

# Efficacy of proton pump inhibitor on nighttime reflux symptoms and associated sleep disturbances in patients with gastroesophageal reflux disease: A real-world study in northern China

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## Research

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# Abstract

## Background

Gastroesophageal reflux disease (GERD) is strongly associated with sleep disturbances. Proton pump inhibitors (PPIs) are the main treatment to improve the symptom of GERD. This study was to investigate the efficacy of PPIs on nighttime GERD symptoms and associated sleep disturbances in general Chinese GERD population.

## Methods

Adult patients with mild or more serious nighttime GERD symptoms were included. The efficacy was evaluated by the relief rate of nighttime GERD symptoms and GERD-related sleep disturbances after 4 weeks PPIs treatment. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index Score (PSQI).

## Results

A total of 750 patients were included in the final analysis. Overall, 51.3% of the patients had achieved a relief of nighttime GERD symptoms after 4 weeks of PPIs treatment. By week 4, the percentages of patients with completely resolved nighttime GERD symptoms and GERD-related sleep disturbances were 32.5% and 51.5%, respectively. PSQI score was significantly improved from  $6.82 \pm 0.12$  at baseline to  $4.56 \pm 0.09$  at 4 weeks ( $P < 0.001$ ).

## Conclusion

PPIs treatment can provide an effective relief of nighttime GERD symptoms and associated sleep disturbances, improving sleep quality of general GERD patients in northern China.

## Trial registration:

Trial registration: ChiCTR, ChiCTR1800017652. Registered 08 August 2018, <http://chictr.org.cn/index.aspx>

## 1. Introduction

Nighttime reflux symptoms of heartburn or acid regurgitation are common among patients with gastroesophageal reflux disease (GERD), affecting about 45–88.9% of this kind of patients [1–5]. While nighttime reflux episodes are less frequently than daytime reflux episodes, they tend to be associated with more severe reflux-related injuries and bothersome [2, 4, 6, 7].

Considerable evidences have confirmed the strong association between GERD and sleep disturbances, such as difficulty falling asleep, arousal during sleep and poor sleep quality, which impair the health-related quality of life (HRQOL) of patients [2, 3, 8–12]. In a nationwide telephone survey of 1,000 US patients with GERD, 79% of respondents experienced nighttime heartburn. In this population, 75% complained of symptoms that affected their sleep, and 40% believed that nighttime reflux events impaired their capability of functioning in the next day [3]. In addition, a patient-reported survey of 11,685 respondents with GERD revealed that 88.9% of the respondents had nighttime reflux symptoms and 68.3% experienced sleep difficulties. Meanwhile, sleep difficulties were associated with a 5.5% increase in overall work impairment and a 10.9% increase in activity impairment [5]. The potential mechanism may be psychoneuroimmunological effect of sleep disturbance [13]. Poor quality of sleep has a great influence on the development of inflammation, cardiovascular disease, carcinogenesis and depression.

Recent studies demonstrate that GERD and GERD-related sleep disturbances were bi-directionally associated. Nighttime reflux symptoms can lead to sleep disturbances, and vice versa sleep disturbances can prolong acid contact time and increase sensory perception [14, 15]. A survey conducted in China suggested that increased nighttime reflux events might play an important role in inducing sleep disturbances in patients with GERD, and patients with GERD along with sleep disturbances were characterized by more serious nighttime acid reflux and erosive esophagitis [16]. Furthermore, nighttime GERD is related to an increased risk of esophagitis and other respiratory complications [17]. Therefore, it is essential to manage nighttime GERD symptoms and GERD-related sleep disturbances effectively for the improvement of HRQOL as well as the prognosis of patients with GERD.

Treatment involving proton pump inhibitors (PPIs) is the first therapeutic strategy for patients with GERD to relieve GERD symptoms and heal the damaged esophageal mucosa [18]. Several clinical trials have demonstrated that PPIs treatment can reduce nighttime GERD symptoms and improve subjective sleep parameters obviously [9, 19–22]. However, the response of nighttime GERD symptoms and GERD-related sleep disturbances to PPIs treatment is not well established in China. Therefore, this real-world study was conducted to elucidate the efficacy of PPIs on nighttime GERD symptoms and associated sleep disturbances in general Chinese GERD population.

## **2. Materials And Methods**

### **2.1 Design and Setting**

This was a multi-center prospective observational study. The patients from 10 tier-3 hospitals in the north of China from July 2017 to March 2018 were recruited. The study was approved by the ethics committee of Tianjin Medical University General Hospital (approval no. IRB2017-113-01) and conducted in accordance with the ethical principles based on the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all participants before study initiation.

### **2.2 Patients**

We included patients aged from 18 to 80, who were diagnosed with GERD for the first time or had history of reflux esophagitis but without any acid suppressive agents taken in the previous 4 weeks. The enrolled patients were required to have experienced with typical heartburn or acid regurgitation of at least mild severity. Patients should also have above symptoms for more than one night per week within the previous 3 months. Exclusion criteria were the presence of any conditions other than GERD-related reflux symptoms or sleep disturbances, active peptic ulcer, history of gastroesophageal surgery, suspected or confirmed malignancy, comorbidity of chronic liver diseases and chronic kidney diseases, severe uncontrolled systemic disorders, such as arrhythmia, chronic obstructive pulmonary disease, asthma as well as heart failure, working night shifts, history of drug or alcohol abuse, mental or psychiatric disorder, women who were pregnant or lactating.

## **2.3 Assessment**

A non-interventional questionnaire survey was performed in all included patients. The PPIs treatment was prescribed by the physicians before patients were enrolled in the study.

Patients were required to document a diary card to record their daily symptoms and fill out a self-administered questionnaire after that at each visit. The diary card and questionnaire comprise the questions regarding nighttime GERD symptoms, GERD-related sleep disturbances, the global Pittsburgh Sleep Quality Index (PSQI) questionnaire, and PPIs treatment regimen. Data were collected on baseline, 2 weeks  $\pm$  3 days and 4 weeks  $\pm$  3 days after the initiation of PPIs therapy. All questionnaires were completed with the guidance of attending investigators.

## **2.4 Symptom and related sleep disturbance**

Nighttime GERD symptoms were defined as typical heartburn or acid regurgitation when patients laid down to sleep at night, being awakened at night by symptoms, having symptoms on awakening in the morning, and being awakened at night by coughing or choking because of fluid or an acid or bitter taste or food in the throat [14]. On a dairy card, patients were required to answer the following questions related with nighttime GERD symptoms or GERD-related sleep disturbances they had experienced last night, which included "Did you experience nighttime GERD symptoms? (yes or no); Did you have trouble falling asleep or unwanted awakenings caused by nocturnal heartburn or acid regurgitation? (yes or no); Which of the following symptoms caused your trouble sleeping? (heartburn, acid regurgitation)". At each evaluation visit, questionnaires were also required to be completed based on the record of dairy card over the previous 7 day, which included "How many days had you experienced nighttime GERD symptoms? (Please write down the cumulative amount of days); How many days had you experienced sleep trouble due to GERD symptoms? (Please write down the cumulative amount of days)". The patients should also self-assess the severity of nighttime GERD symptoms on a point scale ranging from 0 to 4: none (no symptom); mild (symptoms occasional and easily tolerated); moderate (discomforting symptoms causing interference with normal activities); severe (frequently symptoms cause significant restrictions on daily life), and very sever (sever and persistent life limitations due to symptoms).

Complete resolution of nighttime GERD symptoms was defined as had never experienced nighttime GERD symptoms in the previous 7 days. Relief was defined as a more than 50% of reduction in weekly symptomatic days compared with last evaluation visit. Symptom improvement was defined as any decrease compared with last evaluation visit but no more than 50%. Similarly, the improvement of GERD-related sleep disturbances was defined in the same manner. The efficacy was evaluated by the proportion of patients with relief of nighttime GERD symptoms after 4 weeks of PPIs treatment. A responder was defined as someone who achieved complete or relief status.

## 2.5 Sleep quality

The Pittsburgh Sleep Quality Index Score (PSQI) was used to evaluate subjective sleep quality of subjects [23]. The PSQI is a standardized rating scale, which is composed of seven component scores, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Each dimension is rated from 0 to 3, and sum of the seven dimensions yields one global PSQI score. A global PSQI score  $\geq 5$  indicates poor sleep.

## 2.6 Adverse events

Adverse events spontaneously reported by the patients were recorded throughout the survey.

## 2.7 Statistical analysis

Analyses were primarily descriptive. Continuous variables with normal distributions were reported as the mean  $\pm$  standard deviation (SD). Categorical variables were reported as the percentage. The  $\chi^2$  test was used for the categorical variable. Descriptive comparisons were performed using Wilcoxon's rank-sum tests for continuous variable with non-normally distributed data. Friedman test was used to compare the means of repeated continuous variables. All statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA). Statistical significance was defined as two-sided  $P < 0.05$ .

# 3. Results

## 3.1 Participants

Of 1000 patients enrolled in the screening stage, 750 were included in the efficacy evaluations. Flow chart of this study was shown in Fig. 1. The main reasons for the exclusion included early withdraw from the study, major protocol deviation, voluntary discontinuation of PPIs treatment without any post-baseline symptoms, lost of follow-up etc. There were totally 397 male and 353 female with an average age of  $51.21 \pm 0.51$  years old. The nighttime heartburn severity score was  $1.89 \pm 0.78$ , while the PSQI score was  $6.82 \pm 0.12$  at baseline. The demographics and baseline characteristics of the 750 patients in the analysis population were presented in Table 1.

## 3.2 PPIs treatment

In the study, all the patients had taken at least one type of PPIs. Among the 750 patients, 70.13% (526/750) taken PPIs once daily with the standardized dosage recommended by the label information. PPIs treatment strategy was changed during the observation period in 9.1% (68/750) of all patients, of those, 3.20% (24/750) switched to another type of PPIs, while 5.87% (44/750) of the patients increased the PPIs dose. The most commonly prescribed PPIs was rabeprazole (69.1%, 518/750), with a mean daily dose of  $13.61 \pm 6.63$  mg. Other PPIs received by patients including esomeprazole (8.5%, 64/750), lansoprazole (11.3%, 85/750), pantoprazole (4.0%, 30/750) and omeprazole (7.1%, 53/750), with mean daily doses of  $26.65 \pm 12.79$  mg,  $39.19 \pm 16.01$  mg,  $62.67 \pm 41.50$  mg and  $29.06 \pm 10.05$  mg, respectively.

### **3.3 Effect of PPIs on nighttime GERD symptoms and related sleep disturbances**

Overall, 51.3% (385/740) patients were considered to be responders of nighttime GERD symptoms after 4 weeks of PPIs treatment. Among them, 32.5% (244/750) of the patients had achieved complete resolution. The remaining 48.7% (365/750) of patients showed no response to current treatment. For GERD-related sleep disturbances, 78.0% (585/750) patients reported sleep disturbances due to nighttime reflux symptoms at baseline. After 4 weeks PPIs treatment, the respondent rate was up to 70.1% (410/585), while the percentage of patients free from GERD-related sleep disturbances accounted for 53.0% (310/585) of all the patients. Besides, a significantly higher respondent rate of both nighttime GERD symptoms and GERD-related sleep disturbances were achieved at week-4 assessment compared with that at week-2 (34.7%, 260/750 and 47.0%, 275/585, respectively) (both  $P < 0.001$ ; Fig. 2).

PPIs therapy could significantly decrease the severity of nighttime GERD symptoms ( $P < 0.001$ ). The nighttime heartburn severity score at baseline, week-2 and week-4 was  $1.89 \pm 0.78$ ,  $1.14 \pm 0.67$  and  $0.74 \pm 0.67$ , respectively. For nighttime acid regurgitation, the mean scores were  $1.88 \pm 0.78$  at baseline,  $1.07 \pm 0.93$  at 2 weeks and  $0.62 \pm 0.71$  at 4 weeks. Figure 3 showed the change of severity in nighttime symptoms.

### **3.4 Effect on sleep quality**

56.9% (427/750) of patients had poor sleep quality (global PSQI score  $> 5$ ) at baseline. After PPIs treatment, patients' PSQI score was significantly decreased from  $6.82 \pm 0.12$  at baseline to  $5.36 \pm 0.09$  at 2 weeks and  $4.56 \pm 0.09$  at 4 weeks (both  $P < 0.001$ , Fig. 4A). After 2 weeks PPI treatment, the proportion of patients with a total PSQI score  $> 5$  decreased to 40.7% (305/750) ( $P < 0.001$ ) and further decreased to 32.7% (245/750) ( $P < 0.001$ ) at 4 weeks (Fig. 4B).

### **3.5 Comparison of rabeprazole and non-rabeprazole treatment**

According to the type of PPIs, patients were further divided into rabeprazole group and non-rabeprazole group. At 4 weeks, rabeprazole group had a higher proportion of responders of nighttime GERD symptoms (57.5% in rabeprazole vs. 37.5% in non-rabeprazole,  $P < 0.001$ ). Respondent rate of GERD-related sleep disturbances was also significantly higher in rabeprazole group (74.6% in rabeprazole vs.

60.3% in non-rabeprazole,  $P < 0.001$ ). Similarly, rabeprazole group had a significantly less proportion of patients with poor sleep quality after 4 weeks treatment (69.9% in rabeprazole vs. 83.2% in non-rabeprazole,  $P < 0.001$ ) (Fig. 5).

## 3.6 Adverse events

In this study, no active safety data were found throughout the survey.

## 4. Discussion

According to a nationwide survey conducted in China, nighttime GERD symptom is common in Chinese GERD patients, accounting for 56.1% [24]. Among the patients suffering from nighttime GERD symptoms, 80.1% have sleep disturbances, which is significantly higher than those without nighttime GERD symptoms [24]. Such a high prevalence is comparable to that in western countries. However, the incidence of depression is also increasing with aggravation of sleep disturbances. Although, GERD had been considered as a somatopsychic illness, more and more evidences showed there was a relationship between GERD and sleep-wake cycle and mental disorders [25, 26]. Thus, sleep management is recommended for patients with GERD to improve the quality of life and avoid the development of psychological problems [27]. This is the first study that provides real-world data to evaluate the efficacy of PPIs on nighttime GERD symptoms and GERD-related sleep disturbances in Chinese patients. With increased understanding of the interrelationship between sleep disturbances and GERD, it may be helpful to provided better therapeutic strategy.

In the present study, 78.0% patients experienced GERD-related sleep disturbances and 56.9% patients had poor sleep quality at baseline, which were similar with the results of Zhou et al [24]. Overall, 51.3% patients in this study had achieved a relief of nighttime GERD symptoms after 4 weeks of PPIs treatment, which was significantly higher than that at 2 weeks (34.7%). Meanwhile, similar responses to PPIs therapy were also observed in global PSQI score, relief rate of GERD-related sleep disturbances, and complete resolution rate of nighttime GERD symptoms as well as GERD-related sleep disturbances.

The results regarding the efficacy of PPIs therapy on nighttime GERD symptoms and subjective GERD-related sleep dysfunction in our study were consistent with previous studies. A placebo-controlled study of 864 patients with frequent nighttime heartburn reported that lansoprazole 15 mg or 30 mg once daily were highly effective in reducing nighttime heartburn [28]. However, they didn't evaluate the effect of lansoprazole on sleep. Another multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy of esomeprazole and placebo in US demonstrated that 53.1% patients with GERD-related sleep disturbances and moderate-to-severe nighttime heartburn achieved relief of nighttime heartburn, suggesting that esomeprazole 40 mg or 20 mg once daily reduced nighttime heartburn, GERD-related sleep disturbances, and improved sleep quality as well as work productivity in regular activities compared with placebo [20]. Moreover, a multicenter study of 134 GERD patients in Japan found that rabeprazole 10 mg for 8 weeks significantly decreased both FSSG (Frequency Scale for Symptoms of GERD) and PSQI score [9]. Another study in Japan showed that twice daily treatment with rabeprazole for 4 to 8

weeks significantly reduced the frequency of nighttime reflux symptoms, reflux-related sleep disturbances, daytime sleepiness and improved poor sleep quality in GERD patients who were refractory to once daily standard PPI treatment [29]. The findings from current study suggest that PPIs treatment is effectively in improving nighttime GERD symptoms and GERD-related sleep disturbances over a 4-week period in real-world clinical practice in northern China. Moreover, we found that rabeprazole might be more effective in preventing nighttime GERD symptoms, GERD-related sleep disturbances and improving sleep quality, which was also consistent with previous studies. Compared with other PPIs, higher proportion of patients was treated with rabeprazole and received better relief of night-time symptoms [30, 31]. It may be due to that the intragastric pH was maintained longer and higher by rabeprazole during the night, thus, central the nervous system received less sensory stimuli from the intraesophageal lumen that may subconsciously interrupt sleep [32]. Rabeprazole may had a faster onset of action than other kinds of PPIs. However, follow-up period in this study was relative short, therefore, we could not observe the long-term effectiveness of different types of PPIs. Besides, it is unknown that whether the patients take the medicine strictly according to doctor's advice. It's also possible that patients may take medicine sometimes during the day and sometimes at night. Patients may take PPIs on the day-time or for several days in the evening. Longer-term clinical trials in patients with GERD would be needed to test those expectations. Therefore, longer term clinical trials of GERD are still needed to answer these questions.

There were several strengths of this study. First, in this large population based real-world study, we firstly evaluated the efficacy of PPIs treatment in patients with nighttime GERD symptoms and GERD-related sleep disturbances in China. These results will help clinicians to effectively manage patients with nighttime GERD symptoms. Second, our results can be presumed to extend to general GERD patients in northern China. Heartburn and acid regurgitation are both typical reflux symptoms according to the Montreal definition of GERD [33]. In addition, acid regurgitation was reported to more frequently occur at night and more severe than heartburn [34, 35]. Previous studies exploring the effect of PPIs on nighttime GERD symptoms focused merely on nighttime heartburn [20, 22, 28]. In the current study, we enrolled patients with nighttime GERD symptoms with at least mild severity and a frequency of more than one day per week, which represented the majority of GERD patients. Nighttime GERD symptoms included typical heartburn and acid regurgitation. Besides, compared with randomized controlled trials, we included patients with more comorbidities, more concomitant medications and other conditions that were usually excluded by RCTs. Therefore, data in current study can reflect the majority of GERD patients in northern China.

Several limitations need to be considered while interpreting the results in this study. First, data were collected based on patients' self-reported questionnaires, it might be influenced due to recall bias or patient's knowledge of the disease. The available data did not allow consideration of psychological factors and mental disorders that may affect sleep dysfunction. Second, findings in this study mainly represent the situation of target population in northern China, further nationwide researches might be necessary to assess the efficacy of PPIs therapy on the whole target population in China. Third, ambulatory impedance-pH monitoring and polysomnography are not routinely performed in clinical practice. Thus, no objective assessments of nighttime reflux and sleep quality were examined to confirm

the current results. Hence, additional research is needed to evaluate the objective efficacy in China. In addition, efficacy evaluated in our study was the relief rate of nighttime GERD symptoms after 4 weeks of PPIs treatment. Therefore, not all the patients showing no response to current treatment should be considered as real non-responders. It is possible that some of those patients may experience symptoms improvement in a longer duration of therapy. Thus, further efficacy assessment of long-term PPIs treatment is required. Finally, we were failed to evaluate the confounding factors that might interfere with the current data in real-world setting. The causes of PPIs therapy no-response remains unclear in Chinese GERD patients and investigations concerning this issue are thus warranted.

## 5. Conclusions

In summary, nighttime reflux symptoms are common among Chinese patients with GERD, and most patients have experienced GERD-related sleep disturbances. PPIs treatment can provide an effective relief of nighttime GERD symptoms and associated sleep disturbances, improving sleep quality of general GERD patients in northern China.

## List Of Abbreviation

Gastroesophageal reflux disease (GERD); Proton pump inhibitors (PPIs); Pittsburgh Sleep Quality Index Score (PSQI); Health-related quality of life (HRQOL); The mean  $\pm$  standard deviation (SD).

## Declarations

**Ethics approval and consent to participate** The study was approved by the ethics committee of Tianjin Medical University General Hospital (approval no. IRB2017-113-01) and conducted in accordance with the ethical principles based on the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all participants before study initiation.

**Consent for publication** Not applicable

**Availability of data and materials** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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**Competing interests** The authors have no competing of interest to disclose.

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**Authors' contributions** KDS, SM and BW participated in the design of this study. YYH and BY performed the statistical analysis. KS and SM drafted the manuscript. BMW, GLZ, ZHZ, YDL, QY, QJD, GFL, JMW, LLC and RXZ provided data. LPZ, SYW, SL, WZ and KJ collected data. JWZ, SM and XC carried out literature search. BMW and XC carried out manuscript editing. KDS, SM, YYH and BW equally contributed to this work. All authors have read and approved the content of the manuscript.

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## Tables

**Table 1** Demographics and baseline characteristics of patients

Characteristics	Total (n=750)
Age (y)	
Mean (SD)	51.21 (0.51)
Median (rang)	41 (18-79)
Male (n, %)	397, 52.9%
BMI (kg/m <sup>2</sup> )	
Mean (SD)	24.4 (2.9)
Median (range)	24.61(15.82-35.16)
Mean nighttime heartburn severity score (SD)	1.89 (0.78)
Mean nighttime acid regurgitation severity score (SD)	1.88 (0.78)
Mean PSQI score (SD)	6.82 (0.12)
PSQI $\geq$ 5 (n, %)	427 (56.9%)

Data were presented as mean (standard deviation) or n (%)

BMI, body mass index

PSQI, Pittsburgh Sleep Quality Index

## Figures

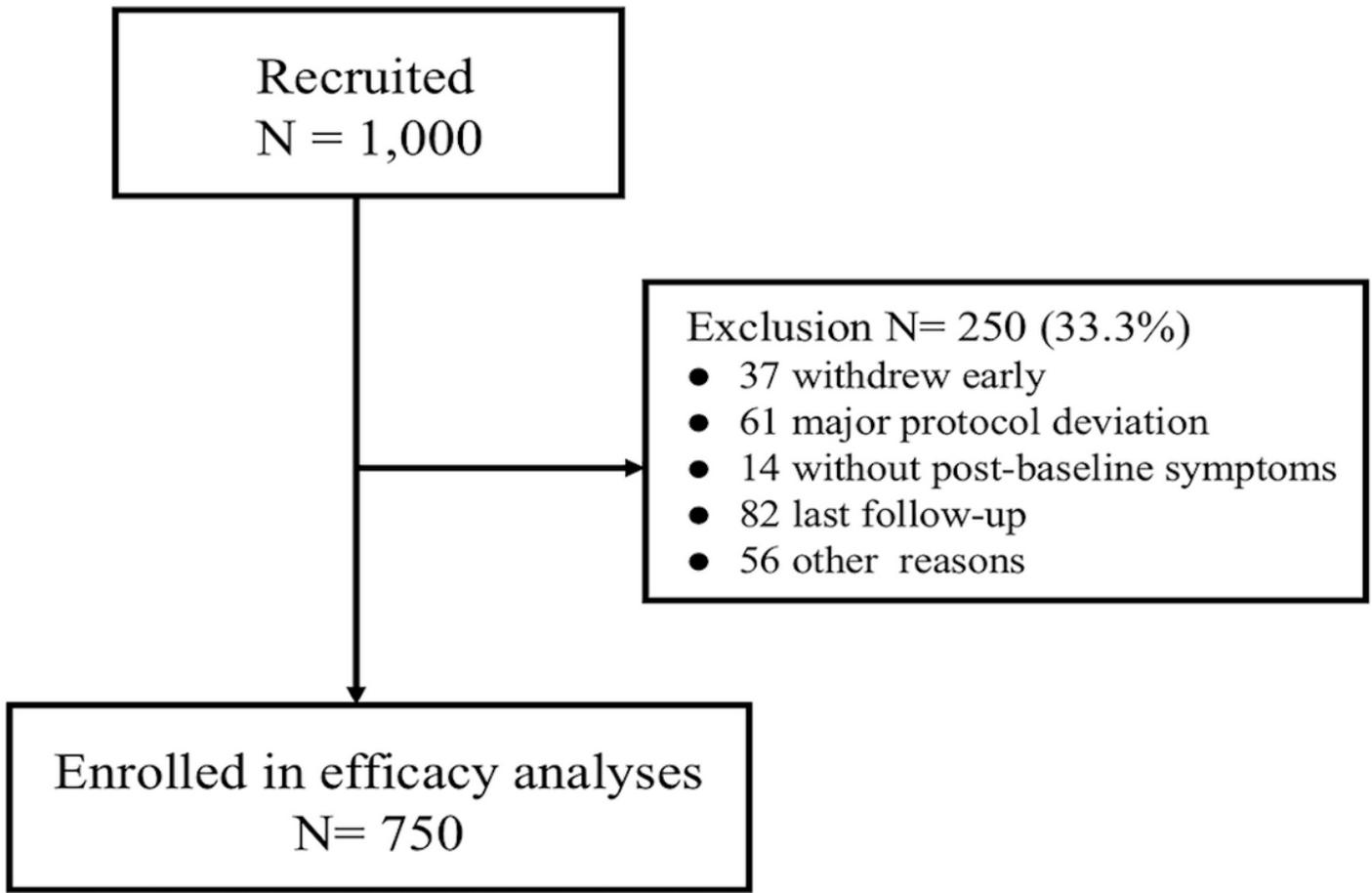


Figure 1

Flow chart of patients.

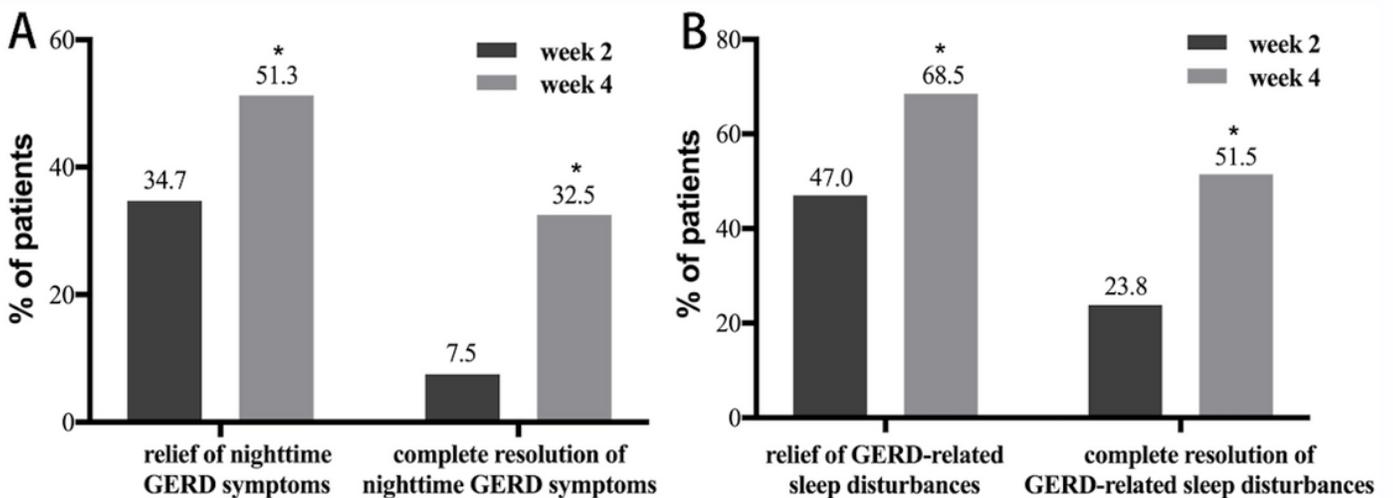
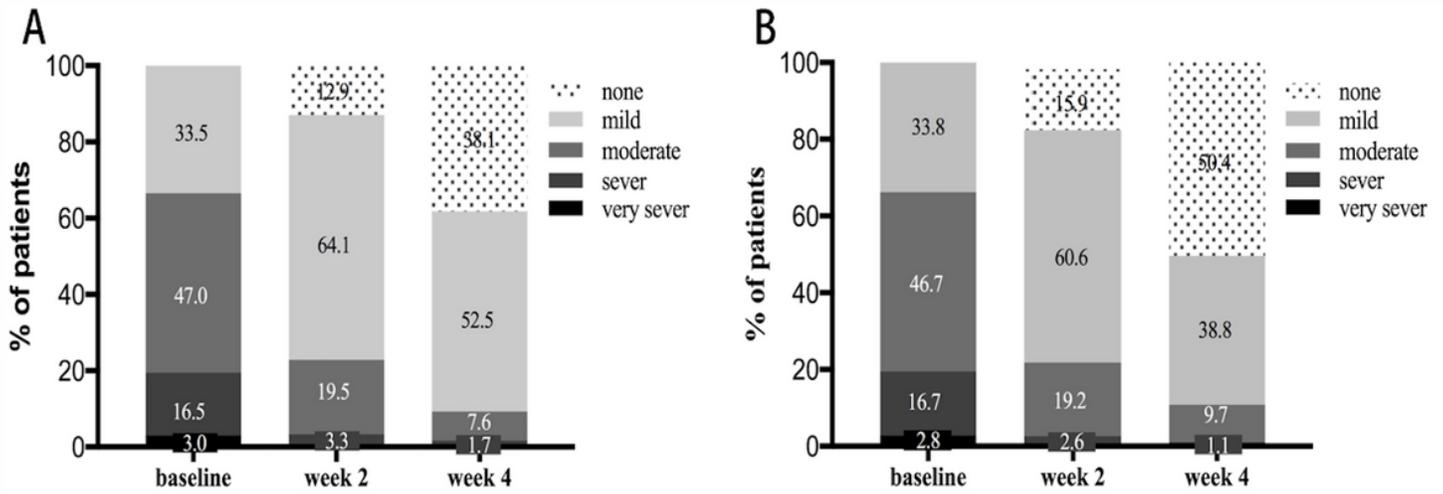


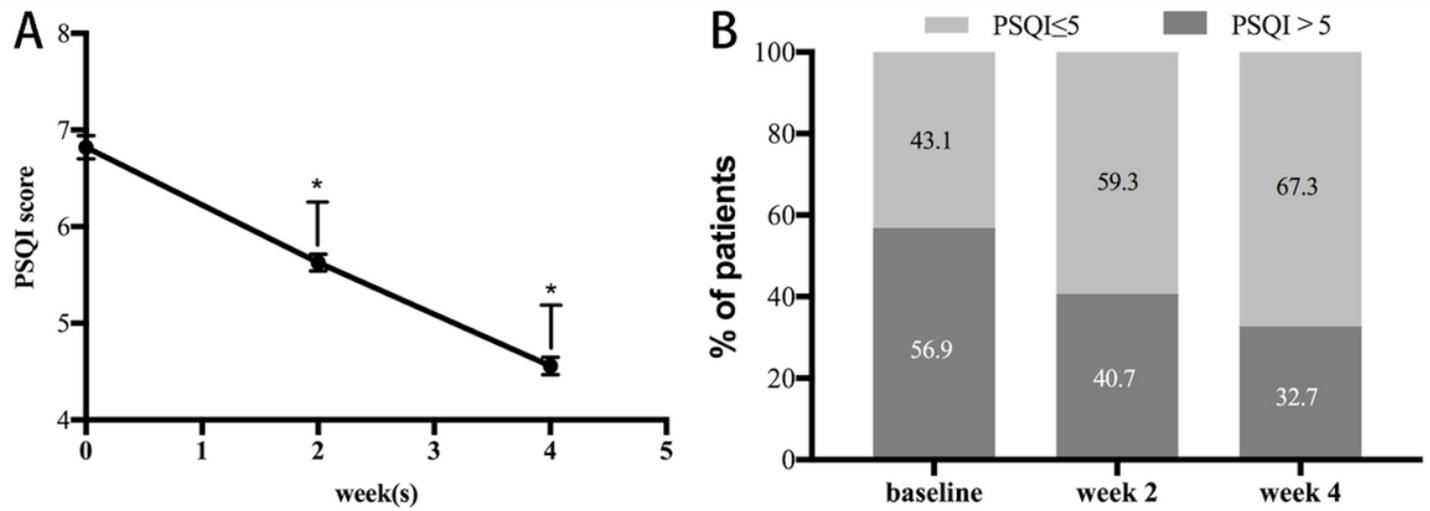
Figure 2

Effect of PPIs treatment on nighttime GERD symptoms (A) and GERD-related sleep disturbances (B) after 2 and 4 weeks. PPIs treatment over 4 weeks or 2 weeks significantly reduced the frequency of nighttime GERD symptoms, as well as GERD-related sleep disturbances. \* $P < .001$  versus baseline.



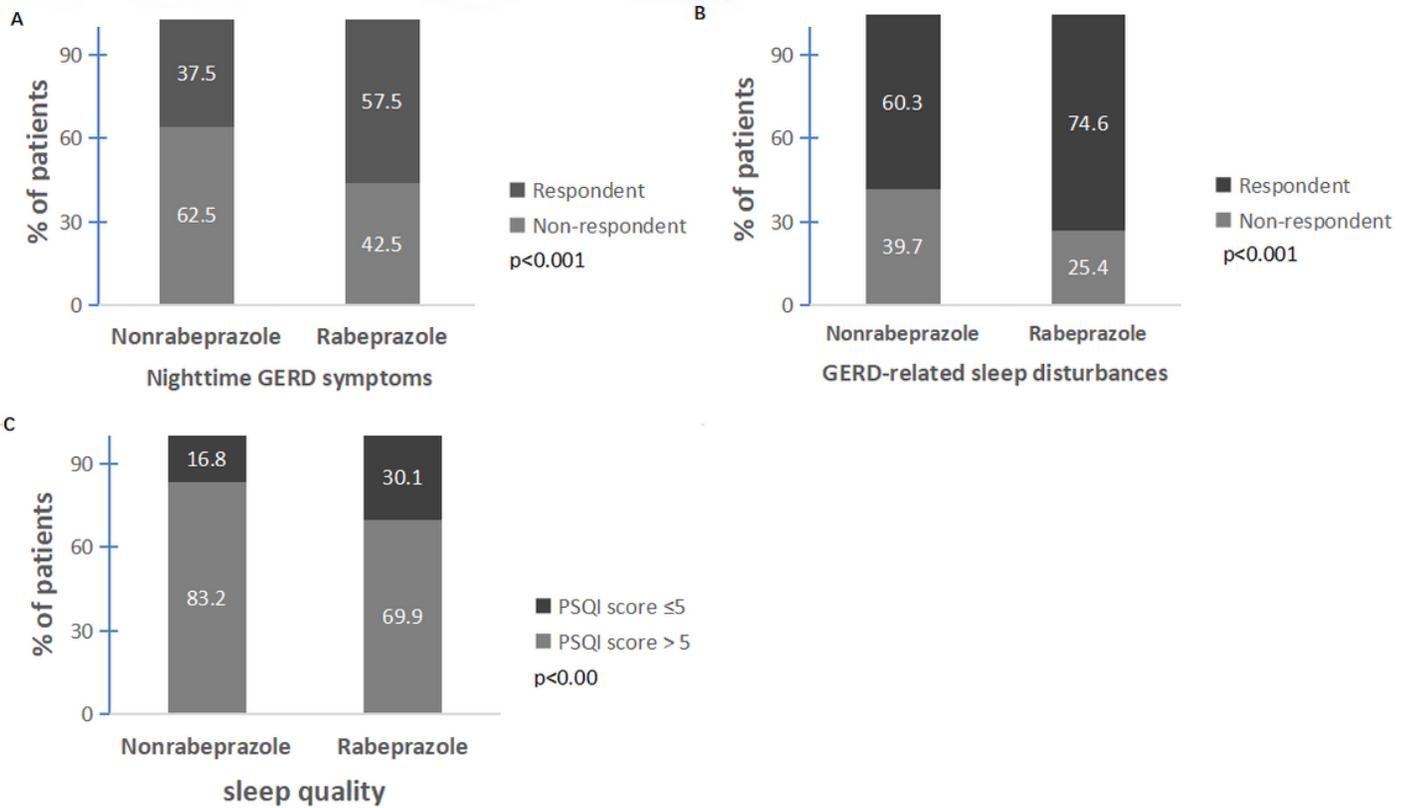
**Figure 3**

Changes in the distribution of nighttime heartburn severity (A) and nighttime acid regurgitation (B) from baseline to week 4.



**Figure 4**

Changes in the mean PSQI score (A) and proportion of patients with a total PSQI score  $\leq 5$  from baseline to week 4 (B). PPIs treatment significantly decreased the mean PSQI score both at week 2 and week 4. PSQI: the Pittsburgh Sleep Quality Index. \* $P < .001$  versus baseline.



**Figure 5**

Effect of rabeprazole and non-rabeprazole on nighttime GERD symptoms (A), GERD-related sleep disturbances (B) and PSQI score (C) at week 4.