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## Systematic review: role of acid, weakly acidic and weakly alkaline reflux in gastroesophageal reflux disease

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Short title: Weakly acidic and weakly alkaline reflux in GERD

## SUMMARY

### Background

The importance of weakly acidic and weakly alkaline reflux in gastroesophageal reflux disease (GERD) is gaining recognition.

### Aim

To quantify the proportions of reflux episodes that are acidic (pH < 4), weakly acidic (pH 4–7) and weakly alkaline (pH > 7) in adult patients with GERD, and to evaluate their correlation with symptoms.

### Methods

Studies were identified by systematic PubMed and Embase searches. Data are presented as sample-size weighted means and 95% confidence intervals.

### Results

In patients with GERD taking a proton pump inhibitor (PPI), 80% (76–84%) of reflux episodes were weakly acidic or weakly alkaline and 83% (78–88%) of reflux symptom episodes were associated with weakly acidic or weakly alkaline reflux episodes. In patients with GERD not taking a PPI, 63% (59–67%) of reflux episodes were acidic and 72% (57–87%) of reflux symptom episodes were associated with acid reflux episodes. Six studies presented data separately for weakly alkaline reflux, which accounted for < 5% of all reflux episodes, both on and off PPI therapy.

### Conclusions

Weakly acidic reflux underlies the majority of reflux episodes in patients with GERD on PPI therapy and is the main cause of reflux symptoms occurring despite PPI therapy.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic disease that affects 10–20% of adults in the USA and Europe (1), and its cardinal symptoms are heartburn and regurgitation (2). GERD develops when the reflux of stomach contents causes troublesome symptoms or complications (2). Episodes of gastroesophageal reflux occur mainly during transient lower esophageal sphincter relaxations (TLESRs) (3). The frequency and duration of TLESRs is similar between individuals with and without GERD. However, as a group, individuals with GERD have an increased risk of reflux occurring during such episodes (3, 4).

The study of gastroesophageal reflux has been revolutionized by the development of combined 24-h esophageal pH and multichannel intraluminal impedance (MII) monitoring (5, 6). MII detects gastroesophageal reflux episodes based on changes in resistance to alternating electrical current between a series of paired electrodes. One of the first studies to combine esophageal pH-monitoring with MII in humans was conducted about a decade ago in a small group of healthy volunteers (7). The investigators noted that only about half of all reflux episodes detected by MII were also detected by pH-metry, concluding that the remainder were due to relatively pH-neutral reflux.

Combined esophageal MII and pH-monitoring allows for the timed correlation of esophageal pH changes with reflux events, and achieves high sensitivity for the detection of acid (pH < 4), weakly acidic (pH 4–7) and weakly alkaline (pH > 7) reflux episodes. Use of this technology is bringing into focus the potential role of weakly acidic and weakly alkaline reflux in GERD and in the production of symptoms that are associated with reflux episodes (8). However, available data on the

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3 proportion of reflux episodes that are acidic, weakly acidic or weakly alkaline in  
4 patients with GERD have not been evaluated using a systematic approach before.  
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8 This systematic review of the literature assesses the proportions of reflux  
9 episodes that are acidic, weakly acidic or weakly alkaline in patients with GERD, and  
10 evaluates how these episodes are associated with use of PPIs and symptoms.  
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## 17 METHODS

### 20 Systematic literature searches

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22 Investigational studies of adult patients with GERD on or off PPI therapy were  
23 identified by systematic searches of the literature to September 2009 in PubMed and  
24 EMBASE. A flow chart of the systematic searches and search strings used is shown in  
25 Figure 1. To be eligible for inclusion, studies needed to provide data on the  
26 proportions of acid (pH < 4), weakly acidic (pH 4–7) and weakly alkaline (pH > 7)  
27 reflux episodes, based on esophageal pH-metry and MII monitoring. Studies reported  
28 in a language other than English were excluded, as were studies that did not report on  
29 the proportion of acid versus weakly acidic and/or weakly alkaline reflux episodes, or  
30 did not provide data sufficient for these proportions to be calculated (e.g. studies  
31 providing only data on the median [not mean] number of episodes per patient, or  
32 studies reporting only on the proportion of time that esophageal pH was acidic and  
33 weakly acidic and/or weakly alkaline). Studies on the effects of surgery on reflux  
34 were not included in this review.  
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### 56 Statistical analysis

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58 Sample-size-weighted means and sample-size-weighted 95% confidence intervals  
59 (CI) were calculated for all pooled prevalence data (9).  
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## RESULTS

The literature searches identified 21 studies involving 664 patients with GERD that fulfilled the inclusion criteria for this review (Figure 1). Twelve of the studies reported the data of 374 patients taking a PPI and 16 studies reported the data of 382 patients not taking a PPI. The majority of the identified studies recruited patients who had a history of reflux symptoms despite taking a PPI. Information on study design is summarized in Table 1. More details on the patient populations and reflux–symptom correlation data are provided in the online supplementary Tables S1, S2 and S3.

Seven of the studies reported data for patients on and off PPI therapy (271 patients in total). Information on the study population, and mean number of reflux episodes and symptom episodes, is shown in Table 2. Overall, the number of reflux episodes did not differ significantly between patients on and off PPI therapy, although one study that reported only on reflux during sleep observed a decrease in the number of reflux episodes with PPI treatment (10). Reflux symptom frequency was 20–70% higher in patients off PPI therapy than in those on PPI therapy in studies of patients who had reflux symptoms despite PPI treatment. The effect was even more pronounced in a study that included only patients with a history of favorable response to PPI therapy, in which the frequency of reflux symptom episodes in those on PPI treatment was 14 times that in patients off PPI therapy (11).

### **Patients with GERD taking a PPI**

The majority of reflux episodes in patients with GERD taking a PPI were of pH > 4, that is, weakly acidic or weakly alkaline (mean: 80%; 95% CI: 76–84%); only a small proportion of reflux episodes were acidic (mean: 20%; 95% CI: 16–24%) (Figure 2).

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4 Three studies presented data separately for weakly alkaline reflux, which accounted  
5  
6 for less than 5% of all reflux episodes (Table S1). The proportion of reflux episodes  
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8 that were acidic versus weakly acidic or weakly alkaline was similar overall during  
9  
10 the 24-h recording period compared with the postprandial period following an  
11  
12 evening meal in a study that assessed the two time periods separately (overall: 18%  
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14 acidic vs 82% weakly acidic/alkaline; postprandial: 20% acidic vs 80% weakly  
15  
16 acidic/alkaline) (12).  
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20 Most reflux-related symptom episodes were associated with reflux episodes  
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22 that were weakly acidic or weakly alkaline (mean: 83%; 95% CI: 78–88%); only a  
23  
24 minority of reflux-related symptoms were associated with acid reflux (mean: 17%;  
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26 95% CI: 12–22%) (Figure 3; Table S3) (13–17). The mean proportion of acid reflux  
27  
28 episodes that were symptomatic was 53% (95% CI: 50–56%), which was similar to  
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30 the mean proportion of weakly acidic or weakly alkaline reflux episodes that were  
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32 symptomatic (47%; 95% CI: 44–50%) (13, 15, 17). In a study that assessed heartburn  
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34 and regurgitation separately, and in which participants could report more than one  
35  
36 symptom during each symptom event, symptomatic acid reflux episodes were just as  
37  
38 commonly associated with heartburn as with regurgitation (67% vs 67%); by contrast,  
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40 symptomatic weakly acidic or weakly alkaline reflux episodes were more commonly  
41  
42 associated with regurgitation (98%, vs 10% with heartburn) (13).  
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### 50 **Patients with GERD not taking a PPI**

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52 In patients with GERD not taking a PPI, the majority of reflux episodes were acidic  
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54 (mean: 63%; 95% CI: 59–67%); the mean proportion of episodes that were weakly  
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56 acidic or weakly alkaline was 37% (95% CI: 33–41%) (Figure 2). Four studies  
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3 presented data separately for weakly alkaline reflux, which accounted for less than  
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5 5% of all reflux episodes (Table S2).  
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8 Most reflux-related symptom episodes were associated with acid reflux  
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10 episodes (mean: 72%; 95% CI: 57–87%); only a minority of reflux-related symptom  
11  
12 episodes were associated with reflux episodes that were weakly acidic or weakly  
13  
14 alkaline (mean: 28%; 95% CI: 13–43%) (Figure 4; Table S3) (11, 13, 14, 18). In a  
15  
16 study that assessed reflux episodes in the postprandial period, the proportion of reflux  
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18 episodes that were acidic versus weakly acidic or weakly alkaline was 64% versus  
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20 36%, respectively, following an evening meal, compared with 61% versus 39%,  
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22 respectively, overall during the 24-h recording period (12).  
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27 The mean proportion of reflux episodes that were symptomatic was slightly  
28  
29 higher for acid reflux than for weakly acidic or weakly alkaline reflux (acidic: 60%;  
30  
31 95% CI: 52–68%; weakly acidic/alkaline: 40%; 95% CI: 32–48%) (13, 18). In a study  
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33 that assessed heartburn and regurgitation separately, and in which participants could  
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35 report more than one symptom during each symptom event, both symptomatic acid  
36  
37 reflux episodes and symptomatic weakly acidic or weakly alkaline reflux episodes  
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39 were more commonly associated with heartburn than with regurgitation (acid –  
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41 heartburn: 84%, regurgitation: 56%; weakly acidic/alkaline – heartburn: 71%,  
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43 regurgitation, 52%) (13).  
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48 The proportion of reflux episodes that were acidic did not differ between  
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50 patients without reflux esophagitis (mean: 65%; 95% CI: 56–74%) and those with  
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52 reflux esophagitis (mean: 63%; 95% CI: 57–69%) in the five studies that reported  
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54 data separately for these two patient groups (Figure 5) (11, 19-22). Similarly, the  
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56 proportion of reflux episodes that were weakly acidic or weakly alkaline did not differ  
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58 between patients without reflux esophagitis (mean: 35%; 95% CI: 26–44%) and those  
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3 with reflux esophagitis (mean: 37%; 95% CI: 31–43%). However, in one study that  
4 reported separately on patients without or with Los Angeles grade A, B and C/D  
5 reflux esophagitis, and with Barrett's esophagus, the proportion of reflux episodes  
6 that were acidic increased with increasing esophageal injury (Table S2); participants  
7 who were on PPI therapy had to discontinue PPI use at least 5 days before the study  
8 (19).  
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## 20 DISCUSSION

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22 Our systematic review of data from 664 patients with GERD shows that the  
23 proportion of reflux episodes that are acidic as opposed to weakly acidic or weakly  
24 alkaline differs considerably between patients who are taking a PPI and those who are  
25 not. In patients taking a PPI, 20% (95% CI: 16–24%) of reflux episodes were acidic,  
26 whereas in patients not on PPI therapy the proportion was 63% (95% CI: 59–67%).  
27  
28 There is a paucity of data on the proportion of reflux episodes that are weakly acidic  
29 and weakly alkaline in individuals with GERD whose symptoms respond to PPI  
30 treatment, with only one of the studies in this review including such a patient  
31 population (23). The overall number of reflux episodes does not differ between  
32 patients on and off PPI therapy, although PPIs may reduce the number of nocturnal  
33 reflux episodes (10). However, patients on PPI therapy have a decreased symptom  
34 frequency compared with those not taking a PPI and, not surprisingly, this is  
35 particularly noticeable in patients who have a history of reduction in reflux symptoms  
36 in response to PPI therapy (11). The decrease in acid reflux with PPIs results from  
37 their ability to elevate gastric and esophageal pH levels, making them effective in the  
38 treatment of acid-related reflux symptoms and complications (24, 25). Most patients  
39 with GERD, with or without reflux esophagitis, experience resolution of their reflux  
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3 symptoms when on PPI therapy (25, 26). However, about 20–40% patients with  
4 GERD report partial- or non-response of their reflux symptoms to PPI therapy in  
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6 clinical studies conducted in the secondary care practice setting (26).  
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11       Refluxate with pH < 4 is not the only type capable of triggering symptoms  
12 during PPI treatment: our review shows that, in patients with GERD who have reflux  
13 symptom episodes despite taking a PPI, more than 80% of reflux-related symptom  
14 episodes (mean: 83%; 95% CI: 78–88%) are associated with weakly acidic or weakly  
15 alkaline reflux. Only a small minority of reflux-related symptoms is associated with  
16 acid reflux in these patients, and improved acid suppression is thus unlikely to address  
17 partial- or non-response to PPI therapy. Furthermore, the majority of patients taking a  
18 PPI were already on twice-daily doses. Recent large clinical trials that evaluated more  
19 potent acid-suppressive agents, such as the dual-release PPI, dexlansoprazole, and the  
20 potassium-competitive acid blocker AZD0865 failed to show clinical superiority of  
21 these agents to traditional PPIs (27, 28).  
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37       The pharmacological inhibition of TLESRs is a promising new approach for  
38 the treatment of GERD and in particular of reflux symptoms that occur despite PPI  
39 therapy. Baclofen, a  $\gamma$ -aminobutyric acid type B (GABA<sub>B</sub>) receptor agonist, has been  
40 shown to inhibit the triggering of TLESRs, thereby reducing acid as well as weakly  
41 acidic and weakly alkaline reflux (29). The clinical use of baclofen is, however,  
42 limited by its adverse effects on the central nervous system, which include dizziness  
43 and somnolence. In a recent proof-of-concept study, the newly developed GABA<sub>B</sub>  
44 receptor agonist lesogaberan, which appears to act predominantly in the periphery,  
45 significantly reduced reflux symptoms in patients with GERD with symptoms despite  
46 PPI therapy, and was well tolerated (30).  
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3 Another potential approach is treatment with a metabotropic glutamate  
4 receptor 5 (mGluR5) antagonist, which has been shown to inhibit TLESRs in animal  
5 studies (29). The mGluR5 negative allosteric modulator ADX10059 significantly  
6 reduced the number of symptomatic reflux episodes in patients with GERD in clinical  
7 trials (31). However, as with baclofen, clinical use of ADX10059 may be limited by  
8 commonly occurring adverse effects on the central nervous system, including  
9 dizziness and nausea (31).  
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19 Antireflux surgery has also been shown to reduce the overall number of reflux  
20 episodes, including those that are acid and weakly acidic or weakly alkaline (32).  
21 However, a study of endoscopic anti-reflux therapy showed significant post-operative  
22 reductions in the number of acid reflux episodes only, with no significant decreases in  
23 the number of weakly acidic or weakly alkaline reflux episodes (33).  
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32 One of the mechanisms through which weakly acidic or weakly alkaline reflux  
33 is believed to generate esophageal symptoms is through mechanical stimulation,  
34 because large volumes of refluxate can trigger heartburn irrespective of its acidity.  
35 Esophageal balloon distension commonly results in heartburn in patients with GERD,  
36 as well as in healthy volunteers, indicating that intra-esophageal mechanical  
37 stimulation can trigger this reflux symptom (34, 35). However, mechanical  
38 stimulation does not explain why, in patients with GERD who are taking a PPI, the  
39 predominant symptom associated with symptomatic weakly acidic or weakly alkaline  
40 reflux episodes seems to be regurgitation, whereas in patients with GERD who are not  
41 taking a PPI it seems to be heartburn (13).  
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55 Proximal esophageal extent of the refluxate is also associated with an  
56 increased likelihood of reflux symptoms. In the study by Zerbib *et al.*, included in this  
57 review, 53% of proximal reflux events were associated with symptoms, compared  
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3 with 34% of distal events ( $P < 0.05$ ) (15). Weakly acidic and weakly alkaline reflux  
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5 was as likely as acid reflux in the proximal esophagus to cause reflux symptoms.

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8 Similarly, Emerenziani *et al.* observed that the frequency of symptomatic reflux  
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10 events in the proximal esophagus was more than twofold that in the distal esophagus  
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12 in patients with GERD, irrespective of acidity (acid reflux – proximal: 25%, distal:  
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14 11%; weakly acidic/alkaline reflux – proximal: 27%, distal: 8%;  $P < 0.05$ ) (23).

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17 Bredenoord *et al.* observed that, compared with individuals without GERD, patients  
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19 with GERD and a positive symptom–reflux association had a significantly higher  
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21 proportion of reflux episodes that reached the proximal esophagus (controls: 20%, vs  
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23 36% and 34% in GERD patients with physiological and pathophysiological  
24  
25 esophageal acid exposure time, respectively;  $P < 0.05$ ) (36).  
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29 The proportion of reflux episodes that were acidic, versus weakly acidic or  
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31 weakly alkaline, in the 2 h following a meal was similar to that during the total 24-h  
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33 monitoring period in patients with GERD on or off PPI therapy in the study by  
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35 Blonski *et al.* (12). However, when restricting the monitoring period to 20-minute  
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37 time windows immediately before and after a meal, Bredenoord *et al.* observed a  
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39 higher proportion of acid reflux episodes in the postprandial than in the preprandial  
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41 period (53% vs 33%;  $P$  not reported) (36). Similarly, Beaumont *et al.* observed a  
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43 significantly enlarged postprandial acid pocket in the stomach of patients with GERD,  
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45 compared with healthy volunteers, as well as an increased number of acid reflux  
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47 episodes in the postprandial period in both healthy volunteers and patients with  
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49 GERD (37).  
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55 Our systematic review of the literature encountered several limitations. These  
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57 included the absence in some studies of relevant baseline patient demographics, such  
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59 as frequency and severity of reflux symptoms and whether or not these responded to  
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3 PPI therapy, as well as inconsistencies between studies in the definitions and methods  
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5 used to define associations between reflux episodes and reflux symptoms. Most  
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7 studies included only individuals who had persistent reflux symptoms despite PPI  
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9 therapy, and this will potentially have led to selection bias in the reported data. In  
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11 addition, the analysis of reflux-related symptom episodes did not examine separately  
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13 the different types of persistent symptoms. It is noteworthy that, despite these  
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15 limitations, the results obtained by our systematic review are remarkably consistent.  
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20 Other limitations include

21  
22 In conclusion, weakly acidic gastroesophageal reflux comprises a substantial  
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24 part of all reflux episodes in patients with GERD on PPI therapy. Whereas the total  
25  
26 number of reflux episodes does not differ between patients on and off PPI therapy, in  
27  
28 those patients who are on PPI therapy, weakly acidic reflux episodes form the large  
29  
30 majority of all reflux episodes. In patients with GERD who have reflux symptoms  
31  
32 despite PPI therapy, weakly acidic reflux episodes are the main cause of these  
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34 symptoms. In future, drugs that prevent the refluxate from reaching the esophagus  
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36 may provide symptom relief in patients with GERD who have an unsatisfactory  
37  
38 response to PPI therapy.  
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For Peer Review

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## Tables and Figure legends

**Table 1.** Overview of the 21 studies included in the review.

Ref.	Patients (n)	PPI status	Persistent GERD symptoms despite PPI therapy	Gastro-esophageal pathology	Number of reflux episodes analysed	Time period of analysis	Meal periods included in analysis
Aanen <i>et al.</i> , 2008 (38)	19	Off PPI	NR	NR	1199	24 h	No
Beaumont and Boeckxstaens, 2009 (39)	23*	On PPI	Yes	HH (n = 11)	1851	24 h	No
Blonski <i>et al.</i> , 2009 (12)	110	Off PPI (n = 40); on PPI (n = 70)	Yes	NR	NR	24 h and 2 h postprandial	Yes
Bredenoord <i>et al.</i> , 2006 (40)	12 <sup>†</sup>	Off PPI	NR	RE (n = 6)	NR	24 h	No
Bredenoord <i>et al.</i> , 2006 (36)	28	Off PPI	NR	NR	NR	24 h	No
Bredenoord <i>et al.</i> , 2008 (41)	14	Off PPI	NR	NR	NR	24 h	No
Bredenoord <i>et al.</i> , 2009 (19)	50 <sup>†</sup>	Off PPI	Pts without RE: no; pts with RE or BE: NR	RE (n = 30); BE (n = 10)	NR	24 h	No
Conchillo <i>et al.</i> , 2008 (20)	26 <sup>†</sup>	Off PPI	NR	RE (n = 13)	NR	24 h	No
Emerenziani <i>et al.</i> , 2008 (11)	52	Off PPI (n = 52); on PPI (n = 12)	No	RE (n = 20)	2984	24 h	NR

Ref.	Patients (n)	PPI status	Persistent GERD symptoms despite PPI therapy	Gastro-esophageal pathology	Number of reflux episodes analysed	Time period of analysis	Meal periods included in analysis
Hemmink <i>et al.</i> , 2008 (42)	30	Off PPI (n = 30); on PPI (n = 30)	Yes	RE (n = 3)	NR	24 h	No
Iwakiri <i>et al.</i> , 2009 (16)	13	On PPI	Yes	None	916	24 h.	No
Khan <i>et al.</i> , 2009 (43)	30 <sup>†</sup>	On PPI	Yes	NR	NR	24h	NR
Orr <i>et al.</i> , 2007 (10)	15	Off PPI (n = 15); on PPI (n = 15)	NR	NR	112	One night	No
Pace <i>et al.</i> , 2007 (21)	20	Off PPI (n = 7); on PPI (n = 13)	NR	RE (n = 6)	1137	24 h	NR
Tutuian <i>et al.</i> , 2008 (17)	120	On PPI	Yes	NR	3547	24 h	NR
Vela <i>et al.</i> , 2001 (13)	12	Off PPI (n = 12); on PPI (n = 12)	NR	NR	478	24 h	NR
Vela <i>et al.</i> , 2003 (18)	9 <sup>†‡</sup>	Off PPI	NR	NR	253	24 h	NR
Weigt <i>et al.</i> , 2007 (14)	32	Off PPI (n = 16); on PPI (n = 16)	NR	NR	3591	24 h	No
Xiao <i>et al.</i> , 2009 (22)	42 <sup>†</sup>	Off PPI	NR	RE (n = 20)	NR	24 h	No
Zerbib <i>et al.</i> , 2008 (15)	20	On PPI	Yes	RE (n = 1); BE (n = 3)	1273	24 h	No

Ref.	Patients (n)	PPI status	Persistent GERD symptoms despite PPI therapy	Gastro-esophageal pathology	Number of reflux episodes analysed	Time period of analysis	Meal periods included in analysis
Zentilin <i>et al.</i> , 2005 (44)	10 <sup>‡</sup>	Off PPI	NR	RE (n = 3)	112	1 h	No

\*The study also included a GABA<sub>B</sub> agonist treatment arm, data for which are not reported here.

†The study also included patients without GERD, for whom the data are not included here.

‡The study also included a GABA<sub>B</sub> agonist or alginate treatment arm, data for which are not reported here.

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; HH, hiatal hernia; NR, not reported; PPI, proton pump inhibitor; pts, patients RE, reflux esophagitis.

**Table 2.** Number of reflux episodes and reflux symptoms in individuals with GERD on and off PPI therapy.

Reference	Mean number of reflux episodes per patient		P value (difference on vs off PPI)	Mean number of reflux symptoms per patient		P value (difference on vs off PPI)	Ratio reflux symptoms off PPI/on PPI
	On PPI	Off PPI		On PPI	Off PPI		
Blonski <i>et al.</i> , 2009 (12)	Overall: 1.7/h Postprandial: 4.5/ h	Overall: 2.3/h Postprandial: 5.1/h	Overall: NS Postprandial: NS	NR	NR	—	—
Emerenziani <i>et al.</i> , 2008 (11)	36/24 h	41/24 h	NS	0.7/24h	10/24 h	NR	14
Hemmink <i>et al.</i> , 2008 (42)	69/24 h	73/24 h	NS	3/24h	5/24 h	< 0.01	1.7
Orr <i>et al.</i> , 2007 (10)	39/night	73/night	< 0.01	NR	NR	—	—
Pace <i>et al.</i> , 2007 (21)	61/24 h	50/24 h	NR	NR	NR	—	—
Vela <i>et al.</i> , 2001 (13)	22/2 h postprandial	18/2 h postprandial	NS	11/2 h postprandial	13/2 h postprandial	NR	1.2
Weigt <i>et al.</i> , 2007 (14)	NR	NR	—	35/24 h	44/24 h	NR	1.3

GERD, gastroesophageal reflux disease; MII-pH, combined multichannel intraluminal impedance and pH monitoring; NR, not reported; NS, not significant; PCP, primary care practitioner; PPI, proton pump inhibitor.

## Figure legends

**Figure 1.** Flow chart of systematic literature searches.

**Figure 2.** The proportion of acid and weakly acidic or weakly alkaline reflux episodes in 374 patients with gastroesophageal reflux disease (GERD) taking a proton pump inhibitor (PPI) (13 treatment arms) and 356 patients with GERD not taking a PPI (22 treatment arms). For studies that reported separately on weakly acidic and weakly alkaline reflux episodes, these data were combined. Symbols denote proportions for each treatment arm and horizontal lines show mean proportions, weighted by the number of patients included in each treatment arm.

**Figure 3.** The proportion of symptom-related reflux episodes that were acidic and weakly acidic or weakly alkaline in 174 patients with gastroesophageal reflux disease on proton pump inhibitor (PPI) therapy. Four studies reported on reflux symptoms combined and one study reported separately on heartburn and regurgitation. The following symptoms were recorded: heartburn, regurgitation (Zerbib et al., 2008); heartburn, regurgitation, acid taste (Vela et al., 2001); heartburn, chest pain, dysphagia, throat pain, oppression (Iwakiri et al., 2009); typical and atypical reflux symptoms (not specified further) (Tutuian et al., 2008); heartburn, regurgitation, chest pain, upper abdominal pain, coughing, sore throat, globus, pressure, burning of the tongue (Weigt et al., 2007). The horizontal line indicates the mean proportion of acid reflux episodes (symptomatic and asymptomatic combined), weighted by the number of patients included in each study.

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3 **Figure 4.** The proportion of symptom-related reflux episodes that were acidic and  
4 weakly acidic or weakly alkaline in 82 patients with gastroesophageal reflux disease  
5 off proton pump inhibitor (PPI) therapy. One study reported separately on patients  
6 without and with reflux esophagitis (RE); three studies did not report on esophageal  
7 injury. The following symptoms were recorded: heartburn, regurgitation (Emerenziani  
8 et al., 2008); heartburn, regurgitation, acid taste (Vela et al., 2001;  
9 Vela et al., 2003); heartburn, regurgitation, chest pain, upper abdominal pain,  
10 coughing, sore throat, globus, pressure, burning of the tongue (Weigt et al., 2007).  
11 The horizontal line indicates the mean proportion of acid reflux, weighted by the  
12 number of patients included in each study.  
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32 **Figure 5.** The proportion of acid and weakly acidic or weakly alkaline reflux episodes  
33 in 177 patients with gastroesophageal reflux disease off proton pump inhibitor (PPI)  
34 therapy without (n = 82; 5 treatment arms) and with (n = 95; 8 treatment arms) reflux  
35 esophagitis. For studies that reported separately on weakly acidic and weakly alkaline  
36 reflux episodes, these data were combined. Symbols denote proportions for each  
37 treatment arm and horizontal lines show mean proportions, weighted by the number of  
38 patients included in each treatment arm.  
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## PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4–5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5, and Figure 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, and Figure 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, and Figure 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, and Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, and Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5, and Figure 1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, and Figure 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, and Figure 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5–6



# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.	5–6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5–6
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1 and 2, and S1–3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 1 and 2, and S1–3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6–9, and Figures 2–4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6–9, and Figures 2–4
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10–13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10–13
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13



# PRISMA 2009 Checklist

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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For Peer Review

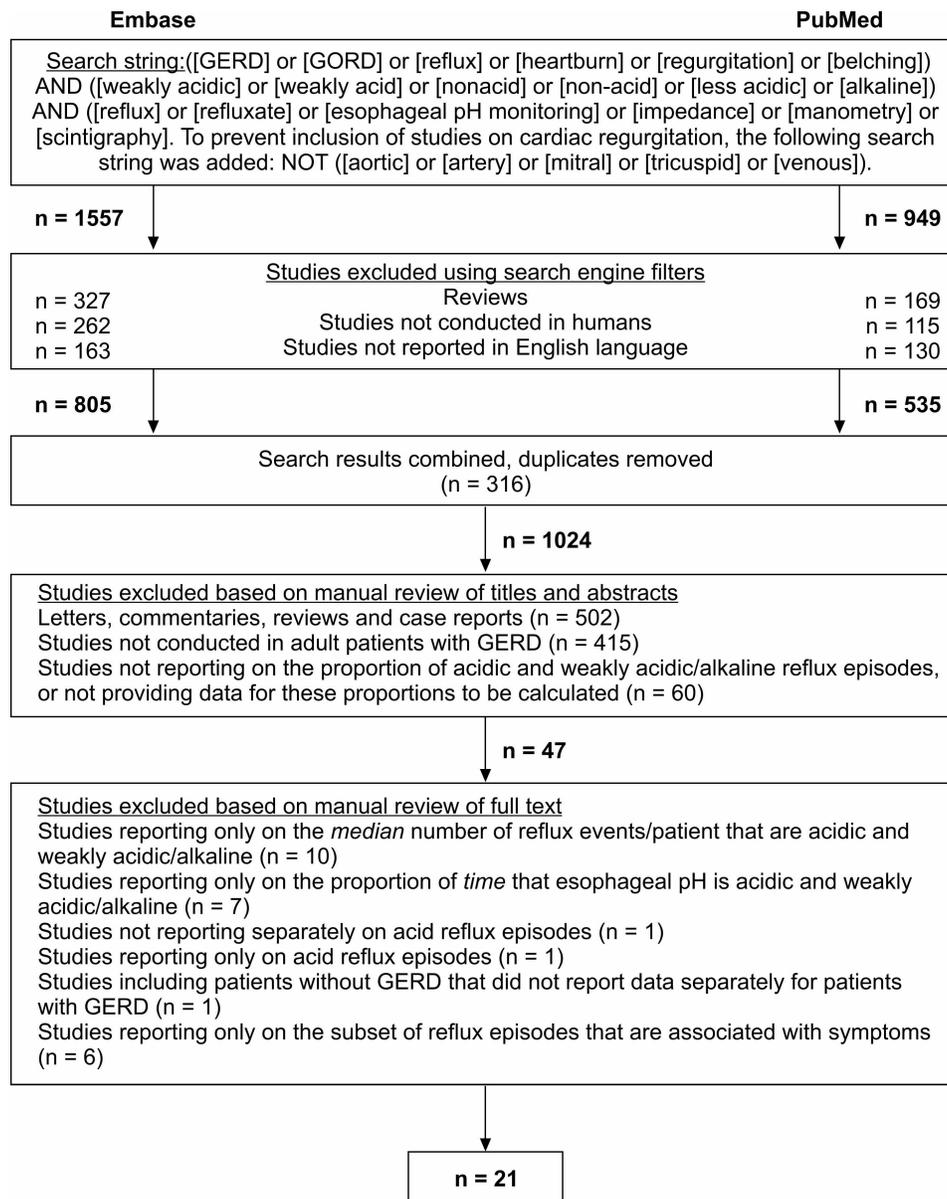


Figure 1. Flow chart of systematic literature searches.  
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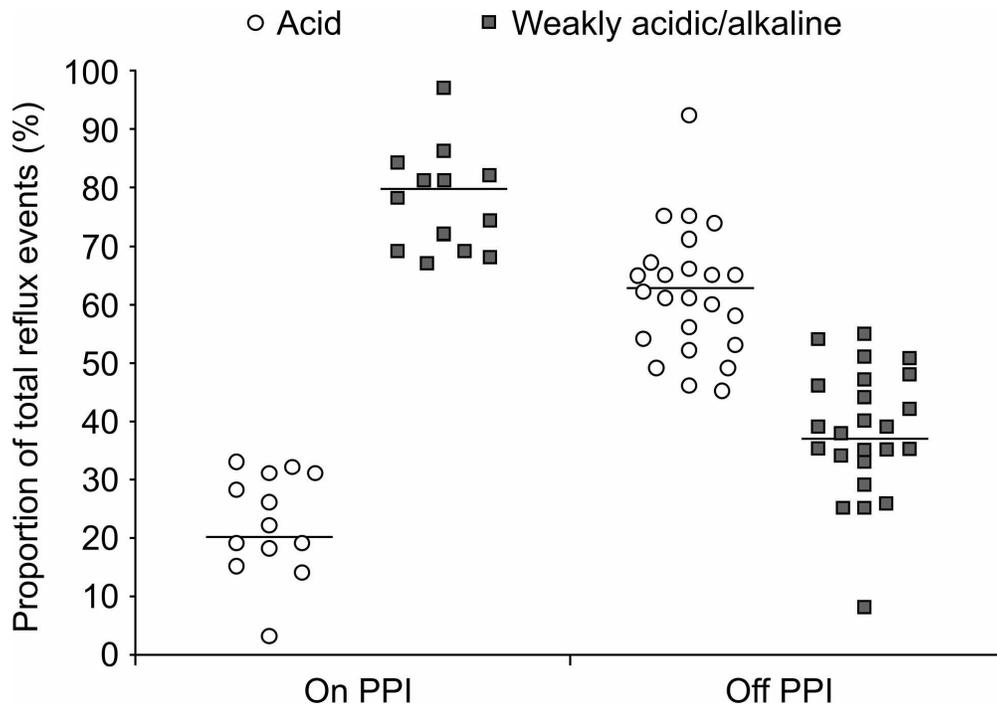
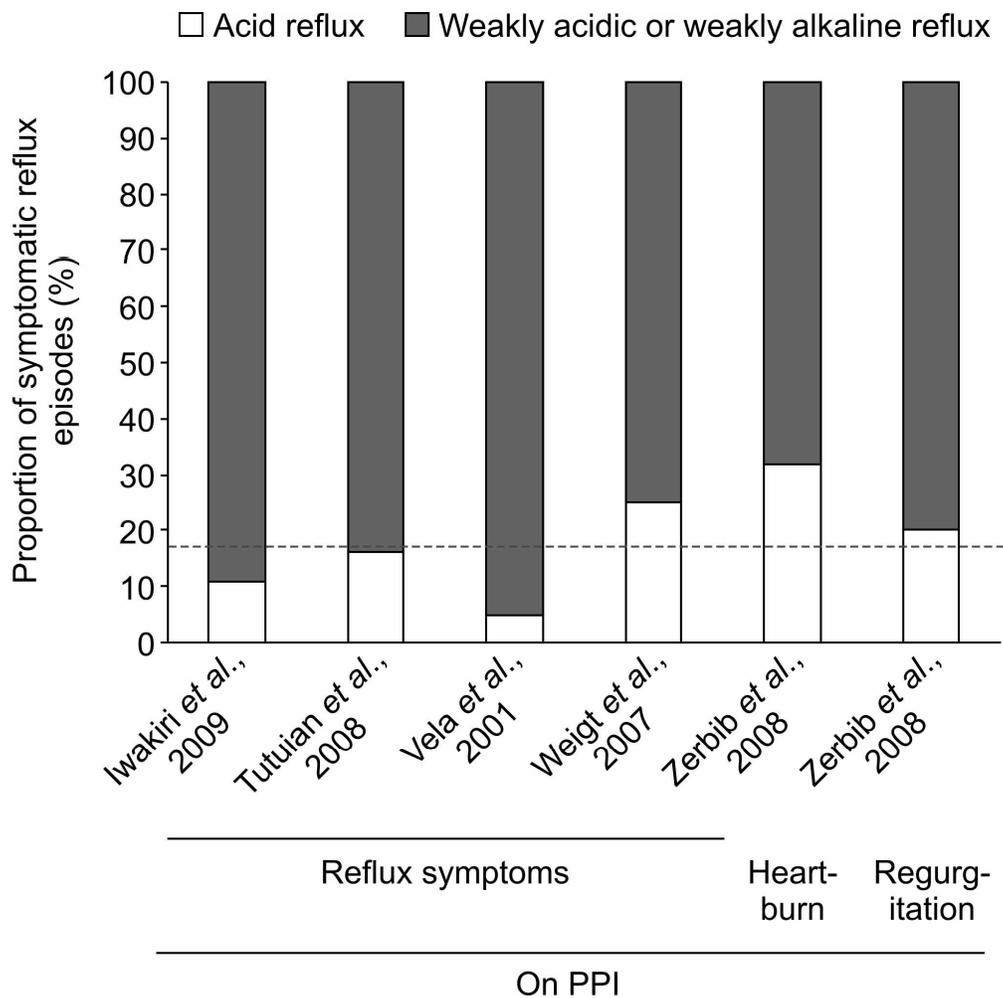


Figure 2. The proportion of acid and weakly acidic or weakly alkaline reflux episodes in 374 patients with gastroesophageal reflux disease (GERD) taking a proton pump inhibitor (PPI) (13 treatment arms) and 356 patients with GERD not taking a PPI (22 treatment arms). For studies that reported separately on weakly acidic and weakly alkaline reflux episodes, these data were combined.

Symbols denote proportions for each treatment arm and horizontal lines show mean proportions, weighted by the number of patients included in each treatment arm.

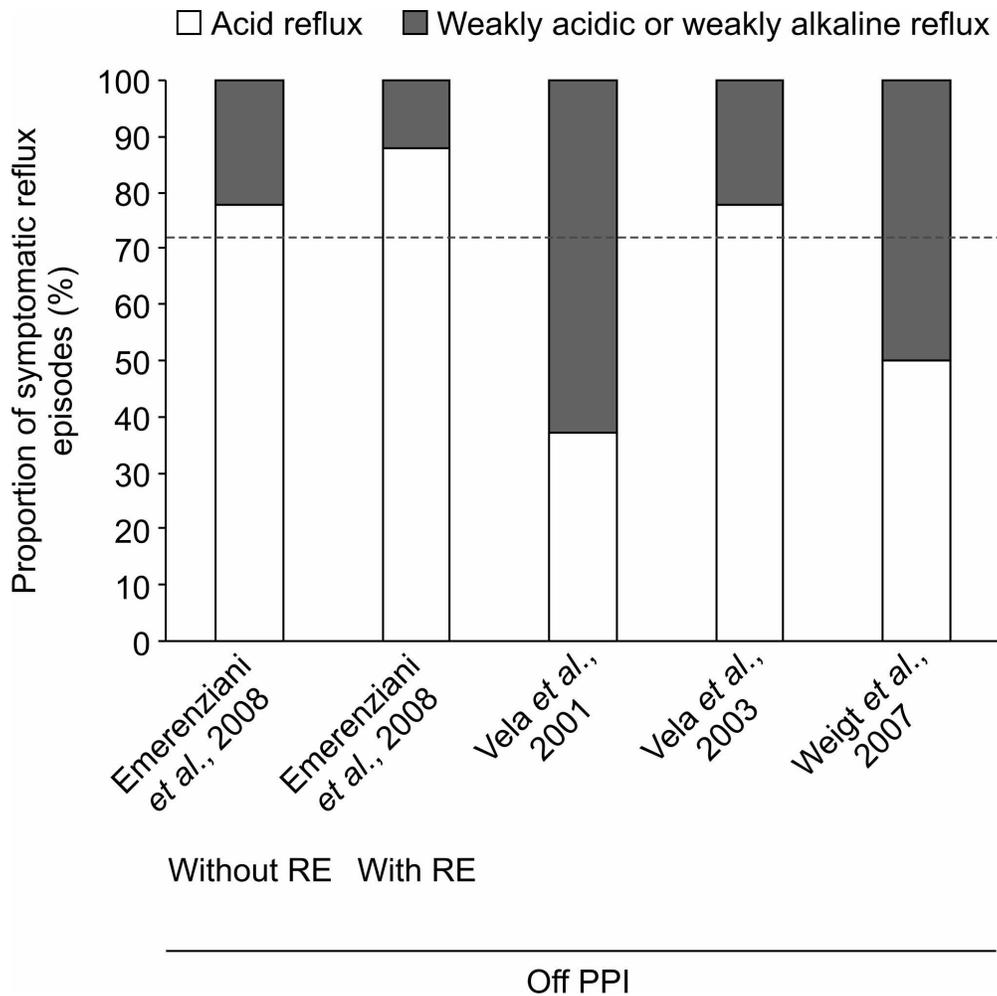
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41 Figure 3. The proportion of symptom-related reflux episodes that were acidic and weakly acidic or  
42 weakly alkaline in 174 patients with gastroesophageal reflux disease on proton pump inhibitor (PPI)  
43 therapy. Four studies reported on reflux symptoms combined and one study reported separately on  
44 heartburn and regurgitation. The following symptoms were recorded: heartburn, regurgitation  
45 (Zerbib et al., 2008); heartburn, regurgitation, acid taste (Vela et al., 2001); heartburn, chest pain,  
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47 specified further) (Tutuian et al., 2008); heartburn, regurgitation, chest pain, upper abdominal pain,  
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49 line indicates the mean proportion of acid reflux episodes (symptomatic and asymptomatic  
50 combined), weighted by the number of patients included in each study.

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41 Figure 4. The proportion of symptom-related reflux episodes that were acidic and weakly acidic or  
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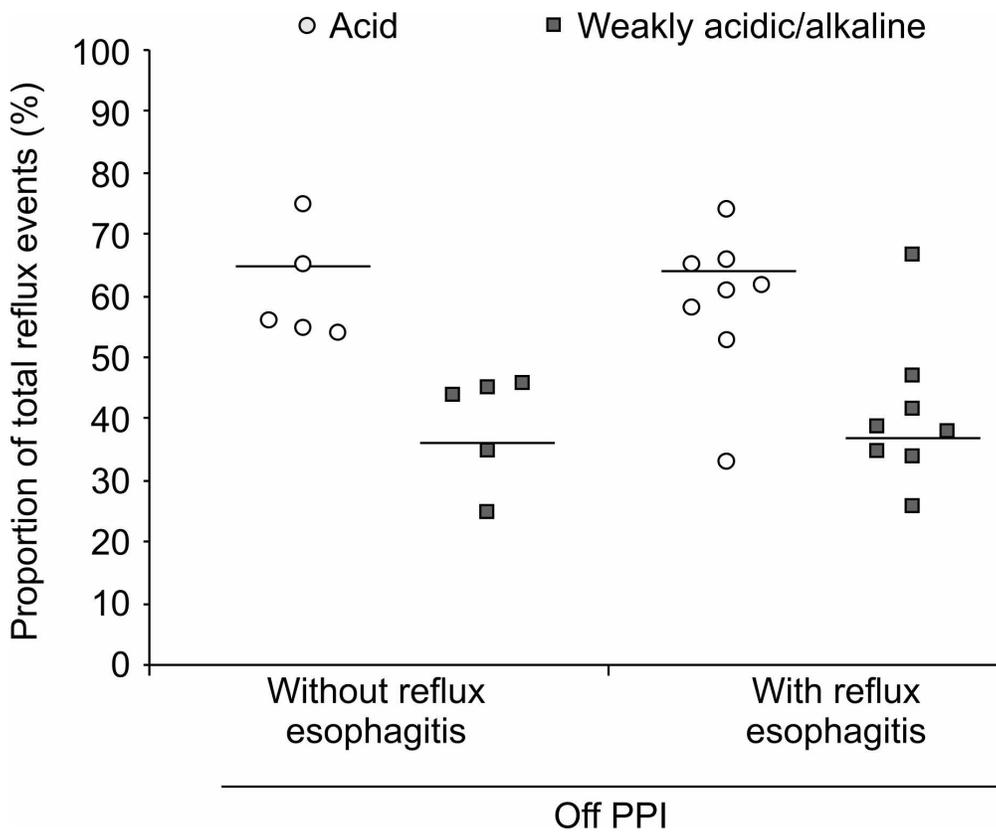


Figure 5. The proportion of acid and weakly acidic or weakly alkaline reflux episodes in 177 patients with gastroesophageal reflux disease off proton pump inhibitor (PPI) therapy without (n = 82; 5 treatment arms) and with (n = 95; 8 treatment arms) reflux esophagitis. For studies that reported separately on weakly acidic and weakly alkaline reflux episodes, these data were combined. Symbols denote proportions for each treatment arm and horizontal lines show mean proportions, weighted by the number of patients included in each treatment arm.

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## Online supplementary materials

**Table S1.** Acid, weakly acidic and weakly alkaline reflux episodes as a proportion of total reflux episodes in individuals with GERD on PPI therapy.

Ref.	Study population on PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Beaumont and Boeckxstaens, 2009 <sup>1</sup>	GERD patients on PPI therapy for typical GERD symptoms (n = 23) (without HH, n = 12; with HH, n = 11) <sup>†</sup> ; 22% of patients reported symptoms during the study	NR	HH-: 694 HH+: 1157	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded	HH-: 32% HH+: 22%	HH-: 68% <sup>‡</sup> HH+: 78% <sup>‡</sup>	NR	
Blonski <i>et al.</i> , 2009 <sup>2</sup>	Patients referred for MII-pH because of persistent reflux symptoms despite PPI therapy (n = 70)	NR	NR	Mean number of acid and weakly acidic/alkaline reflux episodes/h per patient during 24 h; 24-h data were compared with 2-h postprandial data (evening meal)	Total: 18% <sup>‡</sup> Postprandial : 20% <sup>‡</sup>	Total: 82% <sup>‡</sup> Postprandial: 80% <sup>‡</sup>	NR	
Emerenziani <i>et al.</i> , 2008 <sup>3</sup>	Patients with GERD with a history of favorable response to PPI (n = 12); 33% of patients reported symptoms during the study	No	2984; NR separately for patients on/off PPI therapy	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; inclusion of meal periods NR	31% <sup>‡</sup>	69%	NR	

Ref.	Study population on PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Hemmink <i>et al.</i> , 2008 <sup>4</sup>	Patients with typical reflux symptoms despite PPI therapy (n = 30)	Without RE, n = 27; with RE, n = 3 (data NR separately)	NR	Mean number of acid and weakly acidic/alkaline reflux episodes/24 h per patient; meal periods excluded	28% <sup>‡</sup>	69% <sup>‡</sup>	3% <sup>‡</sup>	NR
Iwakiri <i>et al.</i> , 2009 <sup>5</sup>	Patients with heartburn on $\geq 3$ days per week despite double-dose PPI therapy (n = 13)	No	916	Frequency of acid, weakly acidic and weakly alkaline reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded. Symptoms and reflux were considered to be associated if a reflux episode was detected 5 min before the symptom. SI $\geq 50\%$ was considered positive.	14%	82%	4%	5% and 40% of symptoms were associated with acid and weakly acidic/alkaline reflux, respectively; 15% and 39% of patients had a positive SI for acid and weakly acidic/alkaline reflux, respectively
Khan <i>et al.</i> , 2009 <sup>6</sup>	Patients referred for MII-pH because of persistent reflux symptoms despite PPI therapy (n = 30) <sup>¥</sup>	NR	NR	Mean number of acid and weakly acidic/alkaline reflux episodes/24 h per patient; inclusion of meal periods NR	26% <sup>‡</sup>	74% <sup>‡</sup>		NR
Orr <i>et al.</i> , 2007 <sup>7</sup>	Patients with reflux symptoms (history of PPI response NR) (n = 15)	NR	39	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during one night, following a large meal	31% <sup>‡</sup>	69% <sup>‡</sup>		NR

Ref.	Study population on PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Pace <i>et al.</i> , 2007 <sup>8</sup>	Patients with reflux symptoms (history of PPI response NR) (n = 13)	Without RE, n = 9; with RE, n = 4	790	Number of acid and weakly acidic/alkaline reflux episodes for each patient during 24 h; inclusion of meal periods NR	19% <sup>‡</sup> (without RE: 15% <sup>‡</sup> ; with RE: 27% <sup>‡</sup> )	81% <sup>‡</sup> (without RE: 85% <sup>‡</sup> ; with RE: 73% <sup>‡</sup> )		NR
Tutuian <i>et al.</i> , 2008 <sup>9</sup>	Patients referred for MII-pH because of persistent reflux symptoms despite PPI therapy (n = 120)	NR	3547	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; inclusion of meal periods NR. Symptoms and reflux were considered to be associated if a reflux episode was detected 5 min before the symptom.	15%	84%		16% <sup>‡</sup> and 84% <sup>‡</sup> of symptomatic episodes, respectively, were associated with acid and weakly acidic/alkaline reflux episodes; 14% <sup>‡</sup> and 13% <sup>‡</sup> of acid and weakly acidic/alkaline reflux episodes, respectively, were symptomatic

Ref.	Study population on PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Vela <i>et al.</i> , 2001 <sup>10</sup>	Patients with reflux symptoms (history of PPI response NR) (n = 12; correlation of reflux episodes with symptoms conducted in a subset of 5 patients)	NR	261	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; inclusion of meal periods NR. Symptoms and reflux were considered to be associated if a reflux episode was detected 2 min prior to the symptom. SI $\geq 50\%$ and SSI $\geq 10\%$ were considered positive.	3%	97%		60% of acid and 30% of weakly acidic/alkaline reflux episodes were symptomatic; 5% of symptomatic reflux episodes were acid and 95% were weakly acidic/alkaline; 67% of symptomatic acid reflux episodes were associated with heartburn and 67% with regurgitation; 10% of weakly acidic/alkaline reflux episodes were associated with heartburn and 98% with regurgitation.
Weigt <i>et al.</i> , 2007 <sup>11</sup>	Patients with reflux symptoms (history of PPI response NR) (n = 16)	NR	3591 overall, NR separately for patients on/ off PPI therapy	Frequency of weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded. The time difference between symptom and reflux occurrence for the two to be considered associated was NR. SI $\geq 50\%$ was considered positive.	33% <sup>‡</sup>	67%		33% and 21% of symptoms were related to acid and weakly acidic/alkaline reflux episodes, respectively; SI was more often positive regarding weakly acidic/alkaline reflux (12 times) than acid reflux (4 times)

Ref.	Study population on PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Zerbib <i>et al.</i> , 2008 <sup>12</sup>	Patients referred for MII-pH because of persistent reflux symptoms despite PPI therapy (n = 20)	Without RE, n = 16; with RE, n = 1; with BE, n = 3 (data NR separately)	1273	Frequency of weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded	19%	80%	1%	28% of acid and 24% of weakly acidic/alkaline reflux episodes were symptomatic; 21% of symptomatic reflux episodes were acid and 79% were weakly acidic/alkaline; 32% and 68% of heartburn episodes were related to acid and weakly acidic/alkaline reflux episodes, respectively; 20% and 80% of regurgitation episodes were related to acid and weakly acidic/alkaline reflux episodes, respectively

\*Reflux episodes were defined as acidic if pH < 4, as weakly acidic if pH 4–7 and as weakly alkaline if pH > 7.

<sup>†</sup>The study also included a GABA<sub>B</sub> agonist treatment arm, data for which are not reported here.

<sup>‡</sup>Value calculated from data provided in the publication.

<sup>§</sup>Data not reported separately for acid and weakly acidic/alkaline reflux episodes.

<sup>¥</sup>The study also included patients without GERD, for whom the data are not included here.

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; HH, hiatal hernia; MII-pH, combined multichannel intraluminal impedance and pH monitoring; NR, not reported; PPI, proton pump inhibitor; RE, reflux esophagitis; SI, symptom index.

**Table S2.** The proportion of acid, weakly acidic and weakly alkaline reflux episodes as a proportion of total reflux episodes in individuals with GERD off PPI therapy.

Ref.	Study population off PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Aanen <i>et al.</i> , 2008 <sup>13</sup>	Patients with a GERD diagnosis (history of PPI response NR) (n = 19)	NR	1199	Frequency of acid and weakly acidic reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded	52%	47%	1% <sup>†</sup>	NR
Blonski <i>et al.</i> , 2009 <sup>2</sup>	Patients referred for MII-pH therapy to test whether presenting symptoms off PPI therapy are caused by GER (n = 40)	NR	NR	Mean number of acid and weakly acidic/alkaline reflux episodes/h per patient during 24 h; 24-h data were compared with 2-h postprandial data (evening meal)	Total: 61% <sup>†</sup> Postprandial: 64% <sup>†</sup>	Total: 39% <sup>†</sup> Postprandial: 36% <sup>†</sup>		NR
Bredenoord <i>et al.</i> , 2006 <sup>14</sup>	Patients with GERD with time pH < 4 > 6% (history of PPI response NR) (n = 12) <sup>‡</sup>	Without RE, n = 6; with RE, n = 6 (LA grade A, n = 5; B, n = 1)	NR	Mean number of acid and weakly acidic/alkaline reflux episodes per patient during 24 h; meal periods excluded	67%	33%		NR
Bredenoord <i>et al.</i> , 2006 <sup>15</sup>	Patients with GERD (history of PPI response NR) (n = 28) (time pH < 4 < 6%; [pH-], n = 14; time pH < 4 ≥ 6% [pH+], n = 14)	NR	NR	Frequency of acid reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded	pH-: 46% pH+: 71%	pH-: 54% <sup>†</sup> pH+: 29% <sup>†</sup>		NR

Ref.	Study population off PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Brendenoord <i>et al.</i> , 2008 <sup>16</sup>	Patients with GERD selected for Nissen fundoplication (history of PPI response NR) (n = 14)	NR	NR	Mean number of acid and weakly acidic/alkaline reflux episodes per patient during 24 h; meal periods excluded	65% <sup>‡</sup>	35% <sup>‡</sup>		NR
Brendenoord <i>et al.</i> , 2009 <sup>17</sup>	Patients with GERD (patients without RE had a history of favorable response to PPI; history of PPI response NR for patients with RE and BE) (n = 50) <sup>‡</sup>	Without RE, n = 10; with RE, n = 30 (LA grade A, n = 10; B, n = 10; C/D, n = 10), with BE, n = 10	NR	Frequency of acid, weakly acidic and alkaline reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded	Without RE: 54% With RE grade A: 53% With RE grade B: 58% With RE grade C/D: 62% With BE: 66%	Without RE: 45% <sup>†</sup> With RE grade A: 46% <sup>†</sup> With RE grade B: 41% <sup>†</sup> With RE grade C/D: 37% <sup>†</sup> With BE: 33% <sup>†</sup>	1% in all groups	NR
Conchillo <i>et al.</i> , 2008 <sup>18</sup>	Patients with GERD (history of response PPI NR) (n = 26) <sup>‡</sup>	Without RE, n = 13; with RE, n = 13	NR	Mean number of acid and weakly acidic/alkaline reflux episodes/h per patient during 24 h; meal periods excluded	Without RE: 65% <sup>†</sup> With RE: 61% <sup>†</sup>	Without RE: 35% <sup>†</sup> With RE: 39% <sup>†</sup>		NR

Ref.	Study population off PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Emerenziani <i>et al.</i> , 2008 <sup>3</sup>	Patients with GERD with a history of favorable response to PPI (n = 52)	Without RE, n = 32; with RE, n = 20	2984; NR separately for patients on/off PPI therapy	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; inclusion of meal periods NR	Without RE: 75% <sup>‡</sup> With RE: 74% <sup>‡</sup>	Without RE: 25% <sup>‡</sup> With RE: 26% <sup>‡</sup>		In patients without RE, 78% <sup>‡</sup> of symptomatic reflux events were acid and 21% <sup>‡</sup> were weakly acidic/alkaline; in patients with RE, 88% of symptomatic reflux episodes were acid and 12% were weakly acidic/alkaline
Hemmink <i>et al.</i> , 2008 <sup>4</sup>	Patients with typical reflux symptoms despite PPI therapy (n = 30)	Without RE, n = 27; with RE, n = 3 (data NR separately)	NR	Mean number of acid and weakly acidic/alkaline reflux episodes/24 h per patient; meal periods excluded	65% <sup>†</sup>	32% <sup>†</sup>	3% <sup>†</sup>	NR
Orr <i>et al.</i> , 2007 <sup>7</sup>	Patients with reflux symptoms (history of PPI response NR) (n = 15)	NR	73	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during one night, following a large meal	92% <sup>†</sup>	8% <sup>†</sup>		NR
Pace <i>et al.</i> , 2007 <sup>8</sup>	Patients with reflux symptoms (history of PPI response NR) (n = 7)	Without RE, n = 5; with RE, n = 2	347	Number of acid and weakly acidic/alkaline reflux episodes for each patient during 24 h; inclusion of meal periods NR	49% <sup>†</sup> (without RE: 55% <sup>†</sup> ; with RE: 33% <sup>†</sup> )	51% <sup>†</sup> (without RE: 45% <sup>†</sup> ; with RE: 67% <sup>†</sup> )		NR

Ref.	Study population off PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Vela <i>et al.</i> , 2001 <sup>10</sup>	Patients with reflux symptoms (history of PPI response NR) (n = 12; correlation of reflux episodes with symptoms conducted in a subset of 5 patients)	NR	217	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; inclusion of meal periods NR	45%	55%		69% of acid and 57% of weakly acidic/alkaline reflux episodes were symptomatic; 37% of symptomatic reflux episodes were acid and 63% were weakly acidic/alkaline; 84% of symptomatic acid reflux episodes were associated with heartburn and 56% with regurgitation; 71% of weakly acidic/alkaline reflux episodes were associated with heartburn and 52% with regurgitation.
Vela <i>et al.</i> , 2003 <sup>19</sup>	Patients with heartburn (history of PPI response NR) (n = 9) <sup>‡§</sup>	NR	253	Number of total, acid and weakly acidic/alkaline reflux episodes during 24 h; inclusion of meal periods NR Symptoms and reflux were considered to be associated if a reflux episode was detected 5 min before the symptom	60% <sup>†</sup>	40% <sup>†</sup>		49% <sup>†</sup> and 29% <sup>†</sup> of acid and weakly acidic/alkaline reflux episodes were symptomatic, respectively; 72% <sup>†</sup> and 21% <sup>†</sup> of symptoms were related to acid and weakly acidic/alkaline reflux episodes, respectively

Ref.	Study population off PPI therapy	Esophageal injury	Number of reflux episodes analysed	Data analysis	Proportion of reflux episode types*			Correlation of acid vs weakly acidic/alkaline reflux episodes with symptoms
					Acid	Weakly acidic	Weakly alkaline	
Weigt <i>et al.</i> , 2007 <sup>11</sup>	Patients with reflux symptoms (history of PPI response NR) (n = 16)	NR	3591; NR separately for patients on/off PPI therapy	Frequency of weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded	49% <sup>†</sup>	51%		25% and 36% of symptoms were related to acid and weakly acidic/alkaline reflux episodes, respectively; SI was similarly often positive with weakly acidic/alkaline and acid reflux (values NR)
Xiao <i>et al.</i> , 2009 <sup>20</sup>	Patients with GERD (history of PPI response NR) (n = 42) <sup>‡</sup>	Without RE, n = 22; with RE, n = 20	NR	Frequency of acid, weakly acidic and weakly alkaline reflux episodes as a proportion of all reflux episodes during 24 h; meal periods excluded	Without RE: 56% With RE: 65%	Without RE: 43% With RE: 33%	Without RE: 1% With RE: 2%	NR
Zentilin <i>et al.</i> , 2005 <sup>21</sup>	Patients with heartburn (history of PPI response NR) (n = 10) <sup>§</sup>	Without RE, n = 7; with RE, n = 3 (data NR separately)	112	Frequency of acid and weakly acidic/alkaline reflux episodes as a proportion of all reflux episodes during 1 h without meals	75% <sup>¶</sup>	25% <sup>¶</sup>		NR

\*Reflux episodes were defined as acidic if pH < 4, as weakly acidic if pH 4–7 and as weakly alkaline if pH > 7.

<sup>†</sup>Value calculated from data provided in the publication.

<sup>‡</sup>The study also included patients without GERD, for whom the data are not included here.

<sup>§</sup>Data not reported separately for acid and weakly acidic/alkaline reflux episodes.

<sup>¶</sup>Value estimated from graph.

<sup>§</sup>The study also included a GABA<sub>B</sub> agonist or alginate treatment arm, data for which are not reported here.

<sup>‡</sup>Baseline data

BE, Barrett's esophagus; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; LA, Los Angeles classification; MII-pH, combined multichannel intraluminal impedance and pH monitoring; NR, not reported; PPI, proton pump inhibitor; RE, reflux esophagitis.

**Table S3.** Correlation of acid versus weakly acidic/alkaline reflux episodes with symptoms in individuals with GERD on or off PPI therapy.

Ref.	n	Symptoms recorded	Definition of symptom-related reflux episode	Proportion of reflux–symptom episodes associated with acid vs weakly acidic/alkaline reflux			
				On PPI		Off PPI	
				Acid*	Weakly acidic/alkaline*	Acid*	Weakly acidic/alkaline*
Emerenziani <i>et al.</i> , 2008 <sup>3</sup>	52 (of whom 20 had RE)	Heartburn, regurgitation	Reflux $\leq$ 2 min before symptom	N/R	N/R	Without RE: 78%; with RE: 88%	Without RE: 22%; with RE: 12%
Iwakiri <i>et al.</i> , 2009 <sup>5</sup>	13	Heartburn, chest pain, dysphagia, throat pain, oppression	Reflux $\leq$ 5 min before symptom	9%	91%	–	–
Tutuian <i>et al.</i> , 2008 <sup>9</sup>	120	Typical and atypical reflux symptoms (not specified further)	Reflux $\leq$ 5 min before symptom	16% <sup>‡</sup>	84% <sup>‡</sup>	–	–
Vela <i>et al.</i> , 2001 <sup>10</sup>	5 (subset)	Heartburn, regurgitation, acid taste	Reflux $\leq$ 2 min before symptom	5%	95%	37%	63%
Vela <i>et al.</i> , 2003 <sup>19</sup>	9	Heartburn, regurgitation, acid taste	Reflux $\leq$ 5 min before symptom	–	–	78%	22%
Weigt <i>et al.</i> , 2007 <sup>11</sup>	16	Heartburn, regurgitation, chest pain, upper abdominal pain, coughing, sore throat, globus, pressure, burning of the tongue	NR	25%	75%	50%	50%
Zerbib <i>et al.</i> , 2008 <sup>12</sup>	20	Heartburn, regurgitation	Reflux $\leq$ 2 min before symptom	Heartburn: 32%; regurgitation: 20%	Heartburn: 68%; regurgitation: 80%	–	–

\*Reflux episodes were defined as acidic if pH < 4, as weakly acidic if pH 4–7 and as weakly alkaline if pH > 7.

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; RE, reflux esophagitis.

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