors of JGES established editorial and evaluation committees to oversee the production of the updated guidelines; the first committee meeting was convened in October 2010. Agreement was reached with other academic bodies to collaborate in the production process. Searches of the literature included in the PubMed and Japan Centra Revuo Medicina (the Japan Medical Abstracts Society) databases were undertaken, covering the period 1983 to 2011 using the keywords 'endoscopy', 'anticoagulant', 'antiplatelet' and 'antithrombotic' in PubMed and the equivalent Japanese terms in the Japan Medical Abstracts Society search engine.

A draft was produced and reviewed in line with feedback from the peer review committee (Table 1) before final approval at a consensus meeting in June 2011, attended by nine members of the editorial committee, four members of the evaluation committee and the two directors responsible for the project. The team used Delphi Answerpad[11–13] to produce the consensus statements. Where consensus could

Table 1 Editorial committee for the guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment

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Director: Masao Ichinose (Second Department of Internal Medicine, Wakayama Medical University)
Chairperson: Toshiyuki Matsui (Department of Gastroenterology, Fukuoka University Chikushi Hospital)
Working Committee
Chairperson: Kazuma Fujimoto (The Japan Gastroenterological Endoscopy Society: Saga University, Department of Internal Medicine)
Chair of Editorial Committee: Kazuma Fujimoto Committee members:
Choitsu Sakamoto (The Japan Gastroenterological Endoscopy Society: Nippon Medical School, Department of Gastroenterology)
Kazuhide Higuchi (The Japan Gastroenterological Endoscopy Society: Osaka Medical College Second Department of Internal Medicine)
Mototsugu Kato (The Japan Gastroenterological Endoscopy Society: Hokkaido University Hospital, Division of Endoscopy)
Ryuichi Iwakiri (The Japan Gastroenterological Endoscopy Society: Saga University, Department of Gastrointestinal Endoscopy)
Mitsuhiro Fujishiro (The Japan Gastroenterological Endoscopy Society: University of Tokyo, Department of Endoscopy and Endoscopic Surgery)
Shinichiro Uchiyama (The Japanese Society of Neurology, the Japan Stroke Society, the Japanese Society on Thrombosis and Hemostasis: Tokyo Women's Medical University Department of Neurology)
Atsunori Kashiwagi (The Japan Diabetes Society: Shiga University Hospital)
Hisao Ogawa (The Japan Circulation Society: Kumamoto University, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center)
Evaluation Committee:
Chair Yoshikazu Kinoshita (the Japan Gastroenterological Endoscopy Society: Shimane University Second Department of Internal Medicine)
Committee members:
Junji Yoshino (The Japan Gastroenterological Endoscopy Society: Fujita Health University Banbuntane Hotokukai Hospital Department of Internal Medicine)
Tetsuya Mine (The Japan Gastroenterological Endoscopy Society: Tokai University Department of Internal Medicine)
Kazunari Murakami (The Japan Gastroenterological Endoscopy Society: Oita University Department of Gastroenterology)
External Evaluation Committee:
Masahiro Yoshida (Japan Council for Quality Health Care, EBM and Guidelines Division (Medical Information Network Distribution Service): International University of Health and Welfare, Chemotherapy Research Institute)
Masahiro Yasaka (The Japanese Society of Neurology, the Japan Stroke Society, the Japanese Society on Thrombosis and Hemostasis: National Hospital Organization, Kyushu Medical Center Department of Cerebrovascular Medicine and Neurology)
Seiji Hokimoto (The Japan Circulation Society: Kumamoto University Department of Cardiovascular Medicine)
Tetsuo Arakawa (The Japan Gastroenterological Endoscopy Society: Osaka City University Department of Gastroenterology)

not be achieved, statements were revised, and the resulting Delphi evaluations were used in the guidelines.

A similar Delphi evaluation was undertaken at the 82nd JGES symposium in October 2011, with very similar results to the consensus meeting. The final drafts of the explanations accompanying the consensus statements were incorporated, along with evaluations of each statement by the evaluation committee. Given the relatively low level of evidence underpinning the statements, further research carried out by JGES will be needed to validate some of the recommendations.

EVALUATION PROCESS

THE EDITORIAL AND evaluation committees and JGES directors listed in Table 1 (15 persons in total) used Delphi[11–13] voting to reach consensus in areas with little or no scientific evidence except epidemiological evidence. Delphi voting uses a rating scale (1–3, disagree; 4–6, unsure; 7–9, agree), where the results are expressed as the median value and range.

Voting took place at a consensus meeting in June 2011. The prepared statements were subject to a review and approval process, followed by preliminary voting. After further deliberation, the statements were finalized for inclusion in the guidelines. The statements were ranked on a three-point recommendation scale, based on the MINDS recommendation grades[13,14] as follows:

A significant scientific evidence available, highly recommended;
B reasonable scientific evidence available, recommended;
C1 recommended, although scientific evidence not available.

TARGET GROUP

THE TARGET GROUP for the guidelines comprises patients undergoing gastroenterological endoscopy examination and/or treatment while taking antithrombotic therapy. When the patient has severe comorbidities, treatment should be tailored to the individual patient's needs. These guidelines do not cover emergency endoscopic procedures, such as for acute gastroenterological hemorrhage. The guidelines are intended for use by clinicians engaged in gastroenterological endoscopic procedures, as well as their instructors.

ENDOSCOPIC EXAMINATION AND TREATMENT PROCEDURES IN TERMS OF DEGREE OF RISK OF BLEEDING (EXCLUDING EMERGENCY ENDOSCOPIC PROCEDURES)

TABLE 2 CLASSIFIES GASTROENTEROLOGICAL endoscopic examination and treatment procedures into four categories: diagnostic gastroenterological endoscopy without biopsy; endoscopic mucosal biopsy; gastroenterological endoscopy with low risk of bleeding; and gastroenterological endoscopy with high risk of bleeding. Recent evidence suggests that the latter category should be subcategorized into high risk and very high risk, based upon the procedures and techniques used and the target organ.

Table 2 Gastroenterological endoscopic procedures and bleeding risk

1. Diagnostic gastroenterological endoscopic procedures without biopsy:
Upper gastroenterological endoscopy (including transnasal endoscopy)
Lower gastroenterological endoscopy
Endoscopic ultrasonography
Capsule endoscopy
Endoscopic retrograde cholangiopancreatography (ERCP)
2. Endoscopic mucosal biopsy (excluding endoscopic ultrasonography-guided fine-needle aspiration: EUS-FNA)
3. Gastroenterological endoscopic procedures with low bleeding risk:
Balloon-assisted endoscopy
Marking (including clipping, electrocoagulation, tattooing)
Gastroenterological, pancreatic duct, biliary duct stenting (without incision before treatment)
Endoscopic papillary balloon dilation
4. Gastroenterological endoscopic procedures with high bleeding risk:
Polypectomy
Endoscopic mucosal resection
Endoscopic submucosal dissection
Endoscopic duodenal sphincterotomy (papillotomy)
Endoscopic duodenal papillectomy
EUS-FNA
Percutaneous endoscopic gastrostomy (PEG)
Endoscopic treatment of esophageal and gastric varices
Endoscopic gastroenterological dilatation procedures
Endoscopic ablation
Others

DRUG DEFINITIONS (ANTITHROMBOTICS, ANTIPLATELET AGENTS AND ANTICOAGULANTS)

Antithrombotics

THE TERM 'ANTITHROMBOTICS' in the present guidelines encompasses antiplatelet agents such as aspirin and thienopyridine derivatives as well as anticoagulants such as warfarin, heparin and dabigatran. The guidelines do not extend to thrombolytic drugs, low-molecular weight heparin, heparinoids, or i.v. antithrombin preparations.

Antiplatelet agents

Antiplatelet agents are used to maintain circulating platelets in an inactive state, and inhibit aggregation. In arteriosclerotic diseases, atheromatous plaque disruption results in release of physiologically active substances including adenosine diphosphate, thromboxane and thrombin, which activate platelets. This in turn promotes the formation of intraluminal thrombus as a result of platelet aggregation, leading to stenosis or even occlusion. By inhibiting aggregation, antiplatelet agents suppress thrombus formation. For the purposes of these guidelines, antiplatelet drugs have been categorized into aspirin, thienopyridine derivatives and other antiplatelet agents.

Anticoagulants

Anticoagulants include drugs such as warfarin, heparin, heparin formulations such as low molecular weight heparins and heparinoids, and newer drugs such as the direct thrombin inhibitor, dabigatran, and a direct factor Xa inhibitor. For the purposes of the present guidelines, anticoagulants have been categorized into warfarin, unfractionated heparin, and dabigatran. The other anticoagulants must be indicated by future guidelines.

INCIDENCE OF THROMBOEMBOLISM AS A RESULT OF WITHDRAWAL OF TREATMENT

TABLE 3 LISTS GROUPS of patients at increased risk of thromboembolism as a result of withdrawal of antithrombotic therapy. Withdrawal of antithrombotic therapy

Table 3 High-risk conditions of thromboembolism associated with withdrawal of antithrombotic therapy

High-risk conditions associated with withdrawal of antiplatelet agents
Two months following coronary artery bare metal stenting
Twelve months following coronary artery drug eluting stenting
Two months following carotid arterial revascularization (carotid endarterectomy or stenting)
Ischemic stroke or transient ischemic attack with >50% stenosis of major intracranial arteries
Recent ischemic stroke or transient ischemic attack
Obstructive peripheral artery disease ≥ Fontaine grade 3 (rest pain)
Ultrasonic examination of carotid arteries and magnetic resonance angiography of head and neck region where withdrawal is considered high risk of thromboembolism
High-risk conditions associated with withdrawal of anticoagulants†
History of cardiogenic brain embolism
Atrial fibrillation accompanying valvular heart disease
Atrial fibrillation without valvular heart disease but with high risk of stroke
Following mechanical mitral valve replacement
History of thromboembolism following mechanical valve replacement
Anti-phospholipid antibody syndrome
Deep vein thrombosis/pulmonary thromboembolism

†The risk of thromboembolism associated with withdrawal of anticoagulants, such as warfarin, varies considerably. Once thromboembolic complications have occurred, they are often serious. All patients on anticoagulant therapy are treated as high-risk patients.

may have a variety of consequences, some of which may be serious. As a result, all patients taking anticoagulation therapy should be considered high risk.

STATEMENTS 1–12 ON GASTROENTEROLOGICAL ENDOSCOPY

Statement 1

WHEN ASPIRIN, NON-ASPIRIN antiplatelet agents or anticoagulants need to be withdrawn before gastroenterological endoscopy, the prescribing doctor should be consulted beforehand. The patient should be informed of the reasons for the endoscopy, the expected benefits, and any potential complications including hemorrhage. The endoscopy, as a general rule, is carried out with the patient's informed consent.

Delphi scores: median = 9, lowest = 8, highest = 9.

Recommendation: B.

Further information

During gastroenterological endoscopic examination and/or treatment of a patient on antithrombotic therapy, it is necessary to balance the risk of hemorrhage from the antithrombotic therapy with the risk of thromboembolism as a result of withdrawal.[8,15] The risk of hemorrhage depends on the nature of the endoscopic procedure, and the risk of thromboembolism depends on patient comorbidities. It is important to develop a management plan optimized for the individual patient, based on consultation between the endoscopist and the physician prescribing the antithrombotics. The decision to withdraw antithrombotic therapy should not be made by the endoscopist alone.

Previous studies have reported that suspension of aspirin therapy increased the risk of cerebral infarction approximately threefold, with 70% occurring within 10 days of withdrawal.[16,17] Withdrawal of antiplatelet therapy within a year of insertion of a drug eluting coronary stent increased the risk significantly.

Suspension of warfarin therapy causes the patient to revert to a state of hypercoagulability. It has been reported that one in 100 cases of warfarin withdrawal result in thromboembolic complications with poor prognosis.[18–20] In addition to drug withdrawal, the risk of thromboembolism might be increased by dehydration caused by preparation for endoscopic examinations, which should be addressed by adequate fluid replacement.

Statement 2

Diagnostic gastroenterological endoscopy without biopsy can be carried out without withdrawing aspirin, non-aspirin antiplatelet agents, or anticoagulants.

Delphi scores: median = 9, lowest = 8, highest = 9.

Recommendation: B.

Further information

To minimize the risk of thromboembolism, withdrawal of antithrombotic therapy is not required prior to standard gastroenterological endoscopy. Rarely, hemorrhage may occur as a consequence of mucosal lacerations or Mallory–Weiss tears. In patients taking antithrombotics, care should be taken to minimize trauma associated with the procedure; in particular, over-insufflation should be avoided and the procedure should be completed as quickly as possible.

Statement 3

For endoscopic mucosal biopsy, withdrawal of aspirin, non-aspirin antiplatelet agents or anticoagulants is not required when the patient is on antithrombotic monotherapy. If a patient is taking warfarin monotherapy, it should be confirmed that the prothrombin time international normalized ratio (PT-INR) lies within the required therapeutic range. When the patient is on dual or triple antithrombotic therapy,

decisions about withdrawal should be made on a case-by-case basis. Biopsy is inevitably associated with bleeding, regardless of the use of antithrombotics. Hemostasis must be confirmed before extracting the endoscope, and endoscopic hemostatic techniques should be used if bleeding does not stop spontaneously.

Delphi scores: median = 8, lowest = 7, highest = 9.

Recommendation: C1.

Further information

Previous guidelines have recommended withdrawal of antithrombotic therapy for a fixed period to prevent hemorrhagic complications associated with mucosal biopsy.[21] In 2005, JGES recommended 3 or 4 days withdrawal from warfarin, 3 days for aspirin and 5 days for ticlopidine even in low-risk endoscopic procedures requiring biopsy.[2]

The risk of thromboembolism draws more attention than the risk of hemorrhage because of its seriousness. The *Guidelines for Gastroenterological Endoscopy*[3] (version 3, 2006) suggested shortening the duration of withdrawal for several endoscopic procedures, including mucosal biopsy, in which hemostasis for bleeding was relatively easily to carry out.[3] Guidelines for gastroenterological endoscopy in the USA, the UK and Europe allow for the continued use of antithrombotics such as aspirin, thienopyridine derivatives and warfarin around the time of biopsy because of the low risk of hemorrhage.[6,9,10,22] The new JGES guidelines allow mucosal biopsy with continued use of antithrombotics, especially in patients at high risk of thromboembolism. Biopsy with antithrombotics should only be undertaken when absolutely necessary, and caution should be exercised. In patients at low risk of thromboembolism, aspirin can be withdrawn 3 to 5 days before the procedure, and thienopyridine derivatives 5 to 7 days beforehand. Patients taking warfarin therapy should principally be treated as high-risk cases.

The incidence of bleeding complications after mucosal biopsy is 0.002% in the stomach and 0.09% in the large intestine, regardless of antithrombotic use.[23,24] There have been no large randomized studies examining the impact of antithrombotics on bleeding after biopsy. One cross-sectional analysis study conducted with healthy subjects[25] reported no increase in the incidence of bleeding after gastric and duodenal biopsy carried out in those taking antithrombotics in combination with a proton pump inhibitor. A retrospective study in Western Europe showed that the use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, did not increase the incidence of post-biopsy bleeding.[26] Two studies in Japan have reported that antithrombotics, including aspirin, did not increase risk of bleeding after biopsy.[27,28] One cohort study in 12 centers in Japan found no evidence that antithrombotic therapy increased bleeding risk after biopsy, although the number of subjects was small.[29] One case–control study indicated that ongoing aspirin use prior to colonic polypectomy was not associated with post-procedural bleeding.[30] Other studies have indicated that there is no increase in post-biopsy bleeding in patients on warfarin therapy if the PT-INR is within the therapeutic range.[31,32] The incidence of gastrointestinal hemorrhage after biopsy appears to be increased if the PT-INR is ≥3.0,[33] suggesting that mucosal biopsy should not be carried out if the PT-INR was ≥3.0 within the week before biopsy.

Several reports have indicated that aspirin and thienopyridine derivatives prolonged bleeding time, but cilostazol and eicosapentaenoic acid did not.[34–37] Particular care should be taken if antithrombotics have not been withdrawn: (i) the extent of biopsy should be minimized; (ii) the endoscope should not be removed until hemostasis has been confirmed; and (iii) bleeding that does not stop spontaneously should be treated by compression with forceps, sodium alginate and thrombin, or clipping etc.[38] As less acidic gastric conditions preserve platelet aggregation and thus promote hemostasis, an acid suppressant may be prescribed for several days before and after gastric biopsy.[39]

Statement 4

For gastroenterological endoscopic procedures with low bleeding risk, withdrawal of aspirin, non-aspirin antiplatelet agents or anticoagulants is not required. Regarding warfarin, it should be confirmed that the PT-INR is within the therapeutic range.

Delphi scores: median = 9, lowest = 7, highest = 9.

Recommendation: C1.

Further information

No studies have demonstrated a risk of bleeding complications as a result of low-risk gastroenterological endoscopic procedures. One meta-analysis[40] reported 0% incidence of hemorrhagic complications for low-risk endoscopic papillary balloon dilation procedures, and a 2% incidence for high-risk endoscopic transduodenal sphincterotomy procedures, suggesting that risk of bleeding complications for endoscopic procedures with low bleeding risk is negligible in patients taking antithrombotic therapy.

Statement 5

For gastroenterological endoscopic procedures that carry a high risk of bleeding, withdrawal of aspirin monotherapy is not required in patients who would be placed at high risk of thromboembolism by withdrawal. Aspirin can be withdrawn for 3 to 5 days in patients at low risk of thromboembolism.

Delphi scores: median = 8, lowest = 7, highest = 9.

Recommendation: C1.

Further information

Among endoscopic procedures known to carry higher risks of bleeding, the incidence of hemorrhage still varies.

Although the present guidelines do not provide a detailed breakdown, it is important to consider the risk of bleeding associated with a particular procedure; for example, endoscopic submucosal dissection. A case–control study[10] of approximately 30 000 subjects undergoing colonic polypectomy indicated no increase in the risk of bleeding complications in patients taking aspirin. Similarly, a case–control study[41] that enrolled 126 patients undergoing endoscopic duodenal sphincterotomy demonstrated that bleeding complications were not increased in patients taking antithrombotics, the majority of whom were taking aspirin. Retrospective studies of gastric endoscopic submucosal dissection have indicated no increase in bleeding complications if antithrombotics had been withdrawn for 1 week.[42–44] In contrast, one study reported an increased risk of postprocedural bleeding (odds ratio 2.76, 95% confidence interval [95% CI] 1.09–6.98) in patients treated according to the 2005 JGES guidelines who took antithrombotics, corticosteroids or NSAIDs.[45]

A prospective study of 322 patients with colonic tumors >2 cm in diameter indicated that the rate of bleeding complications after endoscopic resection was increased in those who had taken aspirin within 7 days of the procedure (mean withdrawal period: 5.4 days, odds ratio 6.3, 95% CI 1.8–22.5).[46] A retrospective study of 219 cases of gastric and duodenal submucosal dissection in patients taking aspirin monotherapy indicated that the occurrence of bleeding complications appeared to be independent of aspirin withdrawal (0.0% [none of seven patients] *vs* 12.1% [four out of 33 patients]).[47] This study indicated that the rate of postprocedural bleeding complications was not different in the patients in whom aspirin was withdrawn compared to those who had continued to take it (6.6% [10 out of 152 patients]).[47]

The 2009 guidelines published by the American Society for Gastrointestinal Endoscopy (ASGE) recommended continued use of aspirin for gastroenterological endoscopic procedures that carry a high risk of bleeding.[6] The 2011 guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) recommended continued use of aspirin for endoscopic procedures, but recommended that aspirin be withdrawn for 5 days before a procedure with high bleeding risk in patients at low risk of thromboembolism.[10] High bleeding risk procedures were defined as mucosal resection, submucosal dissection, transduodenal sphincterotomy, endoscopic papillary large balloon dilation following transduodenal sphincterotomy, and endoscopic ultrasound-guided fine-needle aspiration of a cystic lesion. The new JGES guidelines, like those of ASGE, recommend the continued use of aspirin in all gastroenterological endoscopic procedures with high bleeding risk. However, in accordance with the 2005 JGES guidelines, aspirin should be withdrawn for 3–5 days in patients at relatively low risk of thromboembolism, in consultation with the prescribing doctor.[2]

The endoscope should only be removed after confirmation that hemostasis has been achieved; any subsequent bleeding should be treated with standard endoscopic techniques, including clipping. Most of the evidence cited in these guidelines comes from studies conducted outside Japan. Ideally, JGES guidelines should be formulated on the basis of high-quality evidence gathered in Japanese patients; therefore, further research is required.

Statement 6

Withdrawal of non-aspirin antiplatelet agents is required in gastroenterological endoscopic procedures that carry a high bleeding risk. Thienopyridine derivatives should be withdrawn for 5 to 7 days, but 1 day is sufficient for all other antiplatelet agents. Replacement with aspirin or cilostazol is required in patients at high risk of thromboembolism.

Delphi scores: median = 8, lowest = 8, highest = 9.

Recommendation: C1.

Further information

Antiplatelet agents other than aspirin have been classified into thienopyridine derivatives and others. Monotherapy with thienopyridine derivatives has been found to increase the risk of bleeding complications after gastroenterological endoscopy procedures that carry a higher risk of bleeding, including colonic polypectomy.[48] The ASGE guidelines also recommend withdrawal of thienopyridine derivatives for 7–10 days before procedures with high bleeding risk.[6] There have been no reports in Japan suggesting an increase in bleeding complications after 5 days of thienopyridine withdrawal as recommended in the 2005 JGES guidelines.[2,3] Taking these data into account, the new guidelines recommend that thienopyridine derivatives should be withdrawn 5–7 days before any high bleeding risk endoscopic procedure.

When it is not feasible to withdraw thienopyridine derivatives, replacement with aspirin is recommended after consultation with the prescribing doctor, a recommendation that concurs with ASGE and ESGE guidelines.[6,10] Alternatively, the Sapporo Consensus, achieved in hospitals based around Sapporo in Japan, recommends that cilostazol, which is available in Japan, may be used instead of aspirin.[38] Cilostazol replacement of antiplatelet agents should be a temporary measure during endoscopic procedures; the prescribing doctor should agree that the replacement strategy will be safe and effective. Cilostazol is contraindicated in patients with congestive cardiac failure; other reported adverse effects include rapid-onset headache and tachycardia. Replacement of antiplatelet agents with cilostazol should be undertaken with care.

There is no definitive evidence base concerning the influence of other antiplatelet agents on hemorrhage at the time of endoscopy. A basic science study has reported that ethyl icosapentate, which has a long serum half-life, does not prolong the bleeding time.[37] Most antiplatelet agents other

than thienopyridine derivatives and aspirin have short serum half-lives and therefore would be expected to have little influence on platelet aggregation or bleeding complications during endoscopic procedures if withdrawn at the correct time.[49] These data support the recommendation of these guidelines that withdrawal 1 day beforehand is sufficient for other antiplatelet agents.

The endoscope should only be removed after confirmation that hemostasis has been achieved; any subsequent bleeding should be treated with standard endoscopic techniques, including clipping.

Statement 7

For gastroenterological endoscopic procedures that carry a high risk of bleeding, warfarin or dabigatran should be replaced with heparin.

Delphi scores: median = 9, lowest = 8, highest = 9.

Recommendation: B.

Heparin replacement

Warfarin has a half-life of approximately 40 h. When the PT-INR lies between 2.0 and 3.0 it takes approximately 4 days for the PT-INR to reach 1.5 after withdrawal.[50] We recommend that warfarin should be replaced with unfractionated heparin 3 to 5 days before endoscopy.[2,3] Unfractionated heparin is usually given as a continuous i.v. infusion of 10 000–20 000 international units (IU) per day, or subcutaneous injection of 10 000–15 000 IU every 12 h.[51,52] The dose is adjusted to attain the required activated partial thromboplastin time (APTT) as quickly as possible. The platelet count should be monitored to detect heparin-induced thrombocytopenia. Intravenous infusion of unfractionated heparin should be suspended at least 3 h before endoscopy, and subcutaneous administration at least 6 h beforehand. After hemostasis has been confirmed, heparin may be resumed and, if the patient can take drugs by mouth, warfarin restarted at the pre-withdrawal dose. Heparin should be discontinued when the PT-INR has returned to the therapeutic range.[53] Dabigatran should be suspended 24–48 h before the procedure, and heparin replacement introduced 12 h later. Warfarin or dabigatran may be resumed after the procedure once hemostasis has been confirmed.

Further information

The most important risk factor for stroke associated with non-valvular atrial fibrillation (NVAF) is a history of stroke or transient ischemic attack (TIA). Stroke is reported to occur at a rate of approximately 12% per year in patients with NVAF.[54] Warfarin is used for both primary and secondary stroke prevention in patients with NVAF.[55]

The Japan Circulation Society *Guidelines on Anticoagulant and Antiplatelet Therapy for Cardiovascular Illnesses*[4] recommend warfarin therapy with a target therapeutic PT-INR range of 2.0–3.0 (1.6–2.6 at age ≥ 75 years) for patients with NVAF and a history of stroke or TIA, or two or more of the following: congestive heart failure, high blood pressure, diabetes, or age ≥75 years. Hemorrhage is the most important complication of warfarin therapy; gastroenterological bleeding is the most common and most likely to be serious.[56] Gastroenterological endoscopic procedures such as polypectomy have been reported to have a high risk of bleeding in the patient taking warfarin.[57,58]

Temporary withdrawal of warfarin therapy for prevention of hemorrhagic complications is required during gastroenterological endoscopic procedures that carry a high risk of bleeding. After withdrawal of warfarin it should be confirmed that PT-INR is <1.5 before the procedure. Warfarin withdrawal is recommended by both the ASGE guidelines[6] and the 2005 JGES guidelines.[2]

Suspension of warfarin in patients requiring anticoagulant therapy results in serious thromboembolism in a proportion of patients.[19,59] A PT-INR <2.0 increases the risk of ischemic stroke in patients with NVAF, and the risk of major stroke increases with PT-INR <1.6.[60] In patients at high risk of thromboembolism, warfarin should be replaced with heparin prior to endoscopy.[61]

Dabigatran is an orally given thrombin inhibitor used to prevent ischemic stroke and systemic embolic events in patients with NVAF. It acts as an anticoagulant through direct and targeted inhibition of the enzymatic activity of thrombin, which plays a key role in the blood coagulation cascade.[62] Dabigatran does not require dietary guidance or PT-INR monitoring. Treatment with dabigatran appears to carry a similar risk of gastrointestinal bleeding to warfarin, even though it has a shorter half-life.[63,64] It should be prescribed with caution in: (i) patients ≥70 years old; (ii) those with impaired renal function (it is contraindicated in patients with a creatinine clearance (C_{Cr}) ≤30 mL/min); (iii) patients with a history of gastroenterological bleeding; and (iv) patients who are taking P-glycoprotein inhibitors, such as itraconazole.

Statement 8

For gastroenterological endoscopic procedures that carry a high risk of bleeding, procedures should be postponed in patients taking aspirin in combination with other antiplatelet agents until the antiplatelet agents have been withdrawn. According to need, the procedures with high bleeding risk can be carried out on monotherapy with aspirin or cilostazol. The withdrawal period for thienopyridine derivatives is 5 to 7 days, and 1 day for all other antiplatelet agents, with the duration of withdrawal being modified to the clinical situation.

Delphi scores: median = 9, lowest = 7, highest = 9.

Recommendation: C1.

Further information

There is no definitive evidence that co-administration of aspirin and other antiplatelet agents increases the risk of bleeding complications after high-risk gastroenterological endoscopic procedures. A retrospective study[48] of 1385 colonic polypectomy procedures undertaken on patients taking aspirin found that clopidogrel increased the rate of post-procedural bleeding (3.5% *vs* 1.0% in patients taking aspirin alone), and that clopidogrel increased the risk of bleeding in patients taking aspirin or NSAIDs by a factor of 3.69 (95% CI 1.60–8.52), suggesting that careful thought should be given to the use of clopidogrel at the time of colonic polypectomy, endoscopic submucosal dissection and other high-risk procedures. A retrospective study of 219 Japanese patients undergoing gastric or duodenal submucosal dissection reported a rate of bleeding complications of 6.6% (10 out of 152 patients) in those not taking antithrombotic therapy; 12.1% (four out of 33 patients) in those in whom antithrombotic monotherapy had been withdrawn before the procedure; 8.3% (one out of 12 patients) in those taking two or more agents that were withdrawn before the procedure; 0.0% (none out of seven patients) in those who remained on aspirin monotherapy; and 46.7% (seven out of 15 patients) in those taking aspirin with one or more other anticoagulants.[48] This suggested that there was an increased risk of bleeding after submucosal dissection in patients taking aspirin and at least one additional antithrombotic.

Nevertheless, patients taking two antithrombotics are at high risk of thromboembolism and withdrawal of antithrombotic therapy should be avoided if possible. The new guidelines recommend that endoscopic procedures that carry a high risk of bleeding should be postponed when the patient needs two antiplatelet agents. High-risk endoscopic procedures, such as the treatment of early cancer, may be undertaken in the patient at high risk of thromboembolism with combination therapy, after combination therapy is temporarily changed to monotherapy with aspirin or cilostazol under discussion between the gastroenterologist and the physician who prescribes dual antiplatelet agents.

We recommend that thienopyridine derivatives should be withdrawn 5 to 7 days before the procedure: 5 days if they are taken as monotherapy and 7 days when taken in combination with aspirin, in accordance with the 2005 JGES guidelines.[2] As other antiplatelet agents have minimal influence on platelet aggregation and generally have a short half-life, the recommended withdrawal period is 1 day. We note that these recommendations require further validation.

Statement 9

For gastroenterological endoscopic procedures that carry a high risk of bleeding, procedures planned in patients taking aspirin in combination with warfarin or dabigatran should be postponed until antithrombotics can be withdrawn. According to need, the procedures can be carried out on aspirin or cilostazol under replacement of warfarin or dabigatran with heparin.

Delphi scores: median = 9, lowest = 7, highest = 9.

Recommendation: C1.

Further information

There is substantial evidence showing that dual antithrombotic therapy induces an increase in the risk of gastrointestinal bleeding as compared with monotherapy, but there is no definitive evidence that co-administration of aspirin and anticoagulants increases the risk of bleeding complications after high-risk gastroenterological endoscopic procedures. A retrospective study of 5593 cases of colonic polypectomy reported no increase in the risk of post-procedural bleeding in patients taking aspirin, but a significant increase in those taking warfarin.[57] This report suggested that warfarin should be replaced with heparin during high-risk endoscopic procedures including polypectomy and submucosal dissection.

Statement 10

For gastroenterological endoscopic procedures that carry a high risk of bleeding, procedures planned in patients taking a non-aspirin antiplatelet agent in combination with warfarin or dabigatran should be postponed until warfarin or dabigatran have been withdrawn. According to need, the procedures can be done on aspirin or cilostazol under replacement of warfarin or dabigatran with heparin.

Delphi scores: median = 9, lowest = 7, highest = 9.

Recommendation: C1.

Further information

There is no definitive evidence that co-administration of non-aspirin antiplatelet agents and anticoagulants increases the risk of bleeding complications after high-risk gastroenterological endoscopic procedures. There have been no reports of the influence of clopidogrel plus other anticoagulants on the endoscopic procedures. This lack of evidence may be explained by the fact that most guidelines[6,10] already recommend withdrawal of both agents, replacing clopidogrel with aspirin and warfarin with heparin.

Statement 11

For gastroenterological endoscopic procedures that carry a high risk of bleeding, procedures planned in patients taking three drugs (aspirin with a non-aspirin antiplatelet agent drug and warfarin or dabigatran) should be postponed until antithrombotics have been withdrawn. According to need, the procedures can be done on aspirin or cilostazol under replacement of warfarin or dabigatran with heparin.

Delphi scores: median = 8, lowest = 7, highest = 9.

Recommendation: C1.

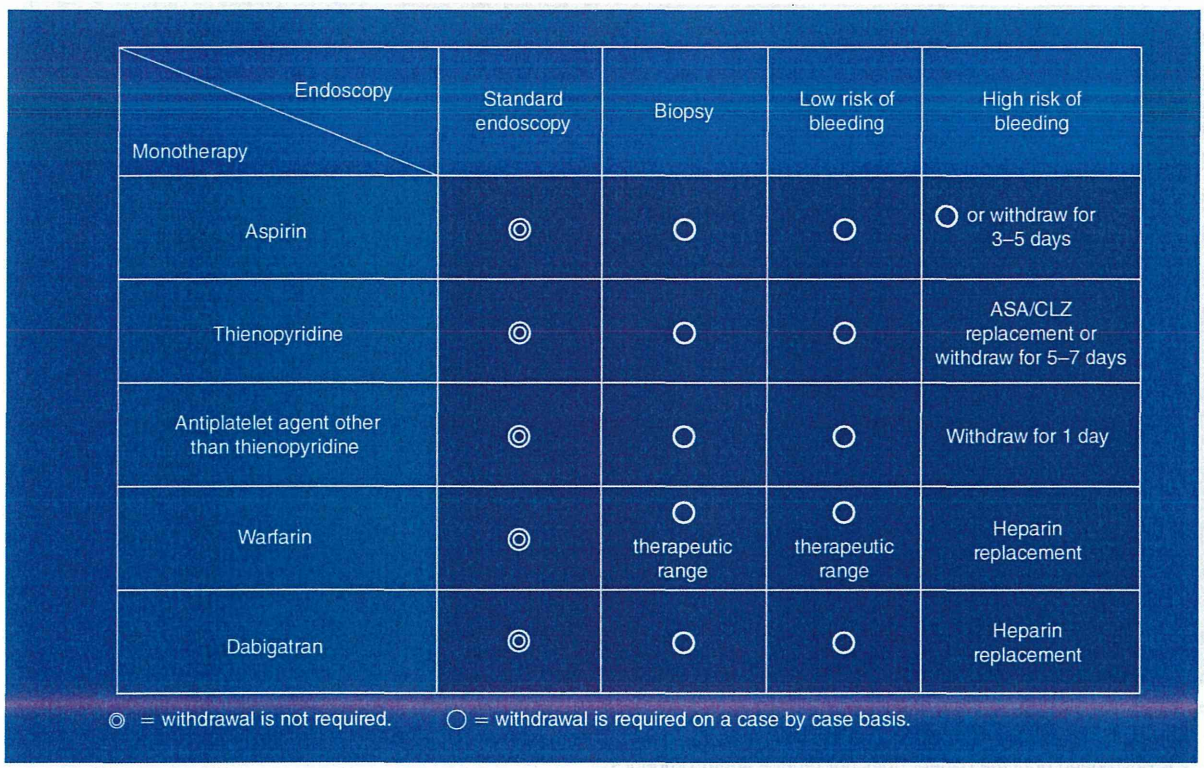

Figure 1 Withdrawal of monotherapy with antiplatelet agents or anticoagulants during gastroenterological endoscopy. ASA, aspirin; CLZ, cilostazol.

Further information

There is no definitive evidence in odds ratio regarding increased bleeding risk of triple therapy with aspirin, a non-aspirin antiplatelet agent and warfarin or dabigatran during high-risk gastroenterological endoscopic procedures.

Statement 12

After temporary withdrawal of antithrombotics, the same regimen should be re-established as soon as hemostasis has been confirmed. Ongoing monitoring for signs of bleeding is required after resumption.

Delphi scores: median = 9, lowest = 8, highest = 9.

Recommendation: C1.

Further information

Oral administration of aspirin, and non-aspirin antiplatelet agents should be resumed as soon as hemostasis is confirmed after the procedure.[2] Anticoagulants should also be resumed without delay. Where heparin replacement has been used, heparin should be resumed after the procedure, and warfarin or dabigatran given when oral intake has been re-established. Warfarin should be given at the pre-withdrawal dose, and heparin can be discontinued when the PT-INR reaches the therapeutic range.[53] Dabigatran, which has a shorter half-life, should be given at the pre-withdrawal dose and heparin can be discontinued immediately.[63]

Ongoing monitoring for signs of bleeding is required after antithrombotic therapy has been resumed. A retrospective study of 3138 colonic polypectomy procedures undertaken in Japan, after which antithrombotic therapy was suspended for 1 week, found evidence of post-procedural bleeding in 1.2% of cases for an average period of 5.1 days (range 1–14 days).[65] A retrospective study of 454 submucosal dissection procedures in Japan, after which antithrombotic therapy was suspended for 1 week, reported post-procedural bleeding in 5.7% of cases with a median period of 2 days (range 0–14 days).[66] Immediate resumption of antithrombotic therapy after gastroenterological endoscopic procedures might increase the risk of post-procedural bleeding, including delayed bleeding more than 2 weeks after the procedure. It is important to ensure that the patient is fully informed of these risks and has given written consent.

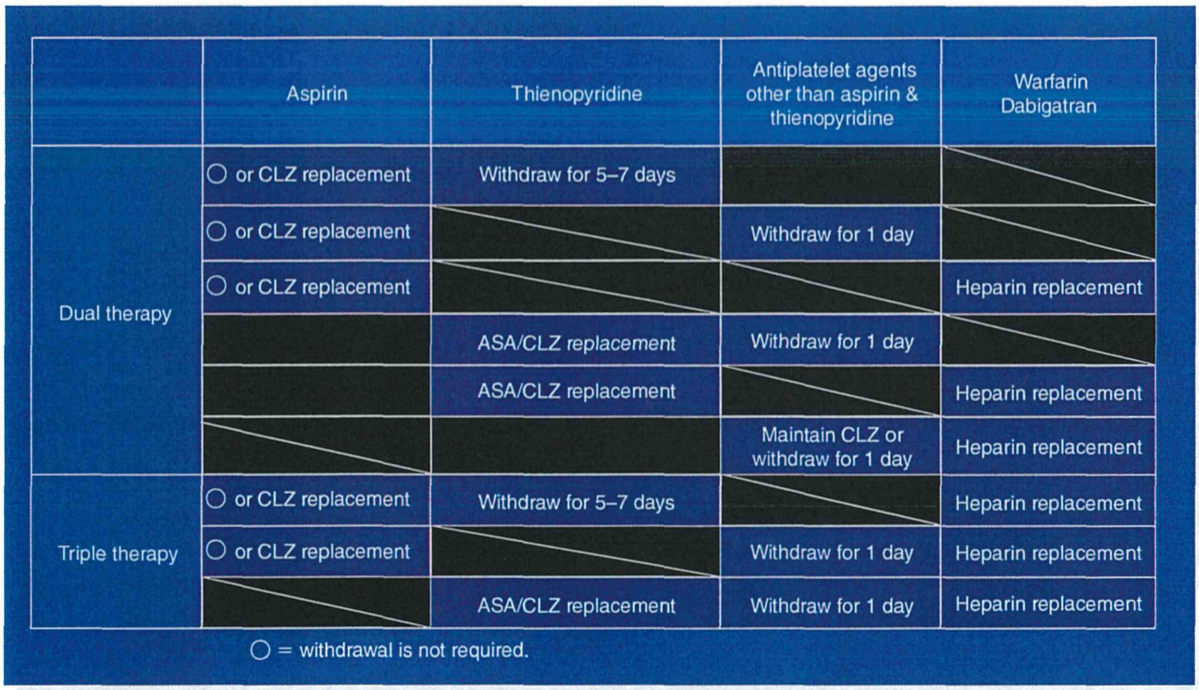

Figure 2 Withdrawal of antiplatelet agents and anticoagulants in combination therapy. ASA, aspirin; CLZ, cilostazol. Biopsy or endoscopy with low bleeding risk is carefully carried out according to the patient's condition. It is preferable that endoscopy with high bleeding risk is postponed until the patient does not require antithrombotics.

SUMMARY OF GUIDELINES

THE GUIDELINES HAVE been summarized in two flowcharts (Figs 1,2).

ACKNOWLEDGMENT

ALL EXPENSES ASSOCIATED with formulation of these guidelines were borne by the Japan Gastroenterological Endoscopy Society. These guidelines have already been published in Japanese (reference[67]).

CONFLICT OF INTERESTS

ALL MEMBERS OF the editorial committee, evaluation committee and peer reviewers of these guidelines were required to declare potential conflicts of interest as follows:

1. The following businesses, companies and industry groups have provided remuneration to committee members (or dependent members of their families) for: executive or consulting work, patent or license fees, lecture fees, manuscript fees or other remuneration of ¥1 million or more; or research expenses of ¥2 million or more; or the committee members (or dependent members of their families) hold stock of ¥1 million or more:
   Astellas Pharma Inc., AstraZeneca Plc, Eisai Co., Ltd, Otsuka Pharmaceutical, CCI, Tsumura & Co., Sanofi Co., Ltd, Daiichi Sankyo Co., Ltd, Takeda Pharmaceutical, Co., Ltd, Mitsubishi Tanabe Pharma Corporation, Nippon Shinyaku Co., Ltd, Nippon Boehringer Ingelheim GmbH, Pfizer Inc., MSD Co., Ltd.
2. The following businesses, companies and industry groups have provided ¥2 million or more to departments with which a committee member is affiliated for: support, collaboration or subcontracting expenses; licensing and transfers; or endowments:
   Astellas Pharma Inc., AstraZeneca Plc, Eisai Co., Ltd, Otsuka Pharmaceutical, Sanofi Co., Ltd, Century Medical Inc., Daiichi Sankyo Co., Ltd, Dainippon Sumitomo Pharma Co., Ltd, Takeda Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Nippon Shinyaku Co., Ltd, Nippon Boehringer Ingelheim GmbH, Pfizer Inc., MSD Co., Ltd.

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1 Japan Gastroenterological Endoscopy Society Postgraduate Education Committee. *Guidelines for Gastroenterological*