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

| |
|---|
| Japan Gastroenterological Endoscopy Society |
| 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.

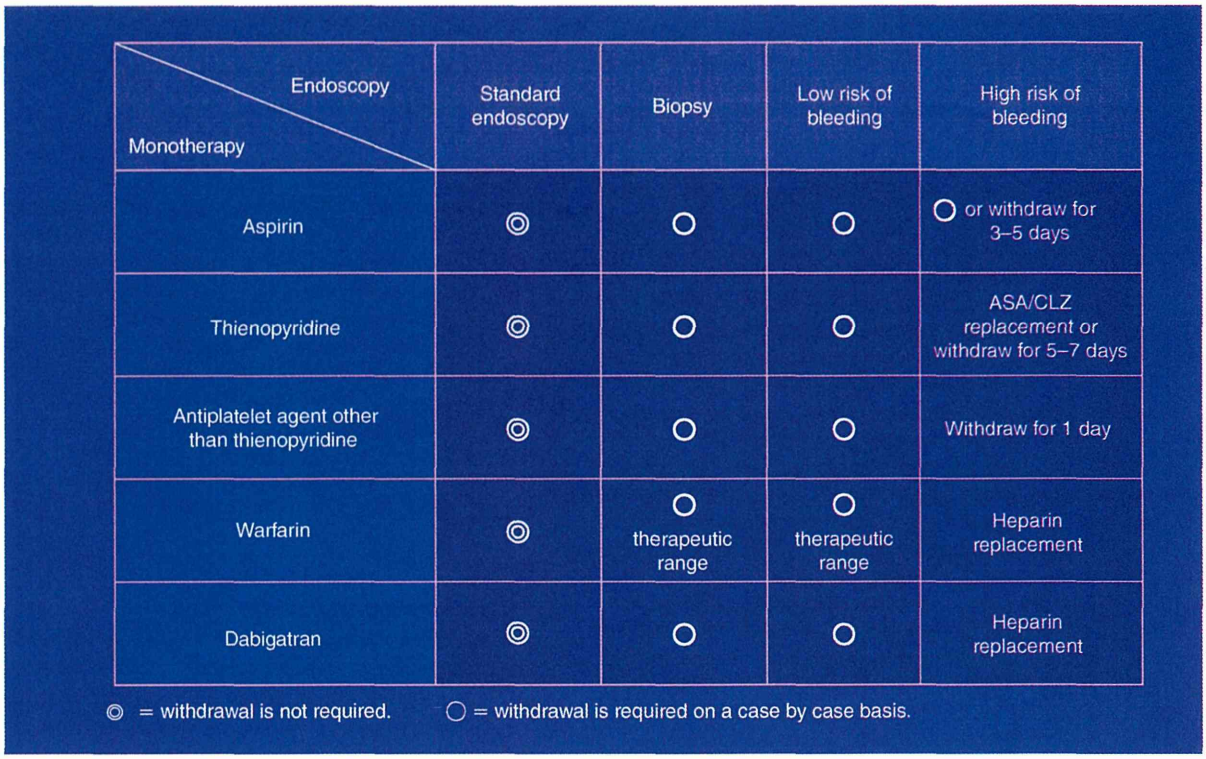


**Figure 1** Withdrawal of monotherapy with antiplatelet agents or anticoagulants during gastroenterological endoscopy. ASA, aspirin; CLZ, cilostazol.

### *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.

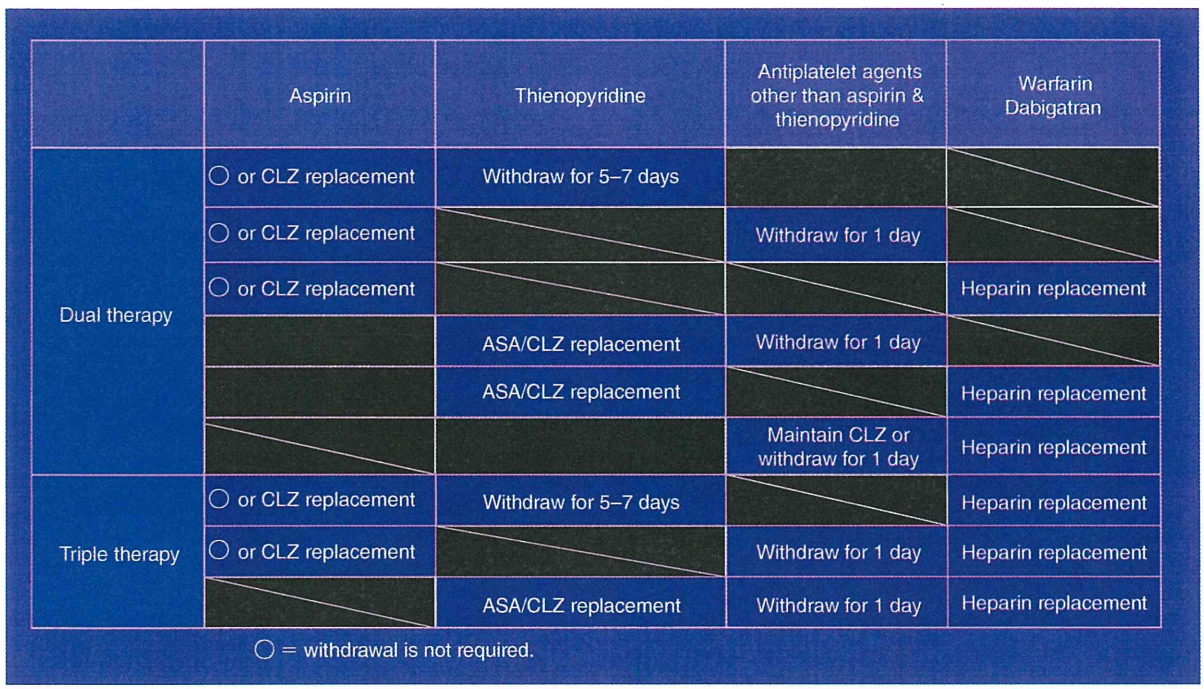


**Figure 2** Withdrawal of antiplatelet agents and anticoagulants in combination therapy. ASA, aspirin; CLZ, cilostazol. Biopsy or endoscopy with low bleeding risk is carefully carried out according to the patient's condition. It is preferable that endoscopy with high bleeding risk is postponed until 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.

## REFERENCES

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

*Endoscopy*. Japan Gastroenterological Endoscopy Society (ed.). Tokyo: Igaku Shoin, 1999. (in Japanese.)
2 Ogoshi K, Kaneko E, Tada M *et al.* Japan Gastroenterological Endoscopy Society Risk Management Committee. Use of anticoagulants and antiplatelet agents during endoscopic procedures. *Gastroenterol. Endosc.* 2005; **47**: 2691–5. (in Japanese.)
3 Japan Gastroenterological Endoscopy Society Postgraduate Education Committee. *Guidelines for Gastroenterological Endoscopy version 3*. Japan Gastroenterological Endoscopy Society (ed.). Tokyo: Igaku Shoin, 2006. (in Japanese.)
4 2008 Report of Joint Study Group. Guidelines on anticoagulant and antiplatelet therapy for cardiovascular illnesses 2009 revised edn. (in Japanese.) Available from URL: http://www.j-circ.or.jp/guideline/pdf/JCS2009_hori_d.pdf
5 Joint Guidelines Committee on Strokes. *2009 Stroke Therapy Guidelines*. Shinohara Y, Ogawa A, Suzuki N, Katayama Y, Kimura A (eds). Kyowa Kikaku, 2009. (in Japanese.)
6 Anderson MA, Ben-Menachem T, Gan SI *et al.* Guidelines: Management of antithrombotic agents for endoscopic procedures. *Gastrointest. Endosc.* 2009; **70**: 1060–70.
7 Becker R, Scheiman J, Dauerman HL *et al.* Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. *Am. J. Gastroenterol.* 2009; **104**: 2903–17.
8 Bhatt DL, Scheiman J, Abraham NS *et al.* ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008; **118**: 1894–909.
9 Veitch AM, Baglin TP, Gershlick AH *et al.* Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures. *Gut* 2008; **57**: 1322–29.
10 Boustière C, Veitch A, Vanbiervliet G *et al.* Endoscopy and antiplatelet agents. European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Endoscopy* 2011; **43**: 445–58.
11 Shiffman RN, Shekelle P, Overhage JM *et al.* Standardized reporting of clinical practice guidelines: A proposal from the Conference on Guideline Standardization. *Ann. Intern. Med.* 2003; **139**: 493–8.
12 Eddy DM. Designing a practice policy: Standards, guidelines and options. *JAMA* 1990; **263**: 3077–82.
13 Ueno F, Matsui T, Matsumoto T *et al.* Evidence-based clinical practice guidelines for Crohn's disease, integrated with formal consensus of experts in Japan. *J. Gastroenterol.* 2013; **48**: 31–72.
14 Takada T, Hirata K, Mayuki T *et al.* Cutting-edge information for the management of acute pancreatitis. *J. Hepatobiliary Pancreat. Sci.* 2010; **17**: 3–12.
15 Becker RC, Scheiman J, Dauerman HL *et al.* American College of Cardiology & American College of Gastroenterology: Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. *J. Am. Coll. Cardiol.* 2009; **54**: 2261–76.
16 Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. *Neurology* 2004; **62**: 1187–9.
17 Maulaz AB, Bezerra DC, Michel P *et al.* Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. *Arch. Neurol.* 2005; **62**: 1217–20.
18 Wahl MJ. Dental surgery in anticoagulated patients. *Arch. Intern. Med.* 1998; **158**: 1610–6.
19 Blacker DJ, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. *Neurology* 2003; **61**: 964–8.
20 Palareti G, Legnani C, Guazzaloca G *et al.* Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants–a prospective study. *Thromb. Haemost.* 1994; **72**: 222–6.
21 Kaneko E, Munakata A, Iwao Y *et al.* Preventing complications associated with colonic endoscopy. *Gastroenterol. Endosc.* 2003; **45**: 1939–45. (in Japanese.)
22 Eisen GM, Baron TH, Dominitz JA *et al.* American Society for Gastrointestinal Endoscopy: Guidelines on the management of antithrombotic and antiplatelet therapy for endoscopic procedures. *Gastrointest. Endosc.* 2002; **55**: 775–9.
23 Sieg A, Hachmoeller-Eisenbach U, Eisenbach T. Prospective evaluation of complications in outpatients GI endoscopy: A survey among German gastroendoscopists. *Gastrointest. Endosc.* 2000; **51**: 37–41.
24 Parra-Blanco A, Kaminaga N, Kojima T *et al.* Hemoclipping for postpolypectomy and postbiopsy colonic bleeding. *Gastrointest. Endosc.* 2000; **51**: 37–41.
25 Whitson MJ, Dikman AE, von Althann C *et al.* Is gastroduodenal biopsy safe in patients receiving aspirin and clopidogrel? *J. Clin. Gastroenterol.* 2011; **45**: 228–33.
26 Shiffman ML, Farrel MT, Yee YS. Risk of bleeding after endoscopic biopsy or polypectomy in patients taking aspirin or other NSAIDS. *Gastrointest. Endosc.* 1994; **40**: 458–62.
27 Ono S, Fujishiro M, Hirano K *et al.* Retrospective analysis on the management of anticoagulants and antiplatelet agents for scheduled endoscopy. *J. Gastroenterol.* 2009; **44**: 1185–9.
28 Tono S, Morita Y, Miura M *et al.* Risks associated with endoscopic biopsy procedures undertaken while administering antiplatelet drugs. *Gastroenterol. Endosc.* 2011; **53**: 3326–35. (in Japanese.)
29 Ono S, Fujishiro M, Kanzaki H *et al.* Conflicting clinical environment about the management of antithrombotic agents during the periendoscopic period in Japan. *J. Gastroenterol. Hepatol.* 2011; **26**: 1434–40.
30 Yousfi M, Gostout CJ, Baron TH *et al.* Postpolypectomy lower gastrointestinal bleeding: Potential role of aspirin. *Am. J. Gastroenterol.* 2004; **99**: 1785–9.
31 Gerson LB, Triadafilopoulos G, Gage BF. The management of anticoagulants in the periendoscopic period for patients with atrial fibrillation: A decision analysis. *Am. J. Gastroenterol.* 2000; **95**: 1717–24.

32 Gerson LB, Michaels L, Ullah N *et al.* Adverse events associated with anticoagulation therapy in the periendoscopic period. *Gastrointest. Endosc.* 2010; **71**: 1211–7.
33 Choudari CP, Rajgopal C, Palmer KR. Acute gastrointestinal haemorrhage in anticoagulated patients: Diagnoses and response to endoscopic treatment. *Gut* 1994; **35**: 464–6.
34 Yamamoto T, Kuyama Y, Kozuma K *et al.* Low-dose aspirin prolongs bleeding after gastric biopsy in Japanese patients. *Thromb. Res.* 2008; **122**: 722–3.
35 Yamamoto T, Kuyama Y, Kozuma K *et al.* Antiplatelet agents and bleeding time after endoscopic biopsy of the gastric antrum in Japanese patients. *Dig. Endosc.* 2010; **22**: 250.
36 Kim JS, Lee KS, Kim YI *et al.* A randomized crossover comparative study of aspirin, cilostazol and clopidogrel in normal controls: Analysis with quantitative bleeding time and platelet aggregation test. *J. Clin. Neurosci.* 2004; **11**: 600–2.
37 Yanagisawa A, Sakata K, Miyagawa M *et al.* Impact of ethyl icosapentate and ticlopidine combination therapy on hemorrhage time and platelet aggregation. *Clin. Rep.* 1992; **26**: 3193–8. (in Japanese.)
38 Mabe K, Hirayama M, Kato M. Withdrawal of anticoagulants and antiplatelet agents during endoscopy. *Gastroenterol. Endosc.* 2010; **52**: 2976–84. (in Japanese.)
39 Li Y, Sha W, Nie Y *et al.* Effect of intragastric pH on control of peptic ulcer bleeding. *J. Gastroenterol. Hepatol.* 2000; **15**: 148–54.
40 Baron TH, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: A metaanalysis of randomized, controlled trials. *Am. J. Gastroenterol.* 2004; **99**: 1455–60.
41 Hussain N, Alsulaiman R, Burtin P *et al.* The safety of endoscopic sphincterotomy in patients receiving antiplatelet agents: A case-control study. *Aliment. Pharmacol. Ther.* 2007; **25**: 579–84.
42 Mannen K, Tsunada S, Hara M *et al.* Risk factors for complications of endoscopic submucosal dissection in gastric tumors: Analysis of 478 lesions. *J. Gastroenterol.* 2010; **45**: 30–6.
43 Okada K, Yamamoto Y, Kasuga A *et al.* Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg. Endosc.* 2011; **25**: 98–107.
44 Ono S, Fujishiro M, Niimi K *et al.* Technical feasibility of endoscopic submucosal dissection for early gastric cancer in patients taking anti-coagulants or antiplatelet agents. *Dig. Liver Dis.* 2009; **41**: 725–8.
45 Tsuji Y, Ohata K, Ito T *et al.* Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J. Gastroenterol.* 2010; **16**: 2913–7.
46 Metz AJ, Bourke MJ, Moss A *et al.* Factors that predict bleeding following endoscopic mucosal resection of large colonic lesions. *Endoscopy* 2011; **43**: 506–11.
47 Tounou S, Morita Y. Risks associated with gastric and duodenal ESD under ongoing low dose aspirin therapy. *Gastroenterol. Endosc.* 2010; **53**: 3326–35. (in Japanese.)
48 Singh M, Mehta N, Murthy UK *et al.* Postpolypectomy bleeding in patients undergoing colonoscopy on uninterrupted clopidogrel therapy. *Gastrointest. Endosc.* 2010; **71**: 998–1005.
49 Uchiyama S, Demaerschalk BM, Goto S *et al.* Stroke prevention by cilostazol in patients with atherothrombosis: Meta-analysis of placebo-controlled randomized trials. *J. Stroke Cerebrovasc. Dis.* 2009; **18**: 482–90.
50 White RH, McKittrick T, Hutchinson R *et al.* Temporary discontinuation of warfarin therapy: Changes in the international normalized ratio. *Ann. Intern. Med.* 1995; **1**: 40–2.
51 Tsuji H. Clinical thrombosis and hemostasis techniques for interns III: Appropriate use of heparin formulations. *J. Thromb. Haemost.* 2008; **19**: 187–90. (in Japanese.)
52 Hirsh J, Warkentin TE, Shaughnessy SG *et al.* Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001; **119** (1 Suppl): 64S–94S.
53 Harrison L, Johnston M, Massicotte MP *et al.* Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann. Intern. Med.* 1997; **15**: 133–6.
54 Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch. Intern. Med.* 1994; **154**: 1449–57.
55 The European Atrial Fibrillation Trial Study Group. The optimal anticoagulation therapy in patients with non-rheumatic atrial fibrillation and recent cerebral ischemia. *N. Engl. J. Med.* 1995; **333**: 5–10.
56 Guerrouij M, Uppal CS, Alklabi A *et al.* The clinical impact of bleeding during oral anticoagulant therapy: Assessment of morbidity, mortality and post-bleed anticoagulant management. *J. Thromb. Thrombolysis* 2011; **31**: 419–23.
57 Hui AJ, Wong RM, Ching JY *et al.* Risk of colonoscopic polypectomy bleeding with anticoagulants and antiplatelet agents: Analysis of 1657 cases. *Gastrointest. Endosc.* 2004; **59**: 44–8.
58 Witt DM, Delate T, McCool KH *et al.* Incidence and predictors of bleeding or thrombosis after polypectomy in patients receiving and not receiving anticoagulation therapy. *J. Thromb. Haemost.* 2009; **7**: 1982–9.
59 Garcia DA, Regan S, Henault LE *et al.* Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch. Intern. Med.* 2008; **14**: 63–9.
60 Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. *Intern. Med.* 2001; **40**: 1183–8.
61 Constans M, Santamaria A, Mateo J *et al.* Low-molecular-weight heparin as bridging therapy during interruption of oral anticoagulation in patients undergoing colonoscopy or gastroscopy. *Int. J. Clin. Pract.* 2007; **61**: 212–7.
62 Connolly SJ, Ezekowitz MD, Yusuf S *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 2009; **361**: 1139–51.
63 Stangier J, Eriksson BI, Dahl OE *et al.* Pharmacokinetic profile of the oral direct thrombin inhibitor dabigatran etexilate in

healthy volunteers and patients undergoing total hip replacement. *J. Clin. Pharmacol.* 2005; **45**: 555–63.
64 Eikelboom JW, Wallentin L, Connolly SJ *et al.* Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011; **123**: 2363–72.
65 Watabe H, Yamaji Y, Okamoto M *et al.* Risk assessment for delayed hemorrhagic complication of colonic polypectomy: Polyp-related factors and patient-related factors. *Gastrointest. Endosc.* 2006; **64**: 73–8.
66 Goto O, Fujishiro M, Kodashima S *et al.* A second-look endoscopy after endoscopic submucosal dissection for gastric epithelial neoplasm may be unnecessary: A retrospective analysis of postendoscopic submucosal dissection bleeding. *Gastrointest. Endosc.* 2010; **71**: 241–8.
67 Fujimoto K, Fujishiro M, Kato M *et al.* Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Gastroenterol. Endosc.* 2012; **54**: 2075–102. (in Japanese.)

J Gastroenterol
DOI 10.1007/s00535-013-0896-9

The Japanese Society of Gastroenterology

ORIGINAL ARTICLE—ALIMENTARY TRACT

# A randomized, placebo-controlled, double-blind clinical trial of rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor: the G-PRIDE study

**Kazunari Tominaga · Mototsugu Kato · Hiroshi Takeda · Yasuyuki Shimoyama · Eiji Umegaki · Ryuichi Iwakiri · Kenji Furuta · Koichi Sakurai · Takeo Odaka · Hiroaki Kusunoki · Akihito Nagahara · Katsuhiko Iwakiri · Takahisa Furuta · Kazunari Murakami · Hiroto Miwa · Yoshikazu Kinoshita · Ken Haruma · Shin'ichi Takahashi · Sumio Watanabe · Kazuhide Higuchi · Motoyasu Kusano · Kazuma Fujimoto · Tetsuo Arakawa · G-PRIDE Study Group**

Received: 15 June 2013 / Accepted: 2 October 2013


**Abstract**
*Background* The aim of this study was to investigate the efficacy of rikkunshito (RKT), a traditional Japanese medicine, combined with proton pump inhibitor (PPI) in patients with PPI-refractory non-erosive reflux disease (NERD).
*Methods* Patients with PPI-refractory NERD ($n = 242$) were randomly assigned to the RKT group [rabeprazole (10 mg/day) + RKT (7.5 g/t.i.d.) for 8 weeks] or the placebo group (rabeprazole + placebo). After the 4- and 8-week treatments, we assessed symptoms and quality of life (QOL) using the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG), Gastrointestinal Symptom Rating Scale (GSRS), and Short-Form Health Survey-8 (SF-8).
*Results* There were no significant differences in FSSG and GSRS score improvement between these groups after the 4- and 8-week treatments. The mental component summary (MCS) scores of the SF-8 improved more in the RKT group (from 45.8 ± 8.1 to 48.5 ± 7.4) than in the placebo group (from 47.7 ± 7.1 to 48.4 ± 7.5) after the 4-week treatment ($P < 0.05$). The 8-week treatment with RKT was more effective for improvement of the degree of

K. Tominaga, M. Kato, H. Takeda, Y. Shimoyama, E. Umegaki, and R. Iwakiri contributed equally to this work.

ClinicalTrials.gov, Number UMIN000005880.

K. Tominaga · T. Arakawa (✉)
Department of Gastroenterology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka, Japan
e-mail: arakawat@med.osaka-cu.ac.jp

M. Kato
Division of Endoscopy, Hokkaido University Hospital, Sapporo, Japan

H. Takeda
Department of Pathophysiology and Therapeutics, Hokkaido University Faculty of Pharmaceutical Sciences, Sapporo, Japan

Y. Shimoyama · M. Kusano
Department of Endoscopy and Endoscopic Surgery, Gunma University Hospital, Maebashi, Japan

E. Umegaki · K. Higuchi
Second Department of Internal Medicine, Osaka Medical College, Takatsuki, Japan

R. Iwakiri
Department of Internal Medicine and Gastrointestinal Endoscopy, Saga Medical School, Saga, Japan

K. Furuta · Y. Kinoshita
Department of Gastroenterology and Hepatology, Shimane University School of Medicine, Izumo, Japan

K. Sakurai
Department of Gastroenterology, Kumamoto University Graduate School of Medicine, Kumamoto, Japan

T. Odaka
Department of Gastroenterology, Chiba University Graduate School of Medicine, Chiba, Japan

H. Kusunoki · K. Haruma
Department of Gastroenterology, Kawasaki Medical School, Kurashiki, Japan

A. Nagahara · S. Watanabe
Department of Gastroenterology, Juntendo University School of Medicine, Tokyo, Japan

K. Iwakiri
Department of Gastroenterology, Nippon Medical School Chiba Hokusoh Hospital, Inzai, Japan

Published online: 18 February 2014

MCS score in patients with a low body mass index (<22) ($P < 0.05$) and significantly improved the acid-related dysmotility symptoms of FSSG in female and elderly patients (≥65 years).

*Conclusion* There were no significant differences in improvement of GERD symptoms in patients with PPI-refractory NERD between these groups. However, RKT may be useful for improving mental QOL in non-obese patients and acid-related dyspeptic symptoms, especially in women and the elderly.

**Keywords** Gastroesophageal reflux · Quality of life · Non-erosive reflux disease · Herbal medicine · Alternative medicine

## Introduction

Recent epidemiological evidences suggest that the incidence of gastroesophageal reflux disease (GERD) is increasing in both Asian and Western countries [1, 2]. This phenomenon may be etiologically due to changes in environmental conditions, such as increased rates of metabolic disorders and decreased rates of *Helicobacter pylori* infection [3–6]. The essential pathophysiology of GERD involves the reflux of gastric contents, including gastric acid concomitant with transient lower esophageal sphincter relaxation (TLESR) [7]. Therefore, a mainstream therapeutic strategy for GERD involves the use of proton pump inhibitors (PPIs) to inhibit acid secretion [8]. However, in clinical practice, troublesome GERD symptoms persist in 20–30 % of patients despite daily treatment with a standard PPI dose [9]. In particular, the PPI resistance rate (40–50 %) in patients without erosion of the esophageal mucosa [non-erosive reflux disease (NERD)] was higher than that in patients with reflux esophagitis (RE) [10]. Therefore, the underlying mechanism of development of NERD is thought to differ from that of RE [2, 11].

It is widely recognized that the persistent GERD symptoms resulting from PPI resistance worsen quality of life (QOL) in patients with PPI-refractory NERD. However, such resistance in these patients may be caused by several factors, including esophageal mucosal hypersensitivity, bile acid reflux, abnormal esophageal motility, gastric motility disorders (gastric reservoir function or emptying), and mental disorders, rather than the acid reflux [2]. Double-dose PPI therapies are currently used in patients with severe RE [12]. Consequently, some regimens using prokinetic agents combined with PPIs have been tested to alleviate the disorders of gastric emptying and esophageal clearance associated with the pathophysiology of GERD [13]. However, these therapeutic regimens have not been proven useful for every type of GERD [8]. Therefore, a suitable and multi-selective therapeutic strategy is needed as soon as possible for such cases.

In Japan, the traditional medication rikkunshito (RKT), in the form of extracted granules for ethical use (product number TJ-43; Tsumura & CO., Tokyo, Japan), has been approved for medicinal use by the Japanese Ministry of Health and Welfare and is widely prescribed for patients with upper gastrointestinal (GI) symptoms [14]. A double-blind trial demonstrated the efficacy of RKT for attenuating upper GI symptoms, such as postprandial fullness, abdominal distention, and gastric discomfort, in patients with functional dyspepsia (FD) diagnosed according to Rome II criteria, which frequently overlaps with NERD [15]. RKT also has pharmacological action similar to that of prokinetic agents, as shown by its attenuation of the gastric dysmotility caused by a nitric oxide-synthesizing enzyme inhibitor and exogenous serotonin [16–18]. In clinical studies, RKT improved nausea in children with GERD by both increasing esophageal clearance and decreasing esophageal acid exposure in a 24-h pH study [19]. These findings suggested the possible therapeutic efficacy of RKT in the treatment of patients with GERD. Based on this, we performed a clinical study and revealed that RKT combined with the standard-dose rabeprazole (RPZ) improved GERD symptoms in patients with PPI-refractory GERD, similar to the effects seen in treatment with a double dose of RPZ in a randomized, parallel comparative study [20]. We think these data must supply one regimen of appropriate therapeutic strategies for the patients. However, if further studies are performed progressively to confirm and/or reconfirm the clinical efficacy of RKT at the next step, an RCT (RKT with PPI vs. placebo with PPI) must be usually conducted. Therefore, we conducted the present study [the Gastroenterology groups-Treatment for PPI-refractory GERD with Rikkunshito: A Multicenter, Randomized, Placebo-controlled, Double-

T. Furuta
Center for Clinical Research, Hamamatsu University School of Medicine, Hamamatsu, Japan

K. Murakami
Department of Gastroenterology, Faculty of Medicine, Oita University, Yufu, Japan

H. Miwa
Division of Upper Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

S. Takahashi
The Third Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

K. Fujimoto
Department of Internal Medicine, Saga Medical School, Saga, Japan

blinded Trial (G-PRIDE)], in which we compared RKT with placebo to verify its therapeutic effects in PPI-refractory NERD.

## Methods

### Subjects

At first, before PPI medication, we have confirmed predominant symptoms of all recruited patients. After confirming that their predominant symptoms were heartburn or regurgitation but not dyspeptic symptoms as a chief complaint, we performed endoscopic examination for all candidate patients to confirm visible esophageal mucosal injury. Next, patients with PPI-refractory NERD (without visible esophageal mucosal injury) were defined as those with persistent GERD symptoms (FSSG score $\geq$8) despite a prior therapy with a standard PPI dose (RPZ 10 mg/day, omeprazole 20 mg/day, or lansoprazole 30 mg/day) for $\geq$4 weeks, because it has been reported that sensitivity, specificity, and accuracy of the FSSG questionnaire were 62, 59, and 60 % in patients with GERD and non-GERD when the cutoff score was set at 8 points as well as most clinical study for patients with GERD symptoms [21]. As a result, 242 patients with PPI-refractory NERD were enrolled in this study from August 2011 to July 2012. Therefore, enrolled patients with PPI-refractory NERD met the following selection criteria: (1) were >20 years of age; (2) had received standard-dose PPI therapy for $\geq$4 weeks before the start of this study for the treatment of NERD; (3) had an FSSG score $\geq$8 after standard-dose PPI therapy for $\geq$4 weeks; (4) planned to receive RPZ (10 mg/day) treatment for $\geq$8 weeks; and (5) provided written informed consent regarding study participation. Exclusion criteria were as follows: (1) esophageal mucosal erosion in endoscopy carried out within 6 months before the registration; (2) the presence of serious complications (liver, kidney, heart, blood, or metabolic disorders); (3) having undergone resection of the upper digestive tract; (4) confirmed presence of a peptic ulcer (excluding ulcer scar) or malignant tumor of the upper digestive tract; (5) inflammatory bowel disease, irritable bowel syndrome (IBS), esophageal stenosis, or esophageal achalasia; (6) diagnosis of a GI motility disorder by the study investigator; (7) suspected organic hepatic/biliary/pancreatic disorders, such as gallstone, hepatitis, and pancreatitis; (8) hemorrhage of the digestive tract, mechanical ileus, or perforation of the digestive tract; (9) taking drugs prohibited for concomitant use (such as anti-ulcer drugs except for rabeprazole, prokinetics, other kampo medicines except for RKT) during the observation period; (10) psychoneurosis; (11) receiving or scheduled to receive an agent that is being developed; (12) lactation, pregnancy, or planned pregnancy during the study or follow-up period; (13) intolerance to oral administration; (14) history of allergy for kampo medicine; and (15) considered ineligible to participate by the chief investigator.

### Study design

This study (UMIN000005880) was a multicenter, randomized, double-blinded, placebo-controlled study that examined the pharmacological efficacy and safety of drug therapy in patients with PPI-refractory NERD in 55 hospitals in Japan. It was performed in accordance with the ethical guidelines for clinical studies and considered the patients' human rights and privacy. The study protocol was approved by the institutional review board of each institution.

### Sample size

The primary variable was FSSG score improvement, and the sample size was obtained as follows: in our previous clinical study [20], 4-week treatment with RKT combined with a standard RPZ dose (10 mg/day) decreased the total FSSG score from 17.6 $\pm$ 6.5 (before treatment) to 12.0 $\pm$ 6.9 in patients with PPI refractory NERD, and the score difference of each case (the effectiveness) was 5.1 $\pm$ 4.8. Additionally, 4-week treatment with double-dose RPZ (20 mg/day) decreased the total FSSG score from 15.5 $\pm$ 7.3 to 10.6 $\pm$ 9.0, and the score difference of each case was 4.0 $\pm$ 7.5. No reports to date have evaluated the efficacy of 4- and 8-week treatments with placebo combined with standard dose RPZ using an FSSG questionnaire. However, Muro et al. [22] evaluated the efficacy of 4- and 8-week treatment with standard dose RPZ in patients with scleroderma and GERD symptoms using an FSSG questionnaire. In that report, the score difference from the 4-week to 8-week treatment was 2.1. Based on this information, we presumed that the score difference was 5.1 and 2.1 in the RKT group and the placebo group, respectively. The standard deviation (SD) adopted 7.5, the maximum value in the previous study. The sample size was based on two-tailed test with a significance level of 0.05, a power level of 0.80, and an anticipated effect size $d$ = difference of means/standard deviation = 7.5. The required sample size was 100 in each group. We assumed 20 % fall off in this trial, and we set a required sample size of 120 in each group for a total of 240 participants.

### Randomization

Patients were randomized to receive RPZ (10 mg once daily) + RKT (7.5 g/day 3 times) (RKT group) or RPZ

(10 mg once daily) + placebo (7.5 g/day 3 times) (placebo group) for 8 weeks according to a computer-generated randomization list provided by a statistician of the site management organization (SMO) (Sogo Rinsho Holdings Co., Ltd, Tokyo, Japan). The placebo was produced with a similar smell and taste to RKT. The RKT and placebo granulated powders appeared identical and were identically packaged and labeled by the SMO to maintain blinding. Patients, investigators, and all other personnel involved in the conduct of the study were blind to treatment. At the baseline period (0 week), eligible patients were assigned a randomization number. These numbers were allocated in sequential order and registered in the patient enrolment center (Sogo Rinsho Holdings) and the allocation was concealed. Emergency envelopes containing the randomization code were kept under lock and key by an SMO (Sogo Rinsho Holdings) and were examined at the end of the trial to ensure that trial blinding had been maintained.

### Study procedures and questionnaire

After written informed consent was obtained from the study participants, the patients with PPI-refractory NERD who met the inclusion criteria and did not meet the exclusion criteria were recruited for this study. Patients were randomly assigned to the RKT group [RPZ (10 mg/day) + RKT (7.5 g/t.i.d.) for 8 weeks] or the placebo group (RPZ + placebo for 8 weeks). RKT was used in the form of a powdered extract obtained by spray drying a hot water extract mixture of the following eight crude herbs: *Atractylodis lanceae rhizoma* (4.0 g), *Ginseng radix* (4.0 g), *Pinelliae tuber* (4.0 g), *Hoelen* (4.0 g), *Zizyphi fructus* (2.0 g), *Aurantii nobilis pericarpium* (2.0 g), *Glycyrrhizae radix* (1.0 g), and *Zingiberis rhizoma* (0.5 g). The fingerprint pattern provided by 3-dimensional high-performance liquid chromatography revealed that RKT contains several low molecular compounds (i.e., hesperidin, liquilitin, liquiritigenin, isoliquilitin, isoliquiritigenin, formononetin glycycoumarin, glycyrrhizin, atractylodin, atractylodinol, 6-shogaol, and 6-gingerol) [18].

Before and after the 4- and 8-week treatments, GERD symptoms were evaluated using the FSSG questionnaire, and GI-related QOL and health-related QOL were evaluated using the Japanese version of the Gastrointestinal Symptom Rating Scale (GSRS), and the acute version of the Short-Form Health Survey-8 (SF-8) questionnaires, similar to what was commonly used in earlier clinical reports [23–26]. The FSSG questionnaire comprises 12 items in two domains: the reflux symptom (RS) domain, in which the sums of the respective scores of items 1, 4, 6, 7, 9, 10, and 12 are calculated; and the acid-related dysmotility symptom (ARD) domain, in which the sums of the respective scores of items 2, 3, 5, 8, and 11, are calculated. The scores were calculated according to the frequency of the symptoms as follows: never, 0; occasionally, 1; sometimes, 2; often, 3; and always, 4, as previously reported. The total score is given by the sum of the RS and ARD scores, and total scores $\geq 8$ indicated probable GERD, as previously validated [21].

The GSRS questionnaire is an inquiry table consisting of 15 items for the evaluation of general GI symptoms. Each GSRS item is rated on a 7-point Likert scale from no discomfort to very severe discomfort. Based on a factor analysis, the 15 GSRS items break down into the following five scales: abdominal pain (abdominal pain, hunger pain, and nausea), reflux syndrome (heartburn and acid regurgitation), diarrhea syndrome (diarrhea, loose stools, and urgent need for defecation), indigestion syndrome (borborygmus, abdominal distension, eructation, and increased flatus), and constipation syndrome (constipation, hard stools, and a feeling of incomplete evacuation).

The SF-8 comprises eight subscales (PF, physical functioning; RP, role limitation due to physical problems; BP, body pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitation due to emotional problems; and MH, mental health). The eight scales are hypothesized to form two distinct, higher-ordered physical and mental health variances. Three scales (PF, RP, and BP) correlate most highly with the physical component and contribute most to the scoring of the physical component summary (PCS) measure. Three scales (MH, RE, and SF) correlated most highly with mental health. VT, GH, and SF had noteworthy correlations with both components. The PCS and mental health component summary (MCS) scores were calculated using a scoring program.

### Primary efficacy endpoints

The primary endpoint consisted of the degree of improvement of FSSG, GSRS, and SF-8 scores after treatment. The degree of improvement was calculated based on the FSSG, GSRS or SF-8 score before and after treatment, using the following mentioned formula. To compare the effects between the two groups, the mean improvement degree was used:

(FSSG and GSRS) improvementdegree($\Delta$)
= [prescores]−[postscores],
(SF - 8) improvement degree($\Delta$) = [postscores]−[prescores]
Prescores: Scores before the start of RPZ + RKT or RPZ + placebotreatment;
Postscores: Scores 4 weeks or 8 weeks after treatment with RPZ + RKT or RPZ + placebo treatment.

### Subgroup analysis and factor analyses related to the RKT responders

Subgroup analysis was pre-planned to perform with respect to each subject's background factors such as age (≥65, ≤64 years), gender (male, female), body mass index (BMI; ≥22, <22). Regarding BMI, we set the cutoff value at 22 for the following reasons. One is that the average BMI for the Japanese general population is about 22. Secondly, we wanted to divide the recruited patients into two groups because that gave a number similar to the other factors (age and sex). Furthermore, features regarding RKT efficacy were examined via classification as ARD and RS scores of the FSSG.

### Adverse events, safety, and tolerability

Safety and tolerability were assessed by recording all adverse events, and changes in hematological and clinical laboratory variables were measured at the screening visit and after the post dose esophagogastroduodenoscopy. An adverse event was defined as any unfavorable or unintended sign, even if it was considered to be causally related to the drugs used in this study.

### Compliance

Treatment compliance was defined as the percentage of the test drug used. A treatment compliance of at least 66.6 % was considered acceptable, as in our previous study [20].

### Statistical analysis

The data obtained from this study were analyzed by a biostatistician of the SMO (Sogo Rinsho Holdings Co.). The efficacy analysis was based on the full analysis set (FAS) population. The primary efficacy variable in each subject was calculated from these scores, and the mean values were compared between the two groups using the Wilcoxon rank-sum test. We employed the *t* test to compare background factors, such as age and BMI. The distributions of gender, current alcohol use, current smoking, and *H. pylori* infection assessed by serum antibody or urea breath test etc., gastric mucosal atrophy, gastric mucosa redness, impaired gastroesophageal flap valve (GEFV) [27], and endoscopic hiatal hernia were compared using Fisher's exact test. Values of $P < 0.05$ were considered significant. The statistically significant differences between each paired group were analyzed using the Mann–Whitney *U*, the repeated measures ANOVA was used for the corrections in multiple comparisons for FSSG, GSRS and SF-8 scores after treatments, and the Steel–Dwass post hoc test was used for the corrections in multiple comparisons for the improvement degree of FSSG, GSRS and SF-8 scores after treatment. All data are expressed as mean ± standard deviation (SD).

## Results

### Background of patients enrolled in the study

There were no marked differences in baseline demographics or clinical characteristics in the two groups except for the rate of current smoking. Furthermore, there were no differences in total FSSG, total GSRS, or SF-8 scores before the start of treatment between the two groups (Table 1).

**Table 1** Patients background factors in the two groups

| | RKT group ($n = 109$) | Placebo group ($n = 108$) | *P* value |
|---|---|---|---|
| Mean age, years (range) | 62.1 (25–85) | 59.4 (22–83) | 0.174[a] |
| Gender, *n* (M/F) | 35/74 | 28/80 | 0.370[b] |
| BMI (mean ± SD) | 22.7 ± 4.0 | 23.0 ± 3.8 | 0.574[a] |
| Current alcohol use, *n* (%) | 22 (20.2) | 26 (24.1) | 0.517[b] |
| Current smoking, *n* (%) | 14 (12.8) | 4 (3.7) | 0.024[b] |
| *Helicobacter pylori*-infection, *n* (%) | 20 (18.3) | 13 (12.0) | 0.115[b] |
| Gastric mucosal atrophy, *n* (%) | 69 (63.3) | 56 (51.9) | 0.096[b] |
| Redness of gastric mucosa, *n* (%) | 14 (12.8) | 7 (6.5) | 0.168[b] |
| Impaired GEFV, *n* (%) (grade III, IV) | 29 (26.6) | 23 (21.3) | 0.173[b] |
| Esophageal hiatal hernia, *n* (%) (grade B and A) | 51 (45.9) | 44 (40,7) | 0.459[b] |
| Concomitant systemic diseases, *n* (%), (with) | 60 (55.0) | 56 (51.9) | 0.785[b] |
| Total FSSG score (mean ± SD) | 17.1 ± 8.1 | 16.5 ± 7.0 | 0.895[c] |
| Overall GSRS score (mean ± SD) | 2.5 ± 0.9 | 2.5 ± 0.8 | 0.624[c] |
| SF-8 PCS score (mean ± SD) | 44.7 ± 6.9 | 45.8 ± 7.5 | 0.114[c] |
| SF-8 MCS score (mean ± SD) | 45.8 ± 8.1 | 47.7 ± 7.1 | 0.057[c] |

*BMI* body mass index, *GEFV* gastroesophageal flap valve, *FSSG* Frequency Scale for the Symptoms of GERD, *GSRS* Gastrointestinal Symptom Rating Scale, *SF-8* Short-Form Health Survey-8, *PCS* physical component summary, *MCS* mental component summary

[a] *t* test

[b] Fisher's exact test

[c] Wilcoxon rank-sum test

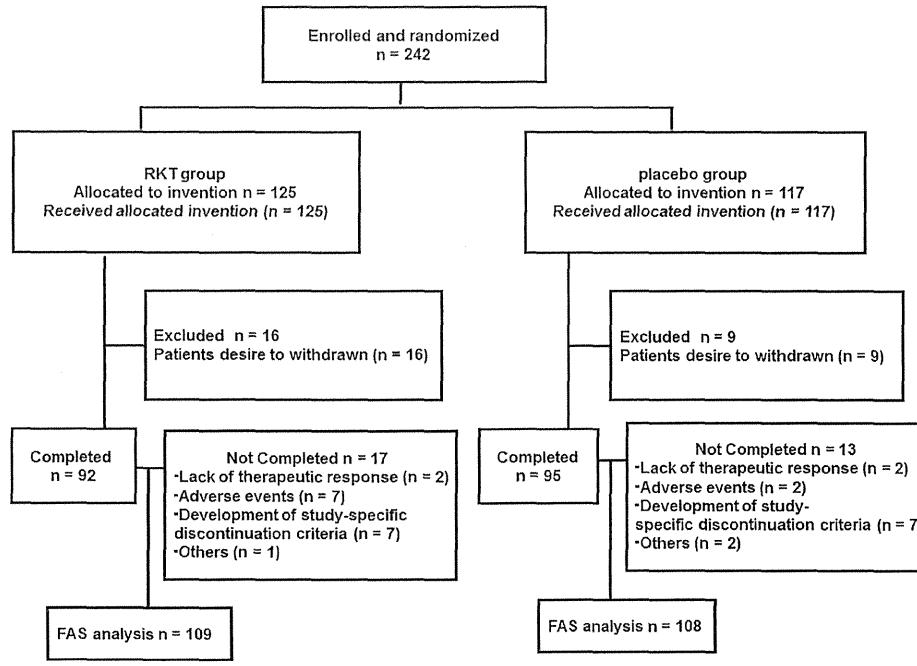


**Fig. 1** Flow of patients throughout the present study. *FAS* full analysis set, *RKT group* RKT (7.5 g/day 3 times) + RPZ (10 mg/day), *placebo group* placebo (7.5 g/day 3 times) + RPZ (10 mg/day)

### Changes in the number of registered patients

Two hundred forty-two patients were randomly assigned to the RKT group ($n = 125$) or the placebo group ($n = 117$) (Fig. 1). Twenty-five patients were excluded from the efficacy assessment because they withdrew from the study after registration. Thus, 217 patients (RKT group: 109, placebo group: 108) were included in the full analysis set (FAS). The number of patients who completed the trial in the RKT group and the placebo group was 92 and 95, respectively.

### Changes in FSSG, GSRS, and SF-8 scores after treatments

The pretreatment and posttreatment scores of FSSG, GSRS, and SF-8 in each group are shown in Table 2. In both groups, the total FSSG and total GSRS scores were significantly decreased after the 4- and 8-week treatment compared to that before treatment ($P < 0.001$). The SF-8 PCS scores in both groups were significantly increased after the 8-week treatment compared to that before treatment. The SF-8 MCS score in the RKT group was significantly increased after the 4- and 8-week treatments, while that in the placebo group was significantly increased after the 8-week treatment compared to the before treatment. There were no significant differences in each score in the 4- and 8-week treatments between the two groups.

### Primary efficacy endpoints

Improvement degrees of FSSG, GSRS, and SF-8 scores in each group are presented in Table 3. The improvement degree of the SF-8 MCS score were significantly higher in the RKT group than in the placebo group after the 4-week treatment ($2.9 \pm 7.8$ vs. $0.8 \pm 7.6$, $P = 0.033$) (Table 3; Fig. 2d). In the 8-week treatment, a similar tendency was observed between the two groups ($3.1 \pm 7.7$ vs. $1.4 \pm 6.6$, $P = 0.099$) (Table 3). However, there were no significant differences in the degrees of improvement of the FSSG, GSRS, and SF-8 PCS scores between the two groups after the 4- and 8-week treatments (Table 3; Fig. 2a–c).

### Subgroup analysis of FSSG, GSRS, and SF-8 scores

Subgroup analyses of FSSG, GSRS, and SF-8 scores of the 8-week treatment were performed based on age ($\geq$65, $\leq$64 years), gender (male, female), and BMI ($\geq$22, <22). In elderly patients, the improvement degree of the ARD scores of FSSG was significantly higher in the RKT group ($3.8 \pm 3.7$) than in the placebo group ($0.8 \pm 3.1$) ($P < 0.001$) (Fig. 3a). In contrast, in younger patients, the improvement degree of the ARD scores of FSSG was significantly higher in the placebo group than in the RKT group ($P < 0.05$) (Fig. 3a). The improvement degree of the ARD scores of FSSG for female patients in the RKT group ($3.3 \pm 3.6$) was significantly higher than that observed in

**Table 2** FSSG, GSRS and SF-8 scores after treatments

| | Week | Mean ± SD (*n*) | | | | *P* value |
|---|---|---|---|---|---|---|
| | | RKT group | | Placebo group | | |
| FSSG | | | | | | |
| Total | 0 | 17.1 ± 8.1 | (107) | 16.5 ± 7.0 | (102) | 0.962 |
| | 4 | 11.8 ± 8.4*** | (99) | 11.5 ± 7.4*** | (98) | 0.903 |
| | 8 | 9.4 ± 8.2*** | (88) | 10.5 ± 8.1*** | (89) | 0.232 |
| RS | 0 | 9.5 ± 5.3 | (107) | 9.2 ± 4.4 | (104) | 0.793 |
| | 4 | 6.3 ± 5.3*** | (102) | 6.1 ± 4.4*** | (99) | 0.978 |
| | 8 | 4.9 ± 5.0*** | (91) | 5.5 ± 4.4*** | (92) | 0.117 |
| ARD | 0 | 7.5 ± 4.0 | (109) | 7.2 ± 3.9 | (104) | 0.739 |
| | 4 | 5.6 ± 3.9*** | (99) | 5.6 ± 4.0** | (103) | 0.701 |
| | 8 | 4.5 ± 3.8*** | (89) | 5.1 ± 4.1*** | (93) | 0.480 |
| GSRS | | | | | | |
| Overall | 0 | 2.5 ± 0.9 | (107) | 2.5 ± 0.8 | (108) | 0.509 |
| | 4 | 2.1 ± 0.9*** | (103) | 2.1 ± 0.6*** | (104) | 0.410 |
| | 8 | 1.9 ± 0.7*** | (92) | 1.9 ± 0.6*** | (94) | 0.487 |
| Reflex syndrome | 0 | 3.2 ± 1.4 | (107) | 2.9 ± 1.3 | (108) | 0.075 |
| | 4 | 2.2 ± 1.2*** | (103) | 2.2 ± 1.0*** | (105) | 0.941 |
| | 8 | 2.0 ± 1.1*** | (92) | 2.1 ± 1.1*** | (94) | 0.559 |
| Abdominal pain | 0 | 2.3 ± 1.1 | (108) | 2.3 ± 1.1 | (108) | 0.944 |
| | 4 | 1.9 ± 1.0** | (103) | 1.9 ± 1.0*** | (105) | 0.742 |
| | 8 | 1.7 ± 0.9*** | (92) | 1.8 ± 0.9*** | (94) | 0.376 |
| Indigestion syndrome | 0 | 2.7 ± 1.2 | (108) | 2.6 ± 1.0 | (108) | 0.424 |
| | 4 | 2.4 ± 1.2 | (103) | 2.3 ± 0.9** | (104) | 0.552 |
| | 8 | 2.1 ± 0.9*** | (92) | 2.2 ± 0.9*** | (94) | 0.381 |
| Diarrhea syndrome | 0 | 1.8 ± 1.0 | (108) | 2.0 ± 1.3 | (108) | 0.486 |
| | 4 | 1.8 ± 1.1 | (103) | 1.7 ± 0.9 | (104) | 0.814 |
| | 8 | 1.6 ± 0.9 | (92) | 1.5 ± 0.7** | (94) | 0.866 |
| Constipation syndrome | 0 | 2.6 ± 1.5 | (108) | 2.4 ± 1.2 | (108) | 0.727 |
| | 4 | 2.2 ± 1.3** | (103) | 2.3 ± 1.0 | (104) | 0.269 |
| | 8 | 2.0 ± 1.0*** | (92) | 2.0 ± 0.9* | (94) | 0.626 |
| SF-8 | | | | | | |
| PCS | 0 | 44.7 ± 6.9 | (107) | 45.8 ± 7.5 | (107) | 0.155 |
| | 4 | 46.6 ± 6.6 | (102) | 46.6 ± 6.9 | (105) | 0.685 |
| | 8 | 47.3 ± 6.4* | (93) | 46.9 ± 6.5 | (92) | 0.754 |
| MCS | 0 | 45.8 ± 8.1 | (107) | 47.7 ± 7.1 | (107) | 0.102 |
| | 4 | 48.5 ± 7.4** | (102) | 48.4 ± 7.5 | (105) | 0.747 |
| | 8 | 49.2 ± 6.9*** | (93) | 49.1 ± 6.8 | (92) | 0.953 |

*FSSG* Frequency Scale for the Symptoms of GERD, *RS* reflux symptom, *ARD* acid-related dysmotility, *GSRS* Gastrointestinal Symptom Rating Scale, *SF-8* Short-Form Health Survey-8, *PCS* physical component summary, *MCS* mental component summary

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ significant differences compared with baseline value (0 week) (repeated measures ANOVA). The statistically significant differences between each paired group were analyzed using the Mann–Whitney *U* analysis and the repeated measures ANOVA for the corrections in multiple comparisons

the placebo group (2.1 ± 3.4) (Fig. 3b). There were no BMI-related differences in FSSG scores between the two groups (Fig. 3c). In patients with a low BMI (<22), the improvement degree of the SF-8 MCS scores was significantly higher in the RKT group (4.3 ± 7.9) than in the placebo group (1.1 ± 5.3) ($P < 0.001$) (Fig. 4c). However, there were no differences in subgroup analyses of GSRS based on age, gender, and BMI between the groups (data not shown). Other factors, such as alcohol use, smoking, *H. pylori* infection, gastric mucosal atrophy, gastric mucosa redness, impaired GEFV, and esophageal hiatal hernia, were not associated with treatment efficacy.

**Table 3** Improvement degree of FSSG, GSRS and SF-8 scores after treatments

| | Week | RKT group mean ± SD (n) | Placebo group mean ± SD (*n*) | *P* value |
|---|---|---|---|---|
| FSSG | | | | |
| ΔTotal | 4 | 5.1 ± 6.9 (97) | 4.6 ± 6.2 (93) | 0.703 |
| | 8 | 7.1 ± 6.8 (87) | 6.1 ± 7.0 (85) | 0.689 |
| ΔRS | 4 | 3.2 ± 4.4 (100) | 3.1 ± 4.2 (96) | 0.736 |
| | 8 | 4.3 ± 4.5 (90) | 3.9 ± 4.6 (90) | 0.738 |
| ΔARD | 4 | 1.8 ± 3.6 (99) | 1.5 ± 3.0 (100) | 0.672 |
| | 8 | 2.8 ± 3.5 (89) | 2.2 ± 3.4 (91) | 0.342 |
| GSRS | | | | |
| ΔOverall | 4 | 0.4 ± 0.9 (101) | 0.4 ± 0.8 (104) | 0.726 |
| | 8 | 0.6 ± 0.8 (90) | 0.6 ± 0.8 (94) | 0.816 |
| ΔReflex syndrome | 4 | 1.0 ± 1.5 (101) | 0.8 ± 1.3 (105) | 0.369 |
| | 8 | 1.2 ± 1.4 (90) | 0.9 ± 1.4 (94) | 0.559 |
| ΔAbdominal pain | 4 | 0.4 ± 1.1 (102) | 0.5 ± 1.0 (105) | 0.717 |
| | 8 | 0.5 ± 1.1 (91) | 0.5 ± 1.0 (94) | 0.376 |
| ΔIndigestion syndrome | 4 | 0.3 ± 1.2 (102) | 0.3 ± 1.0 (104) | 0.820 |
| | 8 | 0.5 ± 1.0 (91) | 0.4 ± 1.1 (94) | 0.381 |
| ΔDiarrhea syndrome | 4 | 0.1 ± 1.1 (102) | 0.3 ± 1.2 (104) | 0.199 |
| | 8 | 0.2 ± 1.1 (91) | 0.5 ± 1.2 (94) | 0.866 |
| ΔConstipation syndrome | 4 | 0.4 ± 1.0 (102) | 0.2 ± 1.0 (104) | 0.245 |
| | 8 | 0.6 ± 1.1 (91) | 0.4 ± 1.0 (94) | 0.626 |
| SF-8 | | | | |
| ΔPCS | 4 | 1.9 ± 6.8 (100) | 0.7 ± 7.4 (104) | 0.277 |
| | 8 | 2.4 ± 6.4 (92) | 1.2 ± 7.4 (92) | 0.454 |
| ΔMCS | 4 | 2.9 ± 7.8 (100) | 0.8 ± 7.6 (104) | 0.033 |
| | 8 | 3.1 ± 7.7 (92) | 1.4 ± 6.6 (92) | 0.099 |

*FSSG* Frequency Scale for the Symptoms of GERD, *RS* reflux symptom, *ARD* acid-related dysmotility symptom, *GSRS* Gastrointestinal Symptom Rating Scale, *SF-8* Short-Form Health Survey-8, *PCS* physical component summary, *MCS* mental component summary

The statistically significant difference between each paired group was analyzed using the Steel–Dwass post hoc test for the corrections in multiple comparisons

### Safety

Adverse events were reported by 19 of 109 patients (17.4 %) receiving RKT and 11 of 108 patients (10.2 %) receiving placebo. Nausea, mild cough, dizziness, and diarrhea were the most commonly reported adverse events. Only one serious adverse event was reported: dizziness occurred in one of 109 patients (0.9 %) treated with RKT, but it was judged as not being treatment-related. No serious adverse events were reported in the 108 patients receiving placebo (data not shown).

## Discussion

The results of the present study—a multicenter, randomized, double-blind, placebo-controlled study to examine the pharmacological efficacy and safety of drug therapy in patients with PPI-refractory NERD in 55 hospitals in Japan—demonstrated that RKT may help improve mental QOL in non-obese patients with PPI-refractory NERD and acid-related dyspeptic symptoms, especially female and elderly patients.

It is widely recognized that patients with NERD respond less to PPI treatment than patients with RE [28]. A double dose of PPI or switching to another kind of PPI is recommended in these cases [29]. However, our earlier study demonstrated that a combination of RKT and RPZ improves troublesome symptoms of PPI-refractory NERD similar to double doses of RPZ [20]. We think these data must supply one of the appropriate therapeutic options in curing PPI-refractory NERD patients. On the other hand, a double dose of PPI can also cure PPI-refractory NERD patients. However, a double dose of PPI is not necessarily used for a long time because of the Japanese insurance system, and it is not always effective for every PPI-refractory NERD patient because of poor QOL. Accordingly, we conducted the present study (the G-PRIDE study)