

On-demand Versus Continuous Maintenance Treatment of Gastroesophageal Reflux Disease With Proton Pump Inhibitors: A Systematic Review and Meta-analysis

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Background/Aims

Long-term maintenance treatment of gastroesophageal reflux disease (GERD) is commonly used to prevent relapse of reflux symptoms; however, due to concerns about safety of long-term proton pump inhibitors (PPI) use, on-demand therapy is recommended as a long-term treatment modality. We compared the efficacy of on-demand and continuous PPI therapy for maintenance treatment of patients with GERD using meta-analysis.

Methods

Core electronic databases were searched for randomized controlled trials comparing on-demand and continuous therapy in GERD patients. The primary outcome was treatment failure of maintenance therapy, and the secondary outcomes included symptomatic relief, patient satisfaction, and amount of PPI use.

Results

Overall, 11 studies were selected in the systematic review and meta-analysis. Compared with continuous PPI therapy, on-demand therapy showed similar outcomes for treatment failure (risk ratio, 1.26; 95% confidence interval [CI], 0.76-2.07), particularly in the non-erosive esophageal reflux disease and mild erosive reflux disease group (risk ratio, 1.48; 95% CI, 0.39-5.63). In studies including severe esophagitis patients, continuous PPI maintenance treatment was more effective (β , 0.127 [95% CI, 0.066-0.188]; $P < 0.001$). Severity of esophagitis was associated with higher efficacies of continuous maintenance therapy. The amount of daily PPI use was about half in the on-demand group compared to the continuous group (risk difference -0.52 ; 95% CI, -0.62 – -0.42).

Conclusions

On-demand PPI therapy shows comparable efficacy to the continuous maintenance treatment in the non-erosive esophageal reflux disease and mild erosive reflux disease group, and can remarkably reduce the amount of PPI use. Therefore, on-demand therapy may be preferentially recommended in the maintenance treatment of GERD unaccompanied by severe esophagitis.

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Key Words

Gastroesophageal reflux; Maintenance; Proton pump inhibitors

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Introduction

Gastroesophageal reflux disease (GERD) is a chronic digestive disorder resulting from the reflux of gastric contents into the esophagus that is often accompanied by troublesome symptoms of heartburn, acid regurgitation, or other extra-esophageal symptoms such as chest pain, chronic cough, hoarseness or globus.¹ GERD imposes an important burden of illness worldwide with an estimated worldwide prevalence of between 8% and 33%.² GERD is heterogeneous and presented with different phenotypes. Erosive reflux disease (ERD) is defined as mucosal defect by endoscopy and occurs in approximately 25% of patients with GERD symptoms.³ Non-erosive reflux disease (NERD) is present in approximately 70% of patients and is characterized by the presence of typical GERD symptoms associated with pathological acid reflux but the absence of demonstrable esophageal mucosal injury on endoscopy.⁴

Currently, acid suppressive therapy with proton pump inhibitors (PPIs) has proved to be the most effective treatment strategy for GERD patients and is recommended as a first-line treatment.⁵ PPIs have shown superiority over histamine H₂-receptor antagonists for controlling symptoms as well as for healing erosions.⁶ Although symptomatic relief and acute healing of esophageal lesions can be achieved by short-term PPI treatments, up to 75% of patients with NERD and up to 90% of patients with ERD experience relapse within 6 months to 1 year after termination of initial treatments.⁷ Therefore, long-term continuous maintenance treatment with PPIs is required for the majority of patients with GERD to adequately control symptoms and to heal mucosal lesions. However, recent studies suggest that long-term PPI treatment can increase the risk of *Clostridium difficile* or other enteric infection, kidney disease, bone fractures, or micronutrient deficiency.⁸ In addition to safety issues, continuous maintenance may have led to unnecessary use of PPIs, increasing overall costs. In the United States, the total expenditure for PPI treatment was over \$11 billion annually.⁹ Therefore, maintenance therapy such as “on-demand” PPI therapy or “intermittent” PPI therapy have been used in clinical practice and their effectiveness has also been studied. On-demand PPI therapy means that patients take a daily dose of a PPI when symptoms recur and stop medication when symptoms resolve. Intermittent PPI therapy is when patients take a regular daily dose of a PPI upon symptom relapse and continue for a pre-specified duration, which is typically 1 or 2 weeks regardless of symptom response. To date, there have been 2 meta-analysis studies comparing on-demand and continuous PPI therapy. Boghossian et al¹⁰

performed a meta-analysis to compare the effects of continuous PPI therapy with stopping or on-demand PPI therapies in 2017.¹⁰ The authors concluded that on-demand PPI therapy may increase risk of “lack of symptom control” compared with continuous PPI use (risk ratio [RR], 1.71; 95% confidence interval [CI], 1.31-2.21), which means lower efficacy of on-demand therapy. However, Khan et al¹¹ reported that on-demand PPI therapy was superior to continuous PPI use in terms of treatment failure (RR, 1.71; 95% CI, 1.31-2.21) in patients with NERD and mild erosive esophagitis.¹¹ These 2 meta-analysis results have drawn conflicting conclusions. Therefore, in this meta-analysis, we intended to comprehensively analyze the treatment failure rates, patient satisfaction, the amount of PPI usage, and symptom relief effects between on-demand PPI and continuous maintenance by synthesizing the studies for GERD patients. In addition, we performed meta-regression to determine whether there is a difference in the effectiveness of 2 treatments according to the presence and severity of ERD and ethnicities.

Materials and Methods

This meta-analysis was conducted in accordance with the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.¹² The need for approval from the institutional review board was waived since this study was performed by reviewing the literatures.

Literature Search Strategy

We searched all relevant studies that evaluated with efficacy of on-demand PPI maintenance and continuous PPI maintenance in GERD patients using PubMed, EMBASE, the Cochrane library, and KoreaMed from inception to December 2020. The following search terms were used: ([gastroesophageal reflux] or [reflux esophagitis] or [erosive esophagitis] or [heartburn]) and ([proton pump inhibitors] or [PPIs]) and ([maintenance] or [on-demand] or [continuous]). The detailed search strategies in each database and the search results are shown in Supplementary Table 1. Cited references in published studies were manually searched to identify other relevant studies.

Study Selection

The inclusion criteria in this study were as follows: (1) patients with GERD including uninvestigated GERD, NERD, and ERD who need PPI maintenance therapy; (2) comparison of on-demand PPI maintenance treatment with continuous PPI maintenance treatment; (3) randomized controlled trials (RCTs) with parallel

design; (4) adults aged over 18 years; and (5) studies available in full-text form. The exclusion criteria were as follows: (1) abstract-only publications or unpublished studies, (2) case reports and narrative reviews, (3) systematic review/meta-analysis, (4) proceedings or study protocols, and (5) studies with insufficient data regarding treatment outcomes. In the first stage of study selection, irrelevant articles were excluded by reviewing the titles and abstracts of the studies retrieved by keyword search. Thereafter, the full texts of selected studies were reviewed in accordance with our inclusion and exclusion criteria.

Quality Assessment

All studies were assessed using Cochrane's "Risk of Bias" tool, which includes the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data addressed over the short and long terms (attrition bias), selective reporting (reporting bias), and other biases.¹³ Two authors (S.J.K. and C.H.T.) independently assessed the methodological quality of all included studies, and any disagreements between the 2 evaluators were resolved by discussion and consensus. If no agreement could be reached, a third investigator (H.K.J.) was consulted.

Data Extraction

The primary outcome of this meta-analysis was treatment failure with maintenance therapy, which means that patients discontinued the allocated maintenance therapy prematurely. The secondary

endpoints were as follows: (1) proportion of patients who achieved successful symptom relief, (2) satisfaction with maintenance therapy, (3) amount of pill usage in each maintenance therapy, and (4) adverse events in both treatment groups. Using a data extraction form that had been developed in advance, 2 reviewers (S.J.K. and C.H.T.) independently extracted the following information: first author, year of publication, study design, country, study period, PPI maintenance dosage, symptom evaluation tools, rates of treatment failure, degree of satisfaction, pill usage during maintenance, and adverse events.

Statistical Methods

Meta-analyses were performed to calculate the pooled RRs with a 95% CI. The Mantel-Haenszel random-effects model was used for binary outcomes, and the inverse variance method was used for continuous outcomes. In addition, we evaluated subgroup analyses according to symptomatic GERD patients who did not undergo endoscopic evaluation, patients with NERD and patients with ERD. Heterogeneity was assessed using the I^2 test to calculate the percentage of total variation across the included articles. Negative values for I^2 were set to zero, and $I^2 \geq 50\%$ indicated the presence of substantial heterogeneity. Meta-regression was performed to investigate sources of heterogeneity (presence and severity of esophagitis and ethnicity). Publication bias was assessed qualitatively by inspecting funnel plots of the logarithmic RR vs their standard errors and quantitatively by Egger's linear regression method test and Begg's rank correlation test when 7 or more studies were available. All P -value were 2-tailed, and $P < 0.05$ was considered statistically

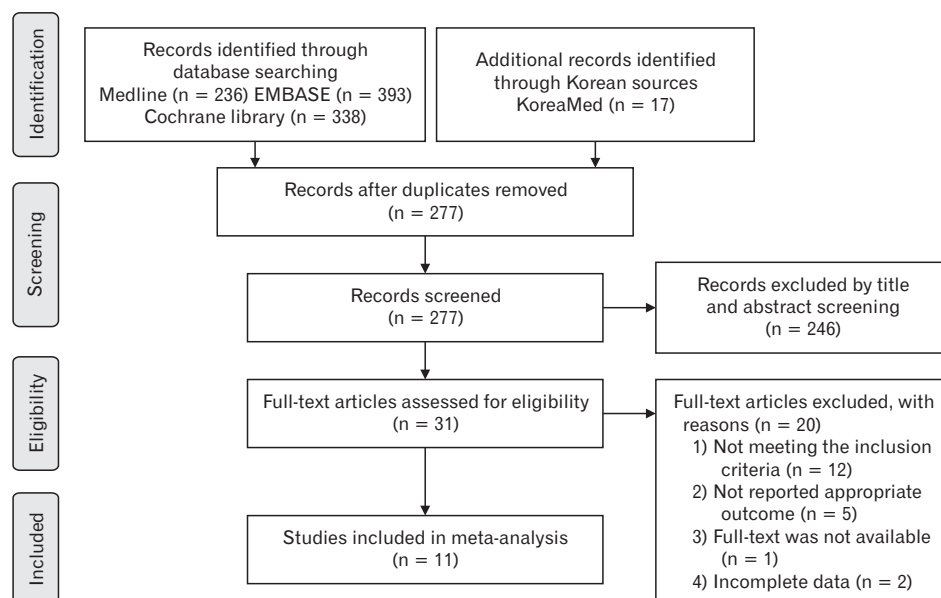


Figure 1. Flow diagram of the studies included in the meta-analysis.

significant in all tests. For meta-analysis, we used Review Manager version 5.3 (RevMan for Windows, the Nordic Cochrane Center, Copenhagen, Denmark) and “meta” packages in R version 3.6.3.

Results

Study Selection

The flow diagram of the selection process, performed in accordance with PRISMA guidelines, is shown in Figure 1. The electronic database search identified a total of 630 records, of which 277 remained after removing duplicates. After screening the titles and abstracts, we excluded 246 irrelevant articles. The full texts of the 31 remaining articles were reviewed for eligibility. Of these, 11 studies met the inclusion criteria, and 20 studies were excluded from the final analysis.

Characteristics of Included Studies

The characteristics of the 11 included studies are summarized in Supplementary Table 1.¹⁴⁻²⁴ The studies were RCTs published between 2004 and 2018, consisting of a total of 6138 GERD patients. The study design was a randomized, open-label study except for 1 study by van der Velden et al,²⁴ which was a randomized, double-blind study. Two studies^{16,20} were conducted in Asian countries, and all other studies were performed in Western countries. Three studies by Hansen et al,¹⁷ Morgan et al,¹⁹ and Szucs et al²² included patients with GERD symptoms. Two studies by Bayerdorffer et al¹⁴ and Tsai et al²³ included patients with NERD. The remaining 6 studies were performed in patients with ERD proven by endoscopy. The detailed GERD definition in each study is described in Supplementary Table 1. Except for 2 studies,^{16,23} the PPI doses for on-demand and continuous maintenance treatment groups were

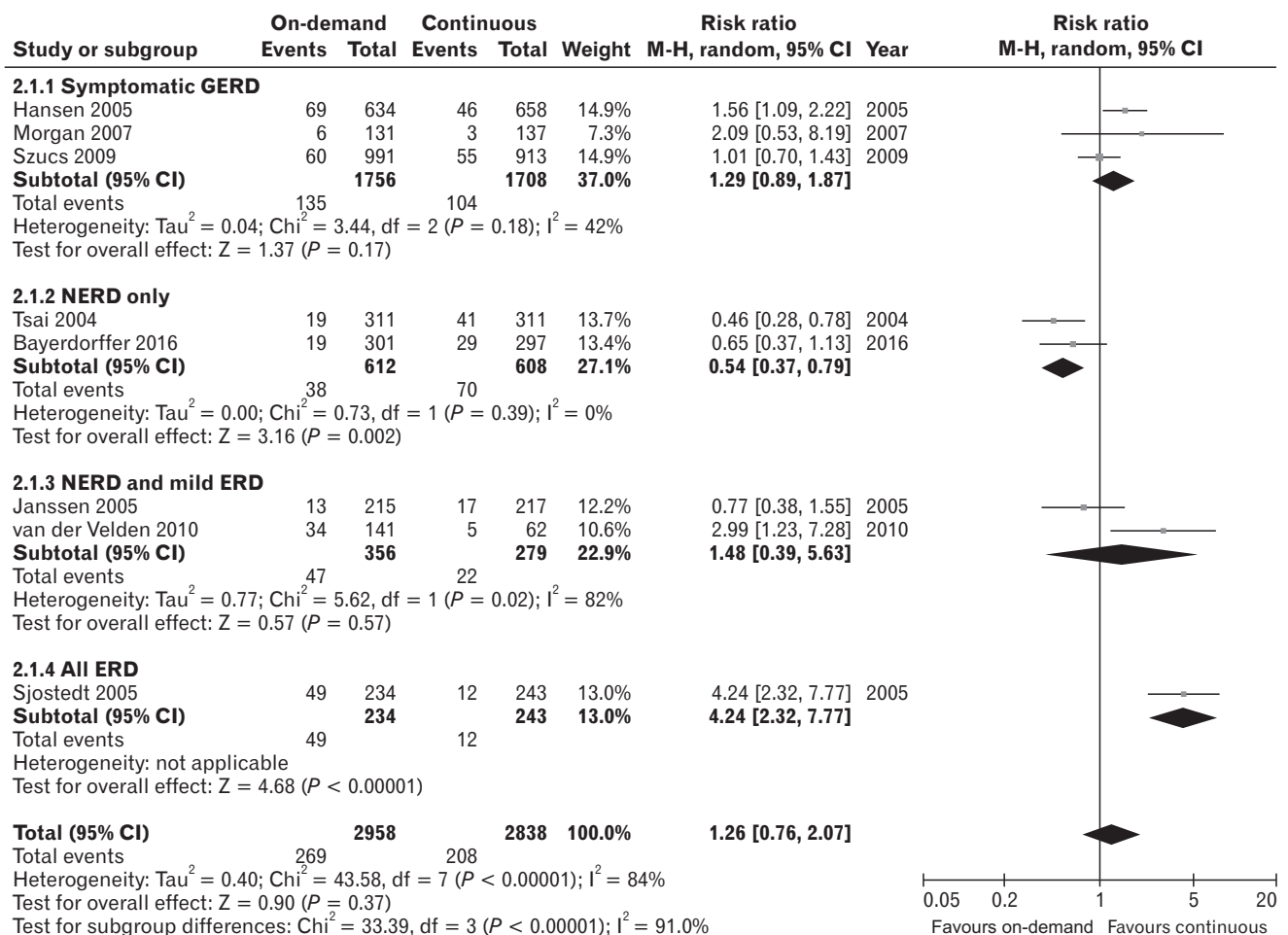


Figure 2. Forest plot of the relative efficacy in terms of the treatment failure between on-demand therapy and continuous therapy. M-H, Mantel-Haenszel; GERD, gastroesophageal reflux disease; NERD, non-erosive esophageal reflux disease; ERD, erosive reflux disease.

the same. In the study by Cho et al,¹⁶ 40 mg esomeprazole was used in the on-demand group and 20 mg esomeprazole was used in the continuous group. In the study by Tsai et al,²³ 20 mg esomeprazole was used in the on-demand group and 15 mg lansoprazole was used in the continuous group. The duration of maintenance therapy in the 2 studies by Cho et al¹⁶ and van der Velden et al²⁴ was 12 and 13 weeks, respectively, and the remaining studies were maintained for 6 months. The risk of bias graph and risk of bias summary of included studies are presented in Supplementary Figure 1 and Supplementary Figure 2, respectively.

Primary Outcomes

A meta-analysis was performed on 8 RCTs that analyzed outcomes for treatment failure. The detailed outcome measurements of each study are summarized in Supplementary Table 2. Treatment failure was observed in 269 of 2958 patients (9.1%) in the on-demand PPI group, and 208 of 2838 patients (7.3%) in the continuous PPI group (Fig. 2). The RR with 95% CI was 1.26 (0.76-2.07) ($P = 0.372$) which means no significant difference between 2 treatments in overall GERD patients. The heterogeneity of studies was 84%. Funnel plot of 8 studies was shown in Supplementary Figure 3 and showed no significant asymmetry. No significant publication bias was detected from Egger's linear regression method test ($P = 0.674$) and Begg's rank correlation test ($P = 0.458$). Subgroup analysis was performed according to the presence or absence of erosive esophagitis. We divided the entire patient group into the symptomatic GERD, NERD only, NERD and mild ERD, and all

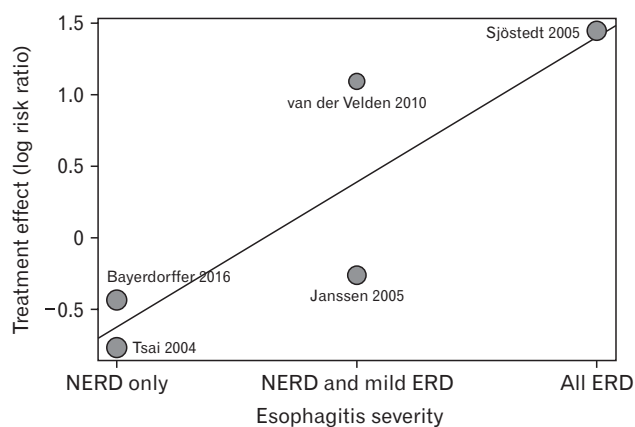


Figure 3. Random-effects univariate meta-regression between treatment failure and esophagitis severity. Each circle represents a study and the size of the circle reflects the influence of that study on the model. The regression prediction is presented by the solid line (1.013 [95% CI, 0.466-1.561], $P < 0.001$). NERD, non-erosive esophageal reflux disease; ERD, erosive reflux disease.

ERD groups as shown in Figure 2. The mild ERD group includes patients with Los Angeles (LA) grade A or B or Savary-Miller grade 1 or 2. No significant difference in treatment failure between the on-demand and continuous groups was found upon meta-analysis in the symptomatic GERD group without endoscopy (RR, 1.29; 95% CI, 0.89-1.87), and the NERD and mild ERD group (RR, 1.48; 95% CI, 0.39-5.63). In the NERD only group, treatment failure was significantly lower in the on-demand group (RR, 0.54; 95% CI, 0.37-0.79). However, in a study including patients with severe erosive esophagitis, treatment failure was significantly lower in the continuous PPI group (RR, 4.24; 95% CI, 2.32-7.77). We performed meta-regression by presence and severity of esophagitis by endoscopy as shown in Figure 3. Severity of esophagitis was associated with higher efficacies of continuous maintenance therapy (β , 1.013 [95% CI, 0.466-1.561]; $P < 0.001$) (Supplementary Table 2). Considering the high heterogeneity of analysis results, subgroup analysis was performed according to PPI types. There was no difference in treatment failure between continuous and on-demand maintenance treatments in the esomeprazole group and other PPI groups (Supplementary Fig. 4 and 5). We also carried out a sensitivity analysis to determine if the omission of each study would undermine the results of meta-analysis. The results of the changes were not obtained after omitting each study, indicating the stability of our analysis (Supplementary Table 3).

Secondary Outcomes

The proportion of patients who achieved successful symptom relief was higher in the continuous PPI group (RR, 1.16; 95% CI, 1.05-1.29) (Fig. 4). Funnel plot of 9 studies is shown in Supplementary Figure 6. No significant publication bias was detected from Egger's linear regression method test ($P = 0.469$) and Begg's rank correlation test ($P = 0.835$). The heterogeneity among studies was significant ($I^2 = 91\%$). Therefore, we performed subgroup analysis according to ethnicity and the presence of esophagitis. There was no significant difference between therapies in the Western symptomatic GERD group (RR, 1.22; 95% CI, 0.94-1.59), in Western NERD only group (RR, 1.05; 95% CI, 0.98-1.13), and in Asian NERD and ERD groups (RR, 1.00; 95% CI, 0.76-1.32). However, continuous PPI maintenance treatment showed more effectiveness in Western NERD and mild ERD group (RR, 1.17; 95% CI, 1.07-1.28) and Western ERD group (RR, 1.37; 95% CI, 1.23-1.52). When the study patient was limited to the NERD and the mild ERD group, continuous maintenance treatment showed a better effect (RR, 1.09; 95% CI, 1.01-1.18) and the number needed to treat (NNT) was 14.3 (95% CI, 7.7-20.9). To identify the sources

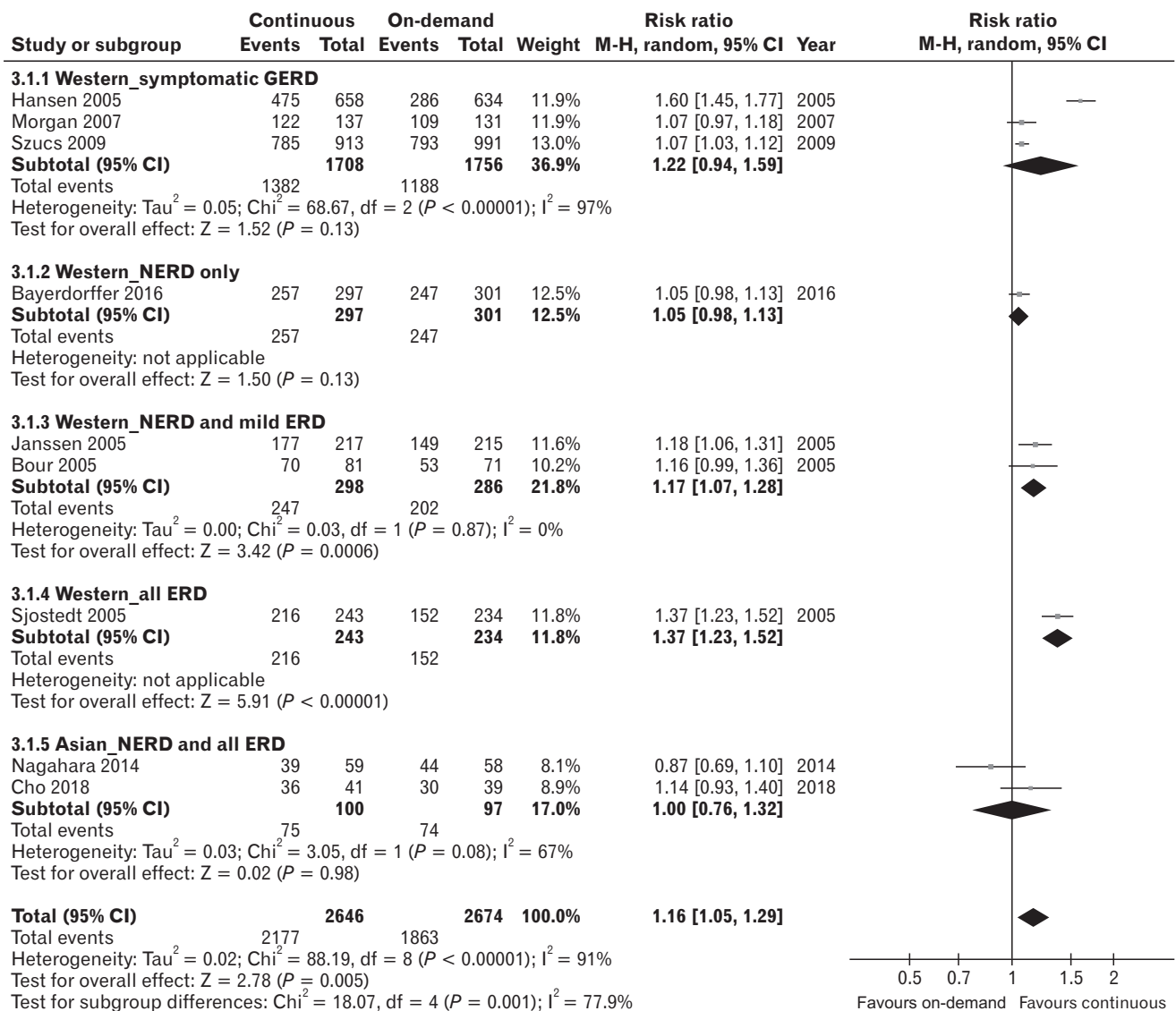


Figure 4. Forest plot of the relative efficacy in terms of the symptom relief between on-demand therapy and continuous therapy. M-H, Mantel-Haenszel; GERD, gastroesophageal reflux disease; NERD, non-erosive esophageal reflux disease; ERD, erosive reflux disease.

of heterogeneity, we performed meta-regression by the presence of esophagitis and ethnicity (Supplementary Fig. 7 and 8). In studies including severe esophagitis patients, continuous PPI maintenance treatment was more effective (β , 0.127 [95% CI, 0.066-0.188]; $P < 0.001$), but no significant difference was observed according to ethnicity (β , -0.179 [95% CI, -0.462-0.105]; $P = 0.218$) (Supplementary Table 2). We also performed subgroup analysis according to PPI types. Continuous therapy was more effective in the studies using esomeprazole, but there was no difference between the 2 groups in the studies using other PPI groups (Supplementary Fig. 9 and 10). Sensitivity analysis did not show changes after omit-

ting each study, indicating the robustness of analysis as shown in Supplementary Table 3.

Pill usage was significantly lower in the on-demand group as shown in Figure 5. In the on-demand group, pill usage per day was less than in the continuous group (risk difference, -0.52; 95% CI, -0.62- -0.42), which means that half of the PPI was used in the on-demand group compared to the continuous group. Patient satisfaction was measured in 6 RCTs. No significant difference in patient satisfaction was found between the 2 groups upon meta-analysis (RR, 0.97; 95% CI, 0.93-1.01) (Supplementary Fig. 11). The frequency of adverse events did not differ between the 2 treatment

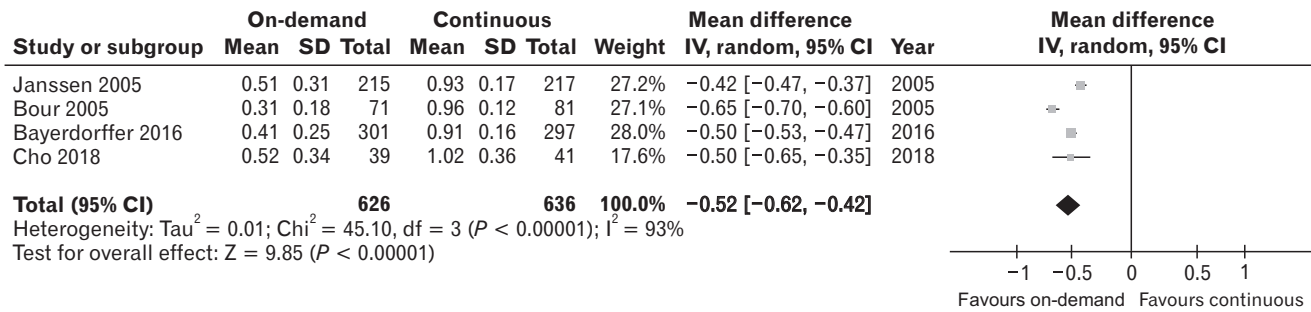


Figure 5. Forest plot of the amount of pill usage between on-demand therapy and continuous therapy. IV, inverse variance.

groups (RR, 1.02; 95% CI, 0.90-1.14) (Supplementary Fig. 12).

Discussion

The meta-analysis of RCTs on maintenance treatment in GERD patients found no difference in treatment failure and satisfaction between the on-demand and continuous PPI maintenance groups. In terms of symptom relief, continuous therapy was more effective than on-demand therapy. However, meta-regression analysis demonstrated that the severity of esophagitis can affect the effectiveness of maintenance therapy. In NERD and mild ERD patients, treatment failure rate was similar in both therapies, and symptom relief was slightly higher in the continuous therapy group, although the clinical significance of this difference does not appear to be large (NNT = 14.3). In terms of treatment failure and symptom relief, continuous maintenance therapy was more effective in studies including severe ERD patients. However, in Asian patients where severe ERD patients are rare, there was no difference in the effect of symptom relief between both maintenance therapies. The amount of pill usage was significantly lower in the on-demand group. Therefore, in GERD patients with NERD and mild ERD patients or Asian patients, on-demand therapy may be preferentially recommended as an effective maintenance therapy.

Although many guidelines recommend on-demand therapy as a maintenance therapy for GERD, few meta-analysis articles have reported its effectiveness. Boghossian¹⁰ reviewed the efficacy of on-demand PPI therapy versus continuous PPI therapy in NERD or mild ERD (LA grade A or B). The authors concluded that on-demand PPI therapy may increase risk of “lack of symptom control” compared with continuous PPI use (RR, 1.71; 95% CI, 1.31-2.21), thereby favoring continuous PPI use. Khan et al¹¹ also performed a meta-analysis comparing on-demand therapy with continuous PPI use in patients with NERD or mild ERD. Their conclusion that on-demand PPI was superior to continuous PPI

(OR, 0.50; 95% CI, 0.35-0.72) in terms of ‘discontinuation of maintenance treatment’ is contrary to the results of the former study. In our study, when limited to NERD and mild ERD patients as in the 2 studies above, continuous maintenance treatment was slightly more effective in symptom relief (RR, 1.09; 95% CI, 1.01-1.18), as in the study of Boghossian, and there was no difference between the 2 groups in treatment failure (RR, 0.85; 95% CI, 0.43-1.66). This result was different from that of Khan’s study.¹¹ This is because van der Velden’s study²⁴ was added to our study due to the difference in inclusion criteria, and the results of this study have an influence on the outcome. However, in studies including moderate to severe esophagitis, continuous therapy showed superior efficacies in terms of treatment failure (RR, 4.24; 95% CI, 2.32-7.70) and symptom relief (RR, 1.37; 95% CI, 1.23-1.52). The American Gastroenterological Association guideline also reports that the use of long-term PPI has a greater benefit than harm in GERD patients with severe esophagitis or complications such as strictures.²⁵

In subgroup analysis, 3 studies included all grades of esophagitis. However, grade C and D esophagitis patients accounted for only 6.0% (7/117) in the Nagahara’s study²⁰ and 2.5% (2/80) in Cho’s study.¹⁶ In the Sjöstedt’s study,²¹ patients with grade C and grade D esophagitis accounted for 17.0% (80/470) and 5.0% (24/470) of all patients, respectively. Therefore, to confirm the effect of maintenance therapy in severe esophagitis such as LA grade C and D, the results of Sjöstedt’s study²¹ should be referenced. Treatment failure was significantly higher (RR, 4.24; 95% CI, 2.32-7.77), and symptom relief was significantly lower (RR, 1.37; 95% CI, 1.23-1.52) in the on-demand PPI group compared to the continuous therapy group. Furthermore, the authors also investigated the cumulative healing rate of esophagitis for up to 6 months. The cumulative proportion of patients in remission on the continuous PPI group was 81.0% compared with only 58.0% in the on-demand PPI group (P < 0.01). In patients with grade C and D esophagitis, relapse rates during on-demand maintenance treatment were as high as 49.0%

and 57.0%, respectively. Therefore, in the maintenance therapy of overall GERD patients, on-demand therapy showed a similar effect to continuous therapy. However, when limited to the patients with severe esophagitis of LA grade C or D, the continuous maintenance therapy could be a better option compared with the on-demand PPI therapy.

Among the 11 studies included in the analysis, 2 were conducted in Asia. Nagahara's study²⁰ was conducted in Japan and Cho's study¹⁶ was conducted in Korea. Both studies included all grades of erosive esophagitis, but the proportion of patients with grade C and D esophagitis were only 6.0% in Nagahara's study²⁰ and 2.5% in Cho's study.¹⁶ According to the results of epidemiologic studies, the proportion of severe erosive esophagitis in Asia is very low compared to that in Western countries. From a multicenter prospective study from Korea, out of 354 erosive esophagitis patients, only 12 patients were grade C and 4 were grade D, and the proportion of grade C and D among all erosive esophagitis was 4.5%.²⁶ This figure is similar to the proportion of grade C and D patients in the 2 Asian studies included in the analysis, and much lower than the proportion (22.0%) found in the Western study by Sjöstedt et al.²¹ The effect of maintenance therapy in the Asian studies also shows different results from Western studies. When symptom relief was an outcome, continuous maintenance therapy was more effective than on-demand therapy in the entire study. However, the results of 2 studies from Asia showed no difference in symptom relief between the on-demand and continuous groups. Therefore, on-demand PPI therapy can be an effective maintenance treatment option in Asian patients with GERD.

Recent studies suggest that long-term PPI use may be associated with adverse events or complications, including enteric infection, bone fracture, kidney diseases, and micronutrient deficiency.⁸ A meta-analysis of 36 case-control studies and 14 cohort studies showed that *C. difficile* infection is associated with PPI use (OR, 1.26; 95% CI, 1.12-1.39).²⁷ An RCT that evaluated the long-term safety of PPIs over 2 years revealed increased events of *C. difficile* infection in PPI group (9 cases in 8791) compared to placebo group (4 cases in 8807), which did not reach statistical significance due to very few number of cases in either group (OR, 2.26, 95% CI, 0.70-7.34).²⁸ According to available evidences, the Food and Drug Administration and Prevention announced that *C. difficile* diarrhea may be associated with PPI use. Other adverse events such as kidney diseases, community-acquired pneumonia, and bone fractures have been demonstrated in case-control studies or cohort studies.²⁹⁻³¹ Therefore, many GERD guidelines recommend that PPIs should be administered at the lowest effective dose. In this

study, the amount of PPI used in the on-demand group was almost half that of the continuous group (-0.52 [-0.62 - -0.42] pill use/day). Therefore, considering the various adverse effects associated with the use of long-term PPI, on-demand maintenance treatment is considered a safer and more cost-effective treatment modality than continuous maintenance treatment.

This study has several limitations. First, as described in the result section and Supplementary Table 1, 10 of the 11 studies included in analysis were open-label studies. On-demand therapy is expected to be difficult to conduct with a double-blind study. Only 1 study performed a double-blind study that showed that symptom control and quality of life were similar in the on-demand and continuous therapies. Since the open-label study is very similar to the actual clinical situation, the interpretation of the results is unlikely to be different significantly. Second, as a result of meta-analysis, the heterogeneity among the studies was high. The inclusion of patients with varying degrees of symptoms and esophagitis may have an effect on the heterogeneity as shown in the meta-regression analysis. Also, as a result of the subgroup analysis by the esophagitis grade, the heterogeneity within each group was significantly reduced. The diversity of outcome measurement also contribute to the high heterogeneity of this study. Third, no studies reported CYP2C19 polymorphism and their effect on PPI maintenance therapy. However, 2 studies used rabeprazole, which is not affected by CYP2C19 polymorphism, reported no difference between the maintenance therapies in terms of "treatment failure" and "symptom relief." Forth, only 2 Asian studies were included in this analysis, and the results between Asian and Western studies show slightly different trends as shown in the analysis. It may be difficult to apply the results of this study to Asian patients. In this regard, more research is needed in the Asian region. Finally, intermittent therapy is another recommended maintenance therapy in some guidelines, and is also known to be an effective maintenance option. However, because of lack of RCTs on the intermittent therapy, its effect cannot be compared with the on-demand or continuous therapy.

In conclusion, the on-demand PPI therapy showed similar efficacies to continuous therapy in the outcome of treatment failure, symptom relief, and patient satisfaction in GERD patients, especially in NERD and mild ERD patients, and Asian patients. The severity of esophagitis significantly influenced the effect of the 2 maintenance therapies. In particular, continuous maintenance treatment seems to be more effective in patients with severe ERD. However, on-demand therapy has the advantage of reducing the amount of PPI usage by half compared to the continuous therapy. Therefore, the on-demand PPI therapy is recommended as an

effective maintenance treatment modality in GERD patients unaccompanied by severe esophagitis.

Supplementary Materials

Note: To access the supplementary tables and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at <http://www.jnmjournal.org/>, and at <https://doi.org/10.5056/jnm21095>.

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